Statistical Analysis Plan

Study ID: 219276

Official Title of Study: A Phase III, Open-label, Randomized, Controlled, Multi-country Study to Evaluate the Immune Response, Safety and Reactogenicity of RSVPreF3 OA Investigational Vaccine When Co-administered with 20-Valent Pneumococcal Conjugate Vaccine (PCV20) in Adults Aged 60 Years and Older.

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STATISTICAL ANALYSIS PLAN

219276 (RSVPreF3 OA) (RSV OA=ADJ-019)

A Phase III, Open-label, Randomized, Controlled, Multi-country Study to Evaluate the Immune Response, Safety and Reactogenicity of RSVPreF3 OA Investigational Vaccine When Co-administered with 20-Valent Pneumococcal Conjugate Vaccine (PCV20) in Adults Aged 60 Years and Older.

AUTHOR: PPD

VERSION NUMBER AND DATE: V2.0, 11JUL2024

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 11JUL2024) for Protocol 219276.

	Name	Signature	Date (DDMmmYYYY)
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Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	**Signature**	**Date (DDMmmYYYY)**
Approved By:	PPD	PPD	
Position:	Lead Statistician		
Company:	GlaxoSmithKline Biologicals		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	17FEB2023	PPD	Not Applicable – First Version
2.0	11JUL2024	PPD	% of participants with OPA titers above LLOQ added. GMFR and 4-fold increase added as part of secondary immunogenicity endpoints analysis. Neurological demyelination summaries added in. Addition of safety sensitivity analysis for solicited administration site events and solicited systemic events as assessed by principal investigator. AEs duration definition and calculations have been updated. Systemic solicited events will now be summarized by dosing visit. Added in further solicited events compliance summaries details. LLOQ and ULOQ values for immunogenicity measures included in Appendix 3. Web posting purpose tables accounted for in text. eDiary compliance ongoing beyond Day 7 tables added.

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LIST OF ABBREVIATIONS

Abbreviation	Term
Ab	Antibodies
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical classification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
Co-Ad	Co-administered
COVID-19	Coronavirus Disease 2019
CSR	Clinical study report
DMC	Data monitoring committee
eCRF	Electronic case report form
ENR	Enrolled set
EoS	End of study
ES	Exposed set
GMFR	Geometric mean fold rise
GMT	Geometric mean titers
HLT	High level term
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean geometric increase
NAb	Neutralizing antibodies
OA	Older adults
OP	Opsonophagocytic
PCV20	20-valent pneumococcal conjugate vaccine
PD	Protocol deviations
PDMP	Protocol Deviations Management Plan
PI	Principal investigator
pIMD	Potential immune-mediated disease

PPS	Per protocol set
PreF3	PreFusion protein 3
PT	Preferred term
RSV	Respiratory syncytial virus
SAP	Statistical analysis plan
SCR	Screened set
SD	Standard deviation
SOC	System Organ Class
ST	Serotype
TEAE	Treatment-emergent adverse event
TFL	Tables, figures and listings
UL	Upper limit
ULOQ	Upper limit of quantification.
WHODD	World Health Organization Drug Dictionary
YOA	Years of age

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of immunogenicity and safety analyses for Protocol 219276 (RSVPreF3 OA) (RSV OA=ADJ-019). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on final protocol dated 06 January 2023.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. Primary Objectives

The primary objectives are:

- To demonstrate the non-inferiority of the 20-valent pneumococcal conjugate vaccine (PCV20) when co-administered with the respiratory syncytial virus (RSV) PreFusion protein 3 (PreF3) Older Adult (OA) (RSVPreF3 OA) investigational vaccine compared to the PCV20 administered alone
- To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine in terms of RSV-A neutralization antibodies when co-administered with the PCV20 vaccine compared to RSVPreF3 OA investigational vaccine administered alone
- To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine in terms of RSV-B neutralization antibodies when co-administered with the PCV20 vaccine compared to RSVPreF3 OA investigational vaccine administered alone

- Note: PCV and RSV-A endpoint will be assessed as co-primary and following the co-primary success, RSV-B will be demonstrated as sequential.

2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the PCV20 vaccine or administered alone
- To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and PCV20 vaccine, co-administered or administered alone

2.3. Statistical Hypotheses

The study includes the following confirmatory primary objectives.

- To demonstrate the non-inferiority of PCV20 when co-administered with the RSVPreF3 OA investgational vaccine compared to PCV20 administered alone in terms of OP Ab titers GMT ratio for each of the pneumococcal vaccine serotypes (ST) at 1 month after the PCV20 vaccine (i.e., at Day 31 [Visit 2] for both study intervention groups).

  Null hypothesis vs. Alternative hypothesis:

  $H_0: \mu_{Control\ group} - \mu_{Co-Ad\ group} > log(2)\ vs. H_a: \mu_{Control\ group} - \mu_{Co-Ad\ group} \leq \log(2)$

  where μ represents the estimated mean of log transformed antibody titers at 1 month after the PCV20 vaccine dose. The null hypothesis will be rejected if the upper limit of the two-sided 95% CI for the group GMT ratio (Control group divided by Co-Ad group) in antibody titers for each of the pneumococcal vaccine STs 1 month after the PCV20 vaccine ≤ 2

- To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the PCV20 vaccine compared to RSVPreF3 OA investigational vaccine administered alone in terms of RSV-A neutralization antibody GMT ratio at 1 month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 [Visit 2] for the Co-Ad group and at Day 61 [Visit 3] for the Control group).

  Null hypothesis vs. Alternative hypothesis:

  $H_0: \mu_{Control\ group} - \mu_{Co-Ad\ group} > log(1.5)\ vs. H_a: \mu_{Control\ group} - \mu_{Co-Ad\ group} \leq \log(1.5)$

  where μ represents the estimated mean of log transformed RSV-A neutralization antibody titers at 1 month after the RSVPreF3 OA investigational vaccine dose. The null hypothesis will be rejected if the upper limit of the two-sided 95% confidence interval (CI) for the study intervention group GMT ratio (Control group divided by Co-Ad group) in RSV-A neutralization antibody titers 1 month after the RSVPreF3 IA investigational vaccine dose ≤ 1.5.

- To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the PCV20 vaccine compared to RSVPreF3 OA investigational vaccine administered alone in terms of RSV-B neutralization antibody GMT ratio at 1 month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 [Visit 2] for the Co-Ad group and at Day 61 [Visit 3] for the Control group).

  Null hypothesis vs. Alternative hypothesis:

  $H_0: \mu_{Control\ group} - \mu_{Co-Ad\ group} > log(1.5)\ vs. H_a: \mu_{Control\ group} - \mu_{Co-Ad\ group} \leq \log(1.5)$

  where μ represents the estimated mean of log transformed RSV-B neutralization antibody titers at 1 month after the RSVPreF3 OA investigational vaccine dose. The null hypothesis will be rejected if the upper limit of the two-sided 95% confidence interval (CI) for the study intervention group GMT ratio (Control group divided by Co-Ad group) in RSV-B neutralization antibody titers 1 month after the RSVPreF3 IA investigational vaccine dose ≤ 1.5.

