Janssen Vaccines & Prevention B.V.*

Statistical Analysis Plan

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

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.

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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Amended Statistical Analysis Plan VAC18193RSV2001_SAP_Amendment 2	3-April-2020
Amended Statistical Analysis Plan VAC18193RSV2001_SAP_Amendment 3	29- May -2020
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Amended Statistical Analysis Plan VAC18193RSV2001_SAP_Amendment 6	23-July-2021
Amended Statistical Analysis Plan VAC18193RSV2001_SAP_Amendment 7	11-July-2022

Amendment 7
Following CBER comments and to align with the Phase 3 studies, the follow-up time, for the End of Efficacy analysis will start from Day 14 Post-Dose instead of Day of Vaccination. Details on the analysis of potential AESIs determined programmatically are included. All AESI analyses will be presented by phase as well as by time interval. The definitions of these time intervals were added. Additionally, for solicited AEs, the denominator for the percentages will be the number of participants with data assessed by the PI in the considered population and phase for a certain regimen (incidence per 100 participants/phase) and risk level.

The Per Protocol Efficacy Set and the follow-up time were updated for the analyses across the three RSV seasons. Analyses focusing on season two and three were added as well. Further, the emergency department visit details were updated to specify that only emergent MRU will be retained. The scoring of the Patient Global Impression of Health (PGI-H) was updated to align with the Phase 3 studies. Additionally, details on the approximate ARI surveillance compliance were added for the analysis across RSV seasons. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was added to the list of respiratory viruses used to define coinfections.

Clarifications were made to the section on the calculation of an ARI duration and determination of new onset or worsening. Information was added to Section 5.1. regarding subject information. And some exploratory immunogenicity assays were added.

The footnote regarding the use of a relative day 365/day 730 was updated to only use such a relative date when no scheduled/unscheduled visit is present and when there is still ARI surveillance present after this date.

Amendment 6 23-July-2021
The primary reason for the amendment: The SAP was amended to align with Protocol Amendment 5 and 6 and to include information on the statistical analysis of the third RSV season and the additional Revaccination Subcohorts. Additionally, very rare events of thrombosis with thrombocytopenia syndrome (TTS) will be followed as an AESI in the Revaccination Subcohorts of this study. The visit window of Day 365 was updated to align with the CTP amendment.

Clarification and/or updates on the analysis were added in the following sections:

- 1.2. Study design updated to include the Revaccination Subcohorts
- 1.6. Changes to Planned Analysis
- 2.1.1. Phase definitions
- 2.1.2. Immunogenicity visit windows
- 2.3. Analysis Sets
- 3.3. Analysis 28 Days Post Second Vaccination in Revaccination Subcohorts A, B, C and D
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- 4.1.1. Demographics and Baseline Characteristics
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- Section 5: Revaccination Subcohorts and Second and Third RSV Season Analysis
- Attachment 1: Transforming Solicited AEs into Analysis Format
- Attachment 10: Clinically Relevant Complication AE terms

Amendment 5 20-April-2021

Clarifications were added in the 'Phase definitions' section.

Amendment 4 11-January-2021

The primary reason for the amendment: The SAP was amended to align with the Protocol Amendment 4 and to include information on the statistical analysis of the second RSV season.

Clarification and/or updates on the analysis were added in the following sections:

- Study design updated to include revaccination subcohort
- Phase definitions
- Analysis Sets
- Season 2 efficacy analysis
- Combination of adverse events
- Immunogenicity visit windows

Moreover, at Section 4.9.1 and 4.10.1 the vaccine efficacy analysis for the clinically relevant diseases and new therapeutic interventions was updated to include an exact Poisson test, instead of an exact Binomial one, to align with the analysis of the primary endpoint.

The exact Binomial and the exact Poisson provide nearly identical vaccine efficacies and confidence intervals (the difference is less than 0.5%).

Finally, tetrachoric and polychoric correlations were used in order to evaluate the correlation of the RiiQ symptoms collected at the site and by the participant, instead of Kendall's rank correlation coefficient .

Other minor corrections in punctuation were made throughout the document.

Amendment 3 (29 May 2020)

The primary reason for the amendment: The SAP was amended:

- To align with CTP amendment 3 (removal of the year 1 vaccination in the description of the design, G-ELISA is now an exploratory immunogenicity endpoint)
- to remove emergency department visits from the hospitalization definition
- to update the definition of a treatment - emergent medical resource
- to add details on how to calculate the percentage of compliance with RiiQ assessments

Some additional small clarifications were made throughout the document.

Amendment 2 (3 April 2020)

The primary reason for the amendment: The SAP was amended to clarify that RT-PCR results from samples that were out of stability are excluded from the analysis, regardless if they were RSV positive or RSV negative.

- For the primary endpoint, those samples received out of stability are not taken into account
- In the sensitivity analysis based on the FAS, those samples that were out of stability are included if they tested RSV positive
- For the multiple imputations model, samples received out of stability are considered missing.

Amendment 1 (1 April 2020)

The primary reason for the amendment: The SAP was amended to align with the Protocol Amendment 2. Moreover, clarification on the analysis were added:

- The definition of the baseline
- EMA and CEC exploratory endpoints added
- Handling missing RiiQ items in calculations of total scores and frailty indexes
- Conditional power algorithm added
- New Concomitant medication definition added
- Handling missing oxygen saturation and respiratory rate in calculation of symptoms added
- The end of the ARI surveillance was updated based on the amended Protocol.

Other minor corrections in punctuation were made throughout the document.

ABBREVIATIONS

AE	adverse event
AESI	Adverse event of special interest
ARI	Acute respiratory infection
AUC	Area under the curve
BMI	body mass index
CI	confidence interval
CP	Conditional power
CDC	Centers for Disease Control and Prevention
CKD	Chronic Kidney Disease
CRF	case report form
CSR	Clinical Study Report
DPS	Data presentation specifications
ECG	Electrocardiogram
eCRF	electronic case report form
ELISA	Enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
FA	Full Analysis Set
ePRO	electronic patient-reported outcome
F protein	fusion protein
FDA	Food and Drug Administration
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IF	Information Fraction
IF	Information Fraction
IF	Information fraction
ITT	Intent-to-Treat
ICS	Intracellular Cytokine Staining
IU/ml	International units per milliliter
IVRS	interactive voice response system
LLOQ	lower limit of quantification
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
MPD	Major Protocol Deviation
NA	Not Applicable
NH	Northern hemisphere
PA	Primary Analysis
PD	Pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)
PP	Per Protocol
POC	Proof of concept
PPE	Per protocol efficacy
PPI	Per protocol immunogenicity
RiiQ	Respiratory Infection Intensity and Impact Questionnaire
RR	Relative ratio
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
RWE	Real world evidence
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
TLF	Tables, Listings and Figures

TTS	Thrombosis with Thrombocytopenia Syndrome
SH	Southern hemisphere
ULOQ	upper limit of quantification
VE	Vaccine Efficacy

1. INTRODUCTION

This is the Statistical Analysis Plan (SAP) applicable for the VAC18193RSV2001 proof-of-concept (POC) study. This SAP is applicable for all analyses up to the end of the third RSV season analysis, as well as for all analyses regarding the Revaccination Subcohorts as described in the clinical trial protocol (CTP) under Section 11.12. Note that the validation of the PRO questionnaires and the correlate of protection analysis will be described in separate SAPs.

This document contains all information needed for performing a full efficacy, safety, and immunogenicity analysis. The tables, listings, and figures (TLF) required for each analysis will be described in separate data presentation specifications (DPS) documents.

1.1. Study Objectives

Please refer to Section 2.1 in the CTP.

1.2. 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 Ad26.RSV.preF/RSV preF protein mixture or placebo intramuscularly (Table 1).

At Day 365, a subcohort of Cohort 1 participants will be identified and will be revaccinated, to assess safety and immunogenicity of a second vaccination. This Revaccination Subcohort (N=240) will consist of at least 120 participants who received active study vaccine on Day 1 and 120 participants who received placebo on Day 1, and who have given informed consent for the additional study procedures. Additional Revaccination Subcohorts were 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 the table below (Table 1).

During all 3 RSV seasons, as well as between the second and third RSV season, participants in cohort 1 will be followed-up twice per week to monitor for symptoms that could indicate an ARI. 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 Subcohorts C and D. Please refer to Section 3.1 in the CTP for further details.

Table 1: Study Design: VAC18193RSV2001

Cohort/Group/ Subcohort	Day 1 Vaccination	Day 365 (Month 12) Revaccination	Month 24 Revaccination	Month 36 Revaccination	Month 48 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	
Revaccination Subcohort 1D[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	
Revaccination Subcohort 2D[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 in the CTP). 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

Table 1: Study Design: VAC18193RSV2001

Cohort/Group/ Subcohort	Day 1 Vaccination	Day 365 (Month 12) Revaccination	Month 24 Revaccination	Month 36 Revaccination	Month 48 Revaccination
		(Amendment 4)	(Amendment 5)		

SH, no sites will be opened in the SH and the study will be performed as a NH study only (see Section 11.12 in the CTP).
[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 Subcohorts C and D 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

1.3. Statistical Hypotheses for Study Objectives

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

- The null hypothesis is that the VE for each of the 3 primary endpoints (see Section 4.4.2) is ≤0%
- The alternative hypothesis is that the VE for at least one of the primary endpoints is >0%

No formal hypothesis on safety and immunogenicity will be tested.

1.4. Sample Size Justification

Please refer to Section 11.2 in the CTP.

1.5. Randomization and Blinding

Please refer to Section 5 in the CTP.

1.6. Changes to Planned Analysis

Additional details were added for several exploratory endpoints.

Moreover, all RT-PCR confirmed RSV cases, during the first RSV season will be evaluated by a Clinical Evaluation Committee (CEC) and classified as mild, moderate, or severe RT-PCR confirmed RSV-mediated diseases. See CEC Charter (EDMS-ERI-51904526) for further details on the CEC responsibilities. Based on the CEC evaluation the following exploratory endpoints were added:

- first occurrence of an RT-PCR confirmed RSV LRI assessed as at least mild by the CEC
- first occurrence of an RT-PCR confirmed RSV LRI assessed as at least moderate by the CEC.
- first occurrence of an RT-PCR confirmed RSV LRI assessed as severe by the CEC.

Finally based on EMA comments two additional exploratory endpoints were added to the analysis of the first RSV season.

In comparison to the immunogenicity analysis described in the CTP (Section 11.9.2) for all Revaccination Subcohorts (and not only for Revaccination Subcohort A with revaccination at day 365) 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.

Categorical BMI was updated to align with the Phase 3 studies to include the categories '< 18.5 kg/m²', '18.5 to < 25 kg/m²', '25 to < 30 kg/m²' and '>= 30 kg/m²'. Additionally, smoking status was updated. Participants who use used nicotine patches or gum are no longer being considered as a smoker. Details were added to the analyses of analgesics and antipyretics to specify the period assignment if usage begins on day of vaccination.

The fourth sensitivity analysis in Section 4.4.2.2. was updated. The specificity for RSV A for the GenMark assay is 93%-96% and for RSV B its 95%-97% which might result in more false positives compared to GeneXpert (specificity of 99-100%). Therefore, the DDL results were used to determine RSV positivity of the ARI for cases where the results of GeneXpert and GenMark differ.

In comparison to the objectives and endpoints in the CTP, first occurrence of RT-PCR-confirmed RSV-mediated LRTD during the second, third, across the second and third and across all three RSV seasons will only be analysed according to Case Definition 1. Additionally, the efficacy endpoints will not be analysed across the first two RSV seasons, only across season 2 and 3 and across all three RSV seasons.

Following CBER comments and to align with the Phase 3 studies, the follow-up time during the RSV Seasons was updated to be defined as the time between 14 days post-vaccination and the occurrence of the first event, instead of as the time between vaccination and the occurrence of the first event. This update is not applied to the primary analysis (described in Section 3.1 and Section 4), but only to the end of efficacy study analysis (described in Section 3.6 and Section 5).

Details on the calculation of duration of an ARI episode were added to Section 4.4.2.1.3. to clarify the approach that was used during the Primary Analysis of the first RSV season. Additionally, a note was added to the description of determining a new onset or worsening to Section 4.4.2.1.1 to clarify the approach for RSV Season 2 and 3.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Study Phases

A baseline (or reference) value for safety and immunogenicity will be defined as the value of the last available assessment prior to the first vaccination on Day 1. If there was no immunogenicity assessment done pre-vaccination, the assessment post-vaccination on Day 1 can be used as the baseline value for the immunogenicity analysis, if available.

A baseline (or reference) value for the efficacy analysis of the first RSV season will be defined as the worst value of the available assessment at Day 1 visit, if Day 1 visit is not available the Day 1 unscheduled visit closest to the day of vaccination will be used. In case two or more assessments are available at the same visit or at the same day of the selected baseline visit (for example assessments both at the eDiary and eDevice) the worst will be used (per question).

A new baseline (or reference) value for the efficacy analysis of the second and third RSV season will be defined as the worst value of the available assessment at Day 365/Day 730 visit, if Day 365/Day 730 visit is not available the Day 365/Day 730 unscheduled visit closest to the relative day 365/day 730 will be used. In case no Day 365/Day 730 visit (schedule or unscheduled) is available then the baseline of the first/second (or first) RSV season will be used. In case two or more assessments are available at the same visit or at the same day of the selected baseline visit (for example assessments both at the eDiary and eDevice) the worst value will be used (per question).

The safety analysis will present all results by period, unless specified otherwise. Immunogenicity results will be presented per analysis time point (see Section 2.1.2) as appropriate. Listings will be shown per phase, period and time point. Efficacy results will be presented across the entire season or per timepoint, where appropriate.

Study day or relative day is defined as follows:

Study Day = visit date - date of Day 1 + 1; if visit date > date of Day 1 (date of first vaccination).

Study Day = visit date - date of Day 1; if visit date < date of Day 1 (date of first vaccination).

2.1.1. Phase Definitions

The phases in the study will be constructed as outlined in Table 2 for all participants, excluding revaccination periods:

Table 2: Phase Definitions all subjects (excluding revaccination periods)

Phase	Phase #	Period	Period #	Interval	
				From	To
Screening	1			Date and time of signing the informed consent form	One minute prior to start of post dose 1 period
Regimen	2	Post-dose	1	Date and time of first vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation from study) b) 23:59 at the date of database cut-off date c) Maximum (28 days after first vaccination at 23:59, scheduled visit 4 weeks after first vaccination at 23:59)

Table 2: Phase Definitions all subjects (excluding revaccination periods)

Phase	Phase #	Period	Period #	Interval	
				From	To
First Year Follow up	3			One minute after Post-dose period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation from study) b) 23:59 at the date of database cut-off date c) 23:59 at the day before the Day 365 visit** (for participants not in Revaccination Subcohort A) d) One minute prior to the revaccination (for Revaccination Subcohort A)
Second Year Follow up	4			One minute after: a) post-revaccination period for participants in Revaccination Subcohort A b) first year follow up phase for the remaining participants	Minimum of: a) 23:59 at the Date of last contact (for early discontinuation or participants that completed the study (Revaccination Subcohort A)) b) 23:59 at the date of database cut-off date (in case of interim) c) 23:59 at the day before the Day 730 visit** (for participants in Revaccination Subcohorts C and D and for ongoing participants in Cohort 1) d) One minute prior to the revaccination (for Revaccination Subcohorts B and 2A)
Third Year Follow up	5			One minute after: a) post-revaccination for participants in Revaccinat	Minimum of: a) 23:59 at the Date of last contact (for early discontinuation or participants that completed the study (Cohort 1 and Revaccination Subcohorts

Table 2: Phase Definitions all subjects (excluding revaccination periods)

Phase	Phase #	Period	Period #	Interval	
				From	To
				ion Subcohorts B and 2A b) Second year follow-up for the remaining participants (except Revaccination Subcohort 1A)	1B and 2A)) b) 23:59 at the date of database cut-off date (in case of interim) c) 23:59 at Day 1 Vaccination + 1094 (for participants in Revaccination Subcohort D) d) One minute prior to the revaccination (for Revaccination Subcohort C and 2B)
Fourth Year Follow up	6			One minute after: a) post-revaccination for participants in Revaccination Subcohorts C and 2B b) Third year follow-up for the participants in Revaccination Subcohort D	Minimum of: a) 23:59 at the Date of last contact (for early discontinuation or participants that completed the study (Participants in Revaccination Subcohorts 2B and C) b) 23:59 at the date of database cut-off date (in case of interim) c) One minute prior to the revaccination (for Revaccination Subcohort D)
Fifth Year Follow up	7			One minute after: a) post-revaccination for participants in Revaccination Subcohort D	Minimum of: a) 23:59 at the Date of last contact (for early discontinuation or participants that completed the study (Revaccination Subcohort D) b) 23:59 at the date of database cut-off date

Additional phases will be applicable for the participants in the Revaccination Cohorts (Table 3):

Table 3: Phase Definitions from revaccination onwards

Phase	Phase #	Period	Period #	Interval	
				From	To
Regimen	8	Post-Revaccination 1[+]	2	Date and time of second vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation from study) b) 23:59 at the date of database cut-off date c) Maximum (28 days after second vaccination at 23:59, scheduled visit 4 weeks after second vaccination at 23:59)
Regimen	9	Post-Revaccination 2[++]	3	Date and time of third vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation from study) b) 23:59 at the date of database cut-off date c) Maximum (28 days after third vaccination at 23:59, scheduled visit 4 weeks after third vaccination at 23:59)

The combination of 'Post dose' period and 'First Year follow up' period will be referred as 'Year One'.
The combination of a 'Post-Revaccination' period and 'XXX Year Follow up' period will be referred as 'Year XXX'. The combination of multiple years will be referred as the 'Overall' phase.

* time refers to hours and minutes

** If Day 365/730/1095/1460/1628 is missing, then the relative day 365/730/1095/1460/1628 will be used to define the end of the 'First/Second/Third/Fourth/Fifth Year follow up' period. For Day 365/Day 730 this will only be done given that there are ARI surveillance questions available after this relative day to avoid creating artificial follow-up phases when there were actually none present.

[+]Only participants that are part of the Revaccination Subcohorts will have a post-revaccination period.

[++]Only participants that are part of the Revaccination Subcohorts 2A and 2B will have a third vaccination, and thus will have a second post-revaccination period.

2.1.2. Immunogenicity Visit Windows

For immunogenicity summaries and tabulations per time point, assessments will be allocated to an analysis visit based on the planned visit as captured in the CRF. Visits that are out of the protocol-defined visit windows (see table below) will not be included in the immunogenicity summaries and tabulations per timepoint. However, they may be included in sensitivity analyses.

Analysis timepoint	Subset	Reference day	Target day (counted from the reference day)	Window
Baseline	Immuno Subset / All Revaccination Subcohorts	Day of vaccination 1	1	(-inf, 1]
Day 15	Immuno Subset / All Revaccination Subcohorts	Day of vaccination 1	15	[15, 18]
Day 85	Immuno Subset	Day of vaccination 1	85	[78, 92]
Day 169	Immuno Subset	Day of vaccination 1	169	[155, 183]
Day 365	Immuno Subset / Revaccination Subcohort 1B, 2B, 1C, 2C, 1D and 2D	Day of vaccination 1	365	[304, 426]
Day 365	Revaccination Subcohorts 1A, 2A	Day of vaccination 2	1	[1]
Day 379	Revaccination Subcohorts 1A, 2A	Day of vaccination 2	15	[15, 18]
Day 393	Revaccination Subcohorts 1A, 2A	Day of vaccination 2	29	[29, 32]
Day 449	Revaccination Subcohorts 1A, 2A	Day of vaccination 2	85	[78, 92]
Day 533	Immuno Subset	Day of vaccination 1	533	[519, 547]
Day 533	Revaccination Subcohorts 1A, 2A	Day of vaccination 2	169	[155, 183]
Day 730	Immuno Subset	Day of vaccination 1	730	[669, 791]
Day 730	Revaccination Subcohort 1A	Day of vaccination 2	365	[334,396]
Day 730	Revaccination Subcohort 1B, 2B	Day of vaccination 2	1	[1]
Day 730	Revaccination Subcohort 2A	Day of vaccination 3	1	[1]
Day 737	Revaccination Subcohort 1B, 2B	Day of vaccination 2	8	[6, 10]
Day 737	Revaccination Subcohort 2A	Day of vaccination 3	8	[6, 10]
Day 744	Revaccination Subcohort 1B, 2B	Day of vaccination 2	15	[15, 18]
Day 744	Revaccination Subcohort 2A	Day of vaccination 3	15	[15, 18]
Day 758	Revaccination	Day of vaccination 2	29	[29, 32]

Analysis timepoint	Subset	Reference day	Target day (counted from the reference day)	Window
	Subcohort 1B, 2B			
Day 758	Revaccination Subcohort 2A	Day of vaccination 3	29	[29, 32]
Day 814	Revaccination Subcohort 1B, 2B	Day of vaccination 2	85	[78, 92]
Day 814	Revaccination Subcohort 2A	Day of vaccination 3	85	[78, 92]
Day 898	Revaccination Subcohort 1B, 2B	Day of vaccination 2	169	[155, 183]
Day 898	Revaccination Subcohort 2A	Day of vaccination 3	169	[155, 183]
Day 912	Immuno Subset	Day of vaccination 1	912	[898, 926]
Day 1095	Revaccination Subcohort 1C and 2C	Day of vaccination 2	1	[1]
Day 1095	Revaccination Subcohort 1B	Day of vaccination 2	365	[334,396]
Day 1095	Revaccination Subcohort 2B	Day of vaccination 3	1	[1]
Day 1095	Revaccination Subcohort 2A	Day of vaccination 3	365	[334,396]
Day 1102	Revaccination Subcohort 2B	Day of vaccination 3	8	[6, 10]
Day 1109	Revaccination Subcohort 1C and 2C	Day of vaccination 2	15	[15, 18]
Day 1109	Revaccination Subcohort 2B	Day of vaccination 3	15	[15, 18]
Day 1123	Revaccination Subcohort 2B	Day of vaccination 3	29	[29, 32]
Day 1179	Revaccination Subcohort 1C and 2C	Day of vaccination 2	85	[78, 92]
Day 1179	Revaccination Subcohort 2B	Day of vaccination 3	85	[78, 92]
Day 1263	Revaccination Subcohort 1C and 2C	Day of vaccination 2	169	[155, 183]
Day 1263	Revaccination Subcohort 2B	Day of vaccination 3	169	[155, 183]
Day 1460	Revaccination Subcohort 1D and	Day of vaccination 2	1	[1]

Analysis timepoint	Subset	Reference day	Target day (counted from the reference day)	Window
	2D			
Day 1460	Revaccination Subcohort 1C and 2C	Day of vaccination 2	365	[334,396]
Day 1460	Revaccination Subcohort 2B	Day of vaccination 3	365	[334,396]
Day 1474	Revaccination Subcohort 1D and 2D	Day of vaccination 2	15	[15, 18]
Day 1544	Revaccination Subcohort 1D and 2D	Day of vaccination 2	85	[78, 92]
Day 1628	Revaccination Subcohort 1D and 2D	Day of vaccination 2	169	[155, 183]

Immunogenicity samples that are not contained in these windows will not be included in the analysis. However, they may be included in sensitivity analyses.

Immunogenicity samples taken during an ARI will be allocated to an analysis timepoint based on the relative day during the ARI and the below windowing. The relative day during the ARI is determined as ARI visit date – ARI onset date +1.

Analysis timepoint	Reference day	Target day (counted from the reference day)	Window
ARI Day 3-5	Onset day of ARI	4	[1,7]
ARI Day 29	Onset day of ARI	29	[22,36]

Immunogenicity samples that are not contained in these windows will not be included in the analysis of ARI samples. However, they may be included in sensitivity analyses.

2.2. Pooling Algorithm for Analysis Centers

Site was not part of the randomization algorithm. Data from all study sites will be pooled together.

2.3. Analysis Sets

Vaccination assignment will follow the as treated principle.

2.3.1. Full Analysis Set (FAS)

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 (i.e., the Safety Subset). The analysis of solicited and unsolicited AEs after revaccination on Day 365 (Month 12)/Day 730 (Month 24)/Day 1095 (Month 36)/Day 1460 (Month 48) will be restricted to participants of the Revaccination Subcohorts that are part of the FAS.

2.3.2. Per Protocol Immunogenicity Population (PPI)

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 (MPD) expected to impact the immunogenicity outcomes (based on the DV.DVSTDTC), will be excluded from the PPI. The list of major protocol deviations to be excluded from the immunogenicity analysis will be documented in the major protocol deviations criteria document that will be finalized prior to database lock. These will also be indicated in the locked database. The analysis of immunogenicity will focus on 5 subsets of the PPI, i.e. the Immuno Subset and the 4 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.

Moreover, immunogenicity samples taken outside of the prespecified visit windows (see Section 2.1.2) will be excluded from the immunogenicity analysis.

The PPI population is the primary immunogenicity population. For key tables, sensitivity immunogenicity analyses will also be performed on the FAS, including participants that are part of the Immuno Subset or the Revaccination Subcohorts for whom immunogenicity measures are available. Excluded samples (samples taken after the natural RSV infection or after major protocol deviations impacting immunogenicity and samples taken outside of the window) will be taken into account as well in the sensitivity analysis.

2.3.3. Per Protocol Efficacy Population (PPE)

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 major protocol deviations 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 RSV season only, the participants of Revaccination Subcohort A will additionally be excluded. For analyses focusing on data from the third RSV season, participants of Revaccination Subcohorts A and B will be excluded. For exploratory analyses focusing on data over season two and three and over all three 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 MPDs expecting to impact the efficacy outcomes and occurring up to the considered season will be **additionally** excluded from the PPE when focusing on data including the second or third RSV season. For exploratory analyses focusing on data over season two and three and over all three RSV seasons, only the data of the season in which the major MPDs expecting to impact the efficacy outcomes occur and the data of the seasons thereafter will be excluded. Note that in case an ARI started in RSV Season 1 or 2 and continues during Season 2 or 3 respectively, all ARI information will be considered part of the first or second year analysis, regardless if they were collected during the second or third year.

2.4. Definition of Subgroups

The following subgroups will be investigated for the primary endpoint and for key immunogenicity assays:

- Age categories (65-74 years, 75-84 years, ≥85 years), as collected
- Risk Level (increased risk/ non-increased risk), as collected (CDC definition)
- Risk Level (CDC definition + Chronic Kidney Disease [CKD] + Diabetes), per Medical History assessment (increased risk/ non-increased risk)
- Sex
- Region (northern and southern hemisphere), if applicable
- Race
- Baseline Frailty (0-0.1: not frail, 0.11-0.2: pre-frail, 0.21-0.45: frail, >0.45 most frail)

Demographic characteristics, study disposition, protocol deviations, safety, immunogenicity, and efficacy might also be analyzed by risk level.

