Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A Phase 2b, randomized, controlled, open-label study to evaluate the immune response and safety of the RSVPreF3 OA investigational vaccine in adults (≥18 years of age) when administered to lung and renal transplant recipients comparing 1 versus 2 doses and compared to healthy controls (≥50 years of age) receiving 1 dose.
Study Number:	219900
Compound Number:	GSK3844766A
Abbreviated Title:	RSV OA=ADJ-023

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s)

Registry	**ID**
ClinicalTrials.gov	NCT05921903
EudraCT	2023-503951-81-00

Statistical Analysis Plan (SAP) Template v3.0 14 September 2022

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
ANCOVA	Analysis of Covariance
CI	Confidence Interval
CIS	Calcineurin inhibitors/Sirolimus
CMI	Cell-Mediated Immunity
COVID-19	Coronavirus Disease 2019
CS	Corticosteroids
CSR	Clinical Study Report
eCRF	electronic Case Report Form
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HA	Healthy Adults
LLOQ	Lower Limit of Quantification
MC	Mycophenolate compound
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean Geometric Increase
MMF	Mycophenolate
OA	Older Adults
PCA	Primary Completion Analysis
pIMD	Potential Immune-Mediated Disease
PPS	Per-Protocol Set

RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRR	Seroresponse rate
ULOQ	Upper Limit of Quantification
YOA	Years of Age

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	26 July 2023	Protocol amendment 1 25 July 2023	Not Applicable	Original version
SAP amendment 1	16 October 2023	Protocol amendment 2 11 October 2023	Section 3.1: Elimination codes were clarified. Section 4.3: Clarification on the analysis done by SOT type and by age group. Analysis by anti - T cell therapy use added. Section 4.3.2.1.2: Difference in SRR between RSV_IC_2 group at Visit 4 and RSV_IC_1 group at Visit 3 and between RSV_HA group at Visit 3 and RSV_IC_2 group at Visit 4 added. Section 4.3.2.3: Analysis of demyelinating disorder SAE from vaccination (Day 1) up to study end (Visit 6) added. Section 6.1.2: Demography and baseline characteristics will not be generated on the Enrolled set.	To align with Output and Programming Specification (OPS) 11 August 2023

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP Amendment 2	27 March 2024	Protocol amendment 2 Final 11 October 2023	To update the age group related to analysis by age group. To update duration analysis in terms of the solicited symptoms. Administration of any medication forbidden by the protocol updated. Definition of baseline definition updated.	To include the right age group of interest. Following the feedback from regulatory the derivation of duration was updated. Concomitant medication considering anti-CD20 or other B-cell monoclonal antibody agents. Considering the nature of the study we do have a visit prior to visit 1 hence definition has been updated.
SAP Amendment 3	23 Jul 2024	Protocol amendment 2 Final 11 October 2023	Added the analysis by immunosuppressive therapy	This update is following the decision taken to replace the subgroup analysis by anti T cell therapies with analysis based on immunosuppressive therapies.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses for primary and secondary objectives to be included in the CSR for Study RSV-OA-ADJ-023 (219900). Details of the planned analyses are provided.

1.1. Objectives, Estimands and Endpoints

Table 1 Objectives, Estimands and Endpoint

Objectives	Endpoints and estimands
Primary	
• To evaluate the humoral immune response against RSV-A following the first and the second dose of RSVPreF3 OA investigational vaccine within 2-dose group in renal and lung SOT patients.	• RSV-A serum neutralizing titers expressed as MGI post-Dose 2 (Visit 4*) over post-Dose 1 (Visit 3*) in renal and lung SOT patients in the 2-dose group.
• To evaluate the humoral immune response against RSV-B following the first and the second dose of RSVPreF3 OA investigational vaccine within 2-dose group in renal and lung SOT patients.	• RSV-B serum neutralizing titers expressed as MGI post-Dose 2 (Visit 4*) over post-Dose 1 (Visit 3*) in renal and lung SOT patients in the 2-dose group.
Secondary-Immunogenicity	
• To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine until 12 months post-study intervention administration in all groups.	• RSV-A and RSV-B serum neutralizing titers expressed as GMT, at pre-study intervention administration, Visit 2* (in a subset of participants), Visit 3*, Visit 4*, Visit 5* and Visit 6* in renal and lung SOT patients (1-dose and 2-dose group), and healthy participants. • RSV-A and RSV-B serum neutralizing titers expressed as group GMT ratio RSV_HA over RSV_IC (pooled RSV_IC_1 and RSV_IC_2 groups) at Visit 2* (in a subset of participants) and Visit 3* and RSV_IC_2 over RSV_IC_1, RSV_HA over RSV_IC_1, and RSV_HA over RSV_IC_2) at Visit 4*, Visit 5* and Visit 6*. • RSV-A and RSV-B serum neutralizing titers expressed as MGI at Visit 2* (in a subset of participants) over Visit 1, and Visit 3* over Visit 1* in RSV_HA and RSV_IC (pooled RSV_IC_1 and RSV_IC_2 groups) and at Visit 4*, Visit 5* and Visit 6* over Visit 1* in RSV_IC_1, RSV_IC_2, RSV_HA groups.
• To evaluate the CMI response following RSVPreF3 OA investigational vaccine administration in a subset of participants in all groups.	• CMI response expressed as group geometric mean of the frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, and IL-17 at pre-study intervention administration, Visit 2*, Visit 3*, Visit 4*, Visit 5* and Visit 6*, in a subset of participants (renal and lung SOT patients (1-dose and 2-dose group), and healthy participants).
Secondary-Safety	
• To evaluate the safety and reactogenicity following RSVPreF3 OA investigational vaccine administration in all groups.	• Percentage of participants reporting each solicited administration site event with onset within 7 days post-study intervention administration (i.e., the day of vaccination and 6 subsequent days).