2.4. Estimands

The primary and secondary estimands to support regulatory decisions are described in the following table:

	Study Intervention	Population	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
Primary	RSVPreF3 OA and PCV20 co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 60 years of age (YOA)	Geometric Mean Titers (GMTs) for opsonophagocytic (OP) antibodies (Ab) titers for each of the pneumococcal vaccine serotypes (STs)	1. Permanently discontinued from study due to any reasons prior to Visit 2 blood sampling 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition prior to Visit 2 blood sampling 4. Vaccine or blood sample taken out of window 5. No pre/ post-vaccine immunogenicity result available	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	Between group 2-sided 95% CI for the group GMT ratio in terms of OP antibody titers for each of the pneumococcal vaccine STs for PCV20 vaccine administered alone (Control) over PCV20 vaccine co-administered with RSVPreF3 investigational vaccine (Co-Ad group) at 1 month after the PCV20 vaccine (at Visit 2 for both groups).
Primary	RSVPreF3 OA and PCV20 co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 60 YOA	GMTs for RSV-A neutralizing Ab titers	1. Permanently discontinued from study due to any reasons within 30 days of vaccine administration (Visit 2 for Co-Ad group; Visit 3 for Control group) 2. Study intervention not administered per protocol	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity	Between group 2-sided 95% CI for the group GMT ratio in terms of RSV-A neutralizing Ab titers for RSVPreF3 investigational vaccine administered alone (Control) over RSVPreF3 investigational vaccine co-

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				3. Prohibited medication or intercurrent medical condition within 30 days of vaccine administration (Visit 2 for Co-Ad group; Visit 3 for Control group) 4. Vaccine or blood sample taken out of window 5. No pre / post-vaccine immunogenicity result available	analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	administered with PCV20 vaccine (Co-Ad group) at 1 month after the RSVPreF3 investigational vaccine (Visit 2 for Co-Ad group; Visit 3 for Control group).
Primary	RSVPreF3 OA and PCV20 co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 60 YOA	GMTs for RSV-B neutralizing Ab titers	1. Permanently discontinued from study due to any reasons within 30 days of vaccine administration (Visit 2 for Co-Ad group; Visit 3 for Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition within 30 days of vaccine administration (Visit 2 for Co-Ad group; Visit 3 for Control group) 4. Vaccine or blood sample taken out of window 5. No post-vaccine immunogenicity result available	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	Between group 2-sided 95% CI for the group GMT ratio in terms of RSV-B neutralizing Ab titers for RSVPreF3 investigational vaccine administered alone (Control) over RSVPreF3 investigational vaccine co-administered with PCV20 vaccine (Co-Ad group) at 1 month after the RSVPreF3 investigational vaccine (Visit 2 for Co-Ad group; Visit 3 for Control group).
Secondary	RSVPreF3 OA and	Adults	Mean Geometric	1. Permanently discontinued	1. Missing data won't be	Within groups antibody MGIs

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	PCV20 co-administered (Co-Ad) or received separately (Control)	aged ≥ 60 YOA	Increase (MGI) for RSV-A neutralizing Ab titers	from study due to any reasons within 30 days of vaccine administration (Visit 2 for Co-Ad group; Visit 3 for Control group 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition 4. Vaccine or blood sample taken out of window 5. No pre or post-vaccine immunogenicity result available	imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	with 2-sided 95% CI for the RSV-A neutralizing Ab titers at 1 month after the RSVPreF3 OA dose (Visit 2 for Co-Ad group; Visit 3 for the Control group) over pre-vaccination for each vaccine administration.
Secondary	RSVPreF3 OA and PCV20 co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 60 YOA	MGI for RSV-B neutralizing Ab titers	1. Permanently discontinued from study due to any reasons within 30 days of vaccine administration (Visit 2, for Co-Ad group; Visit 3 for Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition 4. Vaccine or blood sample taken out of window 5. No pre or post-vaccine immunogenicity result available	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	Within group antibody MGIs with 2-sided 95% CI for the RSV-B neutralizing Ab titers at 1 month after the RSVPreF3 OA dose (Visit 2 for Co-Ad group; Visit 3 for the Control group) over pre-vaccination.
Secondary	RSVPreF3 OA and PCV20 co-	Adults aged ≥ 60	Solicited administration site	1. eDiary not completed on each day	1. Missing data won't be imputed. Compliance to	Percentage and exact 95% CIs of participants with solicited

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	administered (Co-Ad) or received separately (Control)	YOA	events within 7 days after each vaccine administration		eDiary will be captured	administration site events within 7 days after each vaccine administration (Days 1-7 after each vaccine, PCV20 and RSVPreF3 OA) [i.e., date of RSVPreF3 OA vaccine administration for Control group becomes Day 1 for recording events within 7 days]).
Secondary	RSVPreF3 OA and PCV20 co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 60 YOA	Solicited systemic event within 7 days after each vaccine administration	1. eDiary not completed on each day	1. Missing data won't be imputed. Compliance to eDiary will be captured	Percentage and exact 95% CIs of participants with solicited systemic events within 7 days after each vaccine administration (Days 1-7 after each vaccine, PCV20 and RSVPreF3 OA [i.e., date of RSVPreF3 OA vaccine administration for Control group becomes Day 1 for recording events within 7 days]).
Secondary	RSVPreF3 OA and PCV20 co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 60 YOA	Each unsolicited adverse event within 30 days ofeach vaccine administration	1. Permanently discontinued from study due to any reasons prior to Day 31	1. Missing data won't be imputed. Summaries will present the actual data	Percentage and exact 95% CIs of participants with unsolicited adverse events within 30 days after each vaccine administration (Days 1-30 after each vaccine, PCV20 and RSVPreF3 PA [i.e., date of RSVPreF3 OA vaccine administration for

						Control group becomes Day 1 for recording events within 30 days])
Secondary	RSVPreF3 OA and PCV20 co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 60 YOA	Each serious adverse event (SAE) within 6 months of last dose of study intervention	1. Permanently discontinued from study due to any reasons prior to end of study	1. Missing data won't be imputed. Summaries will present the actual data	Percentage and exact 95% CIs of participants with SAEs within 6 months after last dose of study intervention (Days 1 to 6 months [i.e., 180-210]after each vaccine [i.e., date of RSVPreF3 OA vaccine administration for Control group becomes Day 1 for recording events within 6 months]).
Secondary	RSVPreF3 OA and PCV20 co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 60 YOA	Each Potential Immune-Medicated Disease (pIMD) event within 6 months of last dose of study intervention	1. Permanently discontinued from study due to any reasons prior to end of study	1. Missing data won't be imputed. Summaries will present the actual data	Percentage and exact 95% CIs of participants with SAEs within 6 months after last dose of study intervention (Days 1 to 6 months [i.e., 180-210] after each vaccine [i.e., date of RSVPreF3 OA vaccine administration for Control group becomes Day 1 for recording events within 6 months])

[redacted]

2.5. Sample size determination

The target enrollment will be 1090 participants (545 in the group receiving the RSVPreF3 OA investigational vaccine co-administered with PCV20 [Co-Ad group] and 545 in the Control group where RSVPreF3 OA investigational vaccine and PCV20 are administered in a staggered manner). This allows to obtain at least 980 evaluable participants (490 in the Co-Ad group and 490 in the Control group) for the evaluation of the primary objectives, assuming that 10% of the enrolled participants will not be evaluable.

Participants who withdraw from the study will not be replaced.

Each objective will be evaluated with a nominal type I error of 2.5%.

Table A: Overall power to demonstrate primary objectives: non-inferiority of the immunogenicity of RSVPreF3 OA investigational vaccine when co-administered with pneumococcal vaccine (PCV20) as compared to when administered alone- assuming 490 evaluable participants in each group Groups

Endpoint	Standard deviation of log10 concentration	Reference ratio	Non inferiority margin	Type II error	Power
PCV Non-inferiority* (1-sided test with alpha=2.5%)					
GMTs Opsonophagocytic (OP) antibody (Ab)					
3	0.572	1.05	2	<0.01%	>99.99%
7F	0.733	1.05	2	0.01%	99.99%
19A	0.771	1.05	2	0.01%	99.99%
5	0.782	1.05	2	0.02%	99.98%
1	0.789	1.05	2	0.02%	99.98%
14	0.792	1.05	2	0.02%	99.98%
8	0.797	1.05	2	0.03%	99.97%
33F	0.797	1.05	2	0.03%	99.97%
9V	0.825	1.05	2	0.05%	99.95%
10A	0.839	1.05	2	0.06%	99.94%
11A	0.843	1.05	2	0.07%	99.93%
19F	0.845	1.05	2	0.07%	99.93%

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6B	0.882	1.05	2	0.14%	99.86%
4	0.902	1.05	2	0.20%	99.80%
18C	0.910	1.05	2	0.22%	99.78%
6A	0.927	1.05	2	0.29%	99.71%
12F	0.943	1.05	2	0.37%	99.63%
22F	0.966	1.05	2	0.51%	99.49%
15B	1.088	1.05	2	1.96%	98.04%
23F	1.096	1.05	2	2.10%	97.90%
Global Type II error to show non-inferiority				~6.2%	
Global power for PCV					~93.8%
RSV-A Non-inferiority* (1-sided test with alpha = 2.5%)					
GMTs RSV-A neutralization antibody	0.45	1.05	1.5	0.04%	99.96%
RSV-B Non-inferiority* (1-sided test with alpha = 2.5%)					
GMTs RSV-B neutralization antibody	0.45	1.05	1.5	0.04%	99.96%
Global Power for the study				~6.28	~93.7

Abbreviations: Ab=antibody; GMT=geometric mean titer; OA=older adult; OP=opsonophagocytic; PCV=pneumococcal vaccine; RSV=respiratory syncytial virus.

