Statistical Analysis Plan

Study ID: 213569

Official Title of Study: A phase 2b, open-label, multi-center, extension study to evaluate the safety and immunogenicity of a revaccination dose of the RSVPreF3 older adults (OA) investigational vaccine administered intramuscularly 18 months post-Dose 2 in adults 60 years and older who participated in the RSV OA=ADJ-002 study

EudraCT number: 2020-000692-21

Date of Document: 15-07-2021

Statistical Analysis Plan

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eTrack study number and Abbreviated Title	213569 (RSV OA=ADJ-011 EXT:002 MTH20)
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 1 December 2020 Amendment 1 Final: 15 July 2021

APP 9000058193 Statistical Analysis Plan Template V5 (Effective date: 1July2020)

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LIST OF ABBREVIATIONS

AE	Adverse event
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
IU/mL	International units per milliliter
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PD	Protocol Deviation
PPS	Per-Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biologicals Internet Randomisation System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
1 December 2020	First Version	Amendment 1: 4 November 2020
15 July 2021	Amendment 1: Addition of elimination code 2080 in section 4.2.2.1, Addition of section 5.5 Additional analyses due to Covid-19 Pandemic, update of section 10.1.2.3.1.	Amendment 1: 4 November 2020

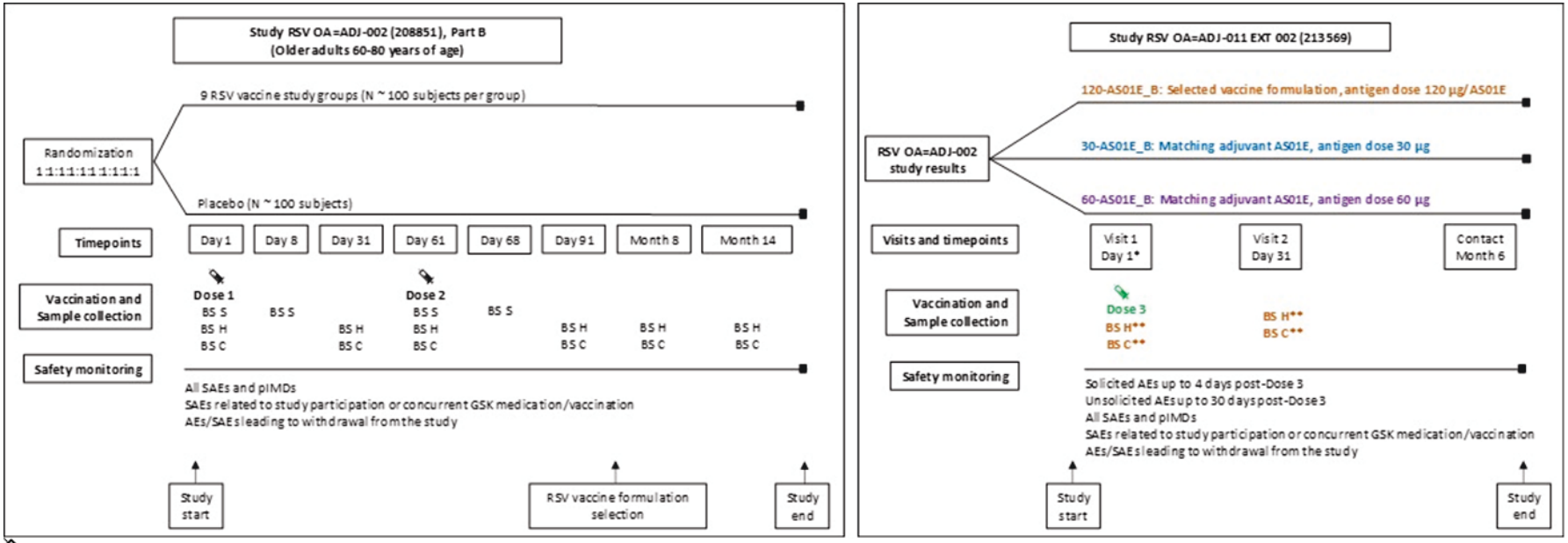
2. OBJECTIVES/ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity following intramuscular (IM) administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for all participants.	• Occurrence of solicited adverse events (AEs) up to 4 days post-Dose 3 (Day 4). • Occurrence of unsolicited AEs up to 30 days post-Dose 3 (Day 31). • Occurrence of serious adverse events (SAEs)/ Potential immune mediated diseases (pIMDs) up to 30 days post-Dose 3 (Day 31).
• To evaluate the humoral immune response following IM administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for participants vaccinated with 2 doses of RSVPreF3 OA investigational vaccine in the parent study.	• Humoral immune response at 1 month post-Dose 3 (Day 31) in terms of: – Neutralizing antibody titers against Respiratory Syncytial Virus (RSV)-A – Neutralizing antibody titers against RSV-B
Secondary	
• To evaluate the humoral and cell-mediated immune (CMI) response following IM administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for participants vaccinated with 2 doses of RSVPreF3 OA investigational vaccine in the parent study.	• Humoral immune response at 1 month post-Dose 3 (Day 31) in terms of: – RSVPreF3-specific Immunoglobulin G (IgG) antibody concentrations • CMI response at 1 month post-Dose 3: – Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α , IFN-γ
• To evaluate the safety and reactogenicity following IM administration of RSVPreF3 OA investigational vaccine up to the study end, for all participants.	• Occurrence of SAEs from vaccination (Day 1) up to study end (Month 6). • Occurrence of pIMDs from vaccination (Day 1) up to study end (Month 6).
Tertiary	
• To further characterize immune responses following IM administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for participants vaccinated with 2 doses of RSVPreF3 OA investigational vaccine in the parent study.	• Any further exploratory immunology such as, but not limited to: – Antibodies against specific protein F epitopes. – Potential new immunological markers for protection. – Frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing one or any combination of immune marker(s) in vitro.

3. STUDY DESIGN

3.1. Overall design

Figure 1 Study design overview



= Vaccination with one of 9 RSVPreF3 OA investigational vaccine formulations or placebo, in RSV OA=ADJ-002 study

= Vaccination of all study participants with RSVPreF3 OA investigational vaccine in current study

N = number of participants; BS S = Blood sample for safety (hematology/biochemistry); BS H = blood sample for humoral immune responses; BS C = blood sample for CMI response

AE = adverse event; SAE = serious adverse event; pIMD = potential immune mediated disease

*Visit 1 (Day 1) = 18 months post-Dose 2 in RSV OA=ADJ-002 study

**Only for the 120-AS01E_B group that received the same, selected formulation of RSVPreF3 OA investigational vaccine in RSV OA=ADJ-002 study

- ***Type of study:*** Extension of study RSV OA=ADJ-002 (208851)
- ***Experimental design:*** Phase 2b, open-label, multi-center study with 3 parallel groups.
- ***Duration:*** Approximately 6 months per participant.
- ***Primary completion date:*** One month post-vaccination , i.e., Day 31 (Visit 2)
- ***Control***: None
- ***Blinding:*** Open-label study
- ***Data collection:*** electronic case report form (eCRF)
- **Study groups**: refer to Figure 1 for an overview of the study groups.
- Group description for analysis

The following group names will be used in the TFLs

Group order in tables	Group label in tables	Group definition for footnote
1	120-AS01E_B	Participants receiving 120 mcg RSVPreF3/AS01E after having received 2 doses of 120 mcg RSVPreF3/AS01E in parent study
2	30-AS01E_B	Participants receiving 120 mcg RSVPreF3/AS01E after having received 2 doses of 30 mcg RSVPreF3/AS01E in parent study
3	60-AS01E_B	Participants receiving 120 mcg RSVPreF3/AS01E after having received 2 doses of 60 mcg RSVPreF3/AS01E in parent study

For the analysis by age category, the following sub-group names will be used in the TFLs

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	60-69Y	60-69 years old participants at dose 1 in parent study
2	70-80Y	70-80 years old participants at dose 1 in parent study

4. ANALYSIS SETS

4.1. Definition

Table 1 Populations for analyses

Analysis Set	Description
Enrolled	Participants who agreed to participate in the clinical study after **completion of the informed consent process.**
Exposed	All participants who received Dose 3 of the study intervention.
Per Protocol	All participants who received Dose 3 of the study intervention and have post-vaccination data minus participants with protocol deviations that lead to exclusion.