Objectives	Endpoints and estimands
	• Percentage of participants reporting each solicited systemic event with onset within 7 days post-study intervention administration (i.e., the day of vaccination and 6 subsequent days). • Percentage of participants reporting unsolicited AEs within 30 days post-study intervention administration (i.e., the day of vaccination and 29 subsequent days). • Percentage of participants reporting SAEs after study intervention administration (Day 1) up to study end (Visit 6). • Percentage of participants reporting pIMDs after study intervention administration (Day 1) up to study end (Visit 6). • Percentage of participants reporting SAEs related to study intervention administration after study intervention administration (Day 1) up to study end (Visit 6). • Percentage of participants reporting pIMDs related to study intervention administration after study intervention administration (Day 1) up to study end (Visit 6). • Percentage of participants reporting fatal SAEs after study intervention administration (Day 1) up to study end (Visit 6). • Percentage of participants reporting AESIs (specific to renal and lung SOT patients) after first study intervention administration (Day 1) up to study end (Visit 6).
Tertiary *(Note that the tertiary objective, endpoints, and estimands are optional and will only be assessed if needed; therefore, not all testing might be performed and reported)*	
CCI [redacted]	

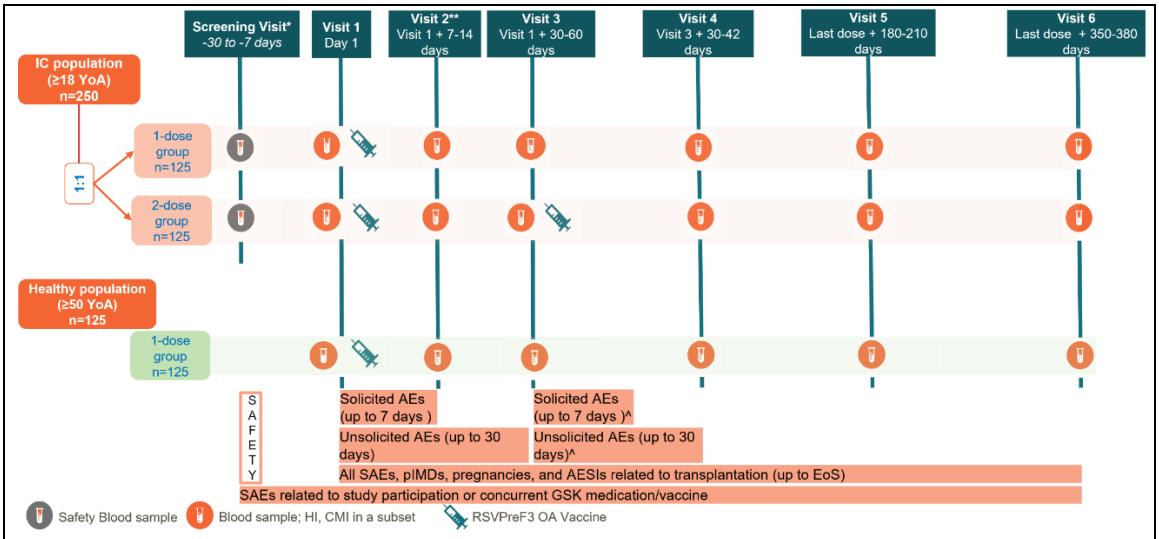
AE = Adverse event; AESI = Adverse event of special interest; CD = Cluster of differentiation; CMI = Cell-mediated immunity; CCI [redacted]; IFN = Interferon; IL = Interleukin; GMT = Geometric mean titer; MGI = Mean geometric increase; CCI [redacted]; OA = Older adult; pIMD = Potential immune-mediated disease; RSV = Respiratory Syncytial Virus; SAE = Serious adverse event; SOT = Solid organ transplant; TNF = Tumor necrosis factor.
MGI is defined as the geometric mean of the within-participant ratios of neutralizing titers.
*Refer to Table 3, Table 4, and Table 5 for details on visits and intervals.

Primary estimand

The primary clinical question of interest is to assess whether a second dose of the RSV OA vaccine increases the immune response in IC population of ≥18 years of age (YOA) in terms of RSV-A and RSV-B neutralizing titers (ED60), MGI from Visit 3 to Visit 4 in eligible participants who complied with the study requirements as defined per protocol (refer to Section 3 for the definition of the PPS used for the primary analysis and to Section 4.2 for the statistical methods).

1.2. Study Design

Table 2 Overview of Study Design and Key Features



Screening Visit: Only in IC population. Blood sample would be collected at screening visit to evaluate participant eligibility.

**Visit 2: Only in a subset of the study population, ~30% of the participants (Visit can occur 7-14 days after first study intervention administration).

^ Solicited and unsolicited AEs after second study intervention administration, only in the IC 2-dose group.

AE = Adverse event; AESI = Adverse event of special interest; CMI = Cell-mediated immunity; EoS = End of study; HI = Humoral immunity; IC = Immunocompromised; pIMD = Potential immune-mediated disease; SAE = Serious adverse event; YoA = Years of age.

Design Features	Phase 2 study to evaluate the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine in IC population (lung and renal transplant recipients) and to assess whether a second dose of the RSV OA vaccine increases the immune response. Blinding: Open label study.
Study intervention	Participants in RSV_IC_1 and RSV_HA groups will receive a single dose of study intervention (RSVPreF3 OA investigational vaccine) at Visit 1 and participants in RSV_IC_2 group will receive two doses of study intervention (RSVPreF3 OA investigational vaccine) at Visit 1 and Visit 3.
Study groups	3 parallel groups: • **RSV_IC_1 group**: IC patients of ≥18 YOA receiving 1 dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1). • **RSV_IC_2 group**: IC patients of ≥18 YOA receiving 2 doses of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1) and Visit 3 (Visit 1 + 30-60 days). • **RSV_HA group**: Healthy adults of ≥50 YOA receiving 1 dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1).
Study intervention Assignment	• Immunocompromised adults ≥18 YoA who received a renal or lung SOT will be randomly assigned in a 1:1 ratio at Visit 1 (Day 1) to RSV_IC_1 group or RSV_IC_2 group to receive either 1 dose or 2 doses of the RSVPreF3 OA investigational vaccine, respectively. • All participants in RSV_HA group (Healthy adults ≥50 YoA) will be assigned to receive the RSVPreF3 OA investigational vaccine.

	Study intervention assignment is generated (permuted block randomization) and stratified by SOT type and CMI subset using a GSK RTSM system. Each IC group may include approximately 65% renal transplant patients and approximately 20% lung transplant patients, and the remaining patients can be freely distributed across the 2 groups. For the healthy participant group, participants will be enrolled in 3 age categories, with approximately 30% of participants 50-59 YoA, approximately 30% of participants 60-69 YoA, and approximately 20% of participants ≥ 70 YoA. The remaining 20% can be distributed freely across the 3 age categories.
Primary Completion Analysis (PCA)	A first analysis will be performed on all immunogenicity, reactogenicity and safety data available and as clean as possible, when data for at least primary and secondary endpoints up to Visit 4 are available for all participants.
Month 6 post-last dose Analysis	A second analysis will be performed on all immunogenicity and safety data available and as clean as possible, when data for at least secondary endpoints up to Visit 5 are available for all participants.
End-of-study Analysis	An end of study analysis will be performed when all data for at least secondary endpoints up to study conclusion (Visit 6) will be available for all participants.

Table 3 Intervals between study visits for IC 1-dose group (RSV_IC_1)

Interval	Optimal length of interval	Allowed interval range
Screening visit → Visit 1	-7 days	-30 to -7 days
Visit 1 → Visit 2*	7 days	7 - 14 days
Visit 1→ Visit 3	30 days	30 - 60 days
Visit 3 → Visit 4	30 days	30 - 42 days
Visit 1 → Visit 5	180 days	180 - 210 days
Visit 1 → Visit 6	365 days	350 - 380 days

*Only in subset of the group.

