Statistical Analysis Plan

Study ID: 219331

Official Title of Study: A Phase III, open-label, randomized, controlled, multicountry study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with Herpes Zoster recombinant subunit (HZ/su) vaccine in adults aged 50 years and older.

NCT number: NCT05966090

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STATISTICAL ANALYSIS PLAN

219331 (RSVPreF3 OA) (RSV OA=ADJ-020)

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 Herpes Zoster recombinant subunit (HZ/su) vaccine in adults aged 50 years and older.

AUTHOR: PPD

VERSION NUMBER AND DATE: V3.0, 23JUL2024

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V3.0 (Dated 23JUL2024) for Protocol 219331.

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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.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	03MAY2023	PPD	Not Applicable – First Version
2.0	27MAR2024	PPD	* Removed 'antibody' word throughout except for sections 3 & 6.6 * Section 10 updated to add in additional age group >= 75 for demography summaries only * Section 15.2.3 updated to remove immunogenicity by age group summaries * Section 16.1.1 re-worded to become clearer with which summaries and listings will be produced * Neurological demyelination pIMD summaries added in * Safety listings added in for: - SAEs leading to study discontinuation or vaccine discontinuation, and - solicited administration site and systemic events leading to study discontinuation or vaccine discontinuation Addition of safety sensitivity analysis for solicited administration site events and solicited systemic events as assessment by principal investigator *AEs duration definition edited and duration tables/figures required have changed. *Systemic solicited events will now be summarized by visit, not by dose.

			*Subgroup tables (race, ethnicity, gender) added for specific secondary immunogenicity and safety endpoints
3.0	23JUL2024		Sections 10 and 16.1.4 updated to account for Web posting purpose tables for demography summary and adverse events summaries respectively. Summary 16.1.2 eDiary compliance ongoing beyond Day 7 tables added. Appendix 3 added for LLOQ and ULOQ values for immunogenicity endpoints.

Table of Contents

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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
GMC	Geometric mean concentration
GMT	Geometric mean titers
HLT	High level term
HZ/su	Herpes zoster subunit
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean geometric increase
NAb	Neutralizing antibodies
OA	Older adults
PD	Protocol deviations
PDMP	Protocol Deviations Management Plan
PI	Principal investigator
pIMD	Potential immune-mediated disease
PPS	Per protocol set
PreF3	PreFusion protein 3

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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 analysis for Protocol 219331 (RSVPreF3 OA) (RSV OA=ADJ-020). 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 version 2.0 dated 17 April 2023.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. Primary Objectives

The primary objectives are:

- To demonstrate non-inferiority of the humoral immune response to two doses of Herpes Zoster recombinant subunit (HZ/su) vaccine when the first dose of HZ/su vaccine is co-administered with the respiratory syncytial virus (RSV) PreFusion protein 3 (PreF3) Older Adult (OA) (RSVPreF3 OA) investigational vaccine, compared to two doses of the HZ/su vaccine administered alone
- To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the first dose of HZ/su vaccine, compared to RSVPreF3 OA investigational vaccine administered alone.

Note: Zoster and RSV-A related endpoints will be assessed as co-primary. RSV-B related endpoints will be assessed as sequential to the success of Zoster and RSV-A.

2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the anti-gE humoral immune response to two doses of HZ/su vaccine, when the first dose of HZ/su vaccine is co-administered with RSVPreF3 OA investigational vaccine or administered alone.
- To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the first dose of HZ/su vaccine or administered alone.

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- To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and the HZ/su vaccine, co-administered or administered alone.

2.3. Statistical Hypotheses

The study includes the following confirmatory primary objectives.

- To demonstrate non-inferiority of the humoral immune response to two doses of HZ/su vaccine when the first dose of HZ/su vaccine is co administered with RSVPreF3 OA investigational vaccine, compared to two doses of HZ/su vaccine administered alone in terms of anti-gE antibodies concentration geometric mean concentration (GMC) ratio at 1-month after the second HZ/su vaccine dose (i.e., at Day 91 [Visit 4] for both study intervention groups).