The primary analysis for immunogenicity will be performed for the 120-AS01E_B group on the Per Protocol set (PPS) for immunogenicity. If the percentage of participants with serological results excluded from the PPS for immunogenicity for the 120-AS01E_B group is at least 10%, a second analysis will be performed on the Exposed Set (ES).

4.2. Criteria for eliminating data from Analysis Sets

4.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study intervention not administered at all in the 011 study), 800 (Fraudulent data) and code 900 (invalid informed consent) will be used for identifying participants eliminated from ES

4.2.2. Elimination from Per-protocol analysis Set (PPS)

For output related to the 011 study only, the PPS as defined below will be applicable. For selected output (e.g. where data from the parent study 002 are shown together with 011 data), a combined PPS, based on the 002 and 011 PPS will be applicable. In the latter case, participants eliminated from the PPS during 002 will also be eliminated from the 011 PPS (even if not eliminated when considering only 011 output).

4.2.2.1. Excluded participants

A participant will be excluded from the PPS analysis under the following conditions.

For codes 1040, 1070, 1080, 1090, 2010, 2040, 2060, 2080: participants will be eliminated from the time at which the condition is met onwards.

For codes 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

When applicable, codes will be allocated to participants as long as they are included in the study.

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis
800	Fraudulent data	All	ES and PPS for analysis of immunogenicity
900	Invalid informed consent	All	ES and PPS for analysis of immunogenicity
1030	Study intervention not administered at all	All	ES and PPS for analysis of immunogenicity
1040	Administration of concomitant vaccine(s) forbidden in the protocol • Any investigational or non-registered vaccine other than the study vaccine used during the study period beginning 30 days before the dose of study vaccine. • Administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of study vaccine administration, with the exception of inactivated, split virion and subunit influenza vaccines which can be administered up to 14 days before or from 14 days after the study vaccination.	All	PPS for analysis of immunogenicity
1070	Vaccine administration not according to protocol • Participant was vaccinated with the correct vaccine but containing a lower volume • Route of the study intervention is not intramuscular • Wrong reconstitution of administered vaccine	Day 1	PPS for analysis of immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis
1080	Vaccine administration after a Temperature deviation • Vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Day 1	PPS for analysis of immunogenicity
1090	Vaccine administration after expiration	Day 1	PPS for analysis of immunogenicity
2010	Protocol violation (inclusion/exclusion criteria)	All	PPS for analysis of immunogenicity
2040	Administration of any medication forbidden by the protocol • Any investigational or non-registered medication or medical device used during the study period beginning 30 days before the dose of study vaccine • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 consecutive days in total) during the period starting 90 days prior to the vaccine dose • Long-acting immune-modifying drugs administered at any time during the study period • Immunoglobulins and/or any blood products or plasma derivatives administered during the period starting 90 days before the dose of study vaccine	Day 1, Day 31	PPS for analysis of immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis
2060	Intercurrent medical condition • Participants may be eliminated from the PPS for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (intercurrent medical condition) or are confirmed to have an alteration of their initial immune status (other than RSV infection)	Day 1, Day 31	PPS for analysis of immunogenicity
2080	Participants did not comply with dosing schedule • Number of days between dose 2 in the parent study RSV OA=ADJ-002 and dose 3 in current study is outside [510-570 days]	Day 1	PPS for analysis of immunogenicity
2090	Participants did not comply with blood sample schedule • Number of days between vaccination at Day 1 and Day 31 blood sample is outside [30-42 days]	Day 31	PPS for analysis of immunogenicity
2100	Serological results not available post-dose • No immunological result at visit 2 for all the following tests: RSV A/B Neutralizing antibody titer, RSVPreF3-specific IgG antibody concentration and RSVPreF3-specific CD4+ T cells frequency	Day 31	PPS for analysis of immunogenicity
2120	Obvious incoherence or abnormality or error in data • Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at laboratory	Day 1, 31	PPS for analysis of immunogenicity

5. STATISTICAL ANALYSES

Standard data derivation rules and stat methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Analysis of demography and baseline characteristics

5.1.1. Analysis planned in the protocol

Demographic characteristics (age at vaccination in years, sex) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variables such as sex.
- Mean, median, standard deviation and range will be provided for continuous data such as age.

The distribution of participants will be tabulated overall, per group and for each age category (60-69 years and 70-80 years).

Withdrawal status will be summarized by group using descriptive statistics:

- The number of participants enrolled into the study as well as the number of participants excluded from PP analyses will be tabulated.
- The numbers of withdrawn participants will be tabulated according to the reason for withdrawal.

5.1.2. Additional considerations

The analysis of demographic characteristics by group will be performed on the ES and on the PPS.

For a given participant and a given demographic variable, missing measurements will not be replaced.

Demography and baseline characteristics will also be summarized by country.

Vital signs (heart rate, respiratory rate, systolic/diastolic blood pressure) and pre-vaccination temperature reported at visit 1 will be summarized by group using descriptive statistics.

Participant disposition in the ES will be reported as a whole and per group, and for each age category (60-69 years and 70-80 years).

A summary of important protocol deviations leading to elimination will be provided by group.

The study population will also be summarized **for web disclosure** as follows:

- Percentage of enrolled participants by country will be tabulated by group,
- Percentage of enrolled participants by age categories (≤64, 65-84, ≥85 YOA) will be tabulated by group.

5.2. Primary endpoint(s)

5.2.1. Analysis planned in the protocol

5.2.1.1. Safety analysis

The safety analysis will be performed on the ES for all participants.

A descriptive analysis by group and overall will present a summary of:

- The number and percentage of participants with at least one administration site event (solicited and unsolicited), with at least one systemic event (solicited and unsolicited) and with any AE during the 4-day or 30-day follow-up period will be tabulated with exact 95% CI after Dose 3. The same computations will be done for Grade 3 AEs, Grade 3 non-serious AEs, related AEs and AEs resulting in a medically attended visit.
- The number and percentage of participants reporting each individual solicited administration site event (any grade, Grade 3, with medically attended visit) and solicited systemic event (any grade, Grade 3, with medically attended visit) during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) will be tabulated for each group after Dose 3.
- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) will be tabulated for each group after Dose 3.
- The number and percentage of participants with any unsolicited AEs during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) with its exact 95% CI will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The same tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. The verbatim reports of unsolicited AEs will be reviewed by a qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.
- The number and percentage of participants with at least one report of SAE/pIMD classified by the MedDRA Preferred Terms and reported during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be tabulated with exact 95% CI. The same tabulation will be done for related SAEs/pIMDs. SAEs/pIMDs will also be described in detail.