*Pass 2019 alpha=2.5%, Two-Sample T-Tests for Non-Inferiority Assuming Equal Variance and Equal mean, Power=100 the Type II error (Beta). The Global Type II error (Beta) has been adjusted using Bonferroni's method (Global Type II error=sum of the individual Type II errors).

For RSV: non-inferiority limit=0.176 (=log10[1.5]).

For each PCV vaccine strain: non-inferiority limit=0.301 (=log10[2.0]).

Reference Ratio=0.0212 (=log10[1.05])

Considering a slight interference of 1.05 in true GMTs in both groups with a common population standard error of 0.45 for the RSV-A and RSV-B neutralizing Ab and the respective SD's for each of the PCV serotype in log10

transformed concentration, the study has at least 93.7% power to meet the primary objectives.

For the same evaluable subjects of 490 subjects, a sensitivity power calculation was performed considering the interference of 1.1 and keeping the other assumptions as it is, a power of ~85% was observed.

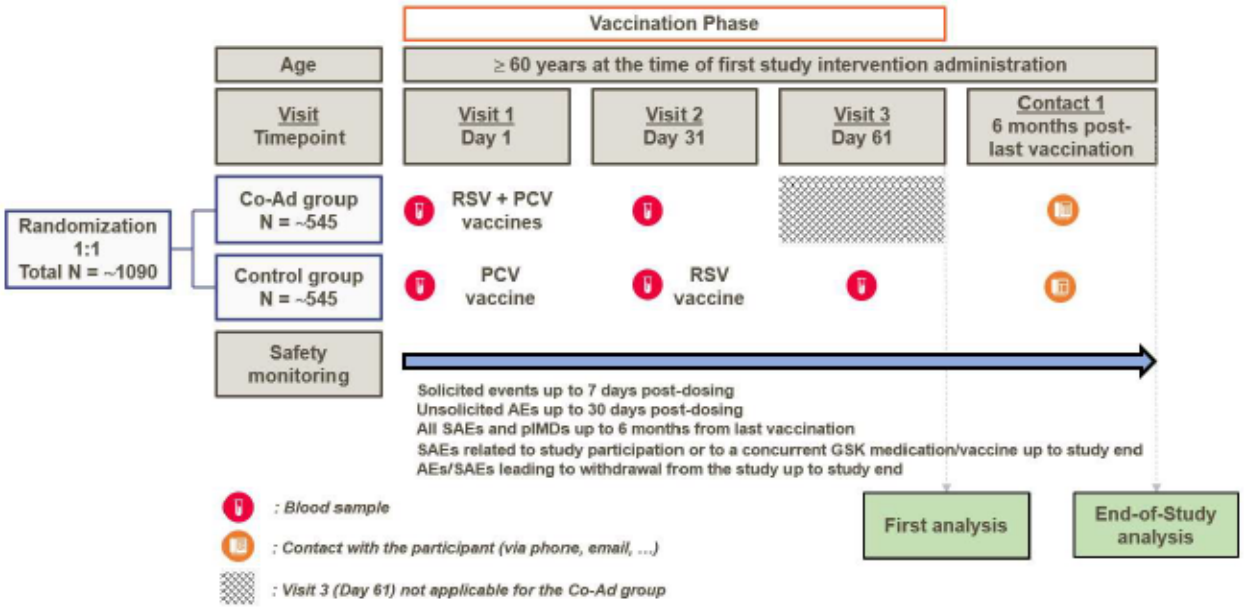
3. STUDY DESIGN

3.1. General Description

This is a phase III, open-label, randomized, controlled, multi-country study in healthy older adults of ≥ 60 YOA with two parallel groups. Participants will be randomly assigned to 2 study groups at Visit 1 (Day 1):

- Co-adminstration (Co-Ad) group: Study intervention administration of RSVPreF3 OA investigational vaccine and PCV20 vaccine co-administered on Visit 1 (Day 1)
- Control group: Study intervention administrations of PCV20 vaccine on Visit 1 (Day 1) and RSVPreF3 OA investigational vaccine on Visit 2 (Day 31).

Figure A: Study Schema



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- AE=Adverse Event; Co-Ad group=Co-Administration group; D=Day; N=Number of participants; PCV=20-valent pneumococcal conjugate vaccine; pIMD=potential Immune-Mediated Disease; RSV=RSVPreF3 OA; SAE=Serious Adverse Event.

- Healthy older adults ≥ 60 YOA will be enrolled in this study according the inclusion and exclusion crtieria (see protocol Section 5.0). Approximately 1090 participants will be randomly assigned to the 2 study intervention groups in a 1:1 ratio prior to intervention to provide approximately 545 enrolled participants in each study intervention group.

The randomization algorithm will use a minimization procedure accounting for age (60-69, 70-79, or ≥ 80 years) and center. Minimization factors will have equal weight in the minimization algorithm. Participants will be enrolled in 3 age categories with a balance between males and females. It is intended to enroll:

- Approximately 40% of participants 60 to 69 YOA, approximately 30% of participants 70 to 79 YOA, and approximately 10% of participants ≥ 80 YOA. The remaining 20% will be distributed freely across the 3 age categories.
- Approximately 40% of participants from each sex. The remaining 20% can be distributed freely across the 2 sexes.

Table A: Study Groups

Study groups	Number of participants	Age (min)	Study interventions
Co-Ad	545	≥ 60 years	RSVPreF3 OA and PCV20 co-administered
Control	545	≥ 60 years	RSVPreF3 OA and PCV20 administered separately

The total duration of the study participation differs for the 2 study intervention groups:

- Co-Ad study intervention group: Total duration is 6 months. There will be 2 study visits on site: Visit 1 on Day 1, when the participants receive study intervention (both RSVPreF3 OA and PCV20 as co-administered), and Visit 2 on Day 31 when blood sampling for vaccine antibody testing will be performed. A safety follow-up visit will be made to the participant approximately 6 months after last vaccine is received) via telephone or by any other convenient means of communication.
- Control study intervention group: Total duration is 7 months. There will be 3 study visits on site: Visit 1 on Day 1, when the participants receive PCV20 vaccine, and Visit 2 on Day 31 when the participants receive RSVPreF3 OA vaccine and blood sampling for PCV20 vaccine antibody testing will be performed, and Visit 3 on Day 61 when blood sampling for RSVPreF3 OA vaccine antibody testing will be performed. A safety follow-up visit will be made to the participant approximately 6 months after last vaccine is received) via telephone or by any other convenient means of communication.

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3.2. Schedule of Events

Schedule of events can be found in Section 1.3 of the protocol.

3.3. Changes to Protocol Defined Analyses

No changes.

4. PLANNED ANALYSES

- There will be no Data Monitoring Committee (DMC) meetings for this study.

4.1. Interim Analysis

There will be no interim analyses for this study.