Additional exploratory subgroup analysis may be performed.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

3.1. DATA MONITORING COMMITTEE REVIEW

The study will be formally monitored by an IDMC. In general, the IDMC will monitor safety data at regular timepoints to ensure the continuing safety of the participants. They will specifically focus on SAEs, adverse events of special interest (AESIs for subcohorts 2A, B, C and D) on

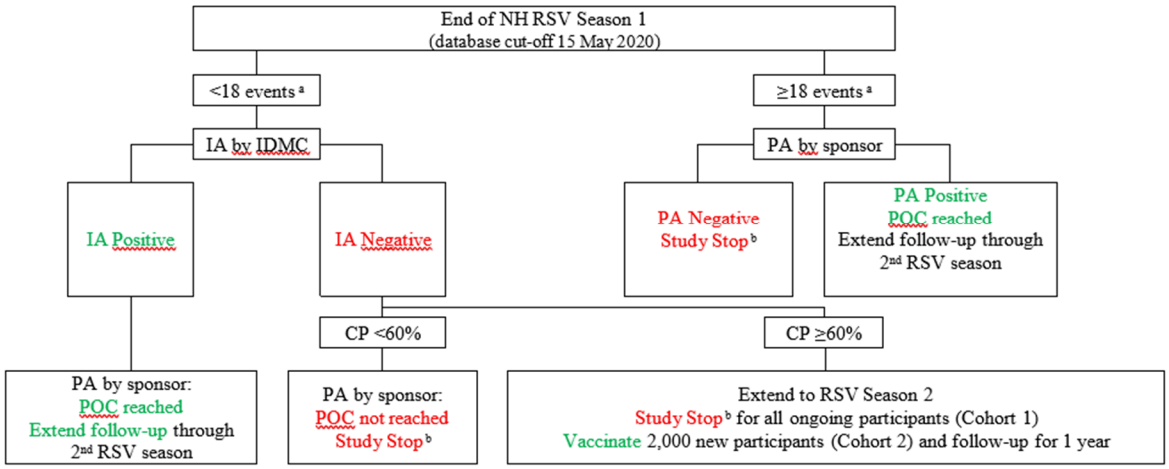
solicited and unsolicited AEs of grade 3 or higher, on unsolicited AEs (UAEs) leading to permanent discontinuation and on related UAEs. The analysis of AEs will be performed according to the specifications in Section 4.2.1. The IDMC members will be informed in case of related deaths and AESIs of study participants. In addition, the IDMC will formally monitor the efficacy endpoints at the time points specified below in the planned analysis plan.

A summary of the planned analysis is provided below, and in Figure 1 (in case the study is performed in the NH only), and in Figure 2 (in case the study is performed in both hemispheres).

In brief:

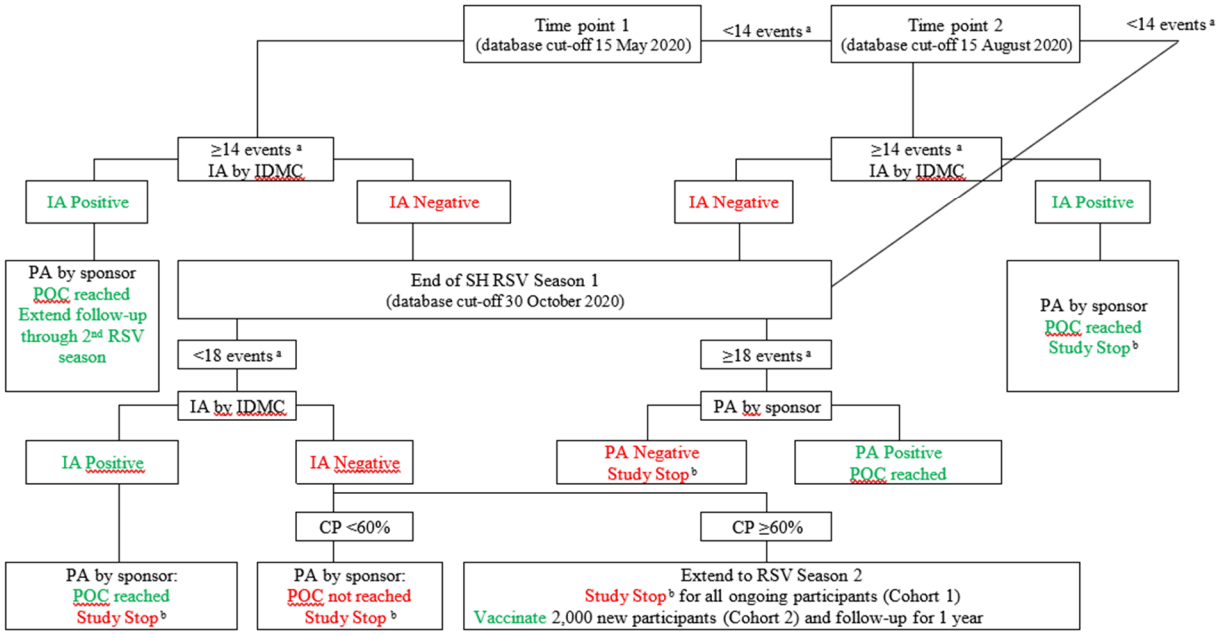
- If participants are only enrolled from the NH, the primary analysis will be performed at the end of the first NH RSV season, except if the incidence is exceptionally low (less than 18 observed RT-PCR-confirmed RSV-mediated lower respiratory tract disease (LRTD) events per Case Definition #2). **In that case, the independent data monitoring committee (IDMC) will perform an interim analysis (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 RSV season or 6 months after the last vaccination 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 (i.e., 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.

Figure 1: Flow Chart 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, 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 2: Flow Chart 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 <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

So 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).

More details regarding the IDMC roles, responsibilities and way of working are included in the IDMC Charter. This SAP will also be used to support the IDMC analyses. The following sections are applicable for the IDMC analyses: Section 4.2, 4.4.1 and 4.4.2.

3.2. Unplanned Snapshot Interim Analysis

An unplanned snapshot interim analysis 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 interim analysis will only be shared with select members of upper management not involved in the conduct of the study.

Since this unplanned snapshot interim analysis 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.

For further details see the Executive Committee Charter.

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

This analysis will be done for each Revaccination Subcohort (A, B, C, and D) 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.

Details on the outputs needed for these analyses are included in Section 5.

3.4. End of Season 2 Analysis

This analysis will include all efficacy, safety, and immunogenicity data collected during the second season. Data collected up to the time of the end of the second RSV season visit will be included in the analysis. 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.

Details on the outputs needed for this analysis are included in Section 5.

3.5. 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.

Details on the outputs needed for this analysis are included in Section 5.

3.6. 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 analysis will be performed on unblinded data.

Details on the outputs needed for this analysis are included in Section 5.

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

This analysis will be done for each Revaccination Subcohort (A, B, C, and D) 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.

Details on the outputs needed for this analysis are included in Section 5.

4. FIRST RSV SEASON ANALYSIS

4.1. SUBJECT INFORMATION

Subject information will be shown for the FA. Certain outputs will also show the Safety subset, PPI, PPE sets for all subjects as well as for the risk level (increased risk/ non-increased risk) subgroups.

4.1.1. Demographics and Baseline Characteristics

Demographic characteristics and screening/baseline characteristics will be summarized with descriptive statistics per vaccine regimen based on the FA, Safety subset, PPI, PPE sets as well based on the risk level of the subjects.

The following demographic and baseline characteristics will be summarized.

- Sex (Female/Male)
- Age (years)
- Age (categorical, 65-74 years, 75-84 years, ≥85 years), as collected

- Race
- Ethnicity
- Region (northern and southern hemisphere), if applicable
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI (categorical, < 18.5 kg/m^2, 18.5 to < 25 kg/m^2, 25 to < 30 kg/m^2, >= 30 kg/m^2)
- Smoking status
- Risk Level (increased risk/ non-increased risk), as collected (CDC definition) *
  - For subjects at increased risk additional subcategories are COPD, CHF, asthma, other chronic heart disease, other chronic lung disease (these categories will be defined based on the medical history of the participants)
- Baseline Frailty
- Baseline Frailty (categorical, 0-0.1: not frail, 0.11-0.2: pre-frail, 0.21-0.45: frail, >0.45 most frail)
- Risk Level (CDC definition + CKD + Diabetes) (increased risk/ non-increased risk), determined by medical history review prior to database lock *
- Number of Comorbidities of interest, based on the categories (CESCAT) from the medical conditions of interest list (see Section 4.1.5.1)

*: If for a participant no medical history records are available then this participant is considered as a non-increased participant, when looking at risk level as collected and for the broad definition.

4.1.2. Disposition Information

The number and percentage of subjects screened, subjects in the FA, PPI, PPE, Safety subset, subjects vaccinated and not randomized, subjects randomized and not vaccinated will be tabulated per vaccine group. The number and percentage of discontinued subjects (study discontinuation and vaccination discontinuation) with the reason of discontinuation will be tabulated for the FA, PPI, PPE and Safety subset per vaccine group, risk level subgroup and overall.

Also, the number of subjects and percentage per phase and period will be tabulated.

4.1.3. Protocol Deviations

Major protocol deviations will be summarized, per vaccine group, increased level subgroup and overall.

There will be special attention to major PDs related to the COVID19 outbreak.

4.1.4. Concomitant Medications

The analysis of concomitant therapies will be done using the WHO drug coded terms. Concomitant medications associated with SAE will be collected through the study, as well as 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.

There will be special attention to:

- analgesics/antipyretics such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin, that started being administered during 7 days following the vaccination (00:00 of day of vaccination + 7 days), based on the safety subset. The following codes will be used for this: N02A (OPIOIDS) and N02B (OTHER ANALGESICS AND ANTIPYRETICS), M01A (ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS) and M01B (ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION). The classes will be added in a footnote in all related tables and listings
- all concomitant medications for the safety subset
- concomitant medications related to SAEs, based on the FAS
- new concomitant medications associated with RT-PCR confirmed RSV ARI episodes and with complications of RT-PCR confirmed RSV ARI based on the PPE set. New concomitant medications are defined as medications not available at baseline or medication with an increased dosage (see Attachment 9: New Concomitant Medications for details), compared to baseline. Baseline medications are all medications reported prior to and at the day of vaccination. In case a baseline medication is reported multiple times then only the last available record reported prior to or at the day of vaccination will be used.

Based on their start and stop date, concomitant therapies will be reported in each applicable phase and period. For the use of analgesics/antipyretics which are taken on the day of vaccination, an exception is made in case the time is before vaccination. In this case, the concomitant medication is also allocated to the post-dose period.

If a concomitant therapy records misses components of its start and/or stop dates (day and/or month and/or year):

- In case of partial start or stop dates, the concomitant therapy records will be allocated to periods using the available partial information, without imputations. If, for example, only month and year are available, these will be compared to the month and the year of the periods, and the concomitant therapy record will be allocated to the period(s) where these date parts match. This rule may lead to assignment to multiple periods. The same rule applies for identifying whether a concomitant therapy was administered during 7 days following a vaccination. If for example, the vaccination was administered on the 30 December 2017 and the concomitant therapy start date is January 2018, then the concomitant therapy will be assumed to have started within 7 days of the vaccination.
- In case of a completely missing start date, the concomitant therapy will be considered as having started before the study.

- In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the study.

4.1.5. Medical History

General medical history will be tabulated.

4.1.5.1. Medical Conditions of Interest

The following medical conditions are of interest:

Categories	Medical Conditions of Interest
Endocrine	Diabetes mellitus
Liver illness	Hepatic cirrhosis
Cancer	Non-malignant tumor
Cardiac illness	Angina
	Arrhythmia
	Valvular (prosthetic aortic or mitral valves)
	Myocardial infarction
	Congestive heart failure (CHF)
Vascular illness	Peripheral vascular
	Hyperlipidemia
	Hypertension
	Cerebrovascular (stroke, transient ischemic attack)
Pulmonary illness	Asthma
	COPD
Renal illness	Chronic renal failure
	Nephrotic syndrome
Neuro-Muscular illness	Seizure disorder
	Spinal cord injury
	Parkinson’s
Gastrointestinal illness	Inflammatory bowel disease (Crohn's, ulcerative colitis)
	Peptic ulcer
	Gastroesophageal reflux disease
Mental Health Diagnoses	Depression
	Anxiety
	Bipolar mood disorder

These medical conditions of interest will be tabulated per category and group.

4.2. SAFETY

Safety analyses will be performed on the FAS. The analysis of solicited and unsolicited AEs will be restricted to the Safety Subset, whereas for the analysis of serious AEs (SAEs) the entire FAS will be used.

Continuous variables will be summarized using the following statistics, as appropriate: number of observations, median, minimum, and maximum. Frequencies and percentages (one decimal place)

will be generated for categorical variables. No formal comparisons between groups will be provided.

Safety data will be analyzed by vaccine regimens and by risk level. Denominator for the percentages is the number of subjects in the considered population and period for a certain regimen (incidence per 100 subjects/phase) and risk level.

Solicited and unsolicited AEs accidently captured for participants outside the Safety Subset, will be listed.

4.2.1. Adverse Events (AE)

Solicited AEs within 7-days post vaccination and unsolicited AEs within the 28-day period following the vaccination are collected only for the Safety Subset. SAE are collected for all participants.

4.2.1.1. Definitions

Solicited AEs shown in the tables and listings will be based on the overall assessment of the investigator. For unsolicited AEs, only the AEs and SAEs within the 28-day period following the vaccination will be presented in the safety tables. SAEs, will be captured and tabulated in outputs covering the whole study period. Unsolicited non-serious adverse events collected outside the 28-day period following the vaccination will be presented through listings. The number of subjects within the Safety subset will be used as a denominator for the solicited and unsolicited AEs, and the number of subjects in the FAS will be used as a denominator for the SAEs. Solicited AEs and unsolicited non-serious AEs should per protocol only be collected for the safety subset. If these would be reported by mistake for non-safety subset subjects, they will be listed separately.

Solicited local AEs will be by definition considered as related to the study vaccine.

The severity of the AEs will be classified as grade 1 to 4. The reporting of solicited AEs will be based on the investigator assessment as document in the CE domain. Solicited events of grade 0, not reported in the CE domain, will therefore not be reported in the AE analysis.

Any ARI recorded as an (S)AE in the eCRF will be excluded from any AE analysis if it is a confirmed RSV infection by RT-PCR (midturbinate swabs and sputum sample, when available) based on the central laboratory or if it is connected with a hospitalized confirmed RSV infection based on an FDA-approved RT-PCR test at the local laboratory.

4.2.1.2. Analysis of Adverse Events

Number and percentage of subjects with at least one particular AE (unsolicited/solicited) will be tabulated. Unsolicited AEs and SAEs will be summarized by System Organ Class and Preferred Term. Solicited AEs will be summarized by class (local, systemic) and preferred term.

For solicited AEs following tables will be provided: summary, by worst severity grade, at least grade 3, related (systemic only), time to onset (in days) and duration (in days) for all events and body temperature.

Note 1: Body temperature will be summarized based on the participants measurements.

Note 2: Duration is defined as number of days from the start of the event until resolution of the event. The time to first onset is defined as (date of first onset – reference date + 1). The reference date is the start date of the vaccination period.

For unsolicited AEs following tables will be provided: summary table (including SAE, fatal outcome, and discontinuation), all events, most frequent, grade 3, permanent stop of vaccine and related.

For SAEs following tables will be provided: all events and all related events.

Listings and/or subject narratives will be provided as appropriate, for those subjects who die, discontinue study vaccinations due to an AE, or experience a severe or serious AE.

4.2.1.3. Phase allocation of Adverse Events

As the analysis of solicited events will be based on the overall assessment of the investigator which is documented in the CE domain, ADAMs will be based on CE. Solicited events are allocated to the phases as described below, however they are always allocated to the respective post-dose period and will never be attributed to the screening phase. Time is not considered while attributing solicited AEs to phases.

For unsolicited AEs, the steps below are followed as well.

Step 1: Allocation of events to the periods:

Adverse events in the SDTM database are allocated to periods based on their start date/time.

- If the start date/time of an event falls between (or on) the start and stop date/time of a period, the AE is attributed to that period (emergent principle).
- In case of partial start or stop dates (i.e. time and/or day and/or month and/or year missing), the events are allocated to the periods using the available partial information on start and end date; no imputation will be done. If, for instance, the AE start date only month and year are available, these data are compared to the month and year information of the periods. This rule may lead to multiplication of the event as a consequence of its assignment to multiple periods.
- In case of a completely missing end date, the date is imputed by the cut-off date of the analysis for subjects still ongoing in the study, and by the end date of the last phase for subjects who discontinued or completed the study.
- In case of a completely missing start date, the event is allocated to the first active treatment phase (post dose 1 period), except if the end date of the AE falls before the start of the first active treatment phase (post dose 1 period).

Step 2: Combination of events:

Overlapping/consecutive events are defined as events of the same subject with the same preferred term which have at least 1 day overlap or for which the start date of an event is 1 day after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

1. If overlapping/consecutive events start in one of the following periods - Screening or follow up (i.e. non-active periods) - followed by an AE in a post-dose period (active period) - they are allocated to their respective periods and are considered as separate events.
2. In case overlapping/consecutive events start within a single period, they are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.
3. In case overlapping/consecutive events start in both an active period followed by a non-active period, they are allocated to the active period only and are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, treatment period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.
4. In case an active period is followed by another active period, and the overlapping/consecutive events start in both periods, they are allocated to their respective period and are considered as separate AEs. In case overlapping/consecutive events start in non-consecutive periods (regardless of active or non-active), they are allocated to their respective period and are considered as separate AEs.
5. In case a non-active period is followed by another non-active period, and the overlapping/consecutive events start in both periods, they are allocated to the first period and they are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

Remarks:

- Events can only be combined into one and the same AE if their start and stop dates are known.
- In case the completely missing end date is imputed (for period allocation), this date is also considered as a complete date.
- Time is not considered when determining overlap of events.

4.2.1.4. Missing Data

Missing data (grade, relationship) will not be imputed. Subjects who do not report an event will be considered as subjects without an event. An AE with a missing severity or relationship will be considered as an AE reported, but will be considered as not reported for the severity or relationship. For example, an AE with missing severity will be considered as an AE reported for

the analysis of any grade but will be considered as not reported for the analysis of grade 3. The analysis of solicited AEs will include the safety data as documented by the investigator.

4.2.2. Vital Signs and Physical Examination Findings

Vital signs (temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) are collected prior to vaccination and during the clinical assessment of an ARI episode for all subjects. The analysis of emerging vital sign abnormalities will be described in the clinical assessment section (Section 4.8).

Temperature will also be collected via the eDiary from vaccination until 7 days after the vaccination for Safety Subset participants. These temperatures will be allocated to predefined temperature intervals (from 37.5° C until 40°C, in steps of half degree increments; eg <37.5, 37.5-<38, 38-<38.5, … >40) and a table will be created, showing the maximum temperatures recorded during the safety follow up of the Safety Subset participants.

Abnormalities resulting from a physical examination will either be documented as medical history or as AE. Therefore, no physical examination specific tables or listings will be generated.

4.3. Immunogenicity Analysis

The analysis of immunogenicity will use the PPI set, focusing on the immunogenicity subset.

4.3.1. Secondary Endpoints

The following humoral and cellular immune responses will be measured as part of the evaluation of secondary objectives:

Immunogenicity against the insert:

Humoral immune response

- RSV A2 neutralizing titers of the vaccine-induced immune response
- Antibodies binding to RSV F protein in post-fusion and/or pre-fusion form (RSV F-protein enzyme-linked immunosorbent assay [ELISA])

Cell-mediated immune response

- ELISpot IFNγ assay (units: SFU/10^6 PBMC). An ELISpot assay is used to quantify the amount of peripheral blood mononuclear cells (PBMCs) able to produce IFNγ upon RSV F-protein peptide stimulation.

Immunogenicity against the vector:

- Adenovirus vector neutralization assay: This assay assesses neutralizing antibody responses against the Ad26 vectors.

4.3.2. Exploratory Endpoints

The following humoral and cellular immune responses may be measured as part of the evaluation of exploratory objectives:

Immunogenicity against the insert:

Humoral immune response

- RSV cross-neutralization of B strains using virus neutralization assay or other surrogate binding assays
- RSV cross-neutralization of other A strains using virus neutralization assay or other surrogate binding assays
- 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.

Cell-mediated immune response

- Analysis of T-cell responses to RSV F protein peptide-stimulated PBMC (ICS)
- Sequencing of B-cells: including but not limited to sequencing of BCR (B-cell receptor) or VH/VL (heavy/light chain characterization) for specificity

Immunogenicity against natural infection:

- Antibodies binding to Ga and/or Gb protein (ELISA)

4.3.3. Handling of Missing and/or Unquantifiable Immune Response Data

Missing immune response data will not be imputed.

Values below the lower limit of quantification (LLOQ) will be imputed based on the type of analysis. For the calculation of the geometric mean titer or medians, values below LLOQ will be imputed to LLOQ/2. While for the calculation of the geometric mean increases, values below LLOQ will be imputed to LLOQ.

For G- Elisa ARI Day 3-5 will be treated similar to a baseline and imputation for actual values and fold rise will follow the above.

For ICS assays: the LLOQ will be used if available and validated. In case no validated LLOQ is available then a provisional cut-off will be provided before DBL (only for total cytokine response). For the individual cytokine combinations of IFNγ, TNFa and IL2, negative values will be imputed with 0. For descriptive statistics or graphs on actual values, values below the LLOQ will also be imputed to a value of LLOQ/2.

Values above the upper limit of quantification (ULOQ) will be imputed to ULOQ.

The LLOQ and ULOQ values per assay will be available in the database.

4.3.4. Immune Response Analysis

No formal hypothesis on immunogenicity will be tested. Key immunogenicity assay results will also be analyzed for the subgroups defined in Section 2.4.

4.3.4.1. Immunogenicity Against the Insert:

4.3.4.1.1. Humoral Assays

For **VNA** and **ELISA** assays following results will be calculated: N, geometric mean[§] and corresponding 95% CI of the actual values and fold increases from baseline will be tabulated and graphically presented. *[§]calculate the mean and corresponding 95%CI of the log_2 transformed values, back-transform this mean [i.e. 2^mean] and CI [i.e. 2^CI].*

Actual values and fold changes from baseline are tabulated and shown as dot plots with dots for subject values, and the corresponding geometric mean and 95% CI per time point for each assay. In addition, GMT plots over time, combining the regimens in one graph (without individual subject dots) will also be created.

Ratios of actual values and of fold changes from baseline between humoral assays may also be presented.

Subject profiles of the actual values over time will be graphically presented.

Reverse distribution curves of the actual values will be provided for selected time points.

In the graphs, original values will be displayed on the log_2 scale.

A scatterplot with the VNA versus ELISA will be provided for the most important time points. In these scatterplots the actual values will be shown, even if they are below the LLOQ, but the LLOQ cut-off will be visualized in the graph per assay if some values are below LLOQ.

Other exploratory parameters maybe analyzed at the discretion of the sponsor.

4.3.4.1.2. Cellular Assays

For **ELISpot** following results will be calculated: N, median, quartiles and minimum and maximum of the actual values will be tabulated and graphically presented.

Tables with the corresponding descriptive statistics will be provided.

Subject profiles of the actual values over time will be graphically presented.

Actual values will be shown as box plots with dots for subject values, and the corresponding median and interquartile range per time point for each assay. In addition, box plots over time, combining the regimens in one graph (without individual subject dots) will also be created. For the graphs, original values will be displayed on the log_{10} scale.

For **ICS** and **PBMC secreted cytokines** (if available) possible analyses may include:

Total Cytokine response: the % of subsets expressing at least IFNγ, TNFa or IL2 will be calculated for CD4 and CD8.

Tables with the corresponding descriptive statistics will be provided.

Subject profiles of the actual values over time will be graphically presented.

Reverse distribution curves of the actual values will be provided for selected time points.

Actual values are shown as box plots with dots for subject values, and the corresponding median and interquartile range per time point for each assay.

In addition, box plots over time, combining the regimens in one graph (without individual subject dots) will also be created.

For all cytokine combinations (IFNg and/or TNFa and/or IL2) bar charts reflecting the median magnitude of each combination will be graphically presented. Tables with the corresponding descriptive statistics will be provided.

Th1 and Th2: Th1 is defined as %RSV-F specific CD4 T-cells IFNγ+ AND/OR IL2+ and Th2 as %RSV-F specific CD4 T-cells IL4+ AND/OR IL13+ AND CD40L+. Subject profiles and graphs of the actual values over time (box-plot type) will be created. In addition, at time points of interest, scatterplots of Th1 vs Th2 might be created.

For the graphs, original values will be displayed on the $\log_{10}$ scale.

Scatterplot with humoral and cellular assays may be provided for the most important time points.

The technical details for the calculation of the ICS values to be used in the graphs will be outlined in the DPS.

4.3.4.2. Immunogenicity Against the Vector

For Ad26-specific **VNA** following statistics will be calculated: N, geometric mean[§(see above for the calculation)] and corresponding 95% CI of the actual values.

Actual values will be tabulated and shown as dot plots with dots for subject values, and the corresponding geometric mean and 95% CI at baseline.

Subject profiles of the assays against the insert will be repeated, highlighting subjects with pre-existing immunity at baseline against the vectors.

Scatterplots with the Adeno assay at baseline versus the assays against the inserts will be provided for the most important time points. In these scatterplots the actual values will be shown, even if they are below the LLOQ.

4.4. EFFICACY

4.4.1. Analysis Specifications

4.4.1.1. Level of Significance

The α-levels for the primary efficacy analysis will be adjusted to:

- Account for multiple analyses. As the total number of events that will be observed is not known in advance, we will initially estimate the proportion of the total number of events (P_{IA}) at the IA and calculate the α level cut-off for the IA using ($P_{IA,}$ 1) as information fraction at the IA and final analysis and the Pocock rule. If the IA is not positive and the study continues, then the α level cut-off at the PA will be calculated based on the α spend at the IA and the IF recalculated using the actual number of events observed at the PA. The specific calculations are given below in Table 4 and Table 5.

And 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[1] .The exact value will be calculated based on the number of events observed for each case definition (see Table 6) at the time of analysis, targeting the same α-level for each of the 3 primary endpoints using the Pocock rule.

Both methods will be combined to come to a single cut-off that will be used to define significance for each case definition. The exact significance level will depend on the number of cases already observed at the time of (interim) analysis.

Table 4 and Table 5 describe how the significance level (alpha) will be spend based on the possible different scenarios. In both tables, event refers to a case based on case definition 2.

Table 4: In Case the Study is Performed at the Northern Hemisphere Only

Number of Events at End of First RSV Season	Interim Analysis	Primary Analysis
≥ 18 events*	***No interim analysis***	***The Primary analysis will be conducted by the Sponsor:*** The full alpha (α= 0.05) will be equally divided across the 3 primary endpoints based on the observed incidence of the 3 case definitions using Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to equally divide the alpha across the 3 endpoints.