Table 4 Intervals between study visits for IC 2-dose group (RSV_IC_2)

Interval	Optimal length of interval	Allowed interval range
Screening visit → Visit 1	-7 days	-30 to -7 days
Visit 1 → Visit 2*	7 days	7 - 14 days
Visit 1→ Visit 3	30 days	30 - 60 days
Visit 3 → Visit 4	30 days	30 - 42 days
Visit 3→ Visit 5	180 days	180 - 210 days
Visit 3 → Visit 6	365 days	350 - 380 days

*Only in subset of the group.

Table 5 Intervals between study visits for healthy participant group (RSV_HA)

Interval	Optimal length of interval	Allowed interval range
Visit 1 → Visit 2*	7 days	7 - 14 days
Visit 1→ Visit 3	30 days	30 - 60 days
Visit 3 → Visit 4	30 days	30 - 42 days
Visit 1 → Visit 5	180 days	180 - 210 days
Visit 1 → Visit 6	365 days	350 - 380 days

*Only in subset of the group.

2. STATISTICAL HYPOTHESES

The primary objective, as outlined in Section 1.1, will be addressed using an estimation approach with no hypothesis testing. For the primary estimand, descriptive analysis will be utilized.

2.1. Multiplicity Adjustment

Given the descriptive nature of the study, no multiplicity adjustment is implemented.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened Set	All participants who were screened for eligibility.	Study Population
Enrolled Set	All participants who entered the study (who were randomized or received study intervention administration or underwent a post-screening study procedure). NOTE: screening failures (who never passed screening even if rescreened) and participants screened (met eligibility) but never enrolled into the study are excluded from the Enrolled Set as they did not enter the study.	Study Population
Exposed Set (ES)	All participants who received the study intervention administration. Analysis per group is based on medical condition (IC versus healthy adults) and according to the randomization (RSV_IC_1 versus RSV_IC_2 group).	Study Population, Safety
Per Protocol Set* (PPS)	All eligible participants • who received the study intervention administration as per protocol • had immunogenicity results pre- and post-dose • complied with blood draw intervals • without intercurrent conditions that may interfere with immunogenicity • without prohibited concomitant medication/vaccination. Analysis per group is based on medical condition (IC versus healthy adults) and according to the randomization (RSV_IC_1 versus RSV_IC_2 group).	Immunogenicity

* Contribution of participants to PPS will be defined by timepoint.

3.1. Criteria for eliminating data from Analysis Sets

Elimination codes will be used to identify participants to be eliminated from analysis. Details are provided below for the Enrolled Set, the Exposed Set (ES) and the Per Protocol Set (PPS).

3.1.1. Elimination from Enrolled Set

The following codes will be used for identifying participants to be eliminated from the Enrolled Set:

- Code 800 (Fraudulent data)
- Code 900 (Invalid informed consent)

3.1.2. Elimination from ES

The following codes will be used for identifying participants to be eliminated from the ES:

- Code 800 (Fraudulent data)
- Code 900 (Invalid informed consent)
- Code 1030 (Study intervention not administered at all)

3.1.3. Elimination from Per-protocol Set (PPS)

A participant will be excluded from the populations for analysis under the following conditions:

- For codes 800, 900, 1030, 1050, 2010 and 2020: participants will be eliminated for all visits.
- For codes 1040, 1070, 1080, 1090, 2040, 2050 and 2080: participants will be eliminated from a specific visit (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.

Table 6 List of elimination codes

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Visit from when it is applicable	Applicable for analysis set/endpoint
800	Fraudulent data	All	All	Enrolled Set, ES, PPS
900	Invalid informed consent	All	All	Enrolled Set, ES, PPS
1030	Study intervention not administered at all	All	All	ES, PPS
1040	Administration of concomitant vaccine(s) forbidden in the protocol: • Use of any investigational or non-registered vaccine other than the study intervention during the period beginning 30 days before the first dose of study intervention, or planned use during the study period up to Visit 6.	All	From the specific visit the condition is met	PPS

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Visit from when it is applicable	Applicable for analysis set/endpoint
	• Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose of study intervention administration and ending 30 days after the last dose of study intervention administration. In the case of COVID-19 and inactivated/subunit/split influenza vaccines, this time window can be decreased to 14 days before and after each study intervention administration. • Live attenuated vaccines should not be administered throughout the study for SOT patients as a part of SoC. • Previous vaccination with the same antigen (RSV) containing vaccine as that of the study intervention, including investigational RSV vaccines.			
1050	Randomization failure: participant not randomized in the correct group	Visit 1	All	PPS
1070	Vaccine administration not according to protocol: • Incomplete vaccination course • Participant was vaccinated with the correct vaccine but containing a lower volume. • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) • Route of the study vaccine is not intramuscular. • Wrong reconstitution of administered vaccine.	Vaccination visit(s) 1 or 1 and 3 as applicable	From the specific visit (1 or 3) the condition is met	PPS
1080	• Vaccine administration after a temperature deviation • Vaccine administered despite a Good Manufacturing Practices (GMP) no-go temperature deviation	Vaccination visit(s) 1 or 1 and 3 as applicable	From the specific visit (1 or 3) the condition is met	PPS
1090	Vaccine administration after expiration	Vaccination visit(s) 1 or 1 and 3 as applicable	From the specific visit (1 or 3) the condition is met.	PPS
2010	Protocol deviation linked to inclusion/exclusion criteria	All	All	PPS
2020	All Pre-dose results are missing	Visit 1	All	PPS
2040	Administration of any medication forbidden by the protocol • Use of any investigational or non-registered product (drug or medical device) other than the study intervention	All	From the specific visit the condition is met.	PPS

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Visit from when it is applicable	Applicable for analysis set/endpoint
	during the period beginning 30 days before the first dose of study intervention, or planned use during the study period up to Visit 6. • Use of anti-CD20 or other B-cell monoclonal antibody agents (e.g., rituximab) as induction, maintenance and/or therapeutic immunosuppressive therapy for the prevention of allograft rejection within 9 months (274 days) of first dose of study. • In healthy participants chronic administration of immune-modifying drugs (defined as more than 14 consecutive days in total) and/or administration of long-acting immune modifying treatments or planned administration at any time up to the end of the study. – Up to 3 months prior to the study intervention administration: o For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed. o Administration of immunoglobulins and/or any blood products or plasma derivatives. – Up to 6 months prior to study intervention administration: long-acting immune modifying drugs including among others immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies, antitumoral medication.			
2050	In healthy participants 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 or are confirmed to have an alteration of their initial immune status.	All	From the specific visit the condition is met.	PPS
2080	Participants did not comply with vaccination schedule for the RSV_IC_2 group. number of days between dose 1 and dose 2 is outside [30-60 days]	Visit 3	Visit 4 and onward for the RSV_IC_2 group	PPS
2090	Participants did not comply with blood sample schedule*: Number of days between vaccination (Visit 1) and blood sample (Visit 2) is outside [7-14] days.	Visit 2, Visit 3, Visit 4, Visit 5, Visit 6	At the specific visit the condition is met	PPS