4.2. First 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 2 (Day 31) (Co-Ad group) or Visit 3 (Day 61) (Control group) are available for all participants. This analysis will be considered as final for those endpoints.

4.3. EOS Analysis

An End of Study analysis will include all data obtained until 6 months post-last dose.

If for any reason the First Analysis could not be performed prior to the EOS Analysis, then the First Analysis will be performed at EOS analysis.

5. ANALYSIS SETS

Agreement and authorization of participants included / excluded from each analysis set will be conducted prior to

production for the interim analysis.

5.1. Process for Analysis Set Assignment

- Definitions for analysis sets are provided below.
- Prior to database lock, a transfer of raw data from the electronic Case Report Form (eCRF) will occur, and participants will be assigned to analysis sets in accordance with the definitions in this SAP and the available data at that time. However, the protocol deviations will be monitored continuously throughout the study.
- Listings presenting participants excluded from each final analysis set and reasons for exclusion will be prepared for sponsor review ahead of database lock in order to allow appropriate related data queries to be issued.
- A Data Review meeting will be held to confirm analysis set assignment, along with protocol deviations review (see protocol deviations management plan [PDMP], to include details of which PDs lead to exclusion from per protocol analyses), for each participant and any changes will be recorded. Changes will be implemented, and an updated analysis set assignment will be approved by the sponsor. The Data Review Plan will be shared with the sponsor for review prior to the Data Review meeting.
- Sponsor authorization of the analysis sets will be necessary prior to database lock. Once approved, analysis sets will be finalized, and the database will be locked.
- After database lock, the final analysis sets will be derived using the final study data, i.e., clinical database (eCRF), eDiary, external vendor data (immunogenicity results) and protocol deviations log.

5.2. Screened Set [SCR]

- All participants who were screened for eligibility.

5.3. Enrolled Set [ENR]

All participants in the SCR who were randomized or received study intervention or have undergone an invasive procedure. For analyses and displays based on ENR, participants will be classified according to randomized intervention.

5.4. Exposed Set [ES]

All participants in the ENR who received a study intervention. Analysis per group is based on the study intervention administered (i.e., study intervention actually received).

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5.5. Per Protocol Set [PPS]

RSV PPS:
All eligible participants in the ES:

- who received RSV vaccine as per protocol in the control group and received both study interventions in the Co-Ad group
- who had immunogenicity results pre- and post-dose for RSV neutralizing titers
- who complied with blood draw interval for RSV samples
- without intercurrent medical conditions* that may interfere with immunogenicity and without prohibited concomitant medication / vaccination up to blood sample post RSV vaccination for control group and Co-Ad group,
- who do not meet any of the criteria for elimination up to blood sample post RSV vaccination for control group and Co-Ad group (i.e., control group participants need to meet all above criteria at Visits 2 and 3; Co-Ad group participants need to meet all above criteria at Visits 1 and 2).

PCV PPS:
All eligible participants in the ES:

- who received PCV vaccine as per protocol in the control group and received both study interventions in the Co-Ad group
- who had immunogenicity results pre- and post-dose for opsonophagocytic antibodies (OP Ab) titers
- who complied with blood draw interval for PCV20 samples
- without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication / vaccination* up to blood sample post PCV20 vaccination for control group and Co-Ad group, and
- who do not meet any of the criteria for elimination up to blood sample post RSV vaccination for control group and Co-Ad group (i.e., control group and Co-Ad group participants need to meet all above criteria at Visits 1 and 2)

*Intercurrent medical conditions that may lead to elimination from the PPS are defined as confirmed immunodeficiency condition, use of prohibited medication, or development of RSV or pneumococcal disease in the interval between study intervention administration and the collection of blood specimen for immunogenicity (i.e., Day 31 for Co-Ad group for PCV20 intervention; Day 31 for Co-Ad group and Day 61 for Control group for RSVPreF3 OA intervention).

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6. GENERAL CONSIDERATIONS

Data will be summarized descriptively (frequency and percentage for categorical data and mean, standard deviation [SD] and range for continuous data, unless specified otherwise). In summary tables for categorical data for which categories are defined on the eCRF, all categories will be presented as specified, even if the participants count within that category is zero.
Unless otherwise specified, all data collected during the trial will be presented in listings for the ENR.

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start / stop day of assessments and events. It will appear in every listing where an assessment date or event date appears.
Reference start date is defined as Day 1 for the day of each vaccination. where study day is the number of days following the latest vaccination.

- If the date of the event is on or after the reference date, then:
  Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings unless otherwise stated.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments) and will be referenced as pre-vaccination. In the case where the last non-missing measurement and the reference start date coincide, and time is not collected, that measurement will be considered pre-vaccination. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as pre-vaccination values.

6.3. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. Windowing Conventions

Allowed time window for each visit will be performed as mentioned in "Schedule of Activities", section 1.3 of protocol. Intervals between study visits are included in Table C: (Co-Ad group) and Table D (Control group).

Table C: Intervals between Study Visits (Co-Ad Group)

Interval	Planned visit interval	Allowed interval (Visit window)
Visit 1 (Day 1 / study intervention administration) → Visit 2 (Day 31)	30 days	30-42 days
Visit 1 → phone contact	180 days	180-210 days

Table D: Intervals between Study Visits (Control Group)

Interval	Planned visit interval	Allowed interval (Visit window)
Visit 1 (Day 1 / study intervention administration) → Visit 2 (Day 31)	30 days	30-42 days
Visit 2 (Day 31 / study intervention administration) → Visit 3 (Day 61)	30 days	30-42 days
Visit 2 → phone contact	180 days	180-210 days

6.5. Statistical Tests

The default significant level will be (5%), CIs will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

95% CI for proportion will be based on exact Clopper-Pearson CI [18].

95% CI for group difference in proportion will be based on Miettinen and Nurminen CI [18].

The group adjusted GMT ratio will be based on a back transformation of group contrast in an ANCOVA model applied to the logarithm-transformed titers.

6.6. Common Calculations

GMT/GMC:

Prior to any statistical analysis that assumes normally distributed observations, antibody concentrations or titers will be log10-transformed. GMT/GMC calculations are performed by taking the inverse logarithm of the mean of the log titer or concentration transformations.

The GMT/GMC will be calculated using the following formula:

$$10^{\frac{\sum_{i=1}^{n} log10\,(t_i)}{n}}$$

where t_i = concentrations or titers for each antibody, n = number of antibodies examined. Non-quantifiable antibody titers or concentrations will be converted as described in Table G for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

MGI is defined as the geometric mean of the within participants ratios of the post-dose titer (at 1 month after the RSVPreF3 OA investigational vaccine dose [Day 31 for Co-Ad group, Day 61 for Control group]) over the pre-dose titer (at pre-vaccination [Day 1 for Co-Ad group and Day 31 for Control group]).

Geometric mean fold rise (GMFR) in serotype-specific OPA titers for PCV is the within participant ratio of OPA GMT at 1 month post PCV vaccination (Day 31 for Co-Ad group and Control group) over pre vaccination (Day 1 for Co-Ad group and Control group).

4-fold rise is defined as a post-vaccination titer ≥ 4 times the LLOQ for that measure (PCV, RSV-A, RSV-B).

Table G: Assay Derivation Rules

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

Note: The Reverse Cumulative Distribution curves (RCC) generated will not use the ULOQ values but the exact value if the exact value is greater than ULOQ.

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For all the assays available for the study, assay derivation rules are included in Table G.

LLOQ and ULOQ values for PCV OP Ab titers and for RSV-A and RSV-B titers and concentrations are as per APPENDIX 3 of this SAP.

6.7. Software Version

All analyses will be conducted using SAS version 9.4 or above.

7. STATISTICAL CONSIDERATIONS

7.1. Adjustments for Covariates and Factors to be Included in Analyses

The following factors will be used in the ANCOVA analyses: age group at vaccination (60 to 69, 70 to 79 or ≥ 80 YOA) and study intervention group (Co-Ad or Control). The following covariate will be used in the ANCOVA: pre-dose $\log_{10}$-transformed titer as covariate. For details, refer to 15.1 and 15.2.