  Null hypothesis vs. Alternative hypothesis:

  $$H_0: \mu_{Control\ group} - \mu_{Co-Ad\ group} > \log 10(1.5)\ vs.\ H_a: \mu_{Control\ group} - \mu_{Co-Ad\ group} \leq \log 10(1.5)$$

  where μ represents the estimated mean of log10 transformed antibody concentration at 1-month after the second HZ/su 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 GMC ratio (Control group versus Co-Ad group) in anti-gE antibody concentration 1-month after the second HZ/su vaccine dose ≤ 1.5.

- To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the first dose of HZ/su vaccine, compared to RSVPreF3 OA investigational vaccine administered alone in terms of:
  - RSV-A neutralzing titers expressed as geometric mean titer (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:

  $$H_0: \mu_{Control\ group} - \mu_{Co-Ad\ group} > \log 10(1.5)\ vs.\ H_a: \mu_{Control\ group} - \mu_{Co-Ad\ group} \leq \log 10(1.5)$$

  where μ represents the estimated mean of log10 transformed RSV-A neutralizing titers at 1 month after

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the RSVPreF3 OA investigational vaccine dose. The null hypothesis will be rejected if the upper limit of the two-sided 95% CI for the study intervention group GMT ratio (Control group versus Co-Ad group) in RSV-A neutralizing titers 1-month after the RSVPreF3 OA investigational vaccine dose ≤ 1.5.

– RSV-B neutralzing titers expressed as geometric mean titer (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:

$H_0: \mu_{Control\ group} - \mu_{Co-Ad\ group} > \log 10(1.5)\ vs.\ H_a: \mu_{Control\ group} - \mu_{Co-Ad\ group} \leq \log 10(1.5)$

where μ represents the estimated mean of log10 transformed RSV-B neutralizing 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% CI for the study intervention group GMT ratio (Control group versus Co-Ad group) in RSV-B neutralizing titers 1-month after the RSVPreF3 OA investigational vaccine dose $\leq$ 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 (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 years of age (YOA)	GMCs for anti-gE antibody (Ab) concentrations.	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition prior to Visit 4 blood sampling 4. HZ/su vaccine doses or blood samples for anti-gE antibody concentrations (for baseline or testing) taken out of window	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.	The least square point estimate and its 2-sided 95% CI for between group GMC ratio derived from an ANCOVA model which includes the treatment group and the age category (age at vaccination: 50 to 59, 60 to 69, or ≥ 70) as fixed effects, and the pre-vaccination log10 transformed titer as covariate, in terms of enzyme linked immunosorbent assay (ELISA) antibody concentration for gE between the Control group over Co-Ad group at 1-month after the second HZ/su vaccination (i.e., at

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				5. No pre / post-vaccine immunogenicity results for anti-gE antibody concentrations available		Day 91 for both Co-Ad and Control groups)
Primary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	GMTs for RSV-A neutralizing titers	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and Visit 3 for Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition prior to 30 days after vaccine administration (Visit 4 for Co-Ad and Visit 3 for Control group) 4. RSVPreF3 OA investigational vaccine or	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.	The least square point estimate and its 2-sided 95% CI for between group GMT ratio derived from an ANCOVA model which includes the treatment group and the age category (age at vaccination: 50 to 59, 60 to 69, or ≥ 70) as fixed effects, and the pre-vaccination log10 transformed titer as covariate, in terms of RSV-A neutralizing titers between Control group over Co-Ad group at 1-month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for Co-Ad group, and at Day 61 for Control group).