Code	Condition under which the code is used	Visit / Contact (timepoints) where the code is checked	Visit from when it is applicable	Applicable for analysis set/endpoint
	Number of days between vaccination (Visit 1) and blood sample (Visit 3) is outside [30-60] days. Number of days between vaccination (Visit 3 and blood sample (Visit 4) is outside [30-42] days. Number of days between vaccination (Visit 1) and blood sample (Visit 5) is outside [180-210] days for RSV_IC_1 and RSV_HA group and Number of days between vaccination (Visit 3) and blood sample (Visit 5) is outside [180-210] days for RSV_IC_2 group. Number of days between vaccination (Visit 1) and blood sample (Visit 6) is outside [350-380] days for RSV_IC_1 and RSV_HA group and Number of days between vaccination (Visit 3) and blood sample (Visit 6) is outside [350-380] days for RSV_IC_2 group.			
2100	Immunological results not available post-vaccination	Visit 2, Visit 3, Visit 4, Visit 5, Visit 6	At the specific visit the condition is met	PPS
2120	Obvious incoherence/abnormality or error in laboratory data • Unreliable released data as a result of confirmed sample mismatch or confirmed inappropriate sample handling at laboratory.	All	At the specific visit the condition is met	PPS

* Refer to Table 3, Table 4, and Table 5 for details on visits and intervals.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

- For the purpose of immunogenicity analyses, any missing or non-evaluable immunogenicity measurement will not be replaced. The descriptive analysis performed for each assay at each time point will exclude participants with a missing or non-evaluable measurement.
- Titers below the assay cut-off (LLOQ) will be replaced by half the assay cut-off (LLOQ/2) and titers above the upper limit of quantification (ULOQ) will be replaced by the ULOQ to compute GMTs, GMRs and MGIs. For the display of reverse cumulative curve, titers below LLOQ and above ULOQ will not be replaced.

- Confidence intervals (CIs) will use 95% confidence levels unless otherwise specified (e.g., primary endpoints analysis, refer to Section 4.2.2). 95% CIs for GMT, GMR and MGI will be based on a back transformation of CI for the mean of log_{10}-transformed values. Exact 95% CIs around proportions are derived using the method of Clopper and Pearson [Clopper, 1934]. 95% CI for group difference in proportion will be based on Miettinen and Nurminen confidence interval [Miettinen, 1985].
- Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.
- Seroresponse rate (SRR) is defined as the proportion of participants having a fold increase in neutralizing titers ≥4.
- The mean geometric increase (MGI) is defined as the geometric mean of the within-participant ratios of the post-vaccination titer over pre-vaccination.

4.1.2. Baseline Definition

The baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.2. Primary Endpoints Analyses

4.2.1. Definition of endpoints

RSV-A and RSV-B neutralizing titers expressed as MGI of post-Dose 2 (Visit 4) over post-Dose 1 (Visit 3) will be computed within the 2-dose group in renal and lung SOT patients.

4.2.2. Main analytical approach

The primary analysis set will be the PPS. If, in RSV_IC_2 group the percentage of vaccinated participants with serological results excluded from the PPS is more than 5%, a second analysis based on the ES will be performed to complement the PPS analysis.

The MGI against RSV-A and RSV-B post-Dose 2 (Visit 4) over post-Dose 1 (Visit 3) will be tabulated with their 2-sided 95% CI for the RSV_IC_2 group.

CIs for MGI will be based on a back transformation of CI for the mean of the difference between log10-transformed values, assuming that log-transformed values are normally distributed with unknown variance.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of endpoints

Refer to Section 1.1 for the definition of secondary safety and immunogenicity (humoral and CMI response) endpoints.

4.3.2. Main analytical approach

4.3.2.1. Immunogenicity analysis: humoral immune response

The analysis will be based on the PPS. If, in any group, the percentage of vaccinated participants with serological results excluded from the PPS is more than 5%, a second analysis based on the ES will be performed to complement the PPS analysis.

4.3.2.1.1. Within groups assessment

For each immunological assay and at each time point that blood samples are collected, the following analysis will be performed by group (the data for RSV_IC_1 and RSV_IC_2 group will also be pooled for dose 1 up to visit 3 (including visit 3)):

- Percentage of participants with neutralizing titers equal to or above pre-defined assay cut-offs and their exact 2-sided 95% CIs will be tabulated. The same computations will be done by SOT type (renal and lung SOT patients), age group (age at first vaccination: 18-49 YOA, 50-59 YOA, and ≥60 YOA in the IC group and 50-59 YOA and ≥60 YOA in the HA group) and immunosuppressive therapy ([All 3 classes: CIS + CS + MC], [Any 2 class combinations of CIS, CS, or MC], and [Any single class: CIS, CS, or MC]).
- SRR, i.e., percentage of participants having a fold increase in neutralizing titers ≥4 and their 2-sided 95% CIs will be tabulated. The same computations will be done by SOT type, age group and immunosuppressive therapy.
- Unadjusted GMTs and their 95% CIs will be tabulated and displayed graphically. The same tabulation will be done by SOT type, age group and immunosuppressive therapy.
- Furthermore, to account for the multiple timepoints at which the blood samples are collected, a mixed effects model (see Section 4.3.3.1) will be fitted, from which the adjusted GMTs and their 95% CIs will be computed and tabulated.
- The kinetics of unadjusted GMTs will be plotted as a function of time for participants with results available at all timepoints (except Visit 2).
- MGIs and their 95% CIs will be tabulated and displayed graphically. The same tabulation will also be done by SOT type and age group and immunosuppressive therapy.
    - MGI (RSV_IC_1, RSV_IC_2, RSV_IC group [pooled RSV_IC_1 and RSV_IC_2 group] and RSV_HA group) with 95% CI, at Visit 2 (in a subset of participants) over Visit 1 and Visit 3 over Visit 1.

- MGI (RSV_IC_1, RSV_IC_2 and RSV_HA group) with 95% CI, at Visit 4, Visit 5 and Visit 6 over Visit 1.

- Distribution of neutralizing titers will be displayed using reverse cumulative curves.

For RSV_IC_2 group and for each immunological assay the following analyses will be performed. The same tabulation will also be done by SOT type, age group and immunosuppressive therapy.