7.2. Multicenter Studies

This study will be conducted by multiple investigators in multiple countries. The participants will be randomized to one of the 2 groups (refer to Table A in section 3.1) which will be performed in a 1:1 ratio prior to intervention to provide approximately 545 enrolled participants per study intervention group.

7.3. Missing Data

Missing data (missing, incomplete or partial dates, AE measurement, prior and concomitant medications and death date) will be handled as per APPENDIX 2 of this SAP.

Missing immunogenicity data will not be imputed. Titers below assay cut-off (i.e., lower limit of quantification or < LLOQ) will be replaced by half the assay cut-off (LLOQ/2) and titers above the assay cut-off (i.e., upper limit of quantification or > ULOQ) will be replaced by the ULOQ for the purpose of GMC/GMT computation.

7.4. Multiple Comparisons / Multiplicity

There are 3 primary endpoints to be accounted for in this study. In order to eliminate the need to adjust alpha, testing for these endpoints will take the following sequence:

- 1st Sequence:
  1) The upper limit (UL) of the 2-sided 95% CI of the GMT ratio (control group divided by Co-Ad group) for each individual pneumococcal vaccine serotype as measured by OP Ab is ≤2.

  AND

  2) The UL of the 2 sided 95% CI of the GMT ratio (control group divided by Co-Ad group) between the control group versus Co-Ad group for RSV-A neutralizing antibody titer one month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

- 2nd Sequence:
  3) The UL of the 2 sided 95% CI of the GMT ratio (control group divided by Co-Ad group) between the control group versus Co-Ad group for RSV-B neutralizing antibody titer one month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

  Testing will progress in the 2nd sequence only if the 1st sequence is a success.

7.5. Examination of Subgroups

Subgroup analyses by age category (60-69, 70-79, ≥60, ≥65, ≥ 80 YOA) will be performed for secondary immunogenicity endpoints, solicited events, unsolicited events, serious AEs and pIMD summaries.

8. Output Presentations

APPENDIX 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics. Statistical output numbering will follow 'ICH E3 Structure and Content of Clinical Study Reports'.

9. Disposition and Withdrawals

All participants who are enrolled in the study (those who received a study intervention, had a blood draw before study intervention administration, or were randomized), i.e., those accounted for in the ENR, will be accounted for in this study.

9.1. Disposition

Participant disposition, withdrawals, and reasons for exclusion from each analysis set, including inclusion as well as exclusion criteria will be presented for the ENR. Participant disposition will be summarized for screen failures from SCR to ENR. Specifically, the number of participants, vaccinated, completed the study, discontinued from the study and the reason for discontinuation will be summarized by study intervention for the ENR. Additionally, the number of participants returning for each visit for the ES will be presented.

A listing of the disposition for all participants with early withdrawal or discontinuation will be provided.

9.2. Protocol Deviations

Protocol deviations (PDs) will be collected in a PD log, as detailed in the PDMP. All PDs will be assessed as either important or non-important. PDs will be reviewed by the sponsor, and their status confirmed by the time that all data

are cleaned for the EOS Analyses. A summary table presenting the number and percentage of participants with important PDs (i.e., those PDs associated to elimination from PPS) and the number and percentage of participants excluded from the PPS analyses will be presented for participants in the ES by study intervention. A listing of all PDs including an indicator of those excluded from the PPS will be provided.

9.2.1. Protocol Deviations Related to Study Conduct

A PD is any non-compliance with the clinical trial protocol, GCP, or protocol deviation guidelines requirements. The non-compliance may be either on the part of the participant, the site principal investigator (PI), the study site staff or the sponsor (or it's delegate).

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ES and PPS. The following demographic and other baseline characteristics will be reported for this study:

- Age (years) – at the time of study intervention
- Age category (60-69, 70-79, ≥60, ≥65, ≥ 80 YOA)
- Sex
- Race (as per Clinical Data Interchange Standards Consortium [CDISC] categories)
- Ethnicity
- Country

Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous variables and frequency counts and percentages for categorical variables.

The number of participants enrolled in each country will be summarized by study intervention.

For web posting purposes, the demographic characteristics including age (based on EudraCT) and country will be presented for the enrolled set and screening set. In addition, the following age categories will be summarized: 18-64, 65-84, and >=85. If the summary of demographics meets the criteria for de-identification, as described in the relevant procedural document, a de-identified version will be produced.

No statistical testing will be carried out for demographic or other baseline characteristics.

11. General Medical / Vaccination History and Examinations

Medical / Vaccination History information will be summarized for the ES.

- Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 25.1 or higher.
- Data captured on the "Medical History" page of the eCRF will be presented by MedDRA System Organ Class (SOC), High Level Terms (HLT) and Preferred Term (PT). Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History section of the eCRF, not the AE section.

- Medical history, classified by the MedDRA Primary SOC, HLT and PTs will be summarized for the ES. A listing of medical / vaccination history data will be provided.

12. Prior, Concomitant and Co-Administered Vaccinations

Prior, concomitant, and co-administered vaccination will be coded with the current version of the World Health Organization Drug Dictionary (WHODD). Concomitant vaccinations during the 30-day follow-up period after each dose and overall will be summarized with exact 95% CI for the ES.

- Prior vaccinations are vaccinations per protocol given to participants prior to the dosing of study intervention and are recorded on the eCRF.
- Concomitant vaccinations are defined as any vaccine that the participant is receiving as of the time of enrolment or receives during the study (other than study interventions) as recorded on the "Concomitant Vaccination" page of the eCRF.

13. Medications

The number and percentage of participants and doses using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days), during the 30-day follow-up period (i.e., on the day of vaccination and 29

subsequent days) and during the 6-month follow-up period (i.e., up to EoS) will be summarized by study intervention group for each study intervention administration and overall will be summarized with exact 95% CIs for the ES.
See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e., concomitant.

- 'Prior' medications are medications which started prior to the dose of study intervention.
- 'Concomitant' medications are medications which started on or after the day of the administration of study intervention.

Further details are in Section 6.7 of the Protocol. Concomitant medications that start within the 7-days follow-up period and within the 30-days follow-up period post each dose will be presented in table summaries (Any, antipyretic action) for the ES and in listings for all medications. This summary will also be repeated for any concomitant medications that start from day of administration up to End of Study.

14. STUDY INTERVENTION EXPOSURE

Exposure to study intervention will be presented for the ES. The date and time of study intervention administration will be taken from the eCRF "Study intervention administration" forms (separate forms for PCV20 and RSVPreF3 OA investigational vaccine). For dosing instructions and route, refer to Table 5 of the Protocol.

15. IMMUNOGENICITY OUTCOMES

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

15.1. Primary Immunogenicity

15.1.1. Primary Immunogenicity Variables & Derivations

The primary immunogenicity endpoints are:

- OP Ab titers for each of the pneumococcal vaccine STs (3, 7F, 19A, 5, 1, 14, 8, 33F, 9V, 10A, 11A, 19F, 6B, 4, 18C, 6A, 12F, 22F, 15B, 23F) expressed as between groups GMT ratio, 1 month after the PCV20 dose (Day 31

for Co-Ad group and for Control group)

- RSV-A neutralizing Ab titers (ED60 and IU/mL) expressed as between groups GMT (ED60) ratio and GMC (IU/mL) ratio, 1 month after the RSVPreF3 OA investigational vaccine dose (Day 31 for Co-Ad group and Day 61 for Control group)
- RSV-B neutralizing Ab titers (ED60 and IU/mL) expressed as between groups GMT (ED60) ratio and GMC (IU/mL) ratio, 1 month after the RSVPreF3 OA investigational vaccine dose (Day 31 for Co-Ad group and Day 61 for Control group)

See 7.4 for details on the handling of multiple primary endpoints.