- The number and percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) and during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be summarized by group.

5.2.1.2. Humoral immune response up to 1 month post-Dose 3

The analysis for immunogenicity will be performed on the PPS for the 120-AS01E_B group only.

At each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified), the analyses below will be performed:

- Percentage of participants with antibody titers/concentrations above the positivity cut-off and their exact 95% CI will be tabulated.
- GMTs/GMCs and their 95% CI will be tabulated and represented graphically.
- Antibody titers/concentrations will be displayed using reverse cumulative curves.
- The mean geometric increase (MGI) i.e. geometric mean of ratios of antibody titers/concentrations of each post-vaccination time point over pre-vaccination, will be tabulated with 95% CI.
- Individual post-vaccination results versus pre-vaccination results will be plotted using scatter plots.
- Distribution of the fold increase of the antibody titers/concentrations (post- over pre-vaccination titers/concentrations) will be tabulated.
- The ratio of fold increase (pre to post) of anti-RSVPreF3-specific antibody concentrations over the fold increase (pre to post) of anti-RSV-A neutralizing antibody titers will be tabulated using descriptive statistics and displayed graphically using scatter plots.
- The fold increase of post-dose 3 (in RSV OA=ADJ-011 EXT:002 MTH20 study) over post-dose 1 (in RSV OA=ADJ-002 study) antibody titers/concentrations will be tabulated using descriptive statistics.

Pre-vaccination will be both pre-Dose 1 in RSV OA=ADJ-002 and pre-Dose 3 in RSV OA=ADJ-011 EXT:002 MTH20.

The immunogenicity analysis will also be performed by age category (60-69 years and 70-80 years, age according to the parent study).

5.2.2. Additional considerations

5.2.2.1. Safety analysis

5.2.2.1.1. Solicited Events

Solicited events will be reported daily during the 4-day (from Day 1 to Day 4) follow up period after vaccination, using structured diaries. Missing or non-evaluable measurements will not be replaced. Therefore, the analysis of solicited events will include only vaccinated participants with documented solicited safety data (i.e., paper diary completed).

In order to summarize the data, the maximum intensity of local injection site erythema/swelling (in mm) and fever (in °C) will be categorized as follows:

Grading	Erythema/swelling	Fever
0:	≤ 20 mm	< 38.0°C (100.4°F)
1:	> 20 - ≤ 50 mm	≥ 38.0°C (100.4°F) - ≤ 38.5°C (101.3°F)
2:	> 50 - ≤ 100 mm	> 38.5°C (101.3°F) - ≤ 39.0°C (102.2°F)
3:	> 100 mm	> 39.0°C (102.2°F)

Fever is defined as temperature ≥ 38.0°C / 100.4°F (regardless of the location of measurement). The preferred location for measuring temperature in this study will be the oral cavity. Body temperature will also be summarized by 0.5°C increments as follows: ≥38.0, >38.5, >39.0, >39.5, >40.0 °C.

Each participant's data will be summarized according to the maximal severity observed during the follow-up period for each event, followed by a summary across participants.

- Compliance in completing solicited events information will be tabulated.
- The number of days with solicited events reported during the 4-day follow-up period will be tabulated for each solicited event, using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same tabulation will be done for Grade 3 solicited events.
- The prevalence of each solicited event (any grade and grade 3) will also be represented graphically per group.

5.2.2.1.2. Unsolicited Adverse Events

For analysis of unsolicited AEs, SAEs, pIMDs and concomitant medications, all vaccinated participants will be considered. Participants who did not report an event or concomitant medication will be considered as participants without the event or the concomitant medication, respectively.

When an unsolicited adverse event occurs more than once for a participant, the maximal severity and strongest relationship to the vaccine group will be counted. The selection of unsolicited AEs reported during the follow-up period will be done using the day of onset.

Listing of AEs/SAEs leading premature withdrawal from study or to interruption of vaccination will be described in detail.

5.2.2.1.3. Combined Solicited and Unsolicited Adverse Events

A summary of participants with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited events will be coded by MedDRA as per the following codes

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Pain	10022086	Injection site pain
Erythema	10015150	Erythema
Swelling	10053425	Injection site swelling
Fever	10016558	Pyrexia

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

5.2.2.1.4. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary.

5.2.2.2. Humoral immune response up to 1 month post-Dose 3

- The kinetics of GMTs/GMCs will be plotted as a function of time for participants with results available at all time points, considering also the results from study RSV OA=ADJ-002 study.

5.3. Secondary endpoint(s)

5.3.1. Analysis planned in the protocol

5.3.1.1. Humoral immune response up to 1 month post-Dose 3

See sections 5.2.1.2 and 5.2.2.2

5.3.1.2. CMI response up to 1 month post-Dose 3

The following parameters will be summarized by group using descriptive statistics (N, geometric mean, min, Q1, median, Q3, max) at each time point for which blood samples are collected for CMI:

- Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 activation markers among IL-2, CD40L, TNF-α, IFN-γ.
- Fold increase of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 activation markers among IL-2, CD40L, TNF-α, IFN-γ, at each post-vaccination time point over pre-vaccination.

- Distribution of the fold increase: the percentage of participants with at least a 2-fold, 4-fold, 6-fold, 8-fold, 10-fold increase post-vaccination as compared to pre-vaccination (Post over Pre) will be tabulated by timepoint and by group.

The immunogenicity analysis will also be performed by age category (60-69 years and 70-80 years, age according to the parent study).

5.3.1.3. SAEs and pIMDs up to 6 months post-Dose 3

- The number and percentage of participants with at least one report of SAE classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. The same tabulation will be done for causally related and fatal SAEs. SAEs will also be described in detail.
- The number and percentage of participants with at least one pIMD classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. The same tabulation will be done for causally related pIMDs. pIMDs will also be described in detail.

5.3.2. Additional considerations

5.3.2.1. CMI response up to 1 month post-Dose 3

Descriptive statistics of the cell-mediated immune response will be tabulated by timepoint and displayed graphically using boxplots (min, Q1, median, Q3, max).

The RSVPreF3-specific CD4+ T cell frequencies will be obtained by subtracting the background value to the antigen-induced value, and by setting to 1 all values less than or equal to zero for geomean calculation and graphical representation. Frequencies will be expressed as the number of cells per million of CD4+ T cells.

More specifically, the frequencies of RSVPreF3-specific CD4+ T cells expressing at least 2 activation markers [$Freq^{2+}$] will be computed as follows:

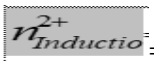
$$Freq^{2+}_{Background} = \frac{n^{2+}_{background}}{N^{CD4}_{Background}} \quad \text{and} \quad Freq^{2+}_{Induction} = \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}},$$

And

$$Freq^{2+}_{specific} = Freq^{2+}_{induction} - Freq^{2+}_{Backgroun}$$

where

$n^{2+}_{Backgroun}$= = number of CD4+ T cells expressing at least 2 activation markers after stimulation with medium only (background)


= number of CD4+ T cells expressing at least 2 activation markers after stimulation with a pool of peptides covering RSVPreF3 (induction)


= Total number of CD4 T cells involved in the assay (background or induction)

For the computation of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 marker(s)** among IL-2, CD40L, TNF-α, IFN-γ, the results **below the LLOQ** of the assay will be replaced by the value of the LLOQ.