- Percentage of participants having a fold increase in neutralizing titers ≥4 and their 2-sided 95% CIs will be tabulated at Visit 4, Visit 5 and Visit 6 from Visit 3.
- MGIs and their 95% CIs will be tabulated at Visit 4, Visit 5 and Visit 6 from Visit 3 and displayed graphically.

Results will be reported using both ED60 and IU/ml units.

4.3.2.1.2. Between groups assessment

Following analyses will be performed for computation of the GMT ratio:

- GMT ratio (RSV_HA group over RSV_IC group (pooled RSV_IC_1 and RSV_IC_2 group) with 95% CI, at Visit 2 (in a subset of participants) and Visit 3 will be derived from ANCOVA model on log_{10}-transformed titers for each neutralization assay. The model will include the group and the baseline log_{10}-transformed titer as covariate. The group GMT ratios will be based on a back transformation of group contrast in the ANCOVA model applied to the logarithmically transformed titers.
- GMT ratio (RSV_IC_2 group over RSV_IC_1 group) with 95% CI, at Visit 4, Visit 5, and Visit 6 will be derived from ANCOVA model on log_{10}-transformed titers for each neutralization assay. The model will include the group, SOT type and the baseline log_{10}-transformed titer as covariate. The group GMT ratios will be based on a back transformation of group contrast in the ANCOVA model applied to the logarithmically transformed titers.
- GMT ratio (RSV_HA group over RSV_IC_1 group) with 95% CI, at Visit 4, Visit 5, and Visit 6 will be derived from ANCOVA model on log_{10}-transformed titers for each neutralization assay. The model will include the group and the baseline log_{10}-transformed titer as covariate. The group GMT ratios will be based on a back transformation of group contrast in the ANCOVA model applied to the logarithmically transformed titers.
- GMT ratio (RSV_HA group over RSV_IC_2 group) with 95% CI, at Visit 4, Visit 5, and Visit 6 will be derived from ANCOVA model on log_{10}-transformed titers for each neutralization assay. The model will include the group and the baseline log_{10}-transformed titer as covariate. The group GMT ratios will be based on a back transformation of group contrast in the ANCOVA model applied to the logarithmically transformed titers.
- GMT ratio (RSV_IC_2 group at Visit 4 over RSV_IC_1 group at Visit 3) with 95% CI will be derived from ANCOVA model.

- GMT ratio (RSV_HA group at Visit 3 over RSV_IC_2 group at Visit 4) with 95% CI will be derived from ANCOVA model.
- The 2-sided 95% CI for the difference in SRR between groups:
  - RSV_HA minus RSV_IC group (pooled RSV_IC_1 and RSV_IC_2) will be computed at Visit 2 and Visit 3
  - RSV_IC_2 minus RSV_IC_1, RSV_HA- minus RSV_IC_2 and RSV_HA minus RSV_IC_1) will be computed at Visit 4, Visit 5 and Visit 6.
  - RSV_IC_2 group at Visit 4 minus RSV_IC_1 group at Visit 3 will be computed.
  - RSV_HA group at Visit 3 minus RSV_IC_2 group at Visit 4 will be computed.

Results will be reported using both ED60 and IU/ml units.

All between-groups analyses of secondary endpoints presented in this Section will be descriptive with the aim to characterize the difference in immunogenicity between groups. These descriptive analyses should be interpreted with caution considering that there is no adjustment for multiplicity for these comparisons.

4.3.2.2. Immunogenicity analysis: CMI response

The analysis will be based on the CMI subset of the PPS. If, in any group, the percentage of vaccinated participants with serological results excluded from the CMI subset of the PPS is more than 5%, a second analysis based on the CMI subset of the ES will be performed to complement the PPS analysis.

At each time point blood samples are collected, the following parameters will be summarized by group (the data for RSV_IC_1 and RSV_IC_2 group will also be pooled for dose 1 up to visit 3 (including visit 3)) using descriptive statistics (N, geometric mean, min, Q1, median, Q3, max) in the CMI subset:

- Frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, measured by intracellular cytokine staining (ICS) using Peripheral Blood Mononuclear Cells (PBMCs)
- The kinetics of the frequency of RSVPreF3-specific CD4+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, measured by ICS, will be plotted as a function of time for participants with results available at all timepoints.
- Fold increase of the frequency of RSVPreF3-specific CD4+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, measured by ICS at the post-vaccination time point over pre-vaccination (Visit 1, Day 1). The percentage of participants with at least a 4-fold increase, post-vaccination as compared to pre-vaccination will be tabulated by timepoint.

- The frequency of RSVPreF3 specific-CD4+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, measured by ICS, will be displayed graphically using boxplots (min, Q1, median, Q3, max)

The above mentioned descriptive within group immunogenicity analysis will also be generated by SOT type (renal and lung SOT patients) in the IC participants by age group and by immunosuppressive therapy.

4.3.2.3. Safety analysis

The safety analysis will be performed per study group (the data for RSV_IC_1 and RSV_IC_2 group will also be pooled for dosing at visit 1) on the ES, as follows:

- The safety follow-up time will be tabulated using descriptive statistics (mean, median, minimum, maximum).
- 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 (solicited and unsolicited) during the 7-day (i.e., the day of vaccination and 6 subsequent days) or 30-day (i.e., the day of vaccination and 29 subsequent days) follow-up period after vaccination will be tabulated with exact 95% CI after each vaccine dose and overall. The same computations will be done for Grade 3 AEs, for Grade 3 non-serious AEs and for AEs resulting in a medically attended visit.

  Those analyses will present all solicited and unsolicited AEs, including SAEs and AESIs (i.e., pIMDs, transplant related AESI and AF) (unless otherwise specified).
- The number and percentage of participants with at least one administration site event (solicited only), with at least one systemic event (solicited only) and with any solicited event during the 7-day (i.e., the day of vaccination and 6 subsequent days) follow-up period after vaccination will be tabulated with exact 95% CI after each vaccine dose and overall. The same computations will be done for Grade 3 AEs, for AEs resulting in a medically attended visit and by SOT type and age group.
- Compliance in completing solicited events information will be tabulated.
- The number and percentage of participants reporting each individual solicited administration site or systemic event (any grade, Grade 3 and resulting in medically attended visit) during the 7-day follow-up period (i.e., the day of vaccination and 6 subsequent days) after vaccination will be tabulated with exact 95% CI after each vaccine dose and overall. The same computations will be done by SOT type and age group.
- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments during the 7-day follow-up period (i.e., the day of vaccination and 6 subsequent days) will be tabulated for each group after each vaccine dose and overall.