Table 4: In Case the Study is Performed at the Northern Hemisphere Only

Number of Events at End of First RSV Season	Interim Analysis	Primary Analysis
<18 events*	***The Interim Analysis will be conducted by the IDMC.*** 1. Calculate the number of events observed (cases based on case definition #2). Suppose x events were observed. 2. In case the study is expanded to a second season (Cohort 2), based on the initial assumptions (2000 additional subjects, with 0.75% RSV incidence and expected 70% VE), 9 additional events are expected during the second season. 3. Based on 1 and 2, obtain the estimated proportion of events already observed ($P_{IA=}$ x/(x+9)) at the interim analysis and calculate the information fraction (IF) of the interim and the primary analysis. The IF, in this case is a 2-component vector containing the estimated proportion of events already observed at the interim analysis and the expected proportion of events at primary analysis (which is 1), so IF=(P_{IA},1) 4. Using this estimated IF and the Pocock's rule, divide the full alpha (α= 0.05) over the two planned analyses (Interim and Primary Analysis) resulting in equal significance cut-offs. This is α' to be used at the IA. 5. This calculated α' will be divided across the 3 primary endpoints based on the observed incidence of the 3 case definitions using Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to divide α' across the 3 endpoints. The use of the Pocock rule results in equal adjusted significance cut-offs for each CD.	***If Interim Analysis is positive or Interim Analysis is negative and Conditional Power < 60% then:*** The same α' will be used and equally divided across the 3 primary endpoints based on the observed incidence of each endpoint using Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to equally divide α' across the 3 endpoints. The use of the Pocock rule results in equal adjusted significance cut-offs for each CD. ***If Interim Analysis is negative and Conditional Power ≥60% then:*** 1. Calculate number of events observed throughout both seasons (x events observed in season 1 and y events observed in season 2) and the corrected IF of the interim and the primary analysis, so IF = (x/ (x + y), 1) 2. The remaining alpha will be spent using a user defined alpha spending function approach based on the α' that was already spent and the corrected IF of step 1. This is α" 3. The new calculated α" will be equally divided across the 3 primary endpoints based on the observed incidence of the 3 case definitions using Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to equally divide α" across the 3 endpoints. The use of the Pocock rule results in equal adjusted significance cut-offs for each CD.

*Number of RT-PCR confirmed RSV-mediated LRTD cases (based on Case Definition #2 based on the PPE).

Table 5: In Case the Study is Performed at the Northern and Southern Hemisphere

Timepoint/ Number of Events	Interim Analysis 1	Interim Analysis 2	Primary Analysis
Time point 1 or Time point 2 / ≥ 14 events*	**The Interim Analysis will be conducted by the IDMC.** 1. Calculate the number of events observed (cases based on case definition #2). Suppose x events were observed. 2. Based on epidemiological/disease transmission modeling and real-world evidence (RWE) (Attachment 2) obtain the estimated number of events expected until the end of the SH season 1. Suppose y additional events are expected. 3. Based on 1 and 2, obtain the estimated proportion of events already observed ($P_{IA=}$ x/ (x + y)) at the interim analysis and calculate the information fraction (IF) of the interim and the primary analysis. The IF, in this case is a 2-component vector containing the estimated proportion of events already observed at the interim analysis and the expected proportion of events at primary analysis (which is 1), so IF=(P_{IA},1) 4. Using this estimated IF and the Pocock's rule, divide the full alpha (α= 0.05) over the two planned analyses (Interim and Primary Analysis) resulting in equal significance cut-offs. This is α' to be used at the IA. 5. This calculated α' will	***No second interim analysis***	***If Interim Analysis 1 is positive, then:*** The same α' will be used and equally divided across the 3 primary endpoints based on the observed incidence of the 3 case definitions using Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to equally divide the alpha across the 3 endpoints. The use of the Pocock rule results in equal adjusted significance cut-offs for each CD.
		No second interim analysis	***If Interim Analysis 1 is negative but at the end of the SH RSV season ≥ 18 events* are observed:*** 1. Calculate number of events observed until the end of the SH RSV season (x observed at the time of the interim analysis and n additional events observed until the end of the SH RSV season). The corrected IF of the interim and the primary analysis is (x / (x + n), 1). 2. The remaining alpha will be spent using a user defined alpha spending function approach based on the α' that was already spent and the corrected IF of step 1. This is α" 3. The new calculated α" will be equally divided across the 3 primary endpoints based on the observed incidence of the 3 case definitions using Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to equally divide α" across the 3 endpoints. The use of the Pocock rule results in equal adjusted significance cut-offs for each CD.
		If Interim Analysis 1 is negative and at the end of the SH RSV season < 18 events*	***If Interim Analysis 2 is positive or Interim Analysis 2 is negative and Conditional Power < 60% then:***

Table 5: In Case the Study is Performed at the Northern and Southern Hemisphere

Timepoint/ Number of Events	Interim Analysis 1	Interim Analysis 2	Primary Analysis
	be divided across the 3 primary endpoints based on the observed incidence of the 3 case definitions using Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to divide α' across the 3 endpoints. The use of the Pocock rule results in equal adjusted significance cut-offs for each CD.	***are observed a second interim analysis will be conducted (potentially 3 analyses will be performed):*** 1. Calculate number of events observed throughout until the end of the SH RSV season (x observed at the time of the interim analysis and n additional events observed until the end of the SH RSV season). In case the study is expanded to a second season (Cohort 2), based on the initial assumptions (2000 additional subjects, with 0.75% RSV incidence and expected 70% VE), 9 additional events are expected during that second season. (Total expected number of events would be x+n+9) 2. Given the α' already spent in the 1st interim analysis, the remaining alpha will be equally spent between the second interim analysis and the primary analysis, using a search over a grid of possible α" with IF (x/(x+n+9), (x + n)/ (x +n+9), 1). The grid search will be performed between the interval α' and α (=0.05), initially by steps of size 0.001 (with possible refinement to smaller steps) until the α" at IA2 and PA are equal to each other up to 3 decimal places. 3. The new calculated α" will be equally divided across the 3 primary endpoints based on the observed incidence of the 3 case definitions using	The same α" will be used and equally divided across the 3 primary endpoints based on the observed incidence of each endpoint using Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to equally divide α' across the 3 endpoints. The use of the Pocock rule results in equal adjusted significance cut-offs for each CD. ***If Interim Analysis 2 is negative and Conditional Power ≥60% then:*** 1. Calculate number of events observed until the end of the second RSV season (x observed at the time of the first interim analysis, n additional events observed at the end of the SH RSV season and y additionally observed at the end of the second season). Total number of events observed throughout is x + n + y 2. The corrected IF of the two interims and the primary analysis is (x / (x + n+ y), (x + n)/ (x + n+ y), 1). 3. Given the α' already spent in the 1st interim analysis and α" has been spent in the 2nd interim analysis, the remaining alpha will be spent using a user defined alpha spending function approach based on α' and α" that were already spent and the corrected IF of step 2. This is α'" 4. The new calculated α'" will be equally divided across the 3 primary endpoints based on the observed incidence of the 3 case definitions using Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to equally divide α'" across the 3 endpoints. The use of the Pocock rule results in equal adjusted significance cut-offs for each

Table 5: In Case the Study is Performed at the Northern and Southern Hemisphere

Timepoint/ Number of Events	Interim Analysis 1	Interim Analysis 2	Primary Analysis
		Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to equally divide α" across the 3 endpoints. The use of the Pocock rule results in equal adjusted significance cut-offs for each CD.	CD.
End of SH RSV season / ≥ 18 events* (and no prior IA performed)	***No interim analysis***	***No interim analysis***	***The Primary analysis will be conducted by the Sponsor:*** The full alpha (α= 0.05) will be equally divided across the 3 primary endpoints based on the observed incidence of the 3 case definitions using Pocock rule. If n_1, n_2 and n_3 are the number of events per CD1, 2 and 3, then the corresponding IF= (n_1/n_3, n_2/n_3, 1) will be used to equally divide the alpha across the 3 endpoints. The use of the Pocock rule results in equal adjusted significance cut-offs for each CD.

* Number of RT-PCR confirmed RSV-mediated LRTD cases (based on Case Definition #2, based on the PPE).

For example: assume in a NH and SH study an IA is performed during the SH RSV season with 18 RT-PCR-confirmed RSV-mediated LRTD events observed. RWE data suggests that during the remainder of the SH season a further 8 events would be observed. So, the expected total number of events at the end of the SH season is 26 and 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 sensitivity analyses the corrected alpha level will be used and for the analyses of secondary and exploratory efficacy endpoints a 5% alpha will be used.

4.4.1.1.1. Conditional Power

Based on Figure 1 and Figure 2, there are two occasions that the IDMC will require to evaluate the conditional power. For a NH only study or a NH and SH study, the conditional power is required if at the end of the respective RSV seasons the incidence is exceptionally low (less than 18 observed RT-PCR-confirmed RSV-mediated lower respiratory tract disease (LRTD) events per Case Definition #2, based on the PPE set) and the interim analysis is negative.

The conditional power is calculated as follows:

1. Calculate the significance level at the IA, α'.
    - Study only performed in the Northern Hemisphere: See *'The Interim Analysis will be conducted by the IDMC'* part in Table 4. Use the significance level resulting from Table 4, step 4 in the corresponding cell.
    - Study performed in the Northern and Southern Hemisphere: see *'If Interim Analysis 1 is negative and at the end of the SH RSV season < 18 events* are observed a second interim analysis will be conducted (potentially 3 analyses will be performed)'* part in Table 5. Use the significance level resulting from Table 5, step 2 in the corresponding cell.
2. Simulate the number of Case definitions #2 expected at the end of the Season 2, 20000 simulations, assuming 900 additional participants per group (1000 per group assuming a 10% drop out rate), a 0.75% RSV incidence and an expected 70% VE.
3. For each of the 20000 simulations, calculate the adjusted significance level used for the final analysis and use an exact Poisson regression to compare active and placebo:
    a. Calculate total number of events observed until the end of the second RSV season (x observed at the time of the interim analysis, n number of events simulated for the second season) for each simulation. Total number of events throughout is x + n
    b. The corrected IF of the interim analysis and the final analysis is (x / (x + n), 1).
    c. Given the α' already spent in the interim analysis, the remaining alpha will be spent using a user defined alpha spending function approach based on α' that was already spent and the corrected IF. This will be α". Note: for each simulation α" will be slightly different.
    d. Use an exact Poisson model to compare active vs placebo, using the total sample size of both seasons and the total number of CD #2 cases across the 2 seasons (observed in season 1 and simulated from season 2). For the Poisson model stratification factors and offsets are not taken into account.
    e. Keep the one-sided p-value and compare it with the significance level from the previous step for each simulation.
2. Finally, the conditional power is the mean number of cases where the p-values obtained from step 3e is smaller than the significance level obtained from step 3c.

For example: assume in a NH only study with 5800 sample size (2900 active and 2900 placebo), at the time of the interim analysis there are in total:

- 5 RT-PCR confirmed RSV-mediated LRTD cases based on Case Definition #2, 4 in the placebo arm and 1 in the active and

Based on Table 4, we expect 9 additional Case Definition #2 events if we expand at season 2, so IF=(0.36,1) for the interim and final analysis. Using the IF and the Pocock's rule the two planned analysis will be evaluated at a 0.02874 significance level.

After simulating 20000 season 2 scenarios under the CTP assumptions, and performing the simulations, the conditional power is 50 %. The study will not be expanded.

4.4.1.2. Data Handling Rules

A sensitivity analysis using multiple imputations will be performed in order to evaluate the impact of missing RT-PCR results on the primary endpoint. RT-PCR results from samples that were out of stability are also considered missing. For ARIs where no RT-PCR result can be linked to the considered ARI episode (based on the rules defined in Section 4.4.2.1.2), the RT-PCR result (positive or negative) will be imputed using the period the ARI occurred, the geographic location (RSV census regions[a]), the age, the risk level of the participants and the severity of the episode as parameters in the model. If a single RT-PCR test is available, no imputation will be performed.

Moreover, the primary analysis model already accounts for drop outs (see Section 4.4.2.2), since participants follow up time is taken into consideration.

4.4.2. Primary Efficacy Endpoints

4.4.2.1. Definition

The three primary efficacy endpoints are first occurrence of RT-PCR confirmed RSV-mediated LRTD according to each of the 3 case definitions shown in Table 6:

Table 6: Case Definitions

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)
RT-PCR confirmation of RSV		

LRTI = lower respiratory tract infection

To meet the primary endpoint criteria for a case definition, the following criteria need to be fulfilled:

[a] https://www.cdc.gov/surveillance/nrevss/rsv/region.html

- The participant must show the necessary number of signs and symptoms (new onset or worsening) according to the considered case definition. Which symptoms will be taken into account and how the number of symptoms will be counted is defined in Section 4.4.2.1.1.
- The considered ARI episode must be RT-PCR confirmed for RSV. RSV RT-PCR confirmation is defined in Section 4.4.2.1.2.

First occurrence of a considered endpoint is defined as the first day of symptoms of the first RSV-confirmed ARI episode where the criteria for the respective case definition are fulfilled on at least one assessment of the considered episode. Only episodes occurring in the first season of the participant are taken into account for the primary analysis.

4.4.2.1.1. Counting Symptoms

During an ARI episode, the participant is asked to daily report symptoms (RiiQ Symptom Scale) and body temperature on the participants device (eDiary). In addition, during the ARI day 3-5 clinical visit, the subject must report symptoms (RiiQ Symptom Scale) and body temperature on the sites device (eDevice) and a clinical assessment is performed by the study staff. In the remainder of the text, assessment will refer to any of the following: to the patient reported outcome on the participants eDiary, to the participant reported outcome on the sites eDevice or to the clinical assessment.

Table 7 shows the LRTI and systemic signs and symptoms that are taken into account for the case definitions and what the corresponding terms are in the RiiQ and the clinical assessment.

Table 7: 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 *or* rhonchi, rales or other sign of consolidation
	Tachypnea		Tachypnea
Systemic Symptoms	Fatigue	Fatigue (tiredness)	Malaise (tiredness)
	Fever		Fever
	Feverishness	Feeling feverish or Fever*	

LRTI =lower respiratory tract infection, RiiQ = Respiratory Infection Intensity and Impact Questionnaire
* Fever defined based on the daily temperature reported from the participants in the eDiary

New onset or worsening of symptoms:

To determine new onset or worsening of symptoms, symptoms should be compared with the respective baseline of the season wherein the episode started:

- Clinical assessment by the site staff will be compared with clinical assessment baseline by the site staff.
- Patient reported outcomes reported on the site's eDevice and on the participants eDiary will be compared with the baseline patient reported outcomes.

Symptoms present during an ARI episode but not at the baseline assessment will be considered as symptoms with a new onset. Symptoms present at the baseline assessment that become worse (higher severity) during the ARI episode will be considered as worsening symptoms.

For assessments that are numerically scored (Decreased oxygen, tachypnea, and fever) new onset or worsening is defined as follows:

- Decreased oxygen saturation is defined as:
  - oxygen saturation of <90% for participants with a baseline oxygen saturation of ≥90% or a missing baseline at randomization (new onset)
  - for participants with baseline oxygen saturation <90%, decreased oxygen saturation is defined as a ≥3% decrease in their oxygen saturation from baseline (worsening).
- Tachypnea is defined by respiratory rate (RR) >20 breaths per minute:
  - For subjects with baseline RR ≤20 or a missing baseline, a value >20 is considered a new onset.
  - For subjects with baseline RR >20 (and ≤25), a value >25 is considered a worsening.
- Fever: all temperatures >37.8ºC during an ARI episode will be considered as a fever, regardless of the baseline temperature of the participant. For example, if a subject has baseline temperature of 37.9 degrees Celsius and during the ARI episode his temperature of is again 37.9 degrees Celsius, it will be counted as a systemic symptom of fever.

Note 1: Shortness of breath and respiratory effort reported at the clinical assessment form will not be taken into account for the case definitions.

Note 2: If a participant at the clinical assessment reported a new onset or worsening of dyspnea and had decreased oxygen saturation, then it counts only as one symptom towards the case definitions. Similarly, if a participant had a new onset or worsening of wheezing and rhonchi, rales or other sign of consolidation, it also counts as one symptom.

Note 3: Example of selecting the baseline of the season in which the ARI started: if an ARI episode starts in Season 2 and continues during Season 3, then all assessments related to that ARI episode will be evaluated in comparison to the Day 365 baseline to determine new onset or worsening.

Missing baseline assessments will not be imputed, in case of missing baseline symptoms the participant will be considered to have no baseline symptoms at all.

Counting of symptoms during an ARI episode:

Counting of the number of symptoms with new onset or worsening will be done per day and per assessment (clinical assessment or patient reported outcome in the eDiary or in the eDevice). Therefore, if a subject has several assessments at the same day (e.g. at ARI day 3-5, or by accident two RiiQs at the eDiary during the same day), the case definitions cannot be met by combining symptoms from different assessments, the required number of symptoms must be attained at one assessment.

For example, if at Day 3 a participant reports in the eDiary mild cough and the study staff reports mild wheezing at the same day, this participant does not meet case definition 2, because the 2 LRTI symptoms are reported by 2 different assessments. The participant would meet the case definition only if both symptoms were reported in the eDiary or if both were reported by the study staff in the clinical assessment.

Note: Patient reported outcomes reported in the eDiary and in the eDevice at the same day can be distinguished by the App type ID linked to the device and by the time of reporting.

4.4.2.1.2. RSV RT-PCR Confirmation of the Considered ARI Episode

Confirmation of RSV infection by RT-PCR (in midturbinate swabs or sputum sample, whenever available) will be performed at the central laboratory (GeneXpert assay only). 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. RT-PCR results from samples that were out of stability are excluded from the analysis, regardless if they were RSV positive or RSV negative (except for the analysis based on the FAS).

Any midturbinate nasal swab and/or sputum sample taken within 7 days after onset of an ARI episode or during the ARI episode will be allocated to that ARI. In case of 2 consecutive ARI episodes, where the second ARI starts within 7 days after the onset of the first episode and the ARI Day 3-5 sample of the first episode is taken while the second episode is ongoing, then the midturbinate nasal swab and/or the sputum sample will be attributed to both ARIs.

4.4.2.1.3. ARI Episode Duration

The duration of an ARI episode is defined as: *Last day of symptoms above baseline - start date of ARI + 1.* The ARI Day 1 and ARI Day 3-5 visits are always taken into account for the duration if there is a new onset or worsening of a symptom. The ARI Day 29 is taken into account for the duration only if the RiiQ assessments reported by the participants on his/her home device go up to or exceed the ARI Day 29 visit date (actual date). In this case, ARI Day 29 site assessments occurring after this last RiiQ assessment reported by the participants on his/her home device (actual day) are not taken into account for the duration. End of Season as well as Day 365 and Day 730 visits are excluded when determining ARI end dates. Only URTI and LRTI symptoms from clinical assessment and patient reported outcome will be used in calculating the duration of an ARI episode (Table 8).

Moreover, for ARIs with no new onset or worsening of symptoms, duration will not be calculated.

For calculating the ARI duration, the following rules may be used:

- For all ARIs the start dates are reported in the CRF (=CE.CESTDTC where CETERM=ACUTE RESPIRATORY INFECTION and CE.CECAT= ‘’).

- Then a temporary end date for each ARI is created:
  - In case a participant has multiple ARIs, the temporary end date is set as a day before the start of the next ARI.
  - In case a participant has only one ARI, the temporary end date is set as the day of database cut off (15 May 2020).
- Search between the ARI start date and the temporary end date, for the last date the participant had a new onset or worsening of URTI or LRTI symptoms (Table 8), at the RiiQ assessments completed on his /her device and set it as '*enddate1'*.
- If the RiiQ assessments, between the ARI start date and the temporary end date, reported by the participants on his/her home device do not reach the actual ARI Day 29 visit date. Search between the 'ARI Day 1' and 'ARI Day 3-5' visits (both scheduled and unscheduled), for the last date the participant had a new onset or worsening of URTI or LRTI symptoms (Table 8), at the assessments collected during these visits and set it as *'enddate2'*.
- If the RiiQ assessments between the ARI start date and the temporary end date reported by the participants on his/her home device go up to or exceed the ARI Day 29 visit date (actual date). Search between the 'ARI Day 1', 'ARI Day 3-5' and 'ARI Day 29' visits (both scheduled and unscheduled), for the last date the participant had a new onset or worsening of URTI or LRTI symptoms (Table 8), at the assessments collected during these visits (clinical assessments and RiiQ) or at the participants device at home (RiiQ) during these dates and set it as '*enddate2*'.
- The ARI episode end date is defined as the maximum between *'enddate1'* and '*enddate2'*.
- And the duration is defined as the *end date – ARI start date +1*

Note 1: in case there is no new onset or worsening after the ARI start date then the ARI end date and the duration are considered missing.

Note 2: the start date of the ARI is always the date reported in the CE domain, even if the subject started reporting symptoms only later in the diary.

For example, see Attachment 8

4.4.2.2. Analysis Methods

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. In case the EOS visit is missing then the 15th of May 2020 will be used. 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 (date of discontinuation).

Note: in case more than one end of season visits are available, the latest will be used to determine the follow up time.

Thus, all participants are included in the analysis according to their follow-up time. The exact one sided p-value corresponding to vaccination group will be compared with the one sided cut-off as described above (Section 4.4.1.1).

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 exact 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 and graphically depicted with forest plots.

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 sensitivity analyses the above Poisson model will be repeated similar to the primary analysis:

- 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). RT-PCR results from samples that were out of stability, but tested RSV positive are taken into account in this analysis.
- based on the PPE set but taking into account only RT-PCR test results from the central laboratory (i.e., excluding the local test results for hospitalized participants)
- based on the PPE set but taking into account only RT-PCR test results from midturbinate swabs (excluding results from sputum samples)
- based on the PPE set but taking into account RT-PCR test results from both GeneXpert assay and GenMark assay, provided that GenMark is available for all ARIs. An ARI episode was considered as positive if GeneXpert is positive (regardless the GenMark result) or GeneXpert is negative but both GenMark and DDL indicate a positive result regardless the subtype.
- based on the PPE set but excluding coinfections with other respiratory viruses, based on GeneXpert and GenMark assay (Attachment 3). This should be detected in one of the scheduled nasal or sputum samples linked to the respective ARI but should not necessarily be detected in the same sample as the one that resulted in RSV confirmation.
- based on the PPE set but excluding coinfections with other respiratory viruses or bacteria based on GeneXpert, GenMark assay and the DDL bacterial assay (Attachment 3). This should be detected in one of the scheduled nasal or sputum samples linked to the respective ARI but should not necessarily be detected in the same sample as the one that resulted in RSV confirmation.
- based on the PPE set but only the participant reported symptoms (eDiary and eDevice) should be used to define case definitions.
- based on the PPE set but only the clinical assessment symptoms should be used to define case definitions
- based on the PPE set with age and increased risk status as collected (instead of as stratified) in case there are many discrepancies between as collected and as stratified.

- based on the PPE set but not taking into account cough for any of the case definitions
- based on the PPE set, but instead of focusing on the first occurrence of RT-PCR confirmed RSV-mediated LRTD, the number of events will be used as dependent variable and the offset will be defined as the time to discontinuation or end of season (whatever comes first). In case the end of season visit is missing, then the 15th of May 2020 will be used as end of season. And in cases, where more than one end of season visits are available, the latest will be used to determine the follow up time.

For these sensitivity analyses, corrected (based on each sensitivity) 2-sided confidence intervals for the VE will be calculated from these models and graphically depicted with forest plots.

Additional sensitivity analyses will include an exact binomial test (Attachment 6), 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.

Moreover, similar Poisson models will be executed for the subgroups defined in Section 2.4. The 95% 2-sided CI for the VE (1-relative risk rate) will be calculated from these regression models (subgroup analyses) and graphically depicted with forest plots.

In case the Poisson model for one of the above analyses does not converge, the model for the considered analysis will be fitted with only the vaccination group as independent variable.

The number of participants (and percentages) fulfilling the case definitions for each analysis (primary, sensitivity and subgroup) in both groups will be calculated and graphically depicted with bar plots.

For subjects with RT-PCR-confirmed RSV-mediated LRTD based on the 3 case definitions, the median duration of the ARI episode and the median number of days meeting each case definition will be summarized. Moreover, time to first occurrence since vaccination of each case definition per group will be graphically presented with reverse Kaplan-Meier curves.

4.4.3. Major Secondary Endpoints

4.4.3.1. Definition

First occurrence of a considered endpoint is defined as the first day of symptoms of the first ARI episode where the criteria for the respective endpoint are fulfilled on at least one assessment of the considered episode. The secondary objectives are defined as follows:

- **First occurrence of any RT-PCR-confirmed RSV ARI**

This is defined as any acute respiratory infection (ARI) in combination with RSV confirmation by RT-PCR in at least one of the samples taken up to 7 days after the onset of the ARI episode or during the ARI episode, see Section 4.4.2.1.2.

Any ARI is defined as new onset or worsening of any of the LRTI and URTI clinical symptoms. Systemic symptoms will not be taken into account. New onset or worsening of symptoms is

determined in a similar way as for the primary endpoint (Section 4.4.2.1.1). Table 8 contains the LRTI and URTI symptoms collected in the RiiQ and the clinical assessment.

ARIs indicated by the site as being initiated in error by the participant, with no RT-PCR swab linked to them will not be taken into account in the analysis.

Table 8: Symptoms of LRTI and URTI as per RiiQ or Clinical Assessment

	RiiQ Term	**Clinical Assessment Term (ARI Days 3-5 Clinical Visit)**
Symptoms of LRTI	Cough	Cough
	Short of breath	Dyspnea *or* decreased oxygen saturation* or Shortness of breath
	Coughing up phlegm (sputum)	Sputum production
	Wheezing	Wheezing; rhonchi, rales or other sign of consolidation
		Tachypnea
		Respiratory Effort
Symptoms of URTI	Sore Throat	Nasal discharge
	Nasal congestion	Pharyngitis
		Sinus tenderness

Any midturbinate nasal swab and/or sputum sample taken within 7 days after onset of an ARI episode or during the ARI episode will be allocated to that ARI. In case of 2 consecutive ARI episodes, where the second ARI starts within 7 days after the onset of the first episode and the ARI Day 3-5 sample of the first episode is taken while the second episode is ongoing, then the midturbinate nasal swab and/or the sputum sample will be attributed to both ARIs.

For calculating the duration of an ARI episode, the first day of symptoms above baseline and the last day of symptoms above baseline will be considered. Days with missing symptom assessments during an ARI episode will be considered part of the ARI episode. For more details, refer to Section 4.4.2.1.3.

Note: Shortness of breath and respiratory effort reported at the clinical assessment form will be take into account for the definition of any ARI disease.

Note: RSV RT-PCR confirmation is defined based on the GeneXpert assay only.

4.4.3.2. Analysis Methods

The number of participants (and percentages) fulfilling the secondary endpoints in both groups will be calculated and graphically depicted with bar plots.