15.1.2. Intercurrent Event Handling and Data Imputation for Primary Immunogenicity Variables

Missing data will not be replaced.

15.1.3. Primary Analysis of Primary Immunogenicity Variables

The primary immunogenicity endpoints will be analyzed as follows:

- For between group assessment GMT/GMC ratio for PCV20 administered alone (Control group) over PCV20 co-administered (Co-Ad group) at 30 days after administration of PCV20 dose (Visit 2, Day 31) and 2-sided 95% CI will be produced for OP Ab titers for each of the pneumococcal vaccine STs, where 2-sided 95% CIs will be derived from an ANCOVA model on $\log_{10}$ transformed titers and presented alongside descriptive GMTs/GMCs and 95% CIs. The ANCOVA model will include the intervention group and age category (age at vaccination: 60 to 69, 70 to 79, or ≥ 80 YOA) as fixed effects, and the pre-dose log10-transformed titer as covariate. Results will be graphically presented using forest plots
- Between groups GMT/GMC ratio for RSVPreF3 OA administered alone (Control group) over RSVPreF3 OA co-administered at 30 days after administration of RSVPreF3 OA dose (Visit 2 for Co-Ad group, Visit 3 for Control group) and 2-sided 95% CI will be produced for RSV-A neutralizing Ab titers (ED60 and IU/mL), where 2-sided 95% CIs will be derived from an ANCOVA model on $\log_{10}$ transformed titers and presented alongside descriptive GMTs/GMCs and 95% CIs. The same ANCOVA model used for the PCV20 GMT ratio will be applied for this summary. Results will be graphically presented using forest plots.
- Between groups GMT/GMC ratio for RSVPreF3 OA administered alone (Control group) over RSVPreF3 OA co-administered at 30 days after administration of RSVPreF3 OA dose (Visit 2 for Co-Ad group, Visit 3 for Control

group) and 2-sided 95% CI will be produced for RSV-B neutralizing Ab titers (ED60 and IU/mL), where 2-sided 95% CIs will be derived from an ANCOVA model on log_{10} transformed titers and presented alongside descriptive GMTs/GMCs and 95% CIs. The same ANCOVA model used for the PCV20 GMT ratio will be applied for this summary. Results will be graphically presented using forest plots.

Missing results will not be replaced.

15.1.4. Sensitivity Analysis for Primary Immunogenicity Variables

All three primary immunogenicity endpoints analyses will be repeated again using a different ANCOVA model. The ANCOVA model will include the study intervention group and age category (age at vaccination: 60-69, 70-79 or ≥80 years) as fixed effects, center as the random effect and the pre-dose log-10 titer as regressors.

15.2. Secondary Immunogenicity

15.2.1. Secondary Immunogenicity Variables & Derivations

The secondary immunogenicity endpoints are:

- Summary of participants with RSV-A neutralizing Ab titers (ED60 and IU/mL) expressed as GMT/GMC at pre-vaccination and at 1 month after the RSVPreF3 OA investigational vaccine dose (Day 31 for Co-Ad group, Day 61 for Control group) will be tabulated.
- Summary of participants with RSV-B neutralizing Ab titers (ED60 and IU/mL) expressed as GMT/GMC at pre-vaccination and at 1 month after the RSVPreF3 OA investigational vaccine dose (Day 31 for Co-Ad group, Day 61 for Control group) will be tabulated.
- MGI for within participants ratios of the post-dose GMT/GMC (at 1-month after the RSVPreF3 OA investigational vaccine dose) over the pre-dose titer (at baseline) for RSV-A neutralizing titers/concentrations will be tabulated.
- MGI for within participants ratios of the post-dose GMT/GMC (at 1-month after the RSVPreF3 OA investigational vaccine dose) over the pre-dose titer (at baseline) for RSV-B neutralizing titers/concentrations will be tabulated.
- Percentage of participants with PCV OP Ab titers for each serotype expressed as GMFR, ratio of OPA GMT at 1-month post-vaccination (Day 31 for Co-Ad group and Control group) over pre-vaccination will be tabulated. This is a within participant comparison.

- Percentage of participants with PCV OP Ab titers for each serotype expressed as participants with a 4-fold increase in OP Ab titers from pre-vaccination (Day 1 for Co-Ad group and Control group) to post-vaccination (Day 31 for Co-Ad group and Control group) will be tabulated.
- Percentage of participants with RSV-A neutralizing Ab titers (ED60 and IU/mL) expressed as GMT/GMC with a 4-fold increase in RSV-A neutralizing Ab titers from pre-vaccination (Day 1 for Co-Ad group and Control group) to 1 month post-vaccination (Day 31 for Co-Ad group, Day 61 for Control group) will be tabulated.
- Percentage of participants with RSV-B neutralizing Ab titers (ED60 and IU/mL) expressed as GMT/GMC with a 4-fold increase in RSV-B neutralizing Ab titers from pre-vaccination (Day 1 for Co-Ad group and Control group) to 1 month post-vaccination (Day 31 for Co-Ad group, Day 61 for Control group) will be tabulated.
- Percentage of participants with RSV-A neutralizing titers/concentrations equal to or above pre-defined assay cut-offs and their 2-sided 95% CIs will be tabulated.
- Percentage of participants with RSV-B neutralizing titers/concentrations equal to or above pre-defined assay cut-offs and their 2-sided 95% CIs will be tabulated.
- Percentages of participants with PCV OP Ab titers for each serotype expressed as those participants with OPA Ab titers ≥ LLOQ (pre-defined assay cut-offs) at pre-vaccination and/or 1 month post-vaccination (Day 31 for Co-Ad group and Control group).

For the derivation of MGI and GMFR refer to 6.6.

15.2.2. Intercurrent Event Handling and Data Imputation for Secondary Immunogenicity Variable(s)

Missing data will not be replaced.

15.2.3. Analysis of Secondary Immunogenicity Variables

The secondary immunogenicity endpoints will be analyzed as follows:

- MGI and 95% CIs for within participants ratios of the post-dose titer (at 1 month after the RSVPreF3 OA investigational vaccine dose) over the pre-dose titer (at pre-vaccination) for RSV-A neutralizing Ab titers (ED60 and IU/mL)
- MGI and 95% CIs for within participants ratios of the post-dose titer (at 1 month after the RSVPreF3 OA investigational vaccine dose) over the pre-dose titer (at pre-vaccination) for RSV-B neutralizing Ab titers (ED60 and IU/mL)

Missing data will not be replaced. Titers below the assay cut-off will be replaced by half the assay cut-off, titers above the upper limit of quantification (ULOQ) will be replaced by the ULOQ.

15.2.4. Within group assessment

For each group, at each time point that blood samples are collected and for each assay (unless otherwise specified):

- Percentage of participants above pre-defined assay cut-off for GMCs and GMTs and their exact 95% CI will be tabulated.
- GMTs and their 95% CI over time will be tabulated and presented graphically (in log10 scale).
- MGI for within participants ratios of the post-dose GMT or GMC (at 1-month after the RSVPreF3 OA investigational vaccine dose) over the pre-dose titer (at baseline) for RSV-A/RSV-B neutralizing titers/concentrations will be tabulated.
- Antibody titers will be displayed using reverse cumulative curves.
- Percentages of participants with GMFR and 95% CIs for within participants ratios of the post-dose titer (at 1 month after the PCV investigational vaccine dose) over the pre-dose titer (at pre-vaccination) for PCV OP Ab titers for each serotype.
- Percentage of participants and 95% CIs for participants with a 4-fold increase in PCV OP Ab titers from pre-dose titer (at pre-vaccination) to post-dose titer (at 1 month after the PCV investigational vaccine dose) for PCV OP Ab titers for each serotype.
- Percentage of participants and 95% CIs for participants with a 4-fold increase in RSV-A neutralizing Ab titers (ED60 and IU/mL) from pre-dose titer (at pre-vaccination) to post-dose titer (at 1 month after the RSV investigational vaccine dose) for RSV-A neutralizing Ab titers (ED60 and IU/mL).
- Percentage of participants and 95% CIs for participants with a 4-fold increase in RSV-B neutralizing Ab titers (ED60 and IU/mL) from pre-dose titer (at pre-vaccination) to post-dose titer (at 1 month after the RSV investigational vaccine dose) for RSV-B neutralizing Ab titers (ED60 and IU/mL).
- Percentage of participants and 95% CIs for participants with OPA Ab titers ≥ LLOQ (pre-defined assay cut-off) at pre-vaccination and/or 1 month post-vaccination (Day 31 for Co-Ad group and Control group) for each serotype.
- The above mentioned descriptive within group immunogenicity analysis will also be generated by age at first vaccination (60-69 YOA, 70-79 YOA, ≥ 60 YOA, ≥65 YOA and ≥80 YOA years).