- The percentage of participants with each solicited administration site event and solicited systemic event (any grade and Grade 3) during the 7-day follow-up period (i.e., the day of vaccination and 6 subsequent days) will be represented graphically for each group after each vaccine dose.
- The number of days for each individual solicited events will be tabulated using descriptive statistics (mean, min, Q1, median, Q3, maximum). The number of days with grade 3 solicited events will be tabulated for each individual solicited events using descriptive statistics (mean, min, Q1, median, Q3, maximum).
- The number and percentage of participants with any unsolicited AEs during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) with its exact 95% CI after each vaccine dose and overall will be tabulated by group and by MedDRA Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT). Similar 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. Similar tabulation will also be done after any dose for any unsolicited AEs and Grade 3 unsolicited AEs done by SOT type and age group. The analyses of unsolicited AEs will include SAEs and AESIs (i.e., pIMDs, transplant related AESI and AF).
- The number and percentage of participants with any non-serious unsolicited AEs during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) with its exact 95% CI after each vaccine dose and overall will be tabulated by group and by MedDRA Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT). Similar tabulation will be done for Grade 3 non-serious unsolicited AEs, for any causally related non-serious unsolicited AEs, for Grade 3 causally related non-serious unsolicited AEs and for non-serious unsolicited AEs resulting in a medically attended visit.
- The number and percentage of participants with any unsolicited AEs reported within 30 minutes following vaccination with its exact 95% CI will be tabulated by group and by MedDRA Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT) after each vaccine dose and overall. Similar tabulation will be done for Grade 3 unsolicited AEs reported within 30 minutes following vaccination.
- The verbatim reports of unsolicited AEs, including SAE and AESI (i.e., pIMDs, transplant related AESI and AF), 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 classified by the MedDRA Primary SOC, HLT and PT from vaccination (Day 1) up to study end (Visit 6) will be tabulated with exact 95% CI. The same computations will be done by SOT type and age group.
- The number and percentage of participants with at least one report of SAE classified by the MedDRA Primary SOC, HLT and PT, related to study intervention administration, from vaccination (Day 1) up to study end (Visit 6) will be tabulated with exact 95% CI.

- The number and percentage of participants with any fatal SAE, from vaccination (Day 1) up to study end (Visit 6) will be tabulated with exact 95% CI. The same computations will be done by SOT type and age group.
- The number and percentage of participants with at least one report of pIMD classified by the MedDRA Primary SOC, HLT and PT from vaccination (Day 1) up to study end (Visit 6) will be tabulated with exact 95% CI. The same computations will be done by SOT type and age group.
- The number and percentage of participants with at least one report of pIMD classified by the MedDRA Primary SOC, HLT and PT, related to study intervention administration, from vaccination (Day 1) up to study end (Visit 6) will be tabulated with exact 95% CI.
- The number and percentage of participants with at least one report of AESI related to organ transplant classified by the MedDRA Primary SOC, HLT and PT from vaccination (Day 1) up to study end (Visit 6) will be tabulated with exact 95% CI. The same computations will be done by SOT type and age group.
- The number and percentage of participants with at least one report of AESI related to organ transplant classified by the MedDRA Primary SOC, HLT and PT, related to study intervention administration, from vaccination (Day 1) up to study end Visit 6) will be tabulated with exact 95% CI.
- The number and percentage of participants with at least one report of AESI (i.e., pIMDs, transplant related AESI and AF) classified by the MedDRA Primary SOC, HLT and PT from vaccination (Day 1) up to study end (Visit 6) will be tabulated with exact 95% CI. The same computations will be done by SOT type and age group.
- The number and percentage of participants with at least one report of AESI (i.e., pIMDs, transplant related AESI and AF) classified by the MedDRA Primary SOC, HLT and PT, related to study intervention administration from vaccination (Day 1) up to study end (Visit 6) will be tabulated with exact 95% CI.
- The number and percentage of participants with demyelinating disorder during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) with its exact 95% CI after each vaccine dose and overall will be tabulated.
- The number and percentage of participants with demyelinating disorder SAE from vaccination (Day 1) up to study end (Visit 6) will be tabulated with exact 95% CI.
- Number of participants with biopsy confirmed following vaccination with allograft rejection will be tabulated.
- All SAEs/AESIs (including pIMDs, transplant related AESI, AF and Fatal) up to study end (Visit 6) will also be described in detail in a tabular listing.
- Listing of participants with declining allograft function based on estimated glomerular filtration rate (eGFR) post-transplantation (all available in eCRF) for renal transplants (from SoC). The decline is defined as a post-vaccination eGFR-value being below the last eGFR value recorded before the first vaccination. as determined by serum creatinine measurements (i.e., fold increase> 1 at post vaccination from Visit 1) will be presented.

- Listing of participants with declining allograft function as determined by FEV1 results for lung transplants (having a CLAD status at post-vaccination worse than for the last CLAD status before first vaccination) will be presented. (i.e., CLAD status at post vaccination vs CLAD status at Visit 1) will be presented.
- List of participants with de novo or anamnestic CCI from vaccination (Day 1) up to 30 days of last vaccination and until study end (Visit 6) will be presented if performed.
- AEs/SAEs (including pIMDs, transplant related AESI, AF and Fatal) leading to study discontinuation from vaccination up to study end will be tabulated.
- For web posting purposes, the number of occurrences and the number and percentage of participants with non-serious AEs (solicited and unsolicited combined) during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) after any doses will be produced by SOC and PT.
- In case of pregnancies, these will be described in detail.
- AF AESIs will be tabulated within the summary of AEs or SAEs according to their classification.

Refer to Section 6.1.5 and Section 6.1.6 for the analysis of concomitant medications and concomitant vaccination.

4.3.3. Additional considerations

4.3.3.1. Mixed-effects model

For the GMTs calculation based on the mixed effects model mentioned in Section 4.3.2.1, ANCOVA model will be fitted including study group (RSV_IC_1, RSV_IC_2 and RSV_HA) and post-vaccination timepoint visits (Visit 3, Visits 4, Visit 5 and Visit 6) as a fixed effects, pre-vaccination log10-transformed titers as a covariate and the response variable is the post-vaccination log10-transformed titers. The PROC MIXED procedure in SAS® will be used to carry out the ANCOVA.

The following SAS codes will be used:

```
     PROC MIXED DATA=SERO method=reml empirical;
CLASS subjid group visit ;
MODEL post-vac=pre-vacc group visit visit*group/ noint s cl;
REPEATED visit/type=un subject=subjid;
LSMEANS visit*group/ E cl;
     ODS OUTPUT LSMEANS=LS;
     RUN;
```

The above SAS codes may be adapted in case of convergence issues.

4.3.3.2. Cell-mediated immune response

The RSVPreF3-specific CD4+/ CD8+ 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 geometric mean calculation and graphical representation. Frequencies will be expressed as the number of cells per million of CD4+/ CD8+ T cells.