For all 3 secondary efficacy endpoints an exact Poisson model, as described in the primary efficacy analysis (see Section 4.4.2.2) will be performed, based on the PPE population. The 95% 2-sided CI for the VE (1-relative risk rate) will be calculated from these regression models and

graphically depicted with forest plots. Moreover, the VE (=1- relative risk) will also be calculated without taking the strata into account, and the 95% 2-sided CI will be based on the exact binomial 95% 2-sided CI (Attachment 6).

Poisson models will be executed also for the subgroups defined in Section 2.4 only for the first occurrence of any RT-PCR-confirmed RSV disease.

In case the Poisson model for one of the above analyses does not converge, the model for the considered analysis will be fitted with only the vaccination group as independent variable.

For participants with any RT-PCR-confirmed RSV disease, the median duration of the ARI episode will be summarized, and time to first occurrence of any RT-PCR-confirmed RSV disease since vaccination per group will be graphically presented with reverse Kaplan Meier curves.

For participants with any RT-PCR-confirmed RSV disease, the different symptom combinations may be summarized.

The PPE set will be used to analyze all secondary exploratory endpoints.

4.4.4. Exploratory Efficacy Variable(s)

4.4.4.1. Definition

Note: For all exploratory endpoints RSV RT-PCR confirmation is defined based on the GeneXpert assay only.

- **First occurrence of any RT-PCR-confirmed RSV A ARI, based on the GenMark assay**

This is defined as any ARI (as defined above) in combination with an RSV confirmation based on GeneXpert and an RSV A confirmation by GenMark in at least one of the samples taken up to 7 days after the onset of the ARI episode or during the ARI episode , see Section 4.4.2.1.2 (one positive sample is sufficient).

- **First occurrence of any RT-PCR-confirmed RSV A ARI , based on the DDL assay**

This is defined as any ARI (as defined above) in combination with an RSV confirmation based on GeneXpert and an RSV A confirmation by DDL in at least one of the samples taken up to 7 days after the onset of the ARI episode or during the ARI episode, see Section 4.4.2.1.2 (one positive sample is sufficient).

- **First occurrence of any RT-PCR-confirmed RSV B ARI ,based on the GenMark assay**

This is defined as any ARI (as defined above) in combination with an RSV confirmation based on GeneXpert and an RSV B confirmation by GenMark in at least one of the samples taken up to 7 days after the onset of the ARI episode or during the ARI episode, see Section 4.4.2.1.2 (one positive sample is sufficient).

- **First occurrence of any RT-PCR-confirmed RSV B ARI , based on the DDL assay**

This is defined as any ARI (as defined above) in combination with an RSV confirmation based on GeneXpert and an RSV B confirmation by DDL in at least one of the samples taken up to 7 days after the onset of the ARI episode or during the ARI episode, see Section 4.4.2.1.2 (one positive sample is sufficient).

- **First occurrence of RT-PCR-confirmed RSV-A-mediated LRTD according each case definition, based on the GenMark assay**

This is defined similarly as the primary endpoint (See Section 4.4.2.1) but taking into account only RSV confirmation based on GeneXpert and RSV A confirmation by GenMark in at least one of the samples taken up to 7 days after the onset of the ARI episode or during the ARI episode, see Section 4.4.2.1.2 (one positive sample is sufficient).

- **First occurrence of RT-PCR-confirmed RSV-A-mediated LRTD according each case definition, based on the DDL assay**

This is defined similarly as the primary endpoint (See Section 4.4.2.1) but taking into account only RSV confirmation based on GeneXpert and RSV A confirmation by DDL in at least one of the samples taken up to 7 days after the onset of the ARI episode or during the ARI episode, see Section 4.4.2.1.2 (one positive sample is sufficient).

- **First occurrence of RT-PCR-confirmed RSV-B-mediated LRTD according each case definition, based on the GenMark assay**

This is defined similarly as the primary endpoint (See Section 4.4.2.1) but taking into account only RSV confirmation based on GeneXpert and RSV B confirmation by GenMark in at least one of the samples taken up to 7 days after the onset of the ARI episode or during the ARI episode, see Section 4.4.2.1.2 (one positive sample is sufficient).

- **First occurrence of RT-PCR-confirmed RSV-B-mediated LRTD according each case definition, based on the DDL assay**

This is defined similarly as the primary endpoint (see Section 4.4.2.1) but taking into account only RSV confirmation based on GeneXpert and RSV B confirmation by DDL in at least one of the samples taken up to 7 days after the onset of the ARI episode or during the ARI episode, see Section 4.4.2.1.2 (one positive sample is sufficient).

- **First occurrence of any RT-PCR-confirmed ARI, other than RSV**

Midturbinate nasal swabs of all ARI episodes may also be tested against other respiratory pathogens. For each one of the following respiratory diseases, the first occurrence of an RT-PCR confirmed disease is defined as any ARI (as defined above) in combination with an RT-PCR confirmation for the specific disease (as defined in Section 4.4.2.1.2). Based on the results from the GenMark Respiratory Panel and/or the GeneXpert panel, RT-PCR confirmed ARI for the respective diseases will be defined as follows:

- **Influenza:** at least one RT-PCR results above LLOQ for at least one influenza strain (A, A H1, A H3, A 2009 H1N1, B), for either the GenMark Respiratory Panel or the GeneXpert panel
- **Parainfluenza:** at least one RT-PCR results above LLOQ for at least one parainfluenza strain (Virus 1, Virus 2, Virus 3)
- **Human Metapneumovirus:** at least one RT-PCR results above LLOQ
- **Human Rhinovirus:** at least one RT-PCR results above LLOQ
- **Adenovirus B/E**: at least one RT-PCR results above LLOQ
- **Adenovirus C**: at least one RT-PCR results above LLOQ
- **Adenovirus B/E and/or C**: at least one RT-PCR results above LLOQ for either strains

Note: this endpoint will be only analyzed if the GenMark panel has run for all ARIs. This is not yet planned for the primary analysis.

- **First occurrence of any RT-PCR-confirmed ARI, other than RSV, according to each case definition**

For each one of the respiratory diseases tested (influenza, parainfluenza, human metapneumovirus, human rhinovirus , adenovirus B/E, adenovirus C and adenovirus B/E and/or C), the first occurrence of an RT-PCR confirmed disease according to the case definitions is defined similar to the primary endpoint (see Section 4.4.2.1), but instead of an RSV RT-PCR confirmation, an RT-PCR confirmation is needed based on the GenMark Respiratory Panel and/or the GeneXpert panel for the different diseases.

Note: this endpoint will be only analyzed if the GenMark panel has run for all ARIs. This is not yet planned for the primary analysis.

- **First occurrence of potential complications of ARI**

This is defined as the first occurrence of any complication linked to an ARI (as defined above) episode.

- **First occurrence of potential complications of respiratory disease linked to an RT-PCR confirmed RSV ARI**

This is defined as the first occurrence of any complication linked to any RSV-confirmed disease (see Section 4.4.3.1)

- **First occurrence of hospitalization linked to an ARI**

This is defined as the first occurrence of a hospitalization linked to an ARI (as defined above) episode. Hospitalization defined in section 12.

- **First occurrence of hospitalization linked to an RT-PCR confirmed RSV ARI**

This is defined as the first occurrence of a hospitalization linked to any RT-PCR-confirmed RSV disease (see Section 4.4.3.1). Hospitalization defined in section 12.

- **First occurrence of RT-PCR-confirmed RSV-mediated LRTD according an ordinal case definition**

The ordinal case definition is defined as follows:

Table 9: 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) (GeneXpert or local lab)	3	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) (GeneXpert or local lab)	2	Case Definition 2 and 3 (not Case definition 1)
1 symptom of LRTI (new onset or worsening) combined with a systemic symptom, 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) (GeneXpert or local lab)	1	Only Case Definition 3 (not Case definitions 1 and 2)
Other	0	No case definition

For subjects fulfilling at least one case definition, the follow-up time is defined as the time between vaccination and the occurrence of the first event with the highest ordinal variable (the event corresponding to the strictest case definition). For non-cases, it is the time between vaccination and the end of season visit. In case the end of season visit is missing then the 15th of May 2020 will be used as end of season. However, for participants that discontinued before having an event, follow-up time is the time between vaccination and the date of last contact (date of discontinuation).

- **Determination of oxygen saturation during clinical assessment during ARI episodes for subjects with an ARI**
- **Determination of oxygen saturation during clinical assessment during ARI episodes for subjects with an RT-PCR confirmed RSV ARI**
- **First occurrence of an RT-PCR confirmed RSV Lower Respiratory Infection (LRI) assessed as at least mild by the CEC**
- **First occurrence of an RT-PCR confirmed RSV LRI assessed as at least moderate by the CEC.**
- **First occurrence of an RT-PCR confirmed RSV LRI assessed as severe by the CEC.**
- **If the G-ELISA assay is available: Explore the relationship between G-ELISA and RT-PCR confirmed RSV infection. Provided a cut-off for G-ELISA FR is found that is sufficiently sensitive and specific, the following objectives will be explored:**
  - First occurrence of serology-confirmed RSV-mediated LRTD according to each case definition
  - First occurrence of any serology-confirmed RSV ARI

- First occurrence of any serology and/or RT-PCR-confirmed RSV ARI
- First occurrence of serology and/or RT-PCR-confirmed LRTD according each case definition

The analyses to explore a cut-off for G-ELISA FR will be described in more detail in the CoP SAP

- **[EMA Endpoints]: First occurrence of RT-PCR confirmed RSV-mediated LRTD according to the following 2 case definitions:**
  - Case Definition 1a: new onset of worsening of >=3 LRTI symptoms based on Table 8, and fever (all temperatures >37.8ºC) or feeling feverish
  - Case Definition 2a: new onset of worsening of >=2 LRTI symptoms based on Table 8, and fever (all temperatures >37.8ºC) or feeling feverish

For both these case definitions, dyspnea and decreased oxygen saturation will count as separate LRTI symptoms.

For example, if a participant has a new onset on cough, dyspnea, decreased oxygen saturation and a fever of 39.0 ºC, this participant fulfils Case Definition 1a.

4.4.4.2. Analysis Methods

For all exploratory efficacy endpoints related to the first occurrence of a disease an exact Poisson model, as described in the primary efficacy analysis (see Section 4.4.2.2) will be performed, based on the PPE population. The 95% exact 2-sided CI for the VE (1-relative risk rate) will be calculated from these regression models and graphically depicted with forest plots. In case of the model does not converge then it will be fitted with only the vaccination group as dependent variable.

For the first occurrence of complications or hospitalizations linked to any ARI and complications or hospitalizations linked to any RT-PCR confirmed RSV disease, the proportion of participants with complications and hospitalizations, will be tabulated separate and an exact Poisson model, as described in the primary efficacy analysis (see Section 4.4.2.2) will be performed, based on the PPE population. The 95% 2-sided CI for the VE (1-relative risk rate) will be calculated from these regression models and graphically depicted with forest plots. In case the Poisson model for one of the above analyses does not converge, the model for the considered analysis will be fitted with only the vaccination group as independent variable.

Complications linked to any ARI and complications linked to any RT-PCR confirmed RSV disease will be summarized by System Organ Class and Preferred Term, per group and per risk level. A summary table including complications with fatal outcomes, complications reported as SAEs and those leading to permanent stop of the vaccination, will also be created. Number of participants with one complication, two complications, three complications or more than 3 complications will also be summarized.

Moreover, for the determination of oxygen saturation the number of subjects (and percentages) with baseline SpO_2 ≥90% and SpO_2 <90% during the ARI episode and the number of subjects

(and percentages) with baseline SpO_2 <90 and that have a ≥2% decrease during ARI episode will be tabulated per group.

4.4.4.3. The Relationship Between the Primary Endpoints and CEC Evaluation

In order to establish the interrelationship between the primary endpoints and RT-PCR confirmed LRIs considered at least moderate by the CEC, the following analyses will be performed restricted to the placebo group. These analyses will be performed in two subgroups of the PPE set:

- participants with any RT-PCR confirmed RSV disease (see above for definition)

In each of those subgroups the following will be calculated: the percentage of subjects having an (RT-PCR confirmed RSV) ARI considered at least moderate by the CEC will be shown for:

- participants meeting Case Definition 1 versus participants not meeting any Case Definition
- participants meeting Case Definition 2 (or 1) versus participants not meeting any Case Definition
- participants meeting Case Definition 3 (or 1 or 2) versus participants not meeting any Case Definition

The corresponding odds ratio (and 95% CI) will be shown as well.

In case of limited number of participants not meeting any case definition:

- participants meeting Case Definition 1 versus participants not meeting Case Definition 1
- participants meeting Case Definition 2 (or 1) versus participants not meeting Case Definition 2 (or 1)
- participants meeting Case Definition 3 (or 1 or 2) versus participants not meeting any Case Definition

The corresponding odds ratio (and 95% CI) will be shown as well.

Moreover, the correlation between the 3 case definitions and the RT-PCR confirmed ARIs assessed by the CEC, will be explored with scatterplots.

Finally the results of the CEC evaluation will be used to explore the creation of a severity score (based on RiiQ and clinical assessment data) with a cut-off to classify an RT-PCR confirmed RSV ARI to having an RT-PCR confirmed RSV LRI assessed at least moderate by the CEC (yes/no). Classification trees (or other classification methods), logistic regression models, combinations of these or other techniques might be used to define a score. An optimal cut-off might be identified based on Receiver operating characteristic (ROC) curves, which might be used to calculate a VE.

The PPE set will be used to analyze all efficacy exploratory endpoints.

4.5. PATIENT-REPORTED OUTCOMES

4.5.1. 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. Based on this questioner, 4 different total scores 2 areas under the curve (AUC) will be calculated:
  - **Total RiiQ Respiratory and Systemic symptom score** is the mean of all scores.
  - **Total RiiQ Respiratory symptom score** is the mean of 6 symptoms, i.e., 2 URTI symptoms (Nasal congestion and Sore throat) and 4 LRTI symptoms (Cough, Wheezing, Shortness of breath, and Coughing up phlegm/sputum)
  - **Total RiiQ Systemic symptom 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).
  - **Total RiiQ Case Definition symptom score** is the mean of 4 LRTI symptoms (Cough, Wheezing, Shortness of breath, and Coughing up phlegm/sputum) and 2 systemic symptoms used in the case definitions, fatigue and feeling feverish
  - Moreover, the **AUC** (Attachment 4) for the change from baseline for the Total RiiQ Respiratory and Systemic symptom score and the Total RiiQ Case Definition symptom score will be calculated.
- **RiiQ Impact Scales (Questions 2 to 4):**
  - **Total RiiQ Impact on Daily Activity score (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. The total score is calculated as the mean of all 7 items (range 0-3).
  - Moreover, the **AUC for the change from baseline for the Total RiiQ Impact on Daily Activity score** will be calculated.
  - **Total 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. The total score is calculated as the mean of all 4 items (range 0-3).
  - **Total 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. The total score is calculated as the mean of all 5 items (range 0-3).

Note 1: Total scores will be calculated based on the number of assessments completed by the participant and in cases where more than 50% of the items needed to calculate the score is not collected (reported as 'Not done'), then the value for that score will be set to missing. For example, if a participant has responded to only 11 out of the 13 RiiQ symptom scale questions the 'Total RiiQ Respiratory and Systemic symptom' score will be the mean of the 11 available

questions. If the participant has only completed 6 or less of the questions, then the Total RiiQ Respiratory and Systemic symptom score will be set to missing.

Note 2: For outputs where the end of season visit is presented, in case there are multiple end of season visits, the worst score across the different scheduled and unscheduled visits will be presented.

4.5.1.1. Analysis Methods

RiiQ scores will be analyzed based on the PPE set, with a major focus participants with any RT-PCR disease (see above for definition) .

For the **total scores**, number of observations, mean, standard error, median, first and third interquartile will be tabulated and means with standard errors will be graphically presented per group and time point for changes from baseline. Moreover, the relationship of the baseline total scores and the worst score reported during the ARI episode will be explored with scatterplots. Furthermore, descriptive statistics of the baseline, the end of season and the change between these two timepoints will be calculated for all participants based on the PPE set, for participants with any RT-PCR-confirmed RSV disease and for participants meeting each of the primary endpoints separately, based on the PPE set.

For the **AUCs** number of observations, median, first and third quartile (q1, q3), minimum and maximum will be calculated and graphically presented with boxplots per group. Scatterplots of the AUC values versus the duration of the ARI episodes will also be created.

Note 1: Everything reported until the resolution of an ARI will be used.

In case two or more assessments are reported at the same day (for example ARI Day 3-5 eDiary and eDevice or two assessments at the same device) then the worst total score will be used. The same applies for the AUC calculations too.

In case a participant experiences two or more ARIs (based on the 'Any ARI' definition, Section 4.4.3.1) during the study then the following rules will be followed in identifying which ARIs data will be used:

- If all fulfil a case definition, then data from the RT-PCR confirmed RSV disease fulfilling the strictest definition will be used (case definition 1> case definition 2> case definition 3)
- If only one fulfils a case definition, then those data will be used
- If none fulfils a case definition or all fulfil the same case definition, then data from the first RT-PCR confirmed RSV disease will be used.
- If none is a RT-PCR confirmed RSV disease, then use:
  - the ARI that fulfils the strictest case definition based on symptoms only (case definition 1> case definition 2> case definition 3) Or
  - the first ARI, in case 2 or more fulfil the same case definition on symptoms only or in case they do not fulfil any case definition on symptoms only.

Note 2: For outputs were only planned visits (ARI Day 3-5, ARI Day 29, End of season) are presented, the worst across the different scheduled and unscheduled visits will be presented per visit.

4.5.2. 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= much better, -2=somewhat better, -1=A little better, 0=About the same, 1=A little worse, 2=somewhat worse, 3= much worse
- **Return to Usual Health.** Participants are being asked whether they have returned to their usual health after developing symptoms suggesting an ARI.
- Number of days a participant took to return to its usual health: This is counted based on the Return to Usual Health question.
  - In case a participant indicated he returned to its usual health (based on the 'Return to usual health' question) on the last day he completed this questionnaire during the considered episode, this is calculated as: *the first day of a series where the participant answered consecutively 'yes' to the 'Return to usual health question' (with no intermittent 'no' answers) - the ARI start date based on the CRF+1* . For the Kaplan-Meier curve this is considered an event.
  - In case a participant indicated he did not return to its usual health (based on the 'Return to usual health' question) on the last day he completed this questionnaire during the considered episode, this is calculated as: *the date of the last reply- the ARI start date based on the CRF + 1*. For the Kaplan-Meier curve this record will be censored.
  - In case a participant never responded to any 'Return to usual health' question during an ARI episode then the number of days will be considered missing.

For example, if 2 participants completed the 'Return to Usual Health' question only for 8 days as indicated in Table 10. For participant 1 the number of days to return to usual health is 5 (*15/11/2019- 11/11/2019 + 1*) and this will be considered an event. For participant 2, the number of days to return to usual health is 8 (*18/11/2019- 11/11/2019 + 1*) and this record will be censored.

Table 10: Example for 'Return to Usual Health' question

	ARI Day 1 - Onset (11/11/2019)	ARI Day 2 (12/11/2019)	ARI Day 3 (13/11/2019)	ARI Day 4 (14/11/2019)	ARI Day 5 (15/11/2019)	ARI Day 6 (16/11/2019)	ARI Day 7 (17/11/2019)	ARI Day 8 (18/11/2019)
Participant 1	No	No	Yes	No	Yes	Yes	Yes	Yes
Participant 2	No	No	Yes	Yes	Yes	No	No	No

Note: in case a participant has two or more different responses at the same day, then the 'No' answer will be taken into account for calculating the number of days a participant took to return to his usual health.

4.5.2.1. Analysis Methods

Patient global impression scores will be analyzed based on the PPE set, with a major focus participants with any RT-PCR disease (see above for definition) .

For the PGI-H, number of observations, mean, standard error, median, first and third quartile, minimum and maximum will be tabulated and means with standard errors will be graphically presented per group and time point for the change from baseline.

For the PGI-C and PGI-S scores, score, number of observations, mean, standard error, median, first and third quartile, minimum and maximum will be tabulated and means with standard errors will be graphically presented per group and time point.

For the PGI-H, descriptive statistics of the baseline, the end of season and the change between these two timepoints will be calculated for all participants based on the PPE set, for participants with any RT-PCR-confirmed RSV disease and for participants meeting each of the primary endpoints separately, based on the PPE set.

The number (and percentage) of participants answering yes and no in the 'Return to Usual Health' question will be calculated per day.

Moreover, the number of days a participant took to return to its usual health will be summarized and graphically presented with Kaplan Meir curves.

In case two or more assessments are reported at the same day (for example eDiary and eDevice or two assessments at the same device) then the worst PGI score (or when looking to Return to Usual Health, the worst answer to this question) will be used.

In case a participant experiences two or more ARIs during the study the same rule as for the RiiQ will be used.

Note 1: For outputs where only planned visits (ARI Day 3-5, ARI Day 29, End of season) are presented, the worst across the different scheduled and unscheduled visits will be presented per visit.

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

The Lawton-Brody IADL questionnaire covers 8 domains (see Attachment 7). Women are scored on all 8 domains; for men, the domains of food preparation, housekeeping, and laundering are excluded from the analysis, regardless if they are filled in. 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.

4.6.1. Analysis Methods

For all participants with any RT-PCR-confirmed RSV disease (see above for definition) from the PPE set, descriptive statistics of the actual values and the change from baseline of the IADL score will be tabulated by sex and group for each timepoint collected.

In case two or more assessments are reported at the same day then the worst total Lawton Brody score will be used. The worst score is the smallest.

In case a participant experiences two or more ARIs during the study the same rule as for the RiiQ will be used.

Note: For outputs were only planned visits (ARI Day 3-5, ARI Day 29, End of season) are presented, the worst across the different scheduled and unscheduled visits will be presented per visit.

4.7. Frailty Index Score

The frailty index score[3] will be calculated from the medical conditions of interest (CETERM, see Section 4.1.5.1) and the Lawton-Brody IADL questionnaire, based on the following equations:

$$\textbf{\textit{Frailty Index for women}} = \frac{25}{33} * \left(\frac{\textbf{\textit{\# of medical conditions the participant has}}}{25}\right) + \frac{8}{33} * \left(1 - \frac{\textbf{\textit{Lawton Brody IADL score}}}{8}\right)$$

$$\textbf{\textit{Frailty Index for men}} = \frac{25}{30} * \left(\frac{\textbf{\textit{\# of medical conditions the participant has}}}{25}\right) + \frac{5}{30} * \left(1 - \frac{\textbf{\textit{Lawton Brody IADL score}}}{5}\right)$$

The range of the frailty index score will be between 0 and 1, with 0 indicating that the participants is not frail and 1 indicating that the participant is most frail.

Moreover, an additional frailty index augmented with the RiiQ data will also be calculated, based on the following equations:

$$\textit{Frailty Index augmented for women} = \frac{25}{34+N}\left(\frac{\#\ of\ medical\ conditions\ the\ participant\ has}{25}\right) + \frac{8}{34+N}\left(1 - \frac{score\ of\ Lawton}{8}\right) + \frac{N}{34+N}\left(\frac{\#\ of\ RiiQ\ symptoms/activities\ the\ participant\ has}{N}\right)$$

$$\textit{Frailty Index augmented for men} = \frac{25}{30+N} * \left(\frac{\#\ of\ medical\ conditions\ the\ participant\ has}{25}\right) + \frac{5}{30+N} * \left(1 - \frac{score\ of\ Lawton}{5}\right) + \frac{N}{30+N}\left(\frac{\#\ of\ RiiQ\ symptoms/activities\ the\ participant\ has}{N}\right),\ for\ men$$

where $N = N_1 + N_2 + N_3 + N_4$ (see below).
Note: For the end of season the medical conditions from baseline are used.

The frailty index will only be calculated for participants that have completed all assessments required for the calculation of the index.

The augmented frailty index will only be calculated for participants that have completed medical conditions of interest, the Lawton Broady, and more than 50% of the RiiQ items required for the calculation of the index (where N>=13).

For calculating the number of RiiQ symptoms/activities the subject has, the following rules will be followed:

- Each one of the assessed RiiQ Respiratory and Systemic symptoms of any grade will count as one (N_1=total number of non-missing symptoms/activities, maximum number 13)
- Each one of the assessed RiiQ Impact on Daily Activities with a severity of 'moderate' or 'great difficulty' will count as one (N_2=total number of non-missing symptoms/activities, maximum number 7)
- If one of the questions in the RiiQ Impact on Emotions scale has a response of 'moderate' or 'extremely' then it will be counted as just one symptom (regardless if all 4 questions have a 'moderate' or 'extremely' response) (N_3= 1, if 1 or more questions with a response of 'moderate' or 'extremely', or 0 otherwise)
- Each one of the following RiiQ Impact on Relationships questions has a response of 'moderate concerned' or 'extremely concerned' will count as one (N_4=total number of non-missing symptoms/activities, maximum number 4):
    1. 'People worrying about you'
    2. 'Being a burden'
    3. 'People wing annoyed with you'
    4. 'Needing to depend on people' or 'People having to do extra things for you'

Note: For end of season frailty calculation, in case two or more assessments are reported at the same day or more than one visit is completed (scheduled and unscheduled visits) then the same rules as in Sections 4.5.1.1 and 4.6.1 will be applied,

4.7.1. Analysis Methods

For both the frailty index and the frailty index augmented with the RiiQ, descriptive statistics of the baseline, the end of season and the change between these two timepoints will be calculated for all participants based on the PPE set, for participants with any RT-PCR-confirmed RSV disease and for participants fulfilling each case definition separately, based on the PPE set.

For the frailty index the following categories will be defined and the number of subjects moving to a different category after the end of the RSV season will be tabulated and graphically presented:

- 0-0.1: not frail
- 0.11-0.2: pre-frail
- 0.21-0.45: frail
- >0.45: most frail

For subjects with any RT-PCR-confirmed RSV disease from the PPE set, the correlation of the baseline frailty index with the total RiiQ scores and with the duration of the ARI episode will be explored with scatterplots.

Finally, the correlation between the two indexes will be explored with scatterplots.

4.8. Clinical Assessment

The clinical assessment consists of 4 different sub-assessments [vital signs, physical examination scoring, upper respiratory and lower respiratory]. Based on the physical examination scoring, upper respiratory and lower respiratory assessments the following total scores will be calculated:

- **Total symptom scores assessed during the clinical assessment** is calculated as the mean of all 4 systemic symptom (cough, sputum levels, Shortness of breath, Malaise (tiredness)).
- **Total upper respiratory score assessed during the clinical assessment** is calculated as the mean of all 3 upper respiratory levels (Nasal Discharge, Pharyngitis and Sinus Tenderness).
- **Total lower respiratory score assessed during the clinical assessment** is calculated as the mean of all 4 lower respiratory levels (Dyspnea, Wheezing, Respiratory Effort and Rales, rhonchi or other).