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				blood sample for RSV neutralizing titers (for baseline or testing) taken out of window 5. No pre / post-vaccine immunogenicity results for RSV-A neutralizing titers available		
Primary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	GMTs for RSV-B neutralizing titers	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and Visit 3 for Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition prior to 30 days after vaccine administration (Visit 4 for Co-	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.	The least square point estimate and its 2-sided 95% CI for between group GMT ratio derived from an ANCOVA model which includes the treatment group and the age category (age at vaccination: 50 to 59, 60 to 69, or ≥ 70) as fixed effects, and the pre-vaccination log10 transformed titer as covariate, in terms of RSV-B neutralizing titers between Control group over Co-Ad group at 1-month after the

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				Ad group and Visit 3 for Control group) 4. RSVPreF3 OA investigational vaccine or blood sample for RSV neutralizing titers (for baseline or testing) taken out of window 5. No pre / post-vaccine immunogenicity results for RSV-B neutralizing titers available	5. Participant excluded from the immunogenicity analysis.	RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for Co-Ad group, and at Day 61 for Control group).
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	Seropositivity rate for anti-gE antibody concentrations	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and 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	Seropositivity rate with exact 95% CI for the anti-gE antibody concentration at pre-vaccination and at 1-month post-second dose of HZ/su vaccine (Visit 4 for Co-Ad group and Control group)

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				3. Prohibited medication or intercurrent medical condition prior to Visit 4 blood sampling 4. HZ/su vaccine doses or blood samples for anti-gE antibody concentrations (for baseline or testing) taken out of window 5. No pre / post-vaccine immunogenicity results for anti-gE antibody concentrations available	analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	GMC for anti-gE antibody concentrations	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or	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	GMCs with 95% CI for the anti-gE antibody concentration at pre-vaccination and at 1-month post-second dose of HZ/su vaccine (Visit 4 for Co-Ad group and Control group)

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				intercurrent medical condition prior to Visit 4 blood sampling 4. HZ/su vaccine doses or blood samples for anti-gE antibody concentrations (for baseline or testing) taken out of window 5. No pre / post-vaccine immunogenicity results for anti-gE antibody concentrations available	analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	Mean Geometric Increase (MGI) for anti-gE antibody concentrations	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition	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.	MGIs of the within participants ratios with 95% CI for the anti-gE antibody concentration at 1-month post-second dose of HZ/su vaccine (Visit 4 for Co-Ad group and Control group) over pre-vaccination.

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				prior to Visit 4 blood sampling 4. HZ/su vaccine doses or blood samples for anti-gE antibody concentrations (for baseline or testing) taken out of window 5. No pre / post-vaccine immunogenicity results for anti-gE antibody concentrations available	4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	Vaccine response rate (VRR) for anti-gE antibody concentrations	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and for Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition	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	VRR for anti-gE antibody concentration with exact 95% CIs at 1-month post-second dose of HZ/su vaccine (Visit 4 for Co-Ad group and Control group) over pre-vaccination (see Section 6.6 for definition of VRR)

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				prior to Visit 4 blood sampling 4. HZ/su vaccine doses or blood samples for anti-gE antibody concentrations (for baseline or testing) taken out of window 5. No pre / post-vaccine immunogenicity result for anti-gE antibody concentrations available	the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	GMTs for RSV-A neutralizing titers.	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and Visit 3 for Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition	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	GMT ratio in terms of RSV-A neutralizing titers at pre-vaccination and at 1-month after the RSVPreF3 investigational vaccine (Visit 2 for Co-Ad group; Visit 3 for Control group)

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				prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and Visit 3 for Control group) 4. RSVPreF3 OA investigational vaccine or blood sample for RSV neutralizing titers (for baseline or testing) taken out of window 5. No pre / post-vaccine immunogenicity results for RSV-A neutralizing titers available	the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately	Adults aged ≥ 50 YOA	MGI for RSV-A neutralizing titers	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and Visit 3 for Control group)	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis.	MGIs of the within participants ratios for the RSV-A neutralizing titers at 1-month after the RSVPreF3 OA dose (Visit 2 for Co-Ad group; Visit 3 for the Control group) over pre-