More specifically, the frequencies of RSVPreF3-specific CD4+/ CD8+ T cells expressing at least 2 activation markers including at least one cytokine [$Freq^{2+}$] 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

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

where

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

$n^{2+}_{Induction}$= number of CD4+ T cells expressing at least 2 activation markers including at least one cytokine 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 activation markers including at least one cytokine among CD40L, 41BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, the results below the lower limit of quantification (LLOQ) of the assay will be replaced by the value of the LLOQ.

4.3.3.3. Atrial Fibrillation (AF) AESIs

Potential AF AESIs will be identified through the MedDRA preferred term of interest atrial fibrillation (10003658). Sites will be prompted via query to complete any necessary additional information for these AESIs in the eCRF. Additional analysis might be performed on those additional data collected for AF AESIs.

AF AESIs will be described in a tabular summary including the characteristics of the AE (seriousness, causality, maximum intensity), time to onset and outcome.

4.4. Tertiary Endpoints Analyses

Analysis of the tertiary endpoints will be described in an amendment of this SAP if the tertiary objective will be evaluated.

4.5. Other Safety Analyses

Not Applicable.

4.6. Other Analyses

4.6.1. Subgroup Analyses

Subgroup analyses of the secondary immunogenicity and safety endpoints will be performed by age group ,SOT type and immunosuppressive therapy described in Section 4.3.2.1.1 and 4.3.2.2

Sub-groups	**Order in tables**	**Label in tables**	**Definition for footnote**
Age group	1	18-49 YOA	18-49 years old participants
	2	50-59 YOA	50-59 years old participants
	3	>=60 YOA	>=60 years old participants
SOT Type	1	LTx	Participants with lung transplant
	2	RTx	Participants with renal transplant
Combination of types of immuno-suppressive therapy in use	1	All 3 classes: CIS + CS + MC	Note: Participants using other class(es) of immunosuppressants in addition to the three classes specified above will also be included in this group. Note: Participants using other class(es) of immunosuppressants in addition to the three classes specified above will also be included in this group.

Sub-groups	Order in tables	Label in tables	Definition for footnote
	2	Any 2 class combinations of CIS, CS, or MC	Participants using any combination of any two of three classes of immunosuppressant: 1) Calcineurin or mTOR inhibitors such as cyclosporine, sirolimus, or tacrolimus, everolimus; 2) Corticosteroids such as prednisone; and 3) Mycophenolate.
	3	Any single class: CIS, CS, or MC	Participants using any single class of immunosuppressant: 1) Calcineurin or mTOR inhibitors such as cyclosporine, sirolimus, or tacrolimus, everolimus; 2) Corticosteroids such as prednisone; and 3) Mycophenolate.
Immuno-suppressive therapy (Mycophenolate) in use	4	Yes	Use of Mycophenolate as immunosuppressive therapy
	5	No	No using of Mycophenolate as immunosuppressive therapy

CIS= Calcineurin inhibitors/Sirolimus, CS= Corticosteroids, MC= Mycophenolate compound

From the concomitant medication dataset the list of immunosuppressants are considered using the key words from “standardized medication name (CMDECOD) containing ("Ciclosporin", "Everolimus", "Sirolimus", "Tacrolimus", "Azathioprine", “Belatacept",) then the participant is considered to be in: CIS

From the concomitant medication dataset the list of immunosuppressants are considered using the key words from “standardized medication name (CMDECOD) containing ("Deflazacort", "Prednisolone", "Prednisone", "Methylprednisolone", “Dexamethasone”) then the participant is considered to be in: CS

From the concomitant medication dataset the list of immunosuppressants are considered using the key words from “standardized medication name (CMDECOD) containing ("Mycophenolate mofetil", "Mycophenolate sodium", "Mycophenolic acid") then the participant is considered to be in: MC.

From the concomitant medication dataset the list of immunosuppressants are considered using the key words from “standardized medication name (CMDECOD) containing ("Basiliximab", " Alemtuzumab ", " Thymoglobulin ", " Muromonab-CD3”, "Mizoribine ", " Immunoglobulin/Immunoglobulins “, " Ofatumumab “ , " Eculizumab " , "Bortezomib " , "Tocilizumab ") then the participant is considered to be in: Other.

4.6.1.1. Mixed-effects model

Not Applicable.

4.7. Interim Analyses

All analyses will be conducted on final data, as clean as possible.

4.7.1. Sequence of analyses

The following analyses will be performed stepwise:

- **PCA** (**Primary completion analysis)**: A first analysis will be performed on all immunogenicity, reactogenicity and safety data available and as clean as possible, when data for at least primary and secondary endpoints up to Visit 4 are available. This analysis will be considered as final for those endpoints*.
- **Month 6 post-last dose**: A second analysis will be performed on all immunogenicity and safety data available and as clean as possible, when data for at least secondary endpoints up to Visit 5 are available. This analysis will be considered as final for those endpoints*.
- An **end of study** analysis will be performed when all data for at least secondary endpoints up to study conclusion (Visit 6) will be available.

  ** Each analysis can be considered as final, as it is based on data that is as clean as possible. However, the consecutive analysis of the same time point might slightly differ at the next analysis e.g., when Visit 5 data are re-analyzed at the time of Visit 6 analysis. If major changes are identified, they will be described in the clinical study report.*

4.7.2. Statistical considerations for interim analysis

No statistical adjustment for interim analysis is required.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 2. (Dated: 11 October 2023).

5. SAMPLE SIZE DETERMINATON

The study is aimed at describing the immune responses and exploring potential differences, between the immune response of IC patients (either after 1 or 2 doses of RSV vaccine) and the immune response of healthy participants. Given the descriptive nature of the study, no multiplicity adjustment is implemented. The sample size for this descriptive study is determined based on the rationale of adequately detecting relevant differences between immune responses:

- **Effect of the second vaccination in IC patients (within-participant comparison)**

In IC patients receiving 2 doses of RSV vaccine, this is evaluated by comparing the response post-Dose 2 (Visit 4) and post-Dose 1(Visit 3). The power and fold-increase that can be detected with a sample size of 100 evaluable participants are shown in Table 7 below.

Table 7 Estimate of the fold-increase that can be detected by power

SD	Power	Fold-increase
0.5	80%	1.39
0.5	90%	1.46
0.4	80%	1.30
0.4	90%	1.35

Paired T-test: alpha (1-sided) = 2.5%, SD of differences = 0.5 (based on RSV OA=ADJ-002 data, 120 ug/AS01E group, V3 vs V6, SD difference neutra RSV-A = 0.23, SD difference neutra RSV-B = 0.40 inflated from 0.4 to 0.5 to account for IC condition)

- **Difference in the humoral immune response of IC patients (1 and 2 doses) vs healthy participants (1 dose)**

100 evaluable participants in each group achieve 80% power to detect actual GMT fold differences of ≥1.55 at 1-sided $\alpha = 2.5\%$ and 1:1 allocation ratio, assuming standard deviation of neutralizing log10-titers of 0.45 and 0.50 in the healthy and IC groups respectively

(Two-sample T-test).