Note: Total scores will be calculated based on the number of assessments completed by the participant and in cases where more than 50% of data needed for a score is not collected (reported as 'Not done'), then the value for that score will be set to missing. For example, if a participant has responded to 2 or 3 out of the 4 systemic score questions the 'Total symptom scores assessed during the clinical assessment' score will be the mean of the 2 or 3 available questions, respectively. If the participant has only completed 1 of the questions, then the score will be set to missing.

4.8.1. Analysis Methods

The clinical assessment will be analyzed based on the PPE set, with a major focus participants with any RT-PCR disease (see above for definition) .

For the **total scores**, descriptive statistics will be tabulated per group and time point for the actual values and the change from baseline and means with standard errors will be graphically presented per group and time point for the change from baseline alone.

For **vital signs** from the clinical assessments questionnaire apart from oxygen saturation, abnormalities emerging after vaccination will be tabulated by worst abnormality grade using Table 11, per timepoint collected. An abnormality will be considered as emerging in a particular period if it is worse than the baseline value. If the baseline is missing, the abnormality is always considered emerging. Cross tabulation of the emerging worst grades of vital signs versus the status at reference will be calculated.

Table 11: Vital Signs Toxicity Grading

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

For the determination of oxygen saturation, the number of participants (and percentages) with baseline SpO_2 ≥90% and SpO_2 <90% during the ARI episode, the number of participants (and percentages) with baseline SpO_2 <90 and that have a ≥3% decrease during ARI episode and the number of participants (and percentages) with missing baseline and SpO_2 <90% during the ARI episode will be tabulated per group.

For symptoms assessed at ARI Day 3-5 both by the site staff on the clinical assessment and by the participant on the RiiQ, tetrachoric and polychoric correlations for the presence and severity, respectively will be calculated, pooling both groups together. Moreover, the correlation between the different RiiQ symptoms collected at the ARI day with most symptoms reported, may be calculated and visualized with a heatmap. Similarly, the correlation between the different clinical assessment symptoms at ARI Day 3-5 may also be explored.

In case two or more assessments are reported at the same day (for example two assessments at the same device) then the worst total score per assessment and the worst vital sign grade per symptom will be used.

In case a participant experiences two or more ARIs (based on the 'Any ARI' definition, Section 4.4.3.1) during the study then the following rules will be followed in identifying which ARIs data will be used:

- If all fulfil a case definition, then data from the RT-PCR confirmed RSV disease fulfilling the strictest definition will be used (case definition 1> case definition 2> case definition 3)
- If only one fulfils a case definition, then those data will be used
- If none fulfils a case definition or all fulfil the same case definition, then data from the first RT-PCR confirmed RSV disease will be used.
- If none is a RT-PCR confirmed RSV-disease, then use:
  - the ARI that fulfils the strictest case definition based on symptoms only (case definition 1> case definition 2> case definition 3) Or
  - the first ARI, in case 2 or more fulfil the same case definition on symptoms only or in case they do not fulfil any case definition on symptoms only.

Note: For outputs were only planned visits (ARI Day 3-5, ARI Day 29, End of season) are presented, the worst across the different scheduled and unscheduled visits will be presented per visit.

4.9. Clinically Relevant Diseases

The following are considered as clinically relevant diseases:

- Hospitalization (as collected on eCRF AE pages (linked via acute respiratory infection form or complications linked to ARI form), medical encounters [Intensive Care Unit and Hospital inpatient department] form and MRU pages [Emerging Hospitalization admissions-Section 4.11])
- Emergency Department visit (as assessed on the eCRF medical encounters form and MRU pages)
- X-ray confirmed pneumonia (as assessed on the eCRF diagnostic tests form: diagnosis of pneumonia confirmed by chest X-ray)
- Radiological confirmed pneumonia (as assessed on the eCRF diagnostic tests form: diagnosis of pneumonia confirmed by chest X-ray, CT-scan or MRI)
- Oxygen saturation < 90% (as indicated on the clinical assessment form)
- Supplemental oxygen (as indicated on the eCRF medical encounters form and the eCRF oxygen supplementation form)
- Exacerbation of disease (COPD and Asthma) (as captured under the eCRF diagnostic tests pages and the pages on measurements during a medically attended ARI)
- Pulmonary function test results supporting diagnosis of LRTD (as captured under the eCRF pages on measurements during a medically attended ARI, where peak expiratory flow, spirometry FVC, FEV1 or FEV6 are indicated as well as that the measurement is clinically significant and supports LRTD)

- Arterial blood gas results supporting diagnosis of LRTD (as captured under the eCRF pages on measurements during a medically attended ARI, where arterial blood gas pH, PaO2, PaCO2, HC03 or oxygen saturation are indicated as well as that the measurement is clinically significant and supports LRTD)

4.9.1. Analysis Methods

The PPE set will be used to analyze all clinically relevant diseases.

The proportion of participants with any RT-PCR confirmed RSV disease leading to clinically relevant diseases and those with RT-PCR-confirmed RSV-mediated LRTD based on the 3 case definitions leading to clinically relevant diseases will be tabulated per group and the corresponding VE (1-relative risk) with an exact Poisson 95% 2-sided CI will be determined and graphically depicted with a forest plot similar to the primary analysis

Depending on their occurrence, the above might be repeated for the different subcategories of clinically relevant disease (with or without calculation of VE).

4.9.2. The Relationship Between the Primary Endpoints and Clinically Relevant Disease

In order to establish the interrelationship between the primary endpoints and clinically relevant diseases, the following analyses will be performed restricted to the placebo group. These analyses will be performed in two subgroups of the PPE set:

- participants with any RT-PCR confirmed RSV disease (see above for definition)
- participants with any ARI (see Any ARI definition, independently of RSV etiology)

In each of those subgroups the following will be calculated: the percentage of subjects having an (RT-PCR confirmed RSV) ARI leading to clinically significant disease will be shown for:

- participants meeting Case Definition 1 versus participants not meeting any Case Definition
- participants meeting Case Definition 2 (or 1) versus participants not meeting any Case Definition
- participants meeting Case Definition 3 (or 1 or 2) versus participants not meeting any Case Definition

The corresponding odds ratio (and 95% CI) will be shown as well

In case of limited number of participants not meeting any case definition:

- participants meeting Case Definition 1 versus participants not meeting Case Definition 1
- participants meeting Case Definition 2 (or 1) versus participants not meeting Case Definition 2 (or 1)
- participants meeting Case Definition 3 (or 1 or 2) versus participants not meeting any Case Definition

The corresponding odds ratio (and 95% CI) will be shown as well

Note: In case a participant experiences two or more ARIs during the study the same rule as for the RiiQ will be used.

Depending on their occurrence, the above might be repeated for the different subcategories of clinically relevant disease or for subgroups.

As a sensitivity check the same analysis will be performed but without taking into account cough for any of the case definitions.

4.10. Therapeutic Interventions

The following are considered as therapeutic interventions of interest:

- New/increased bronchodilator/nebulizer treatment
- New/increased corticosteroid prescription
- New/increased antibiotic prescription
- New/increased antiviral prescription

These will be taken from the concomitant medication pages of the eCRF based on Attachment 5.

The ones linked to an ARI or complication of an ARI will be displayed.

4.10.1. Analysis Methods

The PPE set will be used to analyze the use of therapeutic interventions.

Therapeutic interventions taken at baseline will be summarized for all subjects in the PPE set.

Moreover, the proportion of participants with any RT-PCR confirmed RSV disease utilizing new therapeutic interventions and those with RT-PCR-confirmed RSV-mediated LRTD based on the 3 case definitions utilizing new therapeutic interventions will be tabulated per group and the corresponding VE (1-relative risk) with an exact Poisson 95% 2-sided CI will be determined and graphically depicted with a forest plot, similar to the primary analysis.

Baseline and new interventions are defined as in Section 4.1.4.

Depending on their occurrence, the above might be repeated for the different subcategories of therapeutic interventions or for subgroups (with or without calculation of VE).

4.10.2. The Relationship Between the Primary Endpoints and Use of Therapeutic Interventions

In order to establish the interrelationship between the primary endpoints and use of therapeutic interventions, the following analyses will be performed restricted to the placebo group. These analyses will be performed on two subgroups of the PPE set:

- participants with any RT-PCR confirmed RSV disease (see above for definition)
- participants with any ARI (see Any ARI definition, independently of RSV etiology)

In each of those subgroups the following will be calculated: the percentage of subjects having an (RT-PCR confirmed RSV) ARI utilizing new therapeutic interventions will be shown for:

- participants meeting Case Definition 1 versus participants not meeting any Case Definition
- participants meeting Case Definition 2 (or 1) versus participants not meeting any Case Definition
- participants meeting Case Definition 3 (or 1 or 2) versus participants not meeting any Case Definition

The corresponding odds ratio (and 95% CI) will be shown as well.

In case of limited number of participants not meeting any case definition:

- participants meeting Case Definition 1 versus participants not meeting Case Definition 1
- participants meeting Case Definition 2 (or 1) versus participants not meeting Case Definition 2 (or 1)
- participants meeting Case Definition 3 (or 1 or 2) versus participants not meeting any Case Definition

The corresponding odds ratio (and 95% CI) will be shown as well.

Note: In case a participant experiences two or more ARIs during the study the same rule as for the RiiQ will be used.

Depending on their occurrence, the above might be repeated for the different subcategories of therapeutic interventions.

As a sensitivity check the same analysis will be performed but without taking into account cough for any of the case definitions.

4.11. Medical Resources Use Questionnaire

Medical resource utilization questionnaire data are collected at baseline and during an ARI episode at Day 3-5 and Day 29. The questionnaire contains 4 categories of medical resources and each of them has several subcategories (see Attachment 10 in CTP).

4.11.1. Analysis Methods

The PPE set will be used to analyze the medical resource utilization data.

At baseline the proportion of participants reporting having used the medical resources by category and subcategory will be summarized per group and per risk level.

For participants with any RT-PCR confirmed RSV the proportion of those reporting having used the medical resources by category and subcategory will be summarized per group and per risk level. The number of recorded visits and the length of stay will also be summarized descriptively.

In case two or more assessments are reported at the same day (for example two assessments at the same device) then the worst score per question will be used.

Finally, emerging medical resources utilized during an ARI episode will be summarized per group for all ARI cases, for all RT-PCR confirmed RSV cases, for all negative (or missing) RT-PCR RSV cases and for the 3 case definitions. A treatment - emergent medical resource is defined as a medical resource visit that was related to an ARI or a complication of an ARI (meaning the 'Specify number of visits related to ARI or its complications' question in the MRU is equal or larger to one).

In case a participant experiences two or more ARIs (based on the 'Any ARI' definition, Section 4.4.3.1) during the study then the following rules will be followed in identifying which ARIs data will be used:

- If all fulfil a case definition, then data from the RT-PCR confirmed RSV disease fulfilling the strictest definition will be used (case definition 1> case definition 2> case definition 3)
- If only one fulfils a case definition, then those data will be used
- If none fulfils a case definition or all fulfil the same case definition, then data from the first RT-PCR confirmed RSV disease will be used.
- If none is a RT-PCR confirmed RSV-disease, then use:
  - the ARI that fulfils the strictest case definition based on symptoms only (case definition 1> case definition 2> case definition 3) Or
  - the first ARI, in case 2 or more fulfil the same case definition on symptoms only or in case they do not fulfil any case definition on symptoms only.

Note: For outputs were only planned visits (ARI Day 3-5, ARI Day 29, End of season) are presented, the worst across the different scheduled and unscheduled visits will be presented per visit.

4.12. The Relationship Between the Primary Endpoints and Medical Resource Use

In order to establish the interrelationship between the primary endpoints and medical resource utilization, the following analyses will be performed restricted to the placebo group. These analyses will be performed on two subgroups of the PPE set:

- participants with any RT-PCR confirmed RSV disease (see above for definition)
- participants with any ARI (see Any ARI definition, independently of RSV etiology).

In each of those subgroups the following will be calculated: the percentage of subjects having an (RT-PCR confirmed RSV) ARI and emerging medical resources use will be shown for:

- participants meeting Case Definition 1 versus participants not meeting any Case Definition
- participants meeting Case Definition 2 (or 1) versus participants not meeting any Case Definition
- participants meeting Case Definition 3 (or 1 or 2) versus participants not meeting any Case Definition

The corresponding odds ratio (and 95% CI) will be shown as well.

In case of limited number of participants not meeting any case definition:

- participants meeting Case Definition 1 versus participants not meeting Case Definition 1
- participants meeting Case Definition 2 (or 1) versus participants not meeting Case Definition 2 (or 1)
- participants meeting Case Definition 3 (or 1 or 2) versus participants not meeting any Case Definition

The corresponding odds ratio (and 95% CI) will be shown as well.

Note: In case a participant experiences two or more ARIs during the study the same rule as for the RiiQ will be used.

As a sensitivity check the same analysis will be performed but without taking into account cough for any of the case definitions.

4.13. Connection between Primary Endpoint and Patient reported Measures, clinical assessment and frailty index

In order to establish the interrelationship between the primary endpoints and PROs, the following analyses will be performed restricted to the placebo group. These analyses will be performed on two subgroups of the PPE set:

- participants with any RT-PCR confirmed RSV disease (see above for definition)
- participants with any ARI (see Any ARI definition, independently of RSV etiology)

For the following patient reported measures:

- AUC of the change from baseline for the Total RiiQ Respiratory and Systemic symptom score
- AUC of the change from baseline for the Total RiiQ Case Definition symptom score
- AUC of the change from baseline for the Total RiiQ Impact on Daily Activity score
- The change in IADL score between ARI Day 3-5 and baseline
- The change in augmented frailty score between baseline and end of season

The number of observations, median, first and third quartile, will be calculated for participants meeting each case definition and participants not meeting any case definition or not meeting the considered case definition; this will also be graphically depicted with boxplots.

Note: In case a participant experiences two or more ARIs during the study the same rule as for the RiiQ will be used.

As a sensitivity check the same analysis will be performed but without taking into account cough for any of the case definitions.

4.14. Viral Load

For RSV A viral load, RSV B viral load and their combination, descriptive statistics for ARI Day 1-2, ARI Day 3-5 and for the maximum viral loads observed between the 2 visits, will be calculated for participants with any RT-PCR-confirmed RSV disease and for participants fulfilling the 3 case definitions, by group. The difference and 95% CI of the maximum log10 viral loads between the 2 groups will also be calculated.

For analysis purposes, the qRT-PCR viral load will be imputed with the midpoint on the log scale between the limit of detection (LOD) and LLOQ of the RSV qRT-PCR assay when the result is 'target detected' (TD) but non-quantifiable.

- For the RSV-A qRT-PCR assay, the LOD is 620 copies/mL and the LLOQ is 1000 copies/mL, a result that is TD will be imputed with 2.90 log10 copies/mL.
- For the RSV-B qRT-PCR assay, the LOD is 80 copies/mL and the LLOQ is 250 copies/mL, a result that is TD will be imputed with 2.15 log10 copies/mL.

When the result is 'target not detected' (TND) (meaning below the LOD), for both RSV A and RSV B the value of TND will be imputed with the respective LODs.

In case of co-infection with both subtypes RSV A and B, the rules below will be applied for the overall analyses of viral load from the time the co-infection is detected (i.e. result of TD or >LLOQ), Table 12:

- In case of two quantifiable results: the log10 of the sum of the RSV A and RSV B results in copies/mL will be used.
- In case of a quantifiable result and a TD/TND result: use the imputed TD/TND on the copies/mL scale value and then use the log10 of the sum of the imputed value and the quantifiable result
- In case of two TD results, or one TD and one TND result: use the imputed TD/TND on the copies/mL scale values and then use the log10 of the sum of the imputed values
- In case of two TND results: the log10 of the sum of the RSV A LOD and RSV B LOD results in copies/mL will be used.

Table 12: Rules for coinfections

RSV A	RSV B	Combination
VL value	VL value	VL (RSV A) + VL (RSV B) in copies/ml
VL value	TD	VL (RSV A) + $10^{2.15}$copies/ml
TD	VL value	$10^{2.90}$copies/mL + VL (RSV B)
VL value	TND	VL (RSV A) + 80 copies/mL (LOD of RSV B)
TND	VL value	620 copies/mL (LOD of RSV A) + VL (RSV B)
TD	TD	$10^{2.90}$copies/mL + $10^{2.15}$ copies/mL
TND	TND	620 copies/mL (LOD of RSV A) +80 copies/mL (LOD of RSV B)
TND	TD	620 copies/mL (LOD of RSV A) + $10^{2.15}$ copies/mL
TD	TND	$10^{2.90}$copies/mL + 80 copies/mL

VL: viral load; TD: target detected; TND: target not detected
Note: Log10 transformation should occur after making the sums.

4.15. Approximate ARI surveillance compliance

Participants will receive an ARI surveillance question twice per week questioning whether they have experienced any cold or respiratory infection symptoms. The responsiveness of the participants to this ARI surveillance question will be summarized for both groups.

The approximate number of ARI surveillance questions that each participant is expected to have responded between vaccination (inclusive) and the end of the ARI surveillance or the day of discontinuation (in case of early discontinuation) will be calculated as follows:

1. First the number of weeks between day of vaccination and the end of the ARI surveillance (20th March 2020) or day of discontinuation (in case of early discontinuation) will be calculated.
2. Then the number of weeks that the participant experienced an ARI episode, will be calculated.
3. And finally, the difference of the two (1-2) will be multiplied by 2, since for each week a participant is part of the ARI surveillance journey, we expect to have responses in 2 questionnaires.

For estimating the percentage of compliance per subjects the number of ARI surveillance questions answered after vaccination, until the end of the ARI surveillance period and outside RSV-episodes will be divided by the number obtained in step 3 and will be multiplied by 100.

Note: In case multiple ARI surveillance questions have been answered at the same day, only one will be used.

4.16. ARI MISSING DATA

During the day of vaccination, the end of season visits, the ARI Day 3-5 and ARI Day 29 visit the site will collect the reason for missingness in case there are missing ePro assessments at the sites eDevice. These reasons will be tabulated at baseline and end of season for all participants per assessment and per group. For any ARI episode and for any RT-PCR confirmed RSV ARI the reason of missingness of the different assessments will similarly be tabulated.

Moreover, based on the RiiQ assessments descriptive statistics of the number of days with missing assessments during the first 7 days of an ARI episode, the first 14 days of an ARI episode and during the full ARI episode will be summarized per group. Finally, the percentage of compliance based on the RiiQ assessments will be calculated as follows:

- Compliance over the whole episode is defined as: Nr of days with RiiQ assessments/duration of episode x 100
- Compliance during the first seven days is defined as: Nr of days with RiiQ assessments between day 1 and day 7/ min (duration episode, 7 days) x 100
- Compliance during the first 14 days is defined as: Nr of days with RiiQ assessments between day 1 and day 14/ min (duration episode, 14 days) x 100

For example: For a subject with an ARI episode duration of 21 days with missing RiiQ assessment on day 4, 8 and 19, the compliance over the whole episode is 18/21x100, the compliance during the 1st 7 days is 6/7x100, the compliance over the 1st 14 days is 12/14x100.

4.17. Post-hoc Analyses

Post-hoc some additional analyses were added for season 1.

- Complications aligned with the phase 3 efficacy study (see Section 5.4.1)
- Clinical Relevant Diseases definition aligned with the phase 3 efficacy study (see Section 5.9)
- RIIQ Lower Respiratory Symptom scores (cough, short of breath, coughing op phlegm (sputum) and wheezing) and the respective AUC (see Section 5.5.1.) was added
- The AUC for the change from Day 1 for PGI-H and the AUC for PGI-C and PGI-S, will be calculated (see Section 5.5.2)

5. REVACCINATION SUBCOHORTS AND SECOND AND THIRD RSV SEASON ANALYSIS

The main focus of the year two and three analysis will be RT-PCR confirmed RSV positive ARIs.

Due to the measures implemented against the COVID-19 pandemic in the regions that the study is conducted, the number of RSV reported cases might be limited during the second and/or third RSV season. In such case, the efficacy analysis of year two and/or three will be restricted to a few key tables or listings. In case no RSV cases are reported, then the end of season two and/or three analysis might be restricted to only safety and immunogenicity. At the 'End of Efficacy Study Analysis' results will still be presented across the three year period, however.

5.1. SUBJECT INFORMATION

Demographic characteristics, disposition information, protocol deviations and concomitant medications will be summarized in a similar way to season one for the Revaccination Subcohorts. Some tables might also be created for the PPE sets for the second and third RSV season..

Comorbidities and medical conditions of interest will also be summarized at Day 365/Day 730.

The time that participants are followed in the study will be summarized descriptively, for the FAS and the PPE across the three RSV seasons. The time that participants are followed in the study based on the FAS is defined as the time between vaccination and the minimum between study completion, discontinuation or database cut off. The time that participants are followed in the study based on the PPE across three RSV seasons is defined as the time between vaccination and the minimum between study completion/discontinuation or database cut off or in case the participant had a major protocol deviation impacting efficacy during the second or third year respectively the end of the first RSV Season visit (or first RSV Season cut-off of 20 March 2020

if there would be no visit available) or the day before the planned Day 730 visit (or relative day 730 if no planned day 730 is present) is used. Additionally for participants in Revaccination Subcohort A or B, the end of the first RSV Season visit (or first RSV Season cut-off of 20 March 2020 if there would be no visit available) or the day before the planned Day 730 visit (or relative day 730 if no planned day 730 is present) is used respectively.

5.2. SAFETY

Safety analyses for the second and third RSV season will be performed similarly to the first RSV season (see Section 4.2), based on the FAS. The analysis of solicited and unsolicited AEs will be restricted to the Revaccination Subcohorts.

For the analysis of serious AEs (SAEs) the entire FAS will be used. **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 these participants, 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.

In the Revaccination Subcohorts B, C and D from 1st revaccination onwards and in Revaccination Subcohort 2A from d730 onwards, thrombosis with thrombocytopenia syndrome (TTS) is to be reported to the sponsor as an adverse event of special interest (AESI), within 24 hours of awareness. A potential AESI is defined as thrombotic events or symptomatic thrombocytopenia. For the analysis of serious AEs (SAEs) and (potential) AESIs in the Revaccination Cohorts the FAS will be used as well.

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, C, and D), 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 Subcohorts C and D, 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. 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 Subcohorts C and D.

Different types of SAE tables will be created:

- one focusing on all FAS participants by period until the end of the study or until revaccination.
- one focusing on each Revaccination Subcohort, from revaccination onwards until the end of the study by period.

For related SAEs, SAES resulting in death and AEs leading to discontinuation, tables as described above or listings (depending on the number of occurrences) may be provided.

For AESI analyses, the following subcategories are defined:

- Potential AESIs as identified by the investigator in the database
- Potential AESIs selected programmatically. Those include all reported AEs that are identified by the selection rule:
  - SMQ (Standardised MedDRA Queries) = "EMBOLIC AND THROMBOTIC EVENTS (SMQ)"
    or
  - (SUB_SMQ1 = "HAEMATOPOIETIC THROMBOCYTOPENIA (SMQ)" and SCOPE in ("BROAD","NARROW")) or HLT (higher level term)="Thrombocytopenias"
- Potential AESIs qualified for assessment
  Potential AESIs (programmed/identified by the investigator) that have risk levels assessed by one of the following three criteria are considered 'qualified for assessment':
  - Brighton Collaboration Level (Level 1-5)
  - CDC Tier (non-tier 1/2, tier 1, tier 2)
  - PRAC criteria (confirmed, possible, probable, unlikely, criteria not met)

As AESI (potential, identified by the investigator and/or qualified for assessment) are only collected in the Revaccination Subcohorts B, C and D from 1st revaccination onwards and in Revaccination Subcohort 2A from Day 730 onwards, the analysis of these potential AESI will only include these cohorts/timepoints. Potential AESIs as identified by the investigator, will be tabulated according to the following categories: 'Embolic and thrombotic events (SMQ; Standardised MedDRA Queries)' and 'Haematopoietic Thrombocytopenia (SMQ) (broad) or HLT (higher level term) = 'Thrombocytopenias', and 'Other'. Potential AESI as identified by the investigator, related to study vaccine (investigator assessment), will be tabulated similarly. Potential AESIs qualified for assessment will be tabulated by categories: 'Embolic and thrombotic events (SMQ)' and 'Haematopoietic Thrombocytopenia (SMQ) (broad) or HLT=Thrombocytopenias'.

In addition to the potential AESIs as identified by the investigator in the database, potential AESIs will also be selected programmatically. Those will be tabulated by categories: 'Embolic

and thrombotic events (SMQ)' and 'Haematopoietic Thrombocytopenia (SMQ) (broad) or HLT=Thrombocytopenias'. Potential AESI determined programmatically, related to study vaccine (investigator assessment), will be tabulated similarly. For these, all cohorts and the whole study period will be included in the analyses.

All AESI analyses will be presented by phase as well as by time interval. The definition of the different time intervals can be found below.

Dose	Interval	From	to
Post-vaccination 1	0-28 days post-dose	Date time of the 1st vaccination	Min of:* • 23:59 at the date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum (Date of Vaccination 1 + 28 days at 23:59 , date of scheduled visit 4 weeks after 1st vaccination at 23:59)
	29-56 days post-dose	One minute after the end of the interval 0-28 days post dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Date of Vaccination 1 + 56 days at 23:59
	57 days - 6 months post-dose	One minute after the end of the interval 29-56 days post-dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum (Date of Vaccination 1 + 168 days at 23:59 , date of scheduled visit 168 days post 1st vaccination at 23:59)
	>6 months post-dose	One minute after the end of the interval 57 days - 6 months post-dose	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at the date of DB cut-off for interim analyses • 1 min prior to date time of vaccination 2 for participants in the Revaccination Subcohorts
Post-vaccination	0-28 days	Date time of the	Min of:*

2	post-dose	2nd vaccination	• 23:59 at the date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum (Date of Vaccination 2 + 28 days at 23:59 , date of scheduled visit 4 weeks after 2nd vaccination at 23:59)
	29-56 days post-dose	One minute after the end of the interval 0-28 days post-dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Date of vaccination 2 + 56 days at 23:59
	57 days - 6 months post-dose	One minute after the end of the interval 29-56 days post-dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum(Date of vaccination 2 + 168 days at 23:59 , Day 533 visit at 23:59)
	>6 months post-dose	One minute after the end of the interval 57 days - 6 months post-dose	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at the date of DB cut-off for interim analyses • 1 min prior to date time of vaccination 3 at 23:59 for participants in Revaccination Subcohorts 2A and 2B
Post-vaccination 3	0-28 days post-dose	Date time of the 3rd vaccination	Min of:* • 23:59 at the date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum(Date of vaccination 3 + 28 days at 23:59 , date of scheduled visit 4 weeks after 3rd vaccination at 23:59)
	29-56 days post-dose	One minute after the end of the interval 0-28 days post-dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for

			interim analyses • Date of vaccination 3 + 56 days at 23:59
	57 days - 6 months post-dose	One minute after the end of the interval 29-56 days post-dose	Min of: • 23:59 at date of last contact (for discontinuations) • 23:59 at date of DB cut-off for interim analyses • Maximum(Date of vaccination 3 + 168 days at 23:59 , Day 898 visit at 23:59)
	>6 months post-dose	One minute after the end of the interval 57 days - 6 months post-dose	Min of: • 23:59 at the date of last contact (for discontinuations) • 23:59 at the date of DB cut-off for interim analyses

The combination of the '0 - 28 days post-dose' interval and the '29 - 56 days post-dose' interval will be referred as '0 - 56 days post-dose'.