Pre-vaccination will be both pre-Dose 1 in RSV OA=ADJ-002 and pre-Dose 3 in RSV OA=ADJ-011 EXT:002 MTH20. Frequencies will be tabulated by pre-vaccination category according to LLOQ and (Q1-Q3).

- Mean frequencies of RSVPreF3 specific CD4+ T-cells expressing 1 marker, 2 markers, 3 markers or 4 markers among IL-2, CD40L, TNF-α, at Day 1 and Day 31 will be presented graphically
- Median frequencies of RSVPreF3 specific CD4+ T-cells expressing at least 2 will be plotted as a function of time for participants with results available at all time points, considering also the results from study RSV OA=ADJ-002 study.

5.4. Tertiary endpoints

5.4.1. CMI response up to 1 month post-Dose 3

The following CMI responses will be computed as described in section 5.3.2.1:

- Frequency of RSVPreF3-specific CD8+ T-cells expressing **at least 2 markers** among IL-2, CD40L, TNF-α, IFN-γ, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least 2 markers including at least 1 cytokine*** among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17, as measured by ICS using PBMCs.

  ** cytokines are IL-2, TNF-α, IFN-γ, IL-13, and IL-17*
- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least IFN-γ (Th1-like response)**, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least IL-13 (Th2-like response)**, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least IL-17 (Th17-like response)**, as measured by ICS using PBMCs.
- **Co-expression profile:** Frequency of RSVPreF3-specific CD4+ T-cells expressing **any combination of marker(s) among** CD40L, IL-2, TNF-α, IFN-γ, as measured by ICS using PBMCs, at Day 1 and Day 31 (→15 combinations).

5.5. Additional analyses Due to the Covid-19 Pandemic

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

The overall incidence of COVID-19 AEs and SAEs , COVID-19 AEs leading to study intervention discontinuation, COVID-19 AEs leading to study withdrawal, and severe COVID-19 AEs will be summarized. The incidence of these events at individual PT level can be obtained from the standard AE/SAE summaries.

COVID-19 assessments (confirmed, probable and suspected diagnosis) for participants with COVID-19 AEs will be summarized.

The number and percentage of participants with concomitant vaccination (COVID-19) before and during the study will be tabulated with exact 95% CI.

6. ANALYSIS INTERPRETATION

All analyses are descriptive.

7. INTERIM ANALYSES

7.1. Sequence of analyses

The analyses will be performed stepwise:

- A first analysis will be performed when all data as clean as possible are available for at least primary and secondary endpoints up to Visit 2 (Day 31).
- The final end-of-study analysis will be performed when all data for at least primary and secondary endpoints up to study conclusion (Month 6) are available. All available tertiary endpoints will also be analyzed in this step. Individual listings will only be provided at this stage.

If data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed.

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
End of study analysis	E1_01	CTRS, SR
Analysis up to Day 31	E1_02	CTRS

7.2. Statistical considerations for interim analyses

All analyses will be conducted on final data (as clean as possible) and therefore no statistical adjustment for interim analyses is required.

8. CHANGES TO THE PROTOCOL DEFINED STATISTICAL ANALYSIS

N/A

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1 (Business rules for standard data derivations and statistical methods).

9.1. Handling of missing data

9.1.1. Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following rules will be applied:

- Adverse event start dates with missing day:
  - If the month is not the same as the vaccine dose, then the imputed start date will be the 1st of the month
  - If the event starts in the same month as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the vaccine dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the vaccine dose given during that month.
- Adverse event start dates with missing day and month:
  - If the year is not the same as the vaccine dose, then the imputed start date will be the 1st of January.
  - If the event starts in the same year as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first vaccine dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first vaccine dose given during that year.
  - Adverse event end dates with missing day: the imputed end date will be the last day of the month (30 or 31) or the study conclusion date whichever comes first.
  - Adverse event end dates with missing day and month: the imputed end date will be the last day of the year (31st of December) or the study conclusion date whichever comes first.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains standard rules for data display and derivation for clinical and epidemiological studies.

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a participant prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the case report form (CRF) using the contents of the flag indicating if the event occurred before or after study dose. If 'after study dose' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before study dose' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. dates missing a day and/or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

See also exceptions in section 9.1.1.

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited events

10.1.2.3.1. Studies with paper diaries

For studies using paper diaries which have questions in the CRF indicating the presence or absence of solicited events, the following rules are applicable:

- Denominators for the summary of administration site (or systemic) solicited events will be calculated using the number of participants who respond "Yes" or "No" to the question concerning the occurrence of administration site (or systemic) events.

- When a specific solicited event is marked as having not occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=N for the specified post-dose period for the event in question), all daily measurements will be imputed as Grade 0.
- When a specific solicited event is marked as having occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=Y for the specified post-dose period for the event in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited event summary tables.

The following table shows how participants contribute to each category for a specific solicited event over the Day X to Day Y post-dose period:

Solicited event category	Participants included in the calculation of the numerator
Any	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y or with the adverse event marked as present and at least one missing daily recording between Day X and Day Y
At least grade 1	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All participants with at least one occurrence of the adverse event at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All participants with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

10.1.3. Data derivation

10.1.3.1. Age at first dose in years

When age at first dose is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of first dose. For example:

DOB = 10SEP1983, Date of first dose = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of first dose = 10SEP2018 -> Age = 35 years

10.1.3.2. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

10.1.3.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off and value is <=ULOQ	value
"value" and value is > ULOQ	ULOQ*
All other cases	missing

*This rule will be used to computed descriptive statistics (GMTs, fold increase, etc). All values might be displayed in scatter plots with individual results.

10.1.3.4. Geometric mean titers (GMTs) and concentrations (GMCs)

Geometric Mean Titre (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Non quantifiable antibody titres or concentrations will be converted as described in section 10.1.3.3 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

10.1.3.5. Onset day

The onset day for an event (e.g. AE, concomitant medication/vaccination) is the number of days between the last study dose and the start date of the event. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose).

10.1.3.6. Duration of events

The duration of an event with a start and end date will be the difference between the start and end date plus one day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated as the sum of the individual days with the adverse event reported at grade 1 or higher during the solicited event period.

10.1.3.7. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered systemic events since the administration site flag is not included in the expedited adverse event CRF pages. Unsolicited adverse events with missing administration site flag will also be considered systemic.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

10.1.3.8. Counting rules for occurrences of solicited events

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. Also, in the case of co-administered study interventions, an administration site event recorded for a participant following multiple study interventions will be counted as only one occurrence.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed.

10.1.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values

The maximum and minimum of transformed body temperatures will be displayed with one decimal.

10.1.4.3. Serological summary statistics

For each assay, geometric mean titers (GMT) or concentrations (GMC) and their confidence limits will be presented with one decimal, as well as GMT/GMC fold increase from pre-dose.

The mean, median, standard deviation and quartile values for frequency of RSVPreF3 specific-CD4+ and CD8+ T cells and for the fold increase (post over pre-vaccination) will be presented with one decimal. The minimum and maximum values will be presented with no decimal.

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

11. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934; 26:404-13.