In addition, pooling of IC groups after 1 dose (200 evaluable participants) allows to detect actual GMT fold differences of ≥1.45 with 80% power compared to healthy participants (100 evaluable participants). Two-sample T-test allowing unequal variance: alpha (1-sided) = 2.5%, SD = 0.45 (healthy), 0.5 (IC).

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized. This analysis will be based on the Screened set, Enrolled set, ES.

6.1.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics (age at vaccination in years, sex, race, ethnicity, country, vital signs and Body Mass Index (BMI), SOT type, interval between last transplantation and Visit 1, number of transplantations, Number of rejections, Type of rejection for last transplantation) will be summarized by group using descriptive statistics, as described in Section 4.1.1.

This analysis will be based on the ES, PPS and on the CMI subset of the PPS for all the parameters except vital signs. The vital signs will be summarized based on the ES.

The following age group will be considered in the analysis 18-49 YOA, 50-59 YOA and ≥60 YOA in the IC population and 50-59 YOA and ≥60 YOA in the healthy adults. In addition, for web posting purposes: 18-64 YOA, 65-84 YOA and ≥85 YOA will be summarized on enrolled and screened set. If the summary of demographics meets the criteria for de-identification, as described in the relevant procedural document, a de-identified version should be produced.

The number and percentages of participants with medical history classified by the MedDRA Primary SOC, HLT and PTs will be tabulated by group for the ES.

6.1.3. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to Visit 4 analysis and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset and all deviations leading to exclusions from analysis sets are captured.
- This dataset will be the basis for the summaries of important protocol deviations.

A summary of important protocol deviations will be provided by group, based on the Screened set.

The number of participants screened for the study as well as the number of participants excluded from the Enrolled set, ES and the PPS analyses will be tabulated. These will be based on the Screened set, Enrolled Set and the ES, respectively.

6.1.4. Participant exposure

The number and percentage of participants who received the study intervention will be tabulated by group for the ES.

6.1.5. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary.

The number and percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically) during the 7-day and the 30-day follow-up period after vaccination will be tabulated with exact 95% CI per study group after each dose and overall.

6.1.6. Concomitant Vaccinations

The number and percentage of participants and doses with concomitant vaccination 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 per study group after each dose and overall.

6.1.7. Additional Analyses Due to the COVID-19 Pandemic

Would COVID-19 still be classified as pandemic in one of the study countries, the following analyses will be performed:

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

The overall incidence of COVID-19 AEs (during the 30-day follow-up period), COVID-19 SAEs and COVID-19 AEs leading to study withdrawal (from vaccination up to study end) will be summarized. The incidence of these events will be obtained from standard AE and SAE summaries (i.e., by SOC and PT).

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

The number and percentage of participants with previous or concomitant COVID-19 vaccination, before and during the study (during the 30-day follow-up period after vaccination), will be tabulated with exact 95% CI.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Attributing events to vaccine doses

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 eCRF 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 event will not be attributed to the study vaccination.

6.2.2. Handling of missing data

6.2.2.1. 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.

The following exceptions apply:

- Adverse events 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 events 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 vaccine dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the 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 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 incomplete concomitant medication/vaccination start/end dates will follow the rules above.

6.2.2.2. Laboratory data

Any missing or non-evaluable immunogenicity measurement will not be replaced. The descriptive analysis performed for each assay at each timepoint will exclude participants with a missing or non-evaluable measurement. This is applicable to the standard way of computing geometric mean titers/concentrations (GMTs/GMCs).

Computation of GMTs/GMCs from the mixed effects model inherently accounts for the missingness, under the assumption that the missing data are missing at random (MAR). Participant having missing pre-vaccination titer will be excluded from ANCOVA and mixed effects models (refer Section 4.3.3.1)

6.2.2.3. Daily recording of solicited events

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

6.2.2.4. Unsolicited adverse events

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

As per CDISC Vaccines Therapeutic Area guide, the solicited events which continue beyond the observation period are stored in the Adverse Events (AE) domain, but they do not contribute to the summaries of unsolicited adverse events.

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.

6.2.3. Data derivation

6.2.3.1. Age at vaccination in years and age group

Age will be calculated as the number of years between the year of birth and the year of first vaccination. The age group will be derived based on derived age.

6.2.3.2. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

6.2.3.3. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

6.2.3.4. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

6.2.3.5. 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

6.2.3.6. 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

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

GMT or GMC calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Non quantifiable neutralizing titres or concentrations will be converted as described in Section 6.2.3.6 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

6.2.3.8. Onset day

The onset day for an event (e.g. AE, concomitant medication/vaccination) is the number of days between the 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).

6.2.3.9. 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.

For solicited administration site and systemic events:

The duration of a solicited AE with at least one day Grade > 0 is defined as End date(CEENDY) – Start date(CESTDY) + 1, with Start date defined as the first day with the symptom and End date defined as the last day with the symptom in or beyond the solicited period.

A missing start date will be imputed with the vaccination date.

For paper diaries, if an ongoing symptom has a missing end date, the end date will be considered equal to vaccination date + 29 days. Partial end dates will be imputed according to Section 6.2.2.1

The number of days with grade 3 solicited symptom will be defined considering each day with a known grading=3 (for paper CRF, if the max intensity during the ongoing period is 3, each day of the ongoing period will be counted as grade 3).

The number of days with grade 3 solicited symptom will be defined considering each day with known grading =3 (for paper CRF, if the max intensity during the ongoing period is 3, each day of the ongoing period will be counted as grade 3).

6.2.3.10. Counting rules for combining solicited and unsolicited adverse events

Unsolicited adverse events with missing administration site flag will be considered systemic.

Solicited events will be coded by MedDRA as per the following codes:

Solicited event	Lower level term code	Corresponding Lower level term decode
Pain	10022086	Injection site pain
Redness	10022061	Injection site erythema
Swelling	10053425	Injection site swelling
Fever	10016558	Fever
Headache	10019211	Headache
Fatigue	10016256	Fatigue
Myalgia	10028411	Myalgia
Arthralgia	10003239	Arthralgia

Note that these codes might be adapted depending on the current version of MedDRA at the time of analysis.

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

6.2.3.11. 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.

The intensity of administration site redness/swelling and fever will be scored as follows:

Intensity grade	Redness/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)

6.2.4. Display of decimals

6.2.4.1. Percentages

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

6.2.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, BMI, pre-dose body temperature, age) 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 maxima and minima of transformed height/weight variables will be displayed without decimals.

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

6.2.4.3. Serological summary statistics

For each assay, GMTs and their confidence limits will be presented with one decimal, as well as GMT fold increase from pre-vaccination.

GMT group ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

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.

7. REFERENCES

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

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine*, 1985;4,213-226.