The combination of the '0 - 28 days post-dose' ,'29 - 56 days post-dose' and '57 days - 6 months post-dose' intervals will be referred as '0-6 months post-dose'.

*In case the '0 - 28 days post-dose' interval ends later than 56 days post vaccination then the '29 - 56 days post-dose' interval is not required. For example, if a participant had Day 29 visit at relative day 57, then the following intervals will be created:

0 - 28 days post-dose, lasting from 0 to relative day 57,

57 days - 6 months post-dose, lasting from 58 onwards.

In case the definitions of the time intervals cause overlap, the start date of the latter time interval should always start one minute after the end of the previous one.

For potential AESIs qualified for assessment, potential AESIs as identified by the investigator and potential AESIs determined programmatically, attribution to the intervals will be done similarly to the unsolicited AEs as described in Section 4.2.1.3. For Step 2 of phase allocation of adverse events, the '0 - 28 days post-dose' interval should be treated similar to 'active' periods and the rest as 'non- active' periods.

Further, for solicited AEs, the denominator for the percentages will be the number of participants with data assessed by the PI in the considered population and phase for a certain regimen (incidence per 100 participants/phase) and risk level.

5.3. Immunogenicity Analysis

The analysis of immunogenicity will use the PPI set. For both the Immuno subset and the Revaccination Subcohorts, the immunogenicity analysis will follow the analysis outlined in Section 4.3. Except for Revaccination Subcohort B, Post-F ELISA results will no longer be assessed from Day 365 onwards for the Immuno Subset and Revaccination Subcohorts A, C and D.

In addition, for each Revaccination Subcohort separately, 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 (group 1A, 1B, 1C and 1D respectively) will be calculated for the different assays.

Moreover, 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, 3 or 4 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 point 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 Welch's ANOVA.

A similar analysis might be performed at other timepoints as well.

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 immunogenicity parameters will be made as applicable.

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

Note that tables including descriptive statistics of actual values and fold changes (if applicable) over time might also once be calculated restricted to participants who have data at the last scheduled timepoint included in the respective analyses of the immunosubset and Revaccination Subcohorts. This might also be graphically shown.

5.4. Efficacy Analysis

5.4.1. Exploratory Efficacy Variable(s)

5.4.1.1. Definition

Other exploratory efficacy endpoints are:

- **First occurrence of RT-PCR-confirmed RSV-mediated LRTD during the second RSV season and during the third RSV season according to Case Definition 1**

This is defined similarly as the primary endpoint, but only counted in the respective RSV 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 (see Section 2.1). 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 season two and three and over all three RSV seasons according Case Definition 1**

  This is defined similarly as the primary endpoint but taking into account events over season two and three and over all three 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 (see Section 2.1). 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 season two and three or over all three seasons, first occurrence of a considered endpoint over two or three seasons is defined as the first episode over the two or three periods (regardless A or B strain, unless otherwise specified).

The following exploratory efficacy endpoints, are defined similarly as the corresponding endpoints during the first RSV season (see Section 4.4.3 and 4.4.4), but baseline, new onset or worsening and first occurrence are defined the same way as for RT-PCR-confirmed RSV-mediated LRTD, during the second and third RSV season and over season two and three or over all three RSV seasons. These endpoints might also be explored during the second or third RSV season and across season two and three or across all three RSV seasons.

- **First occurrence of any RT-PCR-confirmed RSV ARI**
- **First occurrence of any RT-PCR-confirmed RSV A ARI, based on the DDL assay**
- **First occurrence of any RT-PCR-confirmed RSV B ARI, based on the DDL assay**
- **First occurrence of RT-PCR-confirmed RSV-A-mediated LRTD according to Case Definition 1, based on the DDL assay**
- **First occurrence of RT-PCR-confirmed RSV-B-mediated LRTD according to Case Definition 1, based on the DDL assay**
- **First occurrence of potential complications (according to the Phase 3 definition; see Section 5.8) of respiratory disease linked to an RT-PCR confirmed RSV ARI**
- **First occurrence of hospitalization linked to an RT-PCR confirmed RSV ARI**
- **First occurrence of pneumonia linked to an RT-PCR confirmed RSV ARI**

  Pneumonia is defined as:
  - X-ray confirmed pneumonia (as assessed on the eCRF diagnostic tests form: diagnosis of pneumonia confirmed by chest X-ray) *OR*

- Radiological confirmed pneumonia (as assessed on the eCRF diagnostic tests form: diagnosis of pneumonia confirmed by chest X-ray, CT-scan or MRI)

5.4.1.2. Analysis Methods

For all exploratory efficacy endpoints an exact Poisson model, as described in the primary efficacy analysis (see Section 4.4.2.2) will be performed, based on the respective PPE population.

For exploratory endpoints regarding only season one data, the follow-up time for cases is defined as the time between 14 days post-vaccination and the occurrence of the first event; for non-cases, it is the time between 14 days post-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 14 days post-vaccination and the occurrence of the first event and for participants that discontinued before having an event, follow-up time is the time between 14 days post-vaccination and the date of last contact (date of discontinuation).

For exploratory endpoints regarding only season two data, the follow-up time for cases in season two is defined as the time between Day 365 visit and the occurrence of the first event (according to the considered endpoint) in the considered season, for non-cases in season two, it is the time between Day 365 visit and the Day 730 (Month 24) visit. However, for participants that discontinued before the end of the second season and had an event in season two (according to the considered endpoint), the follow-up time is defined as the time between Day 365 visit and the occurrence of the first event and for participants that discontinued before having an event in season two, follow-up time is the time between Day 365 visit and the date of last contact. Participants that discontinued prior to 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 three data, the follow-up time for cases in Season three 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 three, 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 three (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 three, 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.

In case Day 365 is missing the analysis, relative date will be used (day of vaccination + 364 days). In case Day 730 is missing the analysis, relative data will be used (day of vaccination + 729 days).

For exploratory endpoints over season two and three, the follow-up time is defined as the time between the Day 365 visit and the occurrence of the first event (according to the considered endpoint) in the two seasons, for non-cases, it is the time between the Day 365 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 (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, follow-up time is the time between the Day 365 visit and the date of last contact. Revaccination Subcohort A participants are not taken into account for these analyses. For Revaccination Subcohort B participants only the second season is taken into account: for cases during the second season, the follow-up time is the time between the Day 365 visit and the occurrence of the first event (according to the considered endpoint), for non-cases it is the time between the Day 365 visit and the Day 730 (Month 24) visit. Note that participants with an MPD expecting to impact the efficacy outcomes in season one or two are not taken into account for these analyses. For participants with an MPD expecting to impact the efficacy outcomes in season three, only the second season can be taken into account: for cases during the second season, the follow-up time is the time between the Day 365 visit and the occurrence of the first event (according to the considered endpoint), for non-cases it is the time between the Day 365 visit and the Day 730 (Month 24) visit.

For exploratory endpoints over three seasons (Season one, Season two and Season three), the follow-up time is defined as the time between 14 days post-vaccination (vaccination day + 14 days) and the occurrence of the first event (according to the considered endpoint) in the three seasons, for non-cases, it is the time between 14 days post-vaccination and the end of the third season visit. However, for participants that discontinued before the end of the third season and had an event (according to the considered endpoint), the follow-up time is defined as the time between 14 days post-vaccination and the occurrence of the first event and for participants that discontinued before having an event, follow-up time is the time between 14 days post-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 14 days post-vaccination and the occurrence of the first event (according to the considered endpoint), for non-cases it is the time between 14 days post-vaccination and end of first season visit. For Revaccination Subcohort B participants only the first two seasons are taken into account: for cases during the first two seasons, the follow-up time is the time between 14 days post-vaccination and the occurrence of the first event (according to the considered endpoint), for non-cases it is the time between 14 days post-vaccination and the Day 730 (Month 24) visit. Note that participants with an MPD expecting to impact the efficacy outcomes in season one are not taken into account for these analyses. For participants with an MPD expecting to impact the efficacy outcomes in season two, only the first season can be taken into account: for cases during the first season, the follow-up time is the time between 14 days post-vaccination and the occurrence of the first event (according to the considered endpoint), for non-cases it is the time between 14 days post-vaccination and the end of the first season visit. For participants with an MPD expecting to impact the efficacy outcomes in season three, only the first and second season can be taken into account: for cases during one of these two seasons, the follow-up time is the time between 14 days post-vaccination and the occurrence of the first event

(according to the considered endpoint), for non-cases it is the time between 14 days post-vaccination and the Day 730 (Month 24) visit.

The 95% exact 2-sided CI for the VE (1-relative risk rate) will be calculated from these regression models and graphically depicted with forest plots. In case of the model does not converge then it will be fitted with only the vaccination group as dependent variable.

Poisson models will be executed also for the subgroups defined in Section 2.4 only for the first occurrence of any RT-PCR-confirmed RSV ARI and for the first occurrence of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition 1 for the second and third RSV season and across the three RSV seasons.

For the same endpoints, the following sensitivity analysis will also be performed, using the same model:

- based on the FAS (which also does not take into account the restriction on the onset [at least 14 days] and will count follow-up from vaccination on Day 1 onwards). RT-PCR results from samples that were out of stability, but tested RSV positive are taken into account in this analysis.
- based on the PPE set but excluding coinfections with other respiratory viruses based on GeneXpert and GenMark assay. This should be detected in one of the scheduled nasal or sputum samples linked to the respective ARI but should not necessarily be detected in the same sample as the one that resulted in RSV confirmation.
- based on the PPE set but only the participant reported symptoms (eDiary and eDevice) should be used to define case definitions.

For the sensitivity analysis focusing on data from the second RSV season only, participants from Revaccination Subcohort A and participants that discontinued earlier than the start of the second RSV season will be excluded. For the sensitivity analysis focusing on data from the third RSV season only, participants from Revaccination Subcohorts A and B and participants that discontinued earlier than the start of the third RSV season will be excluded. For sensitivity analysis focusing on data of RSV season two and three, participants from Revaccination Subcohorts A will be excluded and only data from the second RSV season for participants from Revaccination Subcohort B will be used. For sensitivity analysis focusing on data over three RSV seasons, only the first RSV season data will be used for participants from Revaccination Subcohort A and data from the first two RSV seasons for participants from Revaccination Subcohort B.

Kaplan Meier curves will be plotted for the time to first occurrence for any RT-PCR confirmed RSV ARI and for any RT-PCR confirmed RSV A and B ARI, across the three RSV seasons, based on the PPE set. The respective hazard ratios will also be calculated.

For participants with any RT-PCR-confirmed RSV disease during the second or third RSV season and across three RSV seasons, the median duration of the ARI episode will be summarized.

Complications linked to any RT-PCR confirmed RSV disease across the three RSV seasons will be summarized in a listing.

5.5. PATIENT-REPORTED OUTCOMES

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

For the second and third RSV season, only the total RiiQ Respiratory and Systemic symptom score change from Day 365/Day 730 and the respective AUC will be calculated for RSV ARIs, occurring during the second or third RSV season. For details in calculations see Section 4.5.1.

To align with the phase 3 VAC18193RSV3001 study, also the RiiQ Lower Respiratory Symptom scores (cough, short of breath, coughing op phlegm (sputum) and wheezing) and the respective AUC will be calculated for RSV ARIs during the second and third RSV season. Post-hoc analysis will be done for the first RSV Season.

5.5.1.1. Analysis Methods

The number of observations, median, first and third quartile (q1, q3), minimum and maximum of the AUC will be calculated and graphically presented with boxplots per group, for any RSV ARI, RSV A ARI and RSV B ARI (based on the DDL assay) and for Case Definition 1 occurring during the second or third RSV season and across the three RSV seasons.

Scatterplots of the AUC values versus the duration of the ARI episodes will also be created, for for any RSV ARI and for Case Definition 1 occurring during the second or third RSV season and across the three RSV seasons.

Note that the AUCs for RSV ARIs occurring during the first RSV season are defined based on the change from baseline (Day 1) and the AUCs for ARIs occurring the second or third RSV season are defined based on the change from Day 365/Day 730 (see Section 2.1). In case a participant experience two or more RSV ARIs during the three seasons, the same rule will apply similar to a participant experiencing two or more ARIs during the same season (see Section 4.5.1.1).

5.5.2. Patient Global Impression Scores

The scoring of the Patient Global Impression of Health (PGI-H) will be updated to align with the Phase 3 studies. Participants report their overall impression of their health status today on the following scale: 0=Very good, 1=Good, 2=Fair, 3=Poor, 4=Very poor.

For the second and third RSV season, the same scores will be collected, as in the first RSV season. In addition to the scores indicated in Section 4.5.2, the AUC for the change from Day 365/Day 730 for PGI-H and the AUC for PGI-C and PGI-S, will be calculated.

5.5.2.1. Analysis Methods

The following analysis will be conducted for any RSV ARI, RSV A ARI and RSV B ARI (based on the DDL assay) and in case of the AUC analyses additionally for RT-PCR-confirmed RSV-A-

mediated LRTD and RT-PCR-confirmed RSV-A-mediated LRTD based on Case Definition 1 occurring during the second or third RSV season and across three RSV seasons.

For the AUCs the number of observations, median, first and third quartile (q1, q3), minimum and maximum will be calculated and graphically presented with boxplots per group.

Moreover, the number of days a participant took to return to its usual health will be summarized and graphically presented with Kaplan Meir curves. Hazard ratios will also be calculated, with a cox proportional hazard model with time to return to usual health as dependent variable and group as independent variable.

In case a participant experiences two or more RSV ARIs during the three RSV seasons, the same rule will apply similar to a participant experiencing two or more ARIs during the same season (see Section 4.5.1.1).

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

See Section 4.6.

5.6.1. Analysis Method

For all participants with any RT-PCR-confirmed RSV disease from the PPE set during the first (up to Day 365) or second RSV season (up to Day 730), descriptive statistics of the actual values of the IADL score will be tabulated by sex and group for Day 1 (baseline), Day 365 and Day 730.

5.7. Clinical Assessment

See Section 4.8.

5.7.1. Analysis Methods

Clinical assessments will be analyzed similarly to the first RSV season, as described in Section 4.8.1, for the second or third RSV season and across the three RSV seasons, for participants with any RT-PCR confirmed RSV disease.

Vital signs will only be summarized across the three RSV seasons, for participants with any RT-PCR confirmed RSV disease. An abnormality will be considered as emerging in a particular period if it is worse than the baseline value of the corresponding season.

For ARIs collected during the second or third RSV season, change from the Day 365/Day 730 will be calculated instead of the change from baseline.

In case a participant experience two or more RSV ARIs during the three RSV seasons, the same rule will apply similar to a participant experiencing two or more ARIs during the same season (see Section 4.5.1.1).

5.8. Clinically Relevant Diseases

Clinical relevant diseases associated with RSV ARIs as defined in the phase 3 VAC18193RSV3001 study will be analyzed:

- Hospitalization
- Emergency department visit (as assessed on the eCRF medical encounters form and MRU pages [emerging MRU to be summarized])
- At least one of the following complications: asthma, COPD, respiratory distress, bronchitis, bronchial hyperreactivity, CHF, cardiac arrhythmia, renal impairment or the presence of X-ray or radiological confirmed pneumonia, respiratory arrest and/or failure, pulmonary embolism, pleural effusion, atelectasis, acute coronary events, acute cerebrovascular events, altered mental status, seizure, syncope, systemic inflammatory response syndrome (SIRS), new neurological deficit, asthenia, dehydration or metabolic disturbances.
  See Attachment 10 for the complication terms. These terms will be reported in the AE domain.
  Asthma and chronic obstructive pulmonary disease (COPD) exacerbation supporting LRTD reported in the medically attended ARI form will also be counted, as well as X-ray or radiological confirmed pneumonia from the diagnostic tests form.
- Decreased oxygen saturation defined as oxygen saturation of <92% for participants with a baseline oxygen saturation of ≥92% at randomization; for participants with baseline oxygen saturation <92%, decreased oxygen saturation is defined as a ≥3% decrease in their oxygen saturation from baseline
- Tachypnea (at least Grade 2, see Section 4.8)
- Need of supplemental oxygen
- Hypotension (at least Grade 3, see Section 4.8)
- Pulmonary function test results supporting diagnosis of LRTD
- Arterial blood gas results supporting diagnosis of LRTD

5.8.1. Analysis Methods

The PPE set will be used to analyze all clinically relevant diseases.

For the second and third RSV season and across season two and three and across all three RSV seasons, the following will be calculated. The proportion of participants with any RT-PCR confirmed RSV disease leading to clinically relevant diseases (as defined in Section 4.9 and 5.8) leading to clinically relevant diseases will be tabulated per group and the corresponding VE (1-relative risk) with a 95% CI will be determined and graphically depicted with a forest plot. A Poisson model similar to the primary endpoint will be used.

Any RT-PCR confirmed RSV disease leading to clinically relevant diseases as defined in Section 5.8 will also be summarized for the first RSV season.

The different subcategories of the clinically relevant diseases will be summarized only across the three RSV seasons, for participants with any RT-PCR confirmed RSV disease and RT-PCR-confirmed RSV-mediated LRTD based on Case Definition 1.

In case a participant experiences two or more RSV ARIs during the three RSV seasons, the same rule will apply similar to a participant experiencing two or more ARIs during the same season (see Section 4.5.1.1).

5.9. Therapeutic Interventions

See Section 4.10.

5.9.1. Analysis Methods

The PPE set will be used to analyze the therapeutic interventions. A similar analysis to derive VE as in the first RSV season, limited to any RSV ARI, will be repeated for the second and third RSV season and across season two and three and all three RSV seasons.

The different subcategories of new therapeutic interventions will be summarized only across the three RSV seasons, for participants with any RT-PCR confirmed RSV disease and RT-PCR-confirmed RSV-mediated LRTD based on Case Definition 1.

5.10. Medical Resources Use Questionnaire

See Section 4.11.

5.10.1. Analysis Methods

The PPE set will be used to analyze the medical resource utilization data.

At Day 365 and Day 730 the proportion of participants reporting having used the medical resources by category and subcategory will be summarized per group and per risk level.

The proportion of participants with emerging medical resources utilized, associated with any RT-PCR confirmed RSV ARI or LRTD based on Case Definition 1 across all three RSV seasons, will be summarized per group and per risk level, by MRU category and subcategory. Moreover, for those participants, the number of recorded visits and the length of stay will also be summarized descriptively for the RSV ARI episode.

Finally, the proportion of participants with any RT-PCR confirmed RSV disease with emerging medial resources utilized will be tabulated per group and the corresponding VE (1-relative risk) will be determined as described in Section 5.4.1.2 and graphically depicted with a forest plot, for the second and third RSV season and across season two and three and all three RSV seasons. In case a participant experience two or more RSV ARIs during the three RSV seasons, the same rule will apply similar to a participant experiencing two or more ARIs during the same season (see Section 4.5.1.1).

5.11. The Relationship Between Case Definition 1 and Other Efficacy Endpoints

In order to establish the interrelationship between the first occurrence of RT-PCR confirmed RSV-mediated LRTD according to case definition 1 and the following endpoints:

- Clinically relevant diseases (phase 3)
- Therapeutic interventions
- Emerging medical resource utilization
- Complication (phase 3)
- Hospitalizations
- And none of the above

The percentage of placebo participants having an RT-PCR confirmed RSV ARI and one of the above endpoints during that ARI will be shown for participants meeting Case Definition 1 versus participants not meeting Case Definition 1, with the corresponding odds ratio and 95% CI.

The analysis will be restricted to placebo participants with any RT-PCR confirmed RSV disease, during the three RSV seasons, from the PPE set.

In case a participant experience two or more RSV ARIs during these three RSV seasons, the same rule will apply similar to a participant experiencing two or more ARIs during the same season (see Section 4.5.1.1).

5.12. Connection between Case Definition 1 and patient reported measures, clinical assessment

In order to establish the interrelationship between the first occurrence of RT-PCR confirmed RSV-mediated LRTD according to case definition 1 and PROs, the following analyses will be performed restricted to placebo participants with any RT-PCR confirmed RSV disease, during the three RSV seasons, from the PPE set.

For the AUC of the change from baseline for the Total RiiQ Respiratory and Systemic symptom score and the RiiQ Lower Respiratory Symptom score, the number of observations, median, first and third quartile, will be calculated for participants meeting case definition 1 and participants not meeting case definition 1, this may also be graphically depicted with boxplots.

In case a participant experience two or more RSV ARIs during the three RSV seasons, the same rule will apply similar to a participant experiencing two or more ARIs during the same season (see Section 4.5.1.1).

5.13. Viral Load

Viral loads will be analyzed similar to season one (see Section 4.14) for participants with any RT-PCR-confirmed RSV disease and for participants fulfilling Case Definition 1, during the second or third RSV season and across the three RSV seasons.

The viral load analysis will be conducted separately for RSV A and RSV B infected participants. The overall RSV viral loads will not be calculated.

5.14. Approximate ARI surveillance compliance

The responsiveness of the participants to the ARI surveillance question will be summarized for both groups, for the second and third RSV season, similar to the first RSV season. A summary might be added across the three RSV seasons. For details, refer to Section 4.15. For the second RSV season, however, the number of weeks between the Day 365 visit and the end of the ARI surveillance (Day 730[a]) or day of discontinuation (in case of early discontinuation) will be used in step 1. A similar calculation will be done for the third RSV season based on the Day 730 visit and the end of the ARI surveillance (15th April 2022). Note: in case an ARI episode extends over multiple seasons, the respective duration in the considered season is taken into account for the calculations. Note that as ARI surveillance during the 1st season was stopped at 20 March 2020, for ARIs during the 1st Season, only the duration up to 20 march should be taken into account for the calculation of the approximate ARI surveillance.

5.15. ARI MISSING DATA

The same analysis as in the first RSV season will be conducted, for the second and third RSV season for ARI missing data. See Section 4.16.

[a] For participants without a Day 730 visit, the second RSV season will be cut off at the relative Day 730 (given that they did not discontinue before) to calculate the number of weeks in step 1. Additionally, ARIs starting in the second RSV season lasting longer than this relative Day 730 will also be cut off at the relative Day 730 in step 2. Finally, when calculating the number of surveillance questions answered, the ones after this relative Day 730 visit will not be counted.

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ATTACHMENTS

Attachment 1: Transforming Solicited AEs into Analysis Format

Solicited AEs are recorded by event and relatedness on the CE domain, similar to the format of unsolicited AEs. The reported start date of the AE on the CE domain equals the date of first occurrence of the solicited AE. The last reported date is used as the end date of the AE, regardless of possible changes in grade or time gaps also taking into account if the AE continues after Day 8. The investigators' opinion about the maximum grade over the duration of the AE will be reported. All solicited events are included on the CE domain, even when no such event occurred. In that case, the maximum grade is missing on the CE domain. These records with missing grade will not be used to construct the analysis dataset for solicited AEs. Note: Mapping of CE data to the solicited AE ADaM will occur in a similar way as unsolicited AEs are mapped in the unsolicited AE analysis database. It is possible that the investigators' assessment as captured in CE differs in grade with the diary data (recorded by day on the FA and VS domain). It is the CE data that will be used when creating ADAMs, tables and listings.

Notes:
For solicited AEs time should not be taken into account to allocate an event to a phase, the event is per definition of solicited AEs collected post-dose and should therefore not be allocated to inactive phases.

Duration will be based on the end date – onset date + 1. This duration may differ from the duration in the AE/CE domain because of some remapping before the Season 2 analysis. From that point onwards, the maximum duration for solicited AEs on the CE domain is 8 days. If the AE continues after Day 8, a record will be added to the AE domain, with the same start and end date as the AE had on the CE domain. The duration in the AE domain will differ however, as it will only start counting from Day 8 onwards.

The time to first onset is defined as (date of first onset – reference date + 1). The reference date is the start date of the vaccination period.

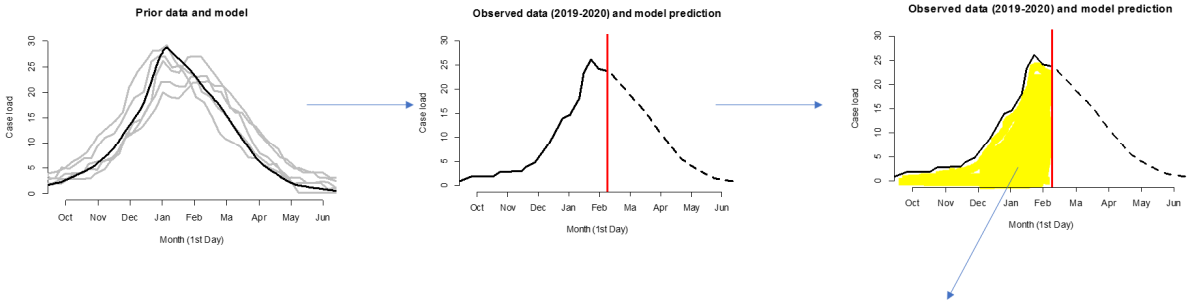
Attachment 2: Real World Evidence

Real World Evidence (RWE) will be used to calculate the information fraction at potential interim analyses. The required RWE consists of:

- historic RSV case data over a time for number of past RSV season and
- continuous reporting of RSV caseloads over the ongoing season in the study region.

Example of these data can be found for Western Australia at https://ww2.health.wa.gov.au/Articles/F_I/Infectious-disease-data/Virus-WAtch (Virus Watch "Current Edition" and "Past Editions") and for New South Wales (Australia) at https://www.health.nsw.gov.au/Infectious/Influenza/Pages/reports.aspx ("Past influenza surveillance reports" and "Monthly surveillance reports"). From previous years, the general distribution of the RSV case load over the season will be described and modeled. The data from the case load for the current RSV season will then be used to estimate the percentage of RSV cases over the complete year that already have been observed by the time of the IA, P_{IA} – see below for a graphical presentation. An effort will be made to identify the relevant RWE data for all study regions. If no data is available for the all study regions, extrapolations may be made from neighboring regions.