Statistical Analysis Plan

Title:	A phase 2b, open-label, multi-center, extension study to evaluate the safety and immunogenicity of a revaccination dose of the RSVPreF3 older adults (OA) investigational vaccine administered intramuscularly 18 months post-Dose 2 in adults 60 years and older who participated in the RSV OA=ADJ-002 study.
eTrack study number and Abbreviated Title	213569 (RSV OA=ADJ-011 EXT:002 MTH20)
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 1 December 2020

APP 9000058193 Statistical Analysis Plan Template V5 (Effective date: 1July2020)

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List of abbreviations

AE	Adverse event
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
IU/mL	International units per milliliter
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PD	Protocol Deviation
PPS	Per-Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biologicals Internet Randomisation System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
1 DEC 2020	First Version	Amendment 1: 4 NOV 2020

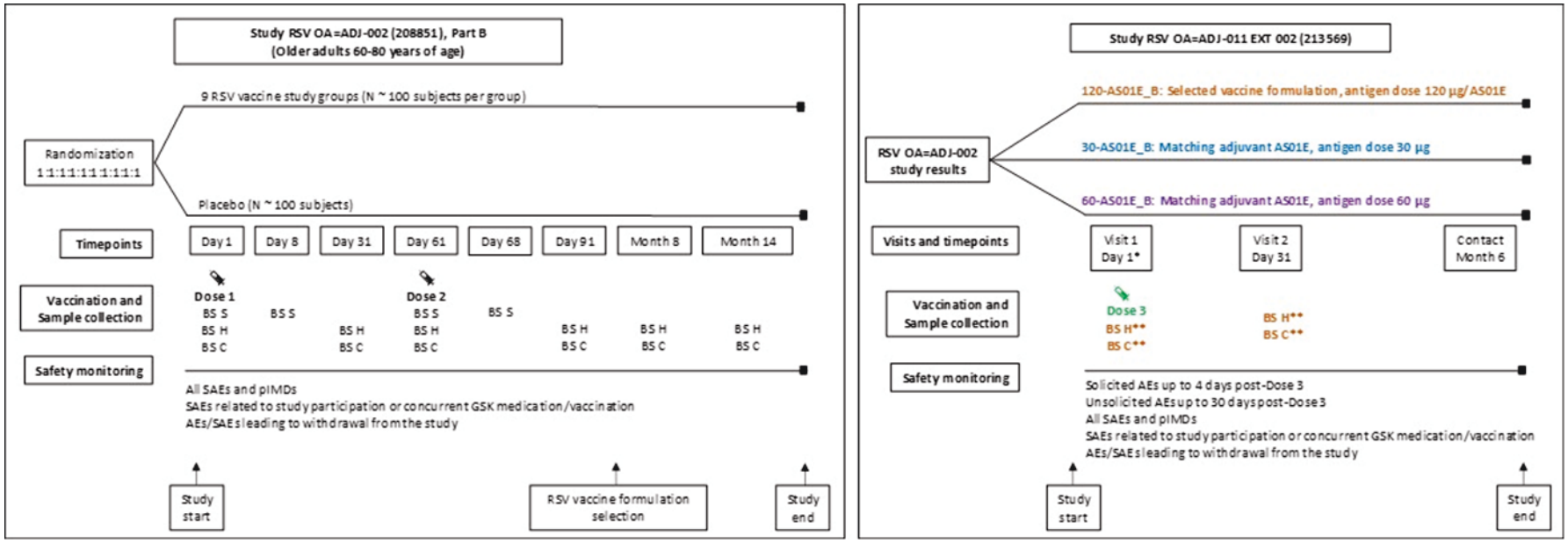
2. OBJECTIVES/ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity following intramuscular (IM) administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for all participants.	• Occurrence of solicited adverse events (AEs) up to 4 days post-Dose 3 (Day 4). • Occurrence of unsolicited AEs up to 30 days post-Dose 3 (Day 31). • Occurrence of serious adverse events (SAEs)/ Potential immune mediated diseases (pIMDs) up to 30 days post-Dose 3 (Day 31).
• To evaluate the humoral immune response following IM administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for participants vaccinated with 2 doses of RSVPreF3 OA investigational vaccine in the parent study.	• Humoral immune response at 1 month post-Dose 3 (Day 31) in terms of: ○ Neutralizing antibody titers against Respiratory Syncytial Virus (RSV)-A ○ Neutralizing antibody titers against RSV-B
Secondary	
• To evaluate the humoral and cell-mediated immune (CMI) response following IM administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for participants vaccinated with 2 doses of RSVPreF3 OA investigational vaccine in the parent study.	• Humoral immune response at 1 month post-Dose 3 (Day 31) in terms of: ○ RSVPreF3-specific Immunoglobulin G (IgG) antibody concentrations • CMI response at 1 month post-Dose 3: ○ Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 markers among IL-2, CD40L, TNF-α , IFN-γ
• To evaluate the safety and reactogenicity following IM administration of RSVPreF3 OA investigational vaccine up to the study end, for all participants.	• Occurrence of SAEs from vaccination (Day 1) up to study end (Month 6). • Occurrence of pIMDs from vaccination (Day 1) up to study end (Month 6).
Tertiary	
• To further characterize immune responses following IM administration of RSVPreF3 OA investigational vaccine up to 1 month post-Dose 3, for participants vaccinated with 2 doses of RSVPreF3 OA investigational vaccine in the parent study.	• Any further exploratory immunology such as, but not limited to: ○ Antibodies against specific protein F epitopes. ○ Potential new immunological markers for protection. ○ Frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing one or any combination of immune marker(s) in vitro.

3. STUDY DESIGN

3.1. Overall design

Figure 1 Study design overview



= Vaccination with one of 9 RSVPreF3 OA investigational vaccine formulations or placebo, in RSV OA=ADJ-002 study

= Vaccination of all study participants with RSVPreF3 OA investigational vaccine in current study

N = number of participants; BS S = Blood sample for safety (hematology/biochemistry); BS H = blood sample for humoral immune responses; BS C = blood sample for CMI response

AE = adverse event; SAE = serious adverse event; pIMD = potential immune mediated disease

*Visit 1 (Day 1) = 18 months post-Dose 2 in RSV OA=ADJ-002 study

**Only for the 120-AS01E_B group that received the same, selected formulation of RSVPreF3 OA investigational vaccine in RSV OA=ADJ-002 study

- ***Type of study:*** Extension of study RSV OA=ADJ-002 (208851)
- ***Experimental design:*** Phase 2b, open-label, multi-center study with 3 parallel groups.
- ***Duration:*** Approximately 6 months per participant.
- ***Primary completion date:*** One month post-vaccination , i.e., Day 31 (Visit 2)
- ***Control***: None
- ***Blinding:*** Open-label study
- ***Data collection:*** electronic case report form (eCRF)
- **Study groups**: refer to Figure 1 for an overview of the study groups.
- Group description for analysis

The following group names will be used in the TFLs

Group order in tables	Group label in tables	Group definition for footnote
1	120-AS01E_B	Participants receiving 120 mcg RSVPreF3/AS01E after having received 2 doses of 120 mcg RSVPreF3/AS01E in parent study
2	30-AS01E_B	Participants receiving 120 mcg RSVPreF3/AS01E after having received 2 doses of 30 mcg RSVPreF3/AS01E in parent study
3	60-AS01E_B	Participants receiving 120 mcg RSVPreF3/AS01E after having received 2 doses of 60 mcg RSVPreF3/AS01E in parent study

For the analysis by age category, the following sub-group names will be used in the TFLs

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	60-69Y	60-69 years old participants at dose 1 in parent study
2	70-80Y	70-80 years old participants at dose 1 in parent study

4. ANALYSIS SETS

4.1. Definition

Table 1 Populations for analyses

Analysis Set	Description
Enrolled	Participants who agreed to participate in the clinical study after **completion of the informed consent process.**
Exposed	All participants who received Dose 3 of the study intervention.
Per Protocol	All participants who received Dose 3 of the study intervention and have post-vaccination data minus participants with protocol deviations that lead to exclusion.