Missing results will not be replaced. Titers and concentrations below the assay cut-off will be replaced by half the assay cut-off, titers above the upper limit of quantification (ULOQ) will be replaced by the ULOQ.

Note: For PCV20 summaries, pre-vaccination is at Visit 1 for Co-Ad group and for Control group. For RSV-A and RSV-B neutralizing titer and concentration summaries, pre-vaccination is at Visit 1 for Co-Ad group and at Visit 2 for Control group.

15.2.5. Secondary Immunogenicity Variables

- The secondary immunogenicity endpoints will be repeated by age group at first vaccination (60-69 YOA, 70-79 YOA, ≥60 YOA, ≥65 YOA and ≥ 80 YOA).

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the ES.

There will be no statistical comparisons between the study intervention groups for safety data.

Secondary Safety Endpoints

- Solicited events
  - Percentage of participants reporting each solicited administration site event (pain, erythema / redness, swelling) with onset within 7 days (i.e., the day of vaccination and 6 subsequent days) following each dose and overall. Percentage of participants reporting each solicited systemic event (fever, headache, fatigue, myalgia, arthralgia) with onset within 7 days (i.e., the day of vaccination and 6 subsequent days) following each dose and overall
- Unsolicited adverse events
  - Percentage of participants reporting unsolicited AE within 30 days (i.e., the day of vaccination and 29 subsequent days) following each dose and overall
- Combined solicited and unsolicited AEs
  - Percentage of participants with combined solicited and unsolicited AEs (any grades, Grade 3, medically attended) during the 4-day (i.e., the day of vaccination and 3 subsequent days), 7-day (i.e., the day of vaccination and 6 subsequent days), and 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days).
- SAEs

CCI [redacted]

PPD [redacted] CCI [redacted]

- Percentage of participants reporting SAEs after vaccine administration (Day 1) up to End of Study (EoS) (6 months after last vaccination)

- pIMDs
  - Percentage of participants reporting pIMDs after vaccine administration (Day 1) up to EoS (6 months after last vaccination), where pIMDs commence after vaccine administration (Day 1) and are not present prior to vaccine administration or are present prior to vaccine administration and worsened after vaccine administration (Day 1).

16.1. Adverse Events

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, version 25.1 or higher. Adverse events will be described using frequency and percentage.

Adverse Events will be grouped by SOC, HLT and PT and summarized by study intervention at time of onset of the AE. The summary tables will present the number and percentage of total participants and number of events, by SOC, HLT, and by PT for each study intervention.

For the summaries of AEs, participants who experience the same AE (in terms of the MedDRA SOC, HLT and PT) more than once will only be counted once for that event in the number of participants but all occurrences of the same event will be counted in the number of events.

Causality, as indicated by the Investigator is classed as "related" and "not related" to RSVPreF3 OA vaccine and to PCV20 vaccine. A "related" AE is defined as an AE with a relationship to study intervention as "related". If a participant reports the same AE more than once within that SOC / PT, the AE with the worst-case relationship to study intervention will be used in the corresponding relationship summaries for each study intervention.

See APPENDIX 2 for handling of partial dates for AEs.

Summaries of events considered causally related by investigator to study intervention will be reported separately for each study intervention (RSVPreF3 OA and PCV20).

Summaries of events by age group will be summarized by age groups: 60-69 YOA, 70-79 YOA, ≥60 YOA, ≥65 YOA and ≥80 based on age at first vaccination.

16.1.1. Solicited Adverse Events

Solicited administration site events and solicited systemic events to be summarized are included in Table H. Intensity scales for solicited events (administration site and systemic) are included in Table I and Table J.

Table H: Solicited events

Solicited administration site events	Solicited systemic events
Pain at Injection Site	Fever
Erythema / Redness at Injection Site	Headache
Swelling at Injection Site	Fatigue
	Myalgia
	Arthralgia

Table I: Intensity scales for solicited events – pain, headache, fatigue, myalgia and arthralgia

Event	Intensity grade	Parameter
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Headache	0	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	None
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	None
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	None
	1	Mild: Arthralgia that is easily tolerated
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

Table J: Intensity scales for solicited events – erythema/swelling and fever

	Erythema/swelling	Fever (Temp °C)
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)

Table K: Solicited events lower level term codes and decodes

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

Solicited events will be summarized and listed as:

- The number and percentage of participants and doses with at least one administration site event (solicited only), with at least one systemic event (solicited only), with any solicited event during 4-day follow-up period and 7-day follow-up period after vaccination, and also events ongoing at the end of the 7 day follow-up period, will be tabulated with exact 95% CI after each dose and overall, by visit. This summary will be repeated by age group.
- The number and percentage of participants, with exact 95% CIs, reporting each solicited event (administration site and/or systemic) will be summarized separately for any grades, Grade 3 and medically attended events during the 4-day follow-up and the 7-day follow-up period (i.e., the day of vaccination and 6 subsequent days), following each dose and overall dose and overall participant. This summary will be repeated by age group.
- The number and percentage of participants, with exact 95% CIs, reporting administration site solicited events (pain, erythema, swelling) will be summarized separately for any grades, Grade 3 and medically attended

events during the 7-day follow-up period (i.e., the day of vaccination and 6 subsequent days) and 4-day follow-up period following each dose and overall and overall participant. This summary will also be repeated by age group.

- The number and percentage of participants, with exact 95% CIs, reporting systemic solicited events (fever, headache, fatigue, myalgia, arthralgia) will be summarized separately for any grades, Grade 3 and medically attended events during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days), 7 day follow-up period and 4-day follow-up period following each dose, overall dose, and overall participant. This summary will also be repeated by age group.
- Duration in days of solicited events will be summarized as follows:

  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 (including grade 3):

  - 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.
  - If a solicited event intensity is still Grade > 0 at day 30, then end date will be considered equal to vaccination date + 29 days.
  - The number of days with grade 3 solicited symptom will be defined considering each day with a known grading=3, irrespective of whether the days are consecutive.

- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments in applicable systemic event summaries.
- The percentage of participants with each solicited administration site event and solicited systemic event (any grade and Grade 3) will be represented graphically for each group after each dose, during the 4-day and 7-day follow-up period.
- All solicited administration site events will be included in a listing.
- All solicited systemic events will be included in a listing.
- Sensitivity analysis will be performed to present differences in severity/intensity scales between participant and principal investigator assessments for solicited events: erythema, swelling and fever. All summaries and

listings aside from this sensitivity analysis are based on the participant assessments – only the sensitivity outputs will be based on the investigator assessment. This will be summarized separately for the solicited administration site events (erythema and swelling) and for the solicited systemic event (fever). The differences between participant and principal investigator assessments will be included in a listing.

16.1.1.1. ENDPOINT LEVEL COMPLIANCE

The study protocol defines a 7-day solicited AE follow-up period.

In terms of compliance for each of Days 1-7, the number/percentage of completed eDiaries will be summarized by study group and by dose, using a frequency table. The denominator for each day will be the number of expected completed eDiaries (i.e., the number of participants).