Estimation of P_{IA}



P_{IA}= proportion of RSV events (of total over season) estimated to have been observed at time of early IA

Attachment 3: Respiratory Viruses Used to Define Coinfections

The following respiratory viruses will be evaluated by the GenMark Respiratory Panel:

- Influenza A
- Influenza A H1
- Influenza A H3
- Influenza A 2009 H1N1
- Influenza B
- Respiratory Syncytial Virus A
- Respiratory Syncytial Virus B
- Parainfluenza Virus 1
- Parainfluenza Virus 2
- Parainfluenza Virus 3
- Human Metapneumovirus
- Human Rhinovirus
- Adenovirus B/E
- Adenovirus C

The following respiratory viruses will be evaluated by the GeneXpert Respiratory Panel:

- Influenza A
- Influenza B
- Respiratory Syncytial Virus
- SARS-COV-2

The following bacteria will be evaluated by the DDL assay:

- Streptococcus pneumoniae
- Staphylococcus aureus
- Haemophilus influenzae
- Moraxella catarrhalis
- Legionella pneumophila/longbeachae
- Mycoplasma pneumoniae
- Chlamydophila pneumoniae
- Bordetella pertussis
- Bordetella parapertussis

Attachment 4: Area Under the Curve Calculation

In the calculation of the AUC, not only the date, but also the timing (the real hours, minutes and seconds as captured in the database should be used, but the AUC result should be reported in hours), of the assessment, is taken into account.

$$\boldsymbol{AUC\ of\ total\ score} = \sum_{\boldsymbol{i=2}}^{\boldsymbol{T}} \frac{[\boldsymbol{TS_{t_i}} + \boldsymbol{TS_{t_{(i-1)}}}]}{\boldsymbol{2}} [\boldsymbol{t_i} - \boldsymbol{t_{(i-1)}}] \quad \textbf{(1)}$$

where

$t_i = (actual)\ timepoint\ i$

$t_{i-1} = (actual)\ timepoint\ (i-1)$

$T = last\ timepoint$

$t_1 = first\ timepoint$

$TS_{t_i} = Total\ score\ at\ \ (actual)\ timepoint\ i$

$TS_{t_{(i-1)}} = Total\ score\ at\ \ (actual)\ timepoint\ (i-1)$

Attachment 5: Therapeutic Interventions of Interest

Corticosteroids prescription

ATC codes	ATC Text
A01AC	Corticosteroids for local oral treatment
A07EA	Corticosteroids acting locally
C05AA	Corticosteroids
D01AC	imidazoles/triazoles in combination with corticosteroids (subset of terms with this ATC code)
D07	CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS
D07A	CORTICOSTEROIDS, PLAIN
D07AA	Corticosteroids, weak (group I)
D07AB	Corticosteroids, moderately potent (group II)
D07AC	Corticosteroids, potent (group III)
D07AD	Corticosteroids, very potent (group IV)
D07B	CORTICOSTEROIDS, COMBINATIONS WITH ANTISEPTICS
D07BA	Corticosteroids, weak, combinations with antiseptics
D07BB	Corticosteroids, moderately potent, combinations with antiseptics
D07BC	Corticosteroids, potent, combinations with antiseptics
D07BD	Corticosteroids, very potent, combinations with antiseptics
D07C	CORTICOSTEROIDS, COMBINATIONS WITH ANTIBIOTICS
D07CA	Corticosteroids, weak, combinations with antibiotics
D07CB	Corticosteroids, moderately potent, combinations with antibiotics
D07CC	Corticosteroids, potent, combinations with antibiotics
D07CD	Corticosteroids, very potent, combinations with antibiotics
D07X	CORTICOSTEROIDS, OTHER COMBINATIONS
D07XA	Corticosteroids, weak, other combinations
D07XB	Corticosteroids, moderately potent, other combinations
D07XC	Corticosteroids, potent, other combinations
D07XD	Corticosteroids, very potent, other combinations
D10AA	Corticosteroids, combinations for treatment of acne
G01B	ANTIINFECTIVES/ANTISEPTICS IN COMBINATION WITH CORTICOSTEROIDS
G01BA	Antibiotics and corticosteroids
G01BC	Quinoline derivatives and corticosteroids
G01BD	Antiseptics and corticosteroids
G01BE	Sulfonamides and corticosteroids
G01BF	Imidazole derivatives and corticosteroids
H02	CORTICOSTEROIDS FOR SYSTEMIC USE
H02A	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
H02B	CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS
H02BX	Corticosteroids for systemic use, combinations
M01BA	Antiinflammatory/antirheumatic agents in combination with corticosteroids

R01AD	Corticosteroids
R03AK	Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics
R03AL	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids
R03BA	Corticosteroids for inhalation
S01BA	Corticosteroids, plain
S01BB	Corticosteroids and mydriatics in combination
S01CA	Corticosteroids and antiinfectives in combination
S01CB	Corticosteroids/antiinfectives/mydriatics in combination
S02B	CORTICOSTEROIDS
S02BA	Corticosteroids
S02C	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S02CA	Corticosteroids and antiinfectives in combination
S03B	CORTICOSTEROIDS
S03BA	Corticosteroids
S03C	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S03CA	Corticosteroids and antiinfectives in combination

Bronchodilator/nebulizer treatment

ATC Code	ATC Text
R03	Drugs for Obstructive Airway Diseases
R03A	Adrenergics Inhalents
R03AA	Alpha-and beta-adrenoreceptor agonists
R03AB	Non Selective beta-adrenoreceptor agonists
R03AC	Selective beta-2-adrenoreceptor agonists
R03AH	Combinations of adrenergics
R03AK	Adrenergics and other drugs for obstructive airway diseases
RO3AL	Adrenergics in combination with corticosteroids or other drugs excl. anticholinergics
R03B	Other Drugs for Obstructive Airways Diseases, Inhalents
R03BA	Glucocorticoids
R03BB	Anticholinergics
R03BC	Antiallergic agents excl. corticosteroids
R03BX	Other Drugs for Obstructive Airways Diseases, Inhalents
R03C	Adrenergics for systemic use
R03CA	Alpha-and beta-adrenoreceptor agonists
R03CB	Non Selective beta-adrenoreceptor agonists
R03CC	Selective beta-2-adrenoreceptor agonists
R03CK	Adrenergics and other drugs for obstructive airway diseases
R03D	Other Systemic Drugs for Obstructive Airways Disease
R03DA	Xanthines
R03DB	Xanthines and Adrenergics

R03DC	Leukotriene receptor agonists
R03DX	Other Systemic Drugs for Obstructive Airways Disease

Antibiotic prescription

ATC Code	ATC Text
A01AB	Antiinfectives and antiseptics for local oral treatment
A02BD	Combinations for eradication of Helicobacter pylori
A07A	Intestinal antiinfectives
D06	Antibiotics and chemotherapeutics for dermatological use
D07C	Corticosteroids, combinations with antibiotics
D09AA	Ointment dressings with antiinfectives
D10AF	Antiinfectives for treatment of acne
G01	Gynecological antiinfectives and antiseptics
J01	Antibacterials for systemic use
J01A	Tetracyclines
J01AA	Tetracyclines
J01B	Amphenicols
J01BA	Amphenicols
J01C	Beta-Lactam Antibacterials, penicillins
J01CA	Penicillins with extended spectrum
J01CE	Beta-lactamase sensitive penicillins
J01CF	Beta-lactamase resistant penicillins
J01CG	Beta-lactamase inhibitors
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors
J01D	Other Beta-Lactam Antibacterials
J01DB	First generation cephalosporins
J01DC	Second generation cephalosporins
J01DD	Third generation cephalosporins
J01DE	Fourth generation cephalosporins
J01DF	Monobactams
J01DH	Carbapenems
J01DI	Other cephalosporins and penems
J01E	Sulfonamides and Trimethroprim
J01EA	Trimethoprim and derivatives
J01EB	Short acting sulfonamides
J01EC	Intermediate-acting sulfonamides
J01ED	Long-acting sulfonamides
J01EE	Combinations of sulfonamides and trimethoprim, incl derivatives
J01F	Macrolides, Lincosamides and Streptogramins
J01FA	Macrolides
J01FG	Streptogramins

J01G	Aminoglycoside Antibacterials
J01GA	Streptomycins
J01GB	Other aminoglycosides
J01M	Qunilone Antibacterials
J01MA	Fluoroquinolones
J01MB	Other quinolones
J01R	Combinations of antibacterials
J01RA	Combinations of antibacterials
J01X	Other Antibacterials
J01XA	Glycopeptide antibacterials
J01XB	Polymyxins
J01XC	Steroid antibacterials
J01XD	Imidazole derivatives
J01XE	Nitrofuran derivatives
J01XX	Other Antibacterials
J0IFF	Lincosamides
R02AB	Antibiotics
S01A	Antiinfectives
S01AA	Antibiotics
S01AB	Sulfonamides
S02A	Antiinfectives
S02AA	Antiinfectives
S02C	Corticosteroids and antiinfectives in combination
S02CA	Corticosteroids and antiinfectives in combination
S03	Antiinfectives
S03AA	Antiinfectives
S03C	Corticosteroids and antiinfectives in combination
S03CA	Corticosteroids and antiinfectives in combination

Antiviral prescription

ATC Codes	ATC Text
D06BB	Antivirals
J05	Antivirals for systemic use
J05A	Direct acting anti-virals
J05AA	Thiosemicarbazones
J05AB	Nucleosides and nucoeotides exc. Reverse transcriptase inhibitors
J05AC	Cyclic amines
J05AD	Phosphonic acid derivatives
J05AE	Protease inhibitors
J05AF	Nucleosides and nucoeotides reverse transcriptase inhibitors

J05AG	Non-nucleoside reverse transcriptase inhibitors
J05AH	Neuraminidase inhibitors
J05AP	Antivirals for treatment of HCV infections
J05AR	Antivirals for treatment of HIV infections
J05AX	Other antivirals
S01AD	Antivirals

Attachment 6: Binomial Exact Test

$$\textbf{Vaccine Efficacy} = 1 - \text{Relative Risk} = 1 - \frac{\#\text{ of Events}_{VX} / \#\text{ of Subjects}_{VX}}{\#\text{ of Events}_{P} / \#\text{ of Subjects}_{P}}$$

$$= 1 - \frac{1}{r} * \frac{\#\text{ of Events}_{VX}}{\#\text{ of Events}_{p}} = 1 - \frac{1}{r} * \frac{\#\text{ of Events}_{VX} / \#\text{ of Events}_{T}}{(\#\text{ of Events}_{T} - \#\text{ of Events}_{VX}) / \#\text{ of Events}_{T}}$$

$$= 1 - \frac{1}{r} * \frac{\#\text{ of Events}_{VX} / \#\text{ of Events}_{T}}{1 - \#\text{ of Events}_{VX} / \#\text{ of Events}_{T}} = 1 - \frac{p}{r * (1 - p)}$$

Where,

$\boldsymbol{r} = \frac{\#\text{ of Subjects}_{VX}}{\#\text{ of Subjects}_{p}}$

$\boldsymbol{p} = \#\text{ of Events}_{VX} / \#\text{ of Events}_{T}$

$\#\ \boldsymbol{of\ Events_{VX}} =$ number of events in the Ad26. RSV. preF group

$\#\ \boldsymbol{of\ Events_{P}} =$ number of events in the Placebo group

$\#\ \boldsymbol{of\ Events_{T}} =$ number of events, regardless the group

Therefore, there is a monotonic link between VE, the vaccine efficacy, and p, the proportion of subjects in the vaccine group among the total cases in the two groups.

Note that, conditional on the total number of events, $\#\ \boldsymbol{of\ Events_{VX}}$ is binomially distributed ($\#\ \boldsymbol{of\ Events_{VX}}, \boldsymbol{n}$) with n the expected proportion of events in the vaccine group under the true vaccine efficacy.

The CI for vaccine efficacy can then be derived from the exact CI from p (Dragalin, Fedorov and Cheuvart, 2002)[5].

Attachment 7: 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 8: Examples of ARI Duration Calculations

Example 1: If a participant had:

- ARI start date: 10/11
- RiiQ assessments on his device: 10/11 - 16/11
- ARI Day 3-5 visit: 14/11
- ARI Day 29 visit: 8/12
- New onset or worsening of LRTI or URTI:
  - RiiQ at subject's device: 10/11-11/11
  - Planned visits: 14/11 and 8/12

Then the ARI episode end date is 14/11 (= max [enddate1, enddate2] = max [11/11, 14/11]) and the duration is 5 days. In case the same participant did not had a new onset or worsening during the ARI Day 3-5 visit then the end date would be 11/11 and the duration 2 days.

	ARI start (CE domain)				**ARI Day 3-5 Visit**	**Duration**
	10/11	11/11	12/11	13/11	14/11	
1	New onset or worsening	New onset or worsening			New onset or worsening	5 days
2	New onset or worsening	New onset or worsening				2 days

Some additional examples below, given the RiiQ assessments reported by the participants on his/her home device do not reach the actual ARI Day 29 visit date:

	ARI start (CE domain)				**ARI Day 3-5 Visit**		**ARI Day 3-5 Unsch. Visit**	**Duration**
	10/11	11/11	12/11	13/11	14/11	15/11	16/11	
1	New onset or worsening	New onset or worsening			New onset or worsening		New onset or worsening	7 days
2	New onset or worsening	New onset or worsening			New onset or worsening			5 days
3	New onset or worsening						New onset or worsening	7 days
4	New onset or worsening							1 day

	ARI start (CE domain)				**ARI Day 1 Unsch. Visit**		**ARI Day 3-5 Visit**	**Duration**
	10/11	11/11	12/11	13/11	14/11	15/11	16/11	
1	New onset or worsening	New onset or worsening			New onset or worsening		New onset or worsening	7 days
2	New onset or worsening	New onset or worsening			New onset or worsening			5 days
3	New onset or worsening	New onset or worsening					New onset or worsening	7 days

Example 2: If a participant had:

- ARI start date: 1/11
- ARI Day 3-5 visit: 4/11
- ARI Day 29 visit: 29/11
- New onset or worsening of LRTI or URTI :
    - RiiQ at subject's device: 1/11-10/11
    - Planned visits: 4/11 and 29/11

If the participant completed the RiiQ assessments from the 1/11 to the 27/11 then the end date would be 10/11 and the duration 10 days. Whereas, if the participant completed the RiiQ assessments from the 1/11 to the 29/11 or to the 30/11 then the end date would be the 29/11 and the duration would be 29 days.

	ARI start (CE domain)								**ARI Day 29 Visit ***		**Duration**
	1/11	1/11	2/11	….	10/11	…	27/11	28/11	29/11	30/11	
1	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ				
1	New onset or worsening	New onset or worsening	New onset or worsening	New onset or worsening	New onset or worsening				New onset or worsening		10 days
2	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	
2	New onset or worsening	New onset or worsening	New onset or worsening	New onset or worsening	New onset or worsening				New onset or worsening		29 days
3	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ	Comp. RiiQ		
3	New onset or worsening	New onset or worsening	New onset or worsening	New onset or worsening	New onset or worsening				New onset or worsening		29 days

*New onset or worsening at 'ARI Day 29' visit is based both on RiiQ collected at the site or by the subject and on the clinical assessments completed at the site.

Example 3: If a participant had:

- ARI start date: 1/11
- ARI Day 3-5 visit: 4/11
- ARI Day 29 visit: 29/11
- New onset or worsening of LRTI or URTI:
  - RiiQ at subject's device: 1/11-28/11
  - Planned visits: 4/11 and 29/11

Example 3: If a participant had:

- ARI start date: 11/11
- RiiQ assessments on his device: 15/11 - 16/11
- ARI Day 3-5 visit: 14/11
- ARI Day 29 visit: 8/12
- New onset or worsening of LRTI or URTI:
  - RiiQ at subject's device: 15/11
  - Planned visits: 14/11

Then the ARI episode end date is 15/11 (= max [enddate1, enddate2] = max [15/11, 14/11]) and the duration is 5 days.

	ARI start (CE domain)			**ARI Day 3-5 Visit**			**Duration**
	11/11	12/11	13/11	14/11	15/11	16/11	
1	No RiiQ completed on participants device	No RiiQ completed on participants device	No RiiQ completed on participants device	No RiiQ completed on participants device New onset or worsening on sites device	New onset or worsening		5 days

Attachment 9: New Concomitant Medications – Increase in dosage Calculation

In case a participant receives the same medication with the same form at baseline and during an ARI episode, then in order to identify whether there was an increase in dose between baseline and ARI episode the medication dose will be calculated by multiplying the dosage per administration with the number of administrations per day or per week, as applicable for both timepoints and compared.

This rule applies for the following medication frequencies:

- Once weekly (1 time per week)
- Twice weekly (2 times per week)
- Three Times weekly (3 times per week)
- Four Times weekly (4 times per week)
- Twice Daily (BID)
- Twice per Month (BIM)
- Every two weeks (Every 2 weeks)
- Every four weeks (Every 4 weeks)
- Weekly (Every week)
- Once
- Per Year
- Every three months (Q3M)
- Daily (QD)
- Four times daily (Q1D)
- Monthly (QM)
- Every Other Day (QOD)
- Three times daily (TID)

For frequencies equal to ‘other’ at baseline, any change to one of the above frequencies will be considered an increase, given that the form remains the same.

For frequencies equal to ‘as necessary’ (PNR) or ‘occasional’, any change to another frequency or dose will be considered as an increase.

A change from ‘as necessary’ (PNR) to ‘occasional’ or ‘other’ will not be considered as an increase.

Moreover, capsule and tablet are considered the same form so to define if there was an increase the dose and the frequency will be used as defined above. The same applies for inhalant and aerosol.

For example:

Standardized Medication Name	Dose per Administration	Dose Units	Dose Form	Dosing Frequency per Interval	Route of Administration	Timepoint
corticosteroids	50.0000	ug	AEROSOL	1 TIME PER WEEK	NASAL	Baseline
corticosteroids	50.0000	ug	AEROSOL	QD	NASAL	During ARI

Baseline dose is 50x1=50 ug per week

During the ARI 50x7=350 ug per week

This is considered an increase in dose for this medication.

Standardized Medication Name	Dose per Administration	Dose Units	Dose Form	Dosing Frequency per Interval	Route of Administration	Timepoint
GUAIFENESIN	600.0000	mg	TABLET	PRN	ORAL	**Baseline**
GUAIFENESIN	1200.0000	mg	TABLET	ONCE	ORAL	**During ARI**

This is considered an increase in dose for this medication since the frequency goes from as necessary to once.

Attachment 10: Clinically Relevant Complication AE terms

Asthma & COPD & bronchial hyperreactivity (Preferred terms)
Acute post asthmatic amyotrophy
Asthma late onset
Obstructive airways disorder
Airway remodelling
Asthma
Bronchospasm
Aspirin-exacerbated respiratory disease
Asthma exercise induced
Status asthmaticus
Asthma-chronic obstructive pulmonary disease overlap syndrome
Asthmatic crisis
Wheezing
Bronchial oedema
Bronchial hyperreactivity
Bronchial obstruction
Bronchostenosis
Obliterative bronchiolitis
Bronchiolitis obliterans syndrome
Bronchitis chronic
Bronchospasm paradoxical
Childhood asthma
Chronic obstructive pulmonary disease
Cough variant asthma
Cystic fibrosis
Cystic fibrosis lung
Infective pulmonary exacerbation of cystic fibrosis
Infective exacerbation of chronic obstructive airways disease
Malignant airway obstruction
Occupational asthma
Reactive airways dysfunction syndrome
Reversible airways obstruction
Severe asthma with fungal sensitisation
Unilateral bronchospasm

Respiratory Distress (Preferred Terms)
Respiratory Distress

Bronchitis (Preferred Terms)
Bronchitis
Bronchitis bacterial
Tracheobronchitis
Bronchitis viral
Allergic bronchitis
Asthma
Pertussis
Bronchitis chemical
Bronchitis chronic
Bronchitis fungal
Bronchitis haemophilus
Bronchitis moraxella
Bronchitis mycoplasmal
Bronchitis pneumococcal
Coxsackie bronchitis
Fibrinous bronchitis
Enterobacter tracheobronchitis
Eosinophilic bronchitis

Bronchitis (Preferred Terms)
Herpes simplex bronchitis
Immune-mediated lung disease
Tracheobronchitis mycoplasmal
Noninfective bronchitis
Obstructive airways disorder
Parainfluenzae viral bronchitis
Parainfluenzae viral laryngotracheobronchitis
Pseudomonas bronchitis
Respiratory syncytial virus bronchitis
Sinobronchitis
Streptococcal bronchitis
Tracheobronchitis bacterial
Tracheobronchitis viral

CHF Exacerbation (Preferred Term)
Cardiac failure congestive

Cardiac Arrhythmia (Preferred Terms)
Chronotropic incompetence
Electrocardiogram repolarisation abnormality
Electrocardiogram RR interval prolonged
Electrocardiogram U wave inversion
Electrocardiogram U wave present
Electrocardiogram U-wave abnormality
Sudden cardiac death
Bezold-Jarisch reflex
Bradycardia
Cardiac arrest
Cardiac death
Cardiac telemetry abnormal
Cardio-respiratory arrest
Central bradycardia
Electrocardiogram abnormal
Electrocardiogram ambulatory abnormal
Electrocardiogram change
Heart rate abnormal
Heart rate decreased
Heart rate increased
Loss of consciousness
Palpitations
Rebound tachycardia
Respiratory sinus arrhythmia magnitude abnormal
Respiratory sinus arrhythmia magnitude decreased
Respiratory sinus arrhythmia magnitude increased
Sudden death
Syncope
Tachycardia
Tachycardia paroxysmal
Bradyarrhythmia
Ventricular asystole
Accessory cardiac pathway
Adams-Stokes syndrome
Agonal rhythm
Atrial conduction time prolongation
Atrioventricular block
Atrioventricular block complete

Cardiac Arrhythmia (Preferred Terms)
Atrioventricular block first degree
Atrioventricular block second degree
Atrioventricular conduction time shortened
Atrioventricular dissociation
Atrioventricular node dysfunction
Bifascicular block
BRASH syndrome
Brugada syndrome
Bundle branch block
Bundle branch block bilateral
Bundle branch block left
Bundle branch block right
Conduction disorder
Defect conduction intraventricular
Electrocardiogram delta waves abnormal
Electrocardiogram PR prolongation
Electrocardiogram PR shortened
Electrocardiogram QRS complex prolonged
Electrocardiogram QT prolonged
Electrocardiogram repolarisation abnormality
Lenegre's disease
Long QT syndrome
Paroxysmal atrioventricular block
Sinoatrial block
Trifascicular block
Ventricular dyssynchrony
Wolff-Parkinson-White syndrome
Nodal arrhythmia
Nodal rhythm
Sinus arrest
Sinus arrhythmia
Sinus bradycardia
Sinus node dysfunction
Wandering pacemaker
Arrhythmia
Heart alternation
Heart rate irregular
Holiday heart syndrome
Pacemaker generated arrhythmia
Pacemaker syndrome
Paroxysmal arrhythmia
Pulseless electrical activity
Reperfusion arrhythmia
Withdrawal arrhythmia
Arrhythmia supraventricular
Atrial fibrillation
Atrial flutter
Atrial parasystole
Atrial tachycardia
Congenital supraventricular tachycardia
Frederick's syndrome
Junctional ectopic tachycardia
Sinus tachycardia
Supraventricular extrasystoles
Supraventricular tachyarrhythmia
Supraventricular tachycardia

Cardiac Arrhythmia (Preferred Terms)
ECG P wave inverted
Electrocardiogram P wave abnormal
Retrograde p-waves
Anomalous atrioventricular excitation
Cardiac fibrillation
Cardiac flutter
Extrasystoles
Tachyarrhythmia
Accelerated idioventricular rhythm
Cardiac fibrillation
Parasystole
Rhythm idioventricular
Torsade de pointes
Ventricular arrhythmia
Ventricular extrasystoles
Ventricular fibrillation
Ventricular flutter
Ventricular parasystole
Ventricular pre-excitation
Ventricular tachyarrhythmia
Ventricular tachycardia
Andersen-Tawil syndrome
Arrhythmia neonatal
Arrhythmogenic right ventricular dysplasia
Atrioventricular node dispersion
Brugada syndrome
Foetal arrhythmia
Foetal heart rate disorder
Foetal tachyarrhythmia
Heart block congenital
Junctional ectopic tachycardia
Long QT syndrome congenital
Lown-Ganong-Levine syndrome
Neonatal bradyarrhythmia
Neonatal tachyarrhythmia
Wolff-Parkinson-White syndrome congenital
Baseline foetal heart rate variability disorder
Bradycardia foetal
Bradycardia neonatal
Cardiac arrest neonatal
Cardio-respiratory arrest neonatal
Foetal cardiac arrest
Foetal heart rate acceleration abnormality
Foetal heart rate deceleration abnormality
Neonatal sinus bradycardia
Neonatal sinus tachycardia
Neonatal tachycardia
Nonreassuring foetal heart rate pattern
Tachycardia foetal

Renal Impairment (Preferred Terms)
Acute kidney injury
Atypical haemolytic uraemic syndrome
Oliguria
Anuria

Renal failure
Cardiorenal syndrome
Chronic kidney disease
End stage renal disease
Renal impairment
Crush syndrome
Diabetic end stage renal disease
Hepatorenal failure
Foetal renal impairment
Prerenal failure
Haemolytic uraemic syndrome
Hepatorenal syndrome
Nail-patella syndrome
Renal injury
Neonatal anuria
Pancreatorenal syndrome
Postoperative renal failure
Postrenal failure
Propofol infusion syndrome
Renal failure neonatal
Renal impairment neonatal
Scleroderma renal crisis
Subacute kidney injury
Traumatic anuria

X-ray or Radiologic Pneumonia (Preferred Terms)
Angiolymphoid hyperplasia with eosinophilia
Charcot-Leyden crystals
Confirmed e-cigarette or vaping product use associated lung injury
Eosinophilia myalgia syndrome
Eosinophilic bronchitis
Eosinophilic granulomatosis with polyangiitis
Eosinophilic pleural effusion
Eosinophilic pneumonia
Eosinophilic pneumonia acute
Eosinophilic pneumonia chronic
Hypereosinophilic syndrome
Loeffler's syndrome
Pneumonitis
Pneumonitis chemical
Probable e-cigarette or vaping product use associated lung injury
Pulmonary eosinophilia
Pulmonary vasculitis
Eosinophil count abnormal
Eosinophil count increased
Eosinophil percentage abnormal
Eosinophil percentage increased
Eosinophilia
Acute lung injury
Acute respiratory distress syndrome
Airway remodelling
Allergic bronchitis
Allergic cough
Allergic respiratory disease
Allergic respiratory symptom
Alveolar lung disease
Alveolar proteinosis

X-ray or Radiologic Pneumonia (Preferred Terms)
Alveolitis
Aspirin-exacerbated respiratory disease
Asthma
Asthma late onset
Asthma-chronic obstructive pulmonary disease overlap syndrome
Asthmatic crisis
Atopic cough
Autoimmune lung disease
Bronchial hyperreactivity
Bronchial obstruction
Bronchiolitis
Bronchiolitis obliterans syndrome
Bronchospasm
Childhood asthma
Complications of transplanted lung
Cough variant asthma
Cystic lung disease
Diffuse alveolar damage
Diffuse panbronchiolitis
Drug reaction with eosinophilia and systemic symptoms
Forced expiratory flow decreased
Forced expiratory volume abnormal
Forced expiratory volume decreased
Fractional exhaled nitric oxide abnormal
Fractional exhaled nitric oxide increased
Functional residual capacity abnormal
Functional residual capacity increased
Goodpasture's syndrome
Granulomatosis with polyangiitis
Hypersensitivity pneumonitis
Hyperventilation
Hypocapnia
Hypoxia
Idiopathic interstitial pneumonia
Immune-mediated lung disease
Interstitial lung disease
Lung hyperinflation
Lung infiltration
Lung opacity
Lung transplant rejection
Lupus pneumonitis
Lymphangioleiomyomatosis
Myalgia
Obliterative bronchiolitis
Obstructive airways disorder
Occupational asthma
Organising pneumonia
PCO2 abnormal
PCO2 decreased
Peak expiratory flow rate abnormal
Peak expiratory flow rate decreased
Pneumonia
PO2 abnormal
PO2 decreased
Polyarteritis nodosa
Prolonged expiration