The primary analysis for immunogenicity will be performed for the 120-AS01E_B group on the Per Protocol set (PPS) for immunogenicity. If the percentage of participants with serological results excluded from the PPS for immunogenicity for the 120-AS01E_B group is at least 10%, a second analysis will be performed on the Exposed Set (ES).

4.2. Criteria for eliminating data from Analysis Sets

4.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study intervention not administered at all in the 011 study), 800 (Fraudulent data) and code 900 (invalid informed consent) will be used for identifying participants eliminated from ES

4.2.2. Elimination from Per-protocol analysis Set (PPS)

For output related to the 011 study only, the PPS as defined below will be applicable. For selected output (e.g. where data from the parent study 002 are shown together with 011 data), a combined PPS, based on the 002 and 011 PPS will be applicable. In the latter case, participants eliminated from the PPS during 002 will also be eliminated from the 011 PPS (even if not eliminated when considering only 011 output).

4.2.2.1. Excluded participants

A participant will be excluded from the PPS analysis under the following conditions.

For codes 1040, 1070, 1080, 1090, 2040, 2060, 2080: participants will be eliminated from the time at which the condition is met onwards.

For codes 2090, 2100, 2120: participants will be eliminated at the specific visit at which the condition is met.

When applicable, codes will be allocated to participants as long as they are included in the study.

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysi
800	Fraudulent data	All	ES and PPS for analysis of immunogenicity
900	Invalid informed consent	All	ES and PPS for analysis of immunogenicity
1030	Study intervention not administered at all	All	ES and PPS for analysis of immunogenicity
1040	Administration of concomitant vaccine(s) forbidden in the protocol • Any investigational or non-registered vaccine other than the study vaccine used during the study period beginning 30 days before the dose of study vaccine. • Administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of study vaccine administration, with the exception of inactivated, split virion and subunit influenza vaccines which can be administered up to 14 days before or from 14 days after the study vaccination.	All	PPS for analysis of immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysi
1070	Vaccine administration not according to protocol • Participant was vaccinated with the correct vaccine but containing a lower volume • Route of the study intervention is not intramuscular • Wrong reconstitution of administered vaccine	Day 1	PPS for analysis of immunogenicity
1080	Vaccine administration after a Temperature deviation • Vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Day 1	PPS for analysis of immunogenicity
1090	Vaccine administration after expiration	Day 1	PPS for analysis of immunogenicity
2010	Protocol violation (inclusion/exclusion criteria)	All	PPS for analysis of immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysi
2040	Administration of any medication forbidden by the protocol • Any investigational or non-registered medication or medical device used during the study period beginning 30 days before the dose of study vaccine • Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 consecutive days in total) during the period starting 90 days prior to the vaccine dose • Long-acting immune-modifying drugs administered at any time during the study period • Immunoglobulins and/or any blood products or plasma derivatives administered during the period starting 90 days before the dose of study vaccine	Day 1, Day 31	PPS for analysis of immunogenicity
2060	Intercurrent medical condition • Participants may be eliminated from the PPS for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (intercurrent medical condition) or are confirmed to have an alteration of their initial immune status (other than RSV infection)	Day 1, Day 31	PPS for analysis of immunogenicity

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysi
2090	Participants did not comply with blood sample schedule • Number of days between vaccination at Day 1 and Day 31 blood sample is outside [30-42 days]	Day 31	PPS for analysis of immunogenicity
2100	Serological results not available post-dose • No immunological result at visit 2 for all the following tests: RSV A/B Neutralizing antibody titer, RSVPreF3-specific IgG antibody concentration and RSVPreF3-specific CD4+ T cells frequency	Day 31	PPS for analysis of immunogenicity
2120	Obvious incoherence or abnormality or error in data • Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at laboratory	Day 1, 31	PPS for analysis of immunogenicity

5. STATISTICAL ANALYSES

Standard data derivation rules and stat methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Analysis of demography and baseline characteristics

5.1.1. Analysis planned in the protocol

Demographic characteristics (age at vaccination in years, sex) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variables such as sex.
- Mean, median, standard deviation and range will be provided for continuous data such as age.

The distribution of participants will be tabulated overall, per group and for each age category (60-69 years and 70-80 years).

Withdrawal status will be summarized by group using descriptive statistics:

- The number of participants enrolled into the study as well as the number of participants excluded from PP analyses will be tabulated.
- The numbers of withdrawn participants will be tabulated according to the reason for withdrawal.

5.1.2. Additional considerations

The analysis of demographic characteristics by group will be performed on the ES and on the PPS.

For a given participant and a given demographic variable, missing measurements will not be replaced.

Demography and baseline characteristics will also be summarized by country.

Vital signs (heart rate, respiratory rate, systolic/diastolic blood pressure) and pre-vaccination temperature reported at visit 1 will be summarized by group using descriptive statistics.

Participant disposition in the ES will be reported as a whole and per group, and for each age category (60-69 years and 70-80 years).

A summary of important protocol deviations leading to elimination will be provided by group.

The study population will also be summarized **for web disclosure** as follows:

- Percentage of enrolled participants by country will be tabulated by group,
- Percentage of enrolled participants by age categories (≤64, 65-84, ≥85 YOA) will be tabulated by group.

5.2. Primary endpoint(s)

5.2.1. Analysis planned in the protocol

5.2.1.1. Safety analysis

The safety analysis will be performed on the ES for all participants.

A descriptive analysis by group and overall will present a summary of:

- The number and percentage of participants with at least one administration site event (solicited and unsolicited), with at least one systemic event (solicited and unsolicited) and with any AE during the 4-day or 30-day follow-up period will be tabulated with exact 95% CI after Dose 3. The same computations will be done for Grade 3 AEs, Grade 3 non-serious AEs, related AEs and AEs resulting in a medically attended visit.
- The number and percentage of participants reporting each individual solicited administration site event (any grade, Grade 3, with medically attended visit) and solicited systemic event (any grade, Grade 3, with medically attended visit) during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) will be tabulated for each group after Dose 3.
- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) will be tabulated for each group after Dose 3.
- The number and percentage of participants with any unsolicited AEs during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) with its exact 95% CI will be tabulated by group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The same tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. The verbatim reports of unsolicited AEs will be reviewed by a qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.

- The number and percentage of participants with at least one report of SAE/pIMD classified by the MedDRA Preferred Terms and reported during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be tabulated with exact 95% CI. The same tabulation will be done for related SAEs/pIMDs. SAEs/pIMDs will also be described in detail.
- The number and percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) and during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be summarized by group.