For compliance of each day beyond Day 7, and for each solicited symptom, the number/percentage of completed eDiaries will be summarized by study group and by dose, using a frequency table. In this summary, the denominator for each symptom will be the number of expected completed diaries (i.e., the number of participants with the symptom on the previous days) and the numerator will be the number of participants with eDiaries completed among the participants contributing to the denominator.

16.1.2. Unsolicited Adverse Events

All unsolicited adverse events summaries will be reported by MedDRA SOC, HLT and PT.
The verbatim reports of unsolicited AEs will be reviewed by a physician 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 above analysis by dose will also be performed.
Unsolicited events will be summarized and listed as:

- 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 will be tabulated by group and by MedDRA SOC, HLT and PT. This summary will be repeated by age group.
  - This summary will be repeated for:
  - Grade 3 unsolicited AEs
  - Considered Causally related by investigator unsolicited AEs
  - Grade 3 considered causally related by investigator unsolicited AEs
  - Unsolicited AEs resulting in a medically attended visit

The above analysis by dose will also be performed.

- 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 will be tabulated by group and by MedDRA SOC, HLT and PT, following each dose.
  - This summary will be repeated for:
    - Grade 3 non-serious AEs (this summary will be repeated by age group)
    - Considered Causally related by investigator non-serious unsolicited AEs
    - Considered Causally related by investigator, Grade 3 non-serious unsolicited AEs
    - Non-serious unsolicited AEs resulting in a medically attended visit
- The number and percentage of participants, with exact 95% CIs, with any unsolicited AEs with onset within 30-minutes of any dose will be tabulated by group and by MedDRA SOC, HLT and PT, following each dose. This summary will be repeated for Grade 3 only unsolicited AEs.
- The number and percentage of participants, with exact 95% CIs, by each AE category (including unsolicited AEs within 30 days of any dose, Grade 3/related/Grade 3 related/medically attended unsolicited AEs within 30 days of any dose, non-serious AEs, serious AEs, pIMDs, fatal serious AEs) will be tabulated by group.

- All of the summaries for unsolicited AEs during the 30-day follow-up period and non-serious unsolicited AEs during the 30-day follow-up period will be repeated by visit.
- A list of unsolicited AEs leading to study discontinuation or vaccine discontinuation (for Control group only) from dose 1 up to the study end will be tabulated by study intervention group (Co-Ad and Control) for each study intervention administration (RSVPreF3 OA, PCV20), by MedDRA, SOC, HLT and PT.
- All unsolicited AEs will be included in a listing.

16.1.3. Solicited and Unsolicited Adverse Events

For clinicaltrials.gov and EudraCT posting purposes, the following summary will be produced:

- The number of occurrence and the number and percentage of participants, with exact 95% CIs, of combined solicited and unsolicited non-serious adverse events (any grades, Grade 3, medically attended) during the 4-day (i.e., the day of vaccination and 3 subsequent days), 7-day (i.e., the day of vaccination and 6 subsequent days), and 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) will be tabulated by MedDRA primary SOC and PT, following each dose and overall dose and overall.
- 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 of any dose will be produced by SOC and PT.

- For web posting purposes, the number of occurrences and the number and percentage of participants with serious AEs, related serious adverse events, fatal serious adverse events, related fatal serious AEs during the 30 day follow up period of any dose will be produced by SOC and PT. Summary of all-cause mortality will also be presented by SOC and PT.

16.1.4. Serious Adverse Events

Analysis of serious adverse events (SAEs) from first vaccination (Visit 1, Day 1) up to 6 months **post-last vaccination**, the reporting period will start at vaccination and will end at approximately 6 months post last vaccination received for Co-Ad group participants (i.e., 180-210 days post last-dose) and approximately 6 months post last vaccination received for Control group participants. SAEs will be summarized by MedDRA SOC, HLT and PT.

SAEs will be summarized and listed as:

- The number and percentage of participants, with exact 95% CIs, with at least one report of SAE with onset after each vaccine administration up to study end (i.e., 6 months post-last vaccination). This summary will be repeated for: This summary will be repeated for:
  - Considered Causally related by investigator SAEs
  - Fatal SAEs
- All SAEs will be included in a listing.
- All SAEs leading to study discontinuation or vaccine discontinuation at any point from first vaccination up to study end will be included in a listing and a tabulated listing.

16.1.5. pIMDs

For analysis of pIMDs from first vaccination (Visit 1, Day 1) up to 6 months **post-last vaccination**, the reporting period will start at vaccination and will end at 6 months post-**last vaccination** (i.e., day of last vaccination+[180-210]). pIMDs will be summarized by MedDRA SOC, HLT and PT.

pIMDs will be summarized and listed as follows:

- The number and percentage of participants, with exact 95% CIs, with at least one report of pIMD (all pIMDs, considered causally related by investigator separately) with onset after each vaccine administration up to study end (i.e., 6 months post-last vaccination) will be summarized.

- All pIMDs will also be described in detail in a listing and in a tabulated listing of pIMDs leading to discontinuation of study will be provided. Classification by new onset vs exacerbations of pIMDs will also be presented.
- The number and percentage of participants, with exact 95% CIs, with at least one report of neurological demyelinating disorder with onset within 30 days of any dose will be summarized. This summary will be repeated for serious neurological demyelinating disorder with onset after each vaccine administration up to study end.

17. DATA NOT SUMMARIZED OR PRESENTED

The other variables and / or domains not summarized or presented are:

- Physical Examination

These domains and / or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

18. REFERENCES

Clopper CJ, 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.

Nauta J. Statistics in Clinical Vaccine Trials. 2010. Heidelberg: Springer.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the following:

Document Headers
All TFL is to include the following header:
Vaccine: RSVPreF3 OA (RSV OA=ADJ-019)
Study 219276 – DELIVERY DESIGNATION

where delivery designation is the name of the current delivery, e.g., DRY RUN, INTERIM ANALYSIS, FINAL ANALYSIS, etc.

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English US

Presentation of Study Intervention Groups

For outputs, intervention groups will be represented as follows and in the given order:

Study Intervention Group	For Tables and Figures	For Listings (include if different to tables)
Co-Ad	Co-Ad	Co-Ad
Control	Control	Control

Presentation of Visits

For outputs, Co-Ad group visits will be represented as follows and in that order:

Long Name (default)	Short Name
Visit 1 (Day 1)	Day 1
Visit 2 (Day 31)	Day 31

For outputs, Control group visits will be represented as follows and in that order:

Long Name (default)	Short Name
Visit 1 (Day 1)	Day 1
Visit 2 (Day 31)	Day 31
Visit 3 (Day 61)	Day 61

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized study intervention group (or intervention received if it's a safety output), first by Co-Ad group then Control group,
- Center-participant ID,
- Date (where applicable).

DECIMAL PLACES

Decimal places for categorical data

- For percentages one decimal will be displayed
- Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

Decimal places for Demographic and baseline characteristics will be as follows:

The mean, median, and SD for continuous baseline characteristics (age) will be presented with one decimal.

Serological Summary Statistics

The number of decimals used when displaying GMTs/GMCs and their CIs is shown in the following table:

GMT/GMC value	Number of decimals
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMT/GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e., the one with the higher number of decimals). For example, if GMT/GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

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

APPENDIX 2. PARTIAL DATE CONVENTIONS

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

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

- AE 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.
- AE 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.
- AE 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.
- AE 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 date will follow the rules above.

Imputed dates will NOT be presented in the listing.

AEs with any missing category details will not be replaced.

APPENDIX 3. LLOQ AND ULOQ VALUES FOR OP AB TITERS FOR MOPA AND LLOQ AND ULOQ VALUES FOR RSV-A AND RSV-B TITERS AND CONCENTRATIONS

LLOQ and ULOQ values for OP Ab Titers for MOPA

CCI

[redacted]

LLOQ and ULOQ values for RSV-A and RSV-B, Titers and Concentrations

CCI

[redacted]