X-ray or Radiologic Pneumonia (Preferred Terms)
Pulmonary granuloma
Pulmonary radiation injury
Pulmonary sensitisation
Pulmonary toxicity
Radiation alveolitis
Radiation pneumonitis
Respiratory alkalosis
Reversible airways obstruction
Rheumatoid lung
Small airways disease
Status asthmaticus
Tachypnoea
Toxic oil syndrome
Transfusion-related acute lung injury
Wheezing
Actinomycotic pulmonary infection
Acute pulmonary histoplasmosis
Atypical mycobacterial pneumonia
Atypical pneumonia
Blastomycosis
Bronchopulmonary aspergillosis
Burkholderia cepacia complex infection
Burkholderia pseudomallei infection
Candida pneumonia
Chlamydial infection
Chronic pulmonary histoplasmosis
Coccidioidomycosis
COVID-19 pneumonia
Embolic pneumonia
Enterobacter pneumonia
Haemophilus infection
Haemorrhagic pneumonia
Hantavirus pulmonary infection
Herpes simplex pneumonia
Histoplasmosis
Infectious pleural effusion
Lung abscess
Metapneumovirus pneumonia
Miliary pneumonia
Paracancerous pneumonia
Parasitic pneumonia
Pleural infection
Pleural infection bacterial
Pleurisy viral
Pneumocystis jirovecii pneumonia
Pneumonia
Pneumonia acinetobacter
Pneumonia adenoviral
Pneumonia anthrax
Pneumonia bacterial
Pneumonia blastomyces
Pneumonia bordetella
Pneumonia chlamydial
Pneumonia cryptococcal
Pneumonia cytomegaloviral
Pneumonia escherichia

X-ray or Radiologic Pneumonia (Preferred Terms)
Pneumonia fungal
Pneumonia haemophilus
Pneumonia helminthic
Pneumonia herpes viral
Pneumonia influenzal
Pneumonia klebsiella
Pneumonia legionella
Pneumonia measles
Pneumonia moraxella
Pneumonia mycoplasmal
Pneumonia necrotising
Pneumonia parainfluenzae viral
Pneumonia pneumococcal
Pneumonia proteus
Pneumonia pseudomonal
Pneumonia respiratory syncytial viral
Pneumonia salmonella
Pneumonia serratia
Pneumonia staphylococcal
Pneumonia streptococcal
Pneumonia toxoplasmal
Pneumonia tularaemia
Pneumonia viral
Pneumonic plague
Post procedural pneumonia
Pulmonary echinococciasis
Pulmonary mucormycosis
Pulmonary nocardiosis
Pulmonary paracoccidioidomycosis
Pulmonary sepsis
Pulmonary sporotrichosis
Pulmonary syphilis
Pulmonary trichosporonosis
Pulmonary tuberculosis
Pyopneumothorax
Septic pulmonary embolism
Tuberculosis
Tuberculous pleurisy
Varicella zoster pneumonia
Acinetobacter infection
Acinetobacter test positive
Adenovirus infection
Adenovirus test positive
Aspergillus infection
Aspergillus test positive
Aspiration tracheal abnormal
Atelectasis
Atypical mycobacterial infection
Atypical mycobacterial lower respiratory tract infection
Auscultation
Avian influenza
Bacterial test positive
Bronchopneumopathy
Burkholderia test positive
Carbon dioxide abnormal
Carbon dioxide increased

X-ray or Radiologic Pneumonia (Preferred Terms)
Chest X-ray abnormal
Chlamydia test positive
Coronavirus infection
Coronavirus test positive
COVID-19
Coxiella test positive
Crepitations
Cryptococcosis
Culture throat positive
Disseminated aspergillosis
Disseminated blastomycosis
Disseminated coccidioidomycosis
Disseminated mucormycosis
Disseminated paracoccidioidomycosis
Disseminated sporotrichosis
Disseminated tuberculosis
Egobronchophony
Empyema
Enterobacter infection
Enterobacter test positive
Escherichia infection
Escherichia test positive
Francisella test positive
Fungal test positive
H1N1 influenza
H2N2 influenza
H3N2 influenza
Haemophilus test positive
Haemoptysis
Hantavirus test positive
Human metapneumovirus test positive
Hypoventilation
Hypoxia
Increased bronchial secretion
Influenza
Influenza A virus test positive
Influenza virus test positive
Klebsiella infection
Klebsiella test positive
Legionella infection
Legionella test positive
Lower respiratory tract congestion
Lower respiratory tract herpes infection
Lower respiratory tract infection
Lower respiratory tract infection bacterial
Lower respiratory tract infection fungal
Lower respiratory tract infection viral
Lung consolidation
Lung infiltration
Lung opacity
MERS-CoV test positive
Metapneumovirus infection
Middle East respiratory syndrome
Moraxella infection
Moraxella test positive
Mucormycosis

X-ray or Radiologic Pneumonia (Preferred Terms)
Mycobacterial infection
Mycobacterium test positive
Mycoplasma infection
Mycoplasma test positive
Nocardiosis
Organising pneumonia
Oxygen saturation abnormal
Oxygen saturation decreased
Paracoccidioides infection
PCO2 abnormal
PCO2 decreased
Percussion test abnormal
Pleural effusion
Pleural rub
Pleuritic pain
Pneumococcal bacteraemia
Pneumococcal infection
Pneumococcal sepsis
Pneumocystis test positive
Pneumovirus test positive
PO2 abnormal
PO2 decreased
Productive cough
Proteus infection
Proteus test positive
Pseudomonas infection
Pseudomonas test positive
Psittacosis
Pulmonary congestion
Pulmonary imaging procedure abnormal
Pulmonary tuberculoma
Q fever
Rales
Respiratory tract infection
Respiratory tract infection bacterial
Respiratory tract infection fungal
Respiratory tract infection viral
Rhonchi
SARS-CoV-1 test positive
SARS-CoV-2 antibody test positive
SARS-CoV-2 test false negative
SARS-CoV-2 test positive
Serratia infection
Serratia test positive
Severe acute respiratory syndrome
Sporotrichosis
Sputum abnormal
Sputum culture positive
Sputum discoloured
Sputum purulent
Staphylococcal infection
Staphylococcus test positive
Streptococcal infection
Streptococcus test positive
Suspected COVID-19
Tachypnoea

X-ray or Radiologic Pneumonia (Preferred Terms)
Tularaemia
Use of accessory respiratory muscles
Venous oxygen saturation abnormal
Venous oxygen saturation decreased

Respiratory Arrest or Failure (Preferred Terms)
Acute respiratory distress syndrome
Acute respiratory failure
Agonal respiration
Apnoea
Apnoeic attack
Bradypnoea
Breath holding
Breath sounds abnormal
Breath sounds absent
Cardio-respiratory distress
Central-alveolar hypoventilation
Chronic respiratory failure
Hypopnoea
Hypoventilation
Hypoventilation neonatal
Infantile apnoea
Lung hypoinflation
Meconium aspiration syndrome
Neonatal respiratory arrest
Neonatal respiratory depression
Neonatal respiratory distress
Neonatal respiratory distress syndrome
Neonatal respiratory failure
Postoperative respiratory distress
Postoperative respiratory failure
Respiratory arrest
Respiratory depression
Respiratory depth decreased
Respiratory distress
Respiratory failure
Respiratory paralysis
Respiratory rate decreased
Adaptive servo-ventilation
Alveolar oxygen partial pressure abnormal
Alveolar oxygen partial pressure decreased
Alveolar-arterial oxygen gradient increased
Anoxia
Asphyxia
Automatic positive airway pressure
Bilevel positive airway pressure
Blood gases abnormal
Blood pH abnormal
Blood pH decreased
Capnogram abnormal
Carbon dioxide abnormal
Carbon dioxide increased
Cardiac arrest
Cardiac arrest neonatal
Cardiopulmonary failure
Cardio-respiratory arrest

Respiratory Arrest or Failure (Preferred Terms)
Cardio-respiratory arrest neonatal
Cheyne-Stokes respiration
Chronic respiratory disease
Clubbing
Continuous positive airway pressure
Cyanosis central
Death neonatal
Dependence on oxygen therapy
Dependence on respirator
Diaphragmatic pacemaker insertion
Dyspnoea at rest
Endotracheal intubation
End-tidal CO2 abnormal
End-tidal CO2 decreased
Hyperbaric oxygen therapy
Hypercapnia
Hypercapnic coma
Hypoxia
Intermittent positive pressure breathing
Irregular breathing
Life support
Lung assist device therapy
Mechanical ventilation
Mechanical ventilation complication
Neonatal anoxia
Neonatal asphyxia
Neonatal hypoxia
Neonatal respiratory acidosis
Neonatal respiratory distress syndrome prophylaxis
Neonatal tachypnoea
Orthopnoea
Oxygen saturation abnormal
Oxygen saturation decreased
Oxygen saturation immeasurable
Oxygen therapy
PaO2/FiO2 ratio decreased
PCO2 abnormal
PCO2 decreased
PCO2 increased
PO2 abnormal
PO2 decreased
Positive end-expiratory pressure
Positive expiratory pressure therapy
Respiration abnormal
Respiratory acidosis
Respiratory disorder
Respiratory disorder neonatal
Respiratory fatigue
Respiratory fume inhalation disorder
Respiratory gas exchange disorder
Respiratory therapy
Tachypnoea
Transient tachypnoea of the newborn
Use of accessory respiratory muscles
Venous oxygen partial pressure abnormal
Venous oxygen partial pressure decreased

Respiratory Arrest or Failure (Preferred Terms)
Venous oxygen saturation abnormal
Venous oxygen saturation decreased
Ventilation perfusion mismatch
Ventilation/perfusion scan abnormal
Wean from ventilator
Weaning failure
Xyphoid retraction
Acute respiratory failure
Agonal respiration
Apnoea
Apnoeic attack
Bradypnoea
Breath holding
Breath sounds abnormal
Breath sounds absent
Central-alveolar hypoventilation
Hypopnoea
Hypoventilation
Hypoventilation neonatal
Infantile apnoea
Lung hypoinflation
Neonatal respiratory arrest
Neonatal respiratory depression
Neonatal respiratory failure
Postoperative respiratory failure
Respiratory arrest
Respiratory depression
Respiratory depth decreased
Respiratory failure
Respiratory paralysis
Respiratory rate decreased
Adaptive servo-ventilation
Alveolar oxygen partial pressure abnormal
Alveolar oxygen partial pressure decreased
Anoxia
Apnoea test abnormal
Asphyxia
Automatic positive airway pressure
Bilevel positive airway pressure
Blood gases abnormal
Blood pH abnormal
Blood pH decreased
Capnogram abnormal
Carbon dioxide abnormal
Carbon dioxide increased
Cardiac arrest
Cardiac arrest neonatal
Cardiopulmonary failure
Cardio-respiratory arrest
Cardio-respiratory arrest neonatal
Cardio-respiratory distress
Cheyne-Stokes respiration
Continuous positive airway pressure
Cyanosis
Cyanosis central
Death neonatal

Respiratory Arrest or Failure (Preferred Terms)
Dependence on oxygen therapy
Dependence on respirator
Diaphragmatic pacemaker insertion
Dyspnoea
End-tidal CO2 abnormal
End-tidal CO2 decreased
Hyperbaric oxygen therapy
Hypercapnia
Hypercapnic coma
Hypoxia
Intermittent positive pressure breathing
Irregular breathing
Life support
Lung assist device therapy
Mechanical ventilation
Mechanical ventilation complication
Neonatal anoxia
Neonatal asphyxia
Neonatal dyspnoea
Neonatal hypoxia
Neonatal respiratory acidosis
Neonatal respiratory distress syndrome prophylaxis
Oxygen saturation abnormal
Oxygen saturation decreased
Oxygen saturation immeasurable
Oxygen therapy
PaO2/FiO2 ratio decreased
PCO2 abnormal
PCO2 increased
PO2 abnormal
PO2 decreased
Positive end-expiratory pressure
Respiration abnormal
Respiratory acidosis
Respiratory disorder
Respiratory disorder neonatal
Respiratory distress
Respiratory fume inhalation disorder
Respiratory gas exchange disorder
Respiratory therapy
Sleep apnoea syndrome
Venous oxygen partial pressure abnormal
Venous oxygen partial pressure decreased
Venous oxygen saturation abnormal
Venous oxygen saturation decreased
Ventilation perfusion mismatch
Ventilation/perfusion scan abnormal
Wean from ventilator
Weaning failure

Pulmonary Embolism (Preferred Terms)
Pulmonary embolism
Anaphylactoid syndrome of pregnancy
Cement embolism
Pulmonary infarction

Metastatic pulmonary embolism
Obstetrical pulmonary embolism
Post procedural pulmonary embolism
Pulmonary artery thrombosis
Pulmonary microemboli
Pulmonary oil microembolism
Pulmonary thrombosis
Pulmonary tumour thrombotic microangiopathy
Pulmonary venous thrombosis
Septic pulmonary embolism

Pleural Effusion (Preferred Terms)
Pleural effusion
Capnothorax
Chylothorax
Haemothorax
Pneumothorax
Congenital chylothorax
Eosinophilic pleural effusion
Traumatic haemothorax
Hepatic hydrothorax
Hydrothorax
Procedural pneumothorax
Pneumothorax spontaneous
Neonatal pneumothorax
Paraneoplastic pleural effusion
Pleuroperitoneal communication
Pneumothorax traumatic

Atelectasis (Preferred Terms)
Atelectasis
Atelectasis neonatal
Tracheobronchitis

Acute Coronary Events (Preferred Terms)
Chest pain
Acute myocardial infarction
Acute coronary syndrome
Myocardial ischaemia
Myocardial infarction
Coronary artery dissection
Coronary artery aneurysm
Angina pectoris
Angina unstable
Prinzmetal angina
Anginal equivalent
Congenital coronary artery malformation
Coronary artery insufficiency
Arteriosclerosis coronary artery
Arteriospasm coronary
Arteritis coronary
Coronary artery disease
Cardiac perfusion defect
Microvascular coronary artery disease
Chest discomfort
Chronic coronary syndrome
Coronary artery stenosis

Acute Coronary Events (Preferred Terms)
Haemorrhage coronary artery
Coronary artery compression
Coronary artery dilatation
Coronary artery embolism
Coronary artery occlusion
Coronary artery perforation
Coronary artery reocclusion
Coronary artery restenosis
Coronary artery thrombosis
Coronary bypass stenosis
Coronary bypass thrombosis
Coronary no-reflow phenomenon
Coronary ostial stenosis
Coronary sinus dilatation
Coronary steal syndrome
Coronary vascular graft occlusion
Coronary vascular graft stenosis
Diabetic coronary microangiopathy
Subendocardial ischaemia
Papillary muscle infarction
Kounis syndrome
Myocardial reperfusion injury
Myocardial stunning
Periprocedural myocardial infarction
Post procedural myocardial infarction
Postinfarction angina
Silent myocardial infarction
Subclavian coronary steal syndrome
Wellens' syndrome

Altered Mental Status (SOC)
Psychiatric disorders

Acute Cerebrovascular Events (Preferred Terms)
Cerebrovascular accident
Subdural haematoma
Superior sagittal sinus thrombosis
Cerebrovascular disorder
Spinal artery embolism
Amaurosis fugax
Amyloid related imaging abnormalities
Amyloid related imaging abnormality-oedema/effusion
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits
Intracranial aneurysm
Brain hypoxia
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery perforation
Cerebral artery stenosis
Cerebral artery thrombosis
Aseptic cavernous sinus thrombosis
Cerebral infarction
Haemorrhagic transformation stroke
Subarachnoid haemorrhage
Cerebral arteriosclerosis
Basal ganglia haemorrhage

Acute Cerebrovascular Events (Preferred Terms)
Basal ganglia haematoma
Basal ganglia infarction
Basal ganglia stroke
Basilar artery aneurysm
Basilar artery occlusion
Basilar artery perforation
Basilar artery stenosis
Vertebrobasilar insufficiency
Basilar artery thrombosis
Benedikt's syndrome
Reversible cerebral vasoconstriction syndrome
Vascular encephalopathy
Haemorrhage intracranial
Blood brain barrier defect
Cerebral congestion
Brain stem haemorrhage
Brain stem embolism
Brain stem haematoma
Brain stem infarction
Brain stem ischaemia
Brain stem microhaemorrhage
Brain stem stroke
Brain stem thrombosis
Capsular warning syndrome
Embolic stroke
Carotid aneurysm rupture
Carotid arterial embolus
Carotid arteriosclerosis
Carotid artery aneurysm
Carotid artery disease
Carotid artery dissection
Carotid artery dolichoectasia
Carotid artery insufficiency
Carotid artery occlusion
Carotid artery perforation
Carotid artery restenosis
Carotid artery stenosis
Carotid artery thrombosis
Cavernous sinus thrombosis
Central nervous system haemorrhage
Central nervous system vasculitis
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebellar atherosclerosis
Cerebellar haemorrhage
Cerebellar embolism
Cerebellar haematoma
Cerebellar infarction
Cerebellar ischaemia
Cerebellar microhaemorrhage
Cerebellar stroke
Cerebral amyloid angiopathy
Cerebral aneurysm perforation
Cerebral aneurysm ruptured syphilitic
Cerebral vasoconstriction
Cerebral arteriovenous malformation haemorrhagic

Acute Cerebrovascular Events (Preferred Terms)
Cerebral arteritis
Intraoperative cerebral artery occlusion
Cerebral artery restenosis
Cerebral haemorrhage
Cerebral capillary telangiectasia
Cerebral circulatory failure
Cerebral gas embolism
Cerebral haematoma
Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal
Traumatic intracranial haemorrhage
Cerebral haemosiderin deposition
Cerebral hyperperfusion syndrome
Cerebral hypoperfusion
Cerebral infarction foetal
Cerebral ischaemia
Cerebral microangiopathy
Cerebral microhaemorrhage
Cerebral microembolism
Cerebral microinfarction
Cerebral reperfusion injury
Cerebral septic infarct
Cerebral small vessel ischaemic disease
Cerebral thrombosis
Cerebral vascular occlusion
Cerebral vasodilatation
Cerebral venous sinus thrombosis
Cerebral venous thrombosis
Cerebrovascular arteriovenous malformation
Foetal cerebrovascular disorder
Cerebrovascular insufficiency
Cerebrovascular pseudoaneurysm
Cerebrovascular stenosis
Charcot-Bouchard microaneurysms
Chronic cerebrospinal venous insufficiency
Claude's syndrome
Spinal vessel congenital anomaly
Giant cell arteritis
Delayed ischaemic neurological deficit
Dural arteriovenous fistula
Embolic cerebellar infarction
Embolic cerebral infarction
Epidural haemorrhage
Extradural haematoma
Jugular vein haemorrhage
Extra-axial haemorrhage
Extraischaemic cerebral haematoma
Haemorrhagic stroke
Intraventricular haemorrhage neonatal
Spinal cord haemorrhage
Subdural haemorrhage
Haemorrhagic cerebral infarction
Hypertensive cerebrovascular disease
Inner ear infarction
Transient ischaemic attack
Internal capsule infarction

Acute Cerebrovascular Events (Preferred Terms)
Internal carotid artery deformity
Intracranial artery dissection
Intracranial haematoma
Ruptured cerebral aneurysm
Intracranial tumour haemorrhage
Intraventricular haemorrhage
Ischaemic cerebral infarction
Ischaemic stroke
Lacunar infarction
Lacunar stroke
Lateral medullary syndrome
Lenticulostriatal vasculopathy
Meningorrhagia
Migrainous infarction
Moyamoya disease
Pituitary infarction
Subarachnoid haemorrhage neonatal
Subdural haemorrhage neonatal
Precerebral artery occlusion
Vertebral artery occlusion
Perinatal stroke
Periventricular haemorrhage neonatal
PHACES syndrome
Pituitary apoplexy
Pituitary haemorrhage
Post cardiac arrest syndrome
Post procedural stroke
Post stroke depression
Precerebral arteriosclerosis
Precerebral artery embolism
Precerebral artery thrombosis
Pseudostroke
Putamen haemorrhage
Susac's syndrome
Reversible ischaemic neurological deficit
Sneddon's syndrome
Spinal artery thrombosis
Spinal cord haematoma
Spinal cord infarction
Spinal epidural haemorrhage
Spinal epidural haematoma
Spinal stroke
Spinal subarachnoid haemorrhage
Spinal subdural haemorrhage
Spinal subdural haematoma
Spinal vascular disorder
Spontaneous internal carotid artery recanalisation
Stroke in evolution
Subarachnoid haematoma
Subclavian steal syndrome
Superficial siderosis of central nervous system
Weber's syndrome
Thalamic infarction
Thalamus haemorrhage
Thrombotic cerebral infarction
Thrombotic stroke

Acute Cerebrovascular Events (Preferred Terms)
Transient aphasia
Transverse sinus stenosis
Transverse sinus thrombosis
Traumatic intracranial haematoma
Vascular cognitive impairment
Vein of Galen aneurysmal malformation
Vertebral artery aneurysm
Vertebral artery arteriosclerosis
Vertebral artery dissection
Vertebral artery perforation
Vertebral artery stenosis
Vertebral artery thrombosis
Vertebrobasilar dolichoectasia
Vertebrobasilar stroke
Wyburn Mason's syndrome

Seizure (Preferred Terms)
1p36 deletion syndrome
2-Hydroxyglutaric aciduria
Acquired epileptic aphasia
Acute encephalitis with refractory, repetitive partial seizures
Alcoholic seizure
Alpers disease
Aspartate-glutamate-transporter deficiency
Atonic seizures
Atypical benign partial epilepsy
Automatism epileptic
Autonomic seizure
Baltic myoclonic epilepsy
Benign familial neonatal convulsions
Benign rolandic epilepsy
Biotinidase deficiency
CDKL5 deficiency disorder
CEC syndrome
Change in seizure presentation
Clonic convulsion
Congenital bilateral perisylvian syndrome
Convulsion in childhood
Convulsions local
Convulsive threshold lowered
CSWS syndrome
Deja vu
Double cortex syndrome
Dreamy state
Drug withdrawal convulsions
Early infantile epileptic encephalopathy with burst-suppression
Eclampsia
Epilepsy
Epilepsy surgery
Epilepsy with myoclonic-atonic seizures
Epileptic aura
Epileptic psychosis
Faciobrachial dystonic seizure
Febrile convulsion
Febrile infection-related epilepsy syndrome
Focal dyscognitive seizures
Frontal lobe epilepsy

Seizure (Preferred Terms)
Gelastic seizure
Generalised onset non-motor seizure
Generalised tonic-clonic seizure
Glucose transporter type 1 deficiency syndrome
GM2 gangliosidosis
Grey matter heterotopia
Hemiconvulsion-hemiplegia-epilepsy syndrome
Hemimegalencephaly
Hyperglycaemic seizure
Hypocalcaemic seizure
Hypoglycaemic seizure
Hyponatraemic seizure
Idiopathic generalised epilepsy
Infantile spasms
Jeavons syndrome
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Lafora's myoclonic epilepsy
Lennox-Gastaut syndrome
Migraine-triggered seizure
Molybdenum cofactor deficiency
Multiple subpial transection
Myoclonic epilepsy
Myoclonic epilepsy and ragged-red fibres
Neonatal epileptic seizure
Neonatal seizure
Parietal lobe epilepsy
Partial seizures
Partial seizures with secondary generalisation
Petit mal epilepsy
Polymicrogyria
Post stroke epilepsy
Post stroke seizure
Postictal headache
Postictal paralysis
Postictal psychosis
Postictal state
Post-traumatic epilepsy
Schizencephaly
Seizure
Seizure anoxic
Seizure cluster
Seizure like phenomena
Severe myoclonic epilepsy of infancy
Simple partial seizures
Status epilepticus
Sudden unexplained death in epilepsy
Temporal lobe epilepsy
Tonic clonic movements
Tonic convulsion
Tonic posturing
Topectomy
Transient epileptic amnesia
Tuberous sclerosis complex
Uncinate fits
Amygdalohippocampectomy
Aura
Corpus callosotomy
Drop attacks
Foaming at mouth

Seizure (Preferred Terms)
Focal cortical resection
Narcolepsy
Preictal state
Seizure prophylaxis
Tongue biting
Altered state of consciousness
Depressed level of consciousness
Loss of consciousness
Clonus
Hypotonia

Syncope (Preferred Terms)
Syncope

Systemic Inflammatory Response (Preferred Terms)
Systemic inflammatory response syndrome

New Neurological Deficit (SOC)
Nervous system disorders

Asthenia (Preferred Terms)
Adult failure to thrive
Asthenia
Autonomic nervous system imbalance
Cachexia
Cancer fatigue
Fatigue
Chronic fatigue syndrome
Decreased activity
Malaise
Lethargy
Listless
Post 5-alpha-reductase inhibitor syndrome
Post treatment Lyme disease syndrome
Sluggishness

Dehydration (Preferred Terms)
Dehydration
Fluid replacement
Fontanelle depressed
Hypovolaemia
Hypovolaemic shock
Skin turgor decreased
Acute kidney injury
Anuria
Aptyalism
Blood pressure ambulatory decreased
Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure orthostatic decreased
Blood pressure systolic decreased
Blood sodium increased
Blood urea nitrogen/creatinine ratio increased
Capillary nail refill test abnormal
Chapped lips
Cheilitis
Delirium
Diastolic hypotension

Dehydration (Preferred Terms)
Disorientation
Dry eye
Dry mouth
Dry skin
Dry throat
Fluid balance negative
Heart rate increased
Hypernatraemia
Hypohidrosis
Hypoosmolar state
Hypotension
Lacrimation decreased
Lid sulcus deepened
Lip dry
Mean arterial pressure decreased
Micturition frequency decreased
Mucosal dryness
Nasal dryness
Oliguria
Orthostatic heart rate response increased
Orthostatic hypotension
Poor venous access
Postural orthostatic tachycardia syndrome
Prerenal failure
Prophylaxis against dehydration
Radial pulse increased
Rapid correction of hyponatraemia
Sinus tachycardia
Sodium retention
Specific gravity urine increased
Subacute kidney injury
Tachycardia
Thirst
Tongue dry
Urine osmolarity increased
Urine output decreased

Metabolic Disturbances (SOC)
Metabolism and nutrition disorders