5.2.1.2. Humoral immune response up to 1 month post-Dose 3

The analysis for immunogenicity will be performed on the PPS for the 120-AS01E_B group only.

At each time point that blood samples are collected for humoral immune response and for each assay (unless otherwise specified), the analyses below will be performed:

- Percentage of participants with antibody titers/concentrations above the positivity cut-off and their exact 95% CI will be tabulated.
- GMTs/GMCs and their 95% CI will be tabulated and represented graphically.
- Antibody titers/concentrations will be displayed using reverse cumulative curves.
- The mean geometric increase (MGI) i.e. geometric mean of ratios of antibody titers/concentrations of each post-vaccination time point over pre-vaccination, will be tabulated with 95% CI.
- Individual post-vaccination results versus pre-vaccination results will be plotted using scatter plots.
- Distribution of the fold increase of the antibody titers/concentrations (post- over pre-vaccination titers/concentrations) will be tabulated.
- The ratio of fold increase (pre to post) of anti-RSVPreF3-specific antibody concentrations over the fold increase (pre to post) of anti-RSV-A neutralizing antibody titers will be tabulated using descriptive statistics and displayed graphically using scatter plots.
- The fold increase of post-dose 3 (in RSV OA=ADJ-011 EXT:002 MTH20 study) over post-dose 1 (in RSV OA=ADJ-002 study) antibody titers/concentrations will be tabulated using descriptive statistics.

Pre-vaccination will be both pre-Dose 1 in RSV OA=ADJ-002 and pre-Dose 3 in RSV OA=ADJ-011 EXT:002 MTH20.

The immunogenicity analysis will also be performed by age category (60-69 years and 70-80 years, age according to the parent study).

5.2.2. Additional considerations

5.2.2.1. Safety analysis

5.2.2.1.1. Solicited Events

Solicited events will be reported daily during the 4-day (from Day 1 to Day 4) follow up period after vaccination, using structured diaries. Missing or non-evaluable measurements will not be replaced. Therefore, the analysis of solicited events will include only vaccinated participants with documented solicited safety data (i.e., paper diary completed).

In order to summarize the data, the maximum intensity of local injection site erythema/swelling (in mm) and fever (in °C) will be categorized as follows:

Grading	Erythema/swelling	Fever
0:	≤ 20 mm	< 38.0°C (100.4°F)
1:	> 20 - ≤ 50 mm	≥ 38.0°C (100.4°F) - ≤ 38.5°C (101.3°F)
2:	> 50 - ≤ 100 mm	> 38.5°C (101.3°F) - ≤ 39.0°C (102.2°F)
3:	> 100 mm	> 39.0°C (102.2°F)

Fever is defined as temperature ≥ 38.0°C / 100.4°F (regardless of the location of measurement). The preferred location for measuring temperature in this study will be the oral cavity. Body temperature will also be summarized by 0.5°C increments as follows: ≥38.0, >38.5, >39.0, >39.5, >40.0 °C.

Each participant's data will be summarized according to the maximal severity observed during the follow-up period for each event, followed by a summary across participants.

- Compliance in completing solicited events information will be tabulated.
- The number of days with solicited events reported during the 4-day follow-up period will be tabulated for each solicited event, using descriptive statistics (mean, min, Q1, median, Q3, maximum). The same tabulation will be done for Grade 3 solicited events.
- The prevalence of each solicited event (any grade and grade 3) will also be represented graphically per group.

5.2.2.1.2. Unsolicited Adverse Events

For analysis of unsolicited AEs, SAEs, pIMDs and concomitant medications, all vaccinated participants will be considered. Participants who did not report an event or concomitant medication will be considered as participants without the event or the concomitant medication, respectively.

When an unsolicited adverse event occurs more than once for a participant, the maximal severity and strongest relationship to the vaccine group will be counted. The selection of unsolicited AEs reported during the follow-up period will be done using the day of onset.

Listing of AEs/SAEs leading premature withdrawal from study or to interruption of vaccination will be described in detail.

5.2.2.1.3. Combined Solicited and Unsolicited Adverse Events

A summary of participants with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited events will be coded by MedDRA as per the following codes

Solicited symptom	**Lower level term code**	**Corresponding Lower level term decode**
Pain	10022086	Injection site pain
Erythema	10015150	Erythema
Swelling	10053425	Injection site swelling
Fever	10016558	Pyrexia

For clintrial.gov and EudraCT posting purposes, a summary of combined solicited and unsolicited non-serious adverse events will be produced by System Organ Class and preferred terms and according to occurrence of each event.

5.2.2.1.4. Concomitant Medication

Medications will be coded using the GSKDRUG dictionary.

5.2.2.2. Humoral immune response up to 1 month post-Dose 3

- The kinetics of GMTs/GMCs will be plotted as a function of time for participants with results available at all time points, considering also the results from study RSV OA=ADJ-002 study.

5.3. Secondary endpoint(s)

5.3.1. Analysis planned in the protocol

5.3.1.1. Humoral immune response up to 1 month post-Dose 3

See sections 5.2.1.2 and 5.2.2.2

5.3.1.2. CMI response up to 1 month post-Dose 3

The following parameters will be summarized by group using descriptive statistics (N, geometric mean, min, Q1, median, Q3, max) at each time point for which blood samples are collected for CMI:

- Frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 activation markers among IL-2, CD40L, TNF-α, IFN-γ.
- Fold increase of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing at least 2 activation markers among IL-2, CD40L, TNF-α, IFN-γ, at each post-vaccination time point over pre-vaccination.
- Distribution of the fold increase: the percentage of participants with at least a 2-fold, 4-fold, 6-fold, 8-fold, 10-fold increase post-vaccination as compared to pre-vaccination (Post over Pre) will be tabulated by timepoint and by group.

The immunogenicity analysis will also be performed by age category (60-69 years and 70-80 years, age according to the parent study).

5.3.1.3. SAEs and pIMDs up to 6 months post-Dose 3

- The number and percentage of participants with at least one report of SAE classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. The same tabulation will be done for causally related and fatal SAEs. SAEs will also be described in detail.
- The number and percentage of participants with at least one pIMD classified by the MedDRA Preferred Terms and reported during the entire study period will be tabulated with exact 95% CI. The same tabulation will be done for causally related pIMDs. pIMDs will also be described in detail.

5.3.2. Additional considerations

5.3.2.1. CMI response up to 1 month post-Dose 3

Descriptive statistics of the cell-mediated immune response will be tabulated by timepoint and displayed graphically using boxplots (min, Q1, median, Q3, max).

The RSVPreF3-specific CD4+ T cell frequencies will be obtained by subtracting the background value to the antigen-induced value, and by setting to 1 all values less than or equal to zero for geomean calculation and graphical representation. Frequencies will be expressed as the number of cells per million of CD4+ T cells.

More specifically, the frequencies of RSVPreF3-specific CD4+ T cells expressing at least 2 activation markers [$\widehat{Freq}^{2+}$] will be computed as follows:

$$Freq^{2+}_{Background} = \frac{n^{2+}_{background}}{N^{CD4}_{Background}} \quad \text{and} \quad Freq^{2+}_{Induction} = \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}},$$

And

$$Freq^{2+}_{Specific} = Freq^{2+}_{Induction} - Freq^{2+}_{Backgroun}$$

where

$n^{2+}_{Backgroun}$ = number of CD4+ T cells expressing at least 2 activation markers after stimulation with medium only (background)

$n^{2+}_{Inductio}$ = number of CD4+ T cells expressing at least 2 activation markers after stimulation with a pool of peptides covering RSVPreF3 (induction)

$N^{CD4}_{Back/Ind}$ = Total number of CD4 T cells involved in the assay (background or induction)

For the computation of the fold increase (post over pre-vaccination) of the frequency of RSVPreF3-specific CD4+ T-cells identified as expressing **at least 2 marker(s)** among IL-2, CD40L, TNF-α, IFN-γ, the results **below the LLOQ** of the assay will be replaced by the value of the LLOQ.

Pre-vaccination will be both pre-Dose 1 in RSV OA=ADJ-002 and pre-Dose 3 in RSV OA=ADJ-011 EXT:002 MTH20. Frequencies will be tabulated by pre-vaccination category according to LLOQ and (Q1-Q3).

- Mean frequencies of RSVPreF3 specific CD4+ T-cells expressing 1 marker, 2 markers, 3 markers or 4 markers among IL-2, CD40L, TNF-α, at Day 1 and Day 31 will be presented graphically
- Median frequencies of RSVPreF3 specific CD4+ T-cells expressing at least 2 will be plotted as a function of time for participants with results available at all time points, considering also the results from study RSV OA=ADJ-002 study.

5.4. Tertiary endpoints

5.4.1. CMI response up to 1 month post-Dose 3

The following CMI responses will be computed as described in section 5.3.2.1:

- Frequency of RSVPreF3-specific CD8+ T-cells expressing **at least 2 markers** among IL-2, CD40L, TNF-α, IFN-γ, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least 2 markers including at least 1 cytokine*** among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17, as measured by ICS using PBMCs.

  ** cytokines are IL-2, TNF-α, IFN-γ, IL-13, and IL-17*
- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least IFN-γ (Th1-like response)**, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least IL-13 (Th2-like response)**, as measured by ICS using PBMCs.
- Frequency of RSVPreF3-specific CD4+ T-cells expressing **at least IL-17 (Th17-like response)**, as measured by ICS using PBMCs.
- **Co-expression profile:** Frequency of RSVPreF3-specific CD4+ T-cells expressing **any combination of marker(s) among** CD40L, IL-2, TNF-α, IFN-γ, as measured by ICS using PBMCs, at Day 1 and Day 31 (→15 combinations).

6. ANALYSIS INTERPRETATION

All analyses are descriptive.

7. INTERIM ANALYSES

7.1. Sequence of analyses

The analyses will be performed stepwise:

- A first analysis will be performed when all data as clean as possible are available for at least primary and secondary endpoints up to Visit 2 (Day 31).
- The final end-of-study analysis will be performed when all data for at least primary and secondary endpoints up to study conclusion (Month 6) are available. All available tertiary endpoints will also be analyzed in this step. Individual listings will only be provided at this stage.

If data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed.

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
End of study analysis	E1_01	CTRS, SR
Analysis up to Day 31	E1_02	CTRS

7.2. Statistical considerations for interim analyses

All analyses will be conducted on final data (as clean as possible) and therefore no statistical adjustment for interim analyses is required.

8. CHANGES TO THE PROTOCOL DEFINED STATISTICAL ANALYSIS

N/A

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1 (Business rules for standard data derivations and statistical methods).

9.1. Handling of missing data

9.1.1. Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following rules will be applied:

- Adverse event start dates with missing day:
  - If the month is not the same as the vaccine dose, then the imputed start date will be the 1st of the month
  - If the event starts in the same month as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the vaccine dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the vaccine dose given during that month.
- Adverse event start dates with missing day and month:
  - If the year is not the same as the vaccine dose, then the imputed start date will be the 1st of January.

- If the event starts in the same year as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first vaccine dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first vaccine dose given during that year.
- Adverse event end dates with missing day: the imputed end date will be the last day of the month (30 or 31) or the study conclusion date whichever comes first.
- Adverse event end dates with missing day and month: the imputed end date will be the last day of the year (31st of December) or the study conclusion date whichever comes first.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains standard rules for data display and derivation for clinical and epidemiological studies.

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a participant prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the case report form (CRF) using the contents of the flag indicating if the event occurred before or after study dose. If 'after study dose' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before study dose' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. dates missing a day and/or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

See also exceptions in section 9.1.1.

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited events

10.1.2.3.1. Studies with paper diaries

For studies using paper diaries which have questions in the CRF indicating the presence or absence of solicited events, the following rules are applicable:

- Denominators for the summary of administration site (or systemic) solicited events will be calculated using the number of participants who respond "Yes" or "No" to the question concerning the occurrence of administration site (or systemic) events.
- When a specific solicited event is marked as having not occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=N for the specified post-dose period for the event in question), all daily measurements will be imputed as Grade 0.
- When a specific solicited event is marked as having occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=Y for the specified post-dose period for the event in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited event summary tables.
- When the occurrence of a specific solicited event is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-dose period for the event in question) but the group of solicited events (administration site or systemic) is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited event summary tables.

The following table shows how participants contribute to each category for a specific solicited event over the Day X to Day Y post-dose period:

Solicited event category	Participants included in the calculation of the numerator
Any	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y or with the adverse event marked as present and at least one missing daily recording between Day X and Day Y
At least grade 1	All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All participants with at least one occurrence of the adverse event at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All participants with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

10.1.3. Data derivation

10.1.3.1. Age at first dose in years

When age at first dose is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of first dose. For example:

DOB = 10SEP1983, Date of first dose = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of first dose = 10SEP2018 -> Age = 35 years

10.1.3.2. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

10.1.3.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off and value is <=ULOQ	value
"value" and value is > ULOQ	ULOQ*
All other cases	missing

*This rule will be used to computed descriptive statistics (GMTs, fold increase, etc). All values might be displayed in scatter plots with individual results.

10.1.3.4. Geometric mean titers (GMTs) and concentrations (GMCs)

Geometric Mean Titre (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Non quantifiable antibody titres or concentrations will be converted as described in section 10.1.3.3 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

10.1.3.5. Onset day

The onset day for an event (e.g. AE, concomitant medication/vaccination) is the number of days between the last study dose and the start date of the event. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose).

10.1.3.6. Duration of events

The duration of an event with a start and end date will be the difference between the start and end date plus one day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated as the sum of the individual days with the adverse event reported at grade 1 or higher during the solicited event period.

10.1.3.7. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered systemic events since the administration site flag is not included in the expedited adverse event CRF pages. Unsolicited adverse events with missing administration site flag will also be considered systemic.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

10.1.3.8. Counting rules for occurrences of solicited events

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. Also, in the case of co-administered study interventions, an administration site event recorded for a participant following multiple study interventions will be counted as only one occurrence.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed.

10.1.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values

The maximum and minimum of transformed body temperatures will be displayed with one decimal.

10.1.4.3. Serological summary statistics

For each assay, geometric mean titers (GMT) or concentrations (GMC) and their confidence limits will be presented with one decimal, as well as GMT/GMC fold increase from pre-dose.

The mean, median, standard deviation and quartile values for frequency of RSVPreF3 specific-CD4+ and CD8+ T cells and for the fold increase (post over pre-vaccination) will be presented with one decimal. The minimum and maximum values will be presented with no decimal.

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

11. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.