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	(Control)			2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition (Visit 4 for Co-Ad group and Visit 3 for Control group) 4. RSVPreF3 OA investigational vaccine or blood sample for RSV neutralizing titers (for baseline or testing) taken out of window 5. No pre / post-vaccine immunogenicity results for RSV-A neutralizing titers available	3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	vaccination.
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered	Adults aged ≥ 50 YOA	GMTs for RSV-B neutralizing titers	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from	GMT ratio in terms of RSV-B neutralizing titers at pre-vaccination and at 1-month after the RSVPreF3 investigational vaccine (Visit 2 for

	(Co-Ad) or received separately (Control)			Ad group and Visit 3 for Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and Visit 3 for Control group) 4. RSVPreF3 OA investigational vaccine or blood sample for RSV neutralizing titers (for baseline or testing) taken out of window 5. No post-vaccine immunogenicity results for RSV-B neutralizing titers available	the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	Co-Ad group; Visit 3 for Control group).

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Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	MGI for RSV-B neutralizing titers	1. Permanently discontinued from study due to any reasons prior to 30 days after vaccine administration (Visit 4 for Co-Ad group and Visit 3 for Control group) 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition (Visit 4 for Co-Ad group and Visit 3 for Control group) 4. RSVPreF3 OA investigational vaccine or blood sample for RSV neutralizing titers (for baseline or testing) taken out of window 5. No pre / post-vaccine immunogenicity results for	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.	MGIs of the within participants ratios for the RSV-B neutralizing titers at 1-month after the RSVPreF3 OA dose (Visit 2 for Co-Ad group; Visit 3 for the Control group) over pre-vaccination.

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				RSV-B neutralizing titers available		
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	Solicited administration site events 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 administration site events within 7 days after each vaccine administration (Days 1-7 after each vaccine, HZ/su 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 (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 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, HZ/su and RSVPreF3 OA [i.e., date of RSVPreF3 OA vaccine administration for Control group

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						becomes Day 1 for recording events within 7 days]).
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	Each unsolicited adverse event within 30 days after each 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 dose/the dose of study intervention (Days 1-30 after each vaccine, HZ/su and RSVPreF3 OA [i.e., date of RSVPreF3 OA vaccine administration for Control group becomes Day 1 for recording events within 30 days])
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately	Adults aged ≥ 50 YOA	Each serious adverse event (SAE) up to study end (6 months after last vaccination)	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 all SAEs after last dose of study intervention up to study end (Days 1-183 after each vaccine [i.e., date of RSVPreF3 OA vaccine administration for Control

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	(Control)					group becomes Day 1 for recording events within 6 months]).
Secondary	RSVPreF3 OA (one dose) and HZ/su (two doses) co-administered (Co-Ad) or received separately (Control)	Adults aged ≥ 50 YOA	Each Potential Immune-Medicated Disease (pIMD) event up to study end (6 months after last vaccination)	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 all pIMDs up to study end (Days 1-183 after each vaccine [i.e., date of RSVPreF3 OA vaccine administration for Control group becomes Day 1 for recording events within 6 months])

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2.5. Sample size determination

The target enrollment will be approximately 530 participants (approximately 265 in the Co-Ad group and approximately 265 in the Control group) to obtain approximately 450 evaluable participants (approximately 225 in the Co-Ad group and approximately 225 in Control group) for the evaluation of the primary objectives, assuming that approximately 15% of the enrolled participants will not be evaluable (participants withdrawn or excluded from the PPS).

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 Non-Inferiority Objectives: Assuming 225 Evaluable Subjects in Each Group

Endpoint	Standard deviation of log_{10} concentration	Reference ratio	Non inferiority margin	Type II error	Power
HZ/su vaccine Non-inferiority* (1-sided test with alpha=2.5%)					
GMCs Anti-gE ELISA Ab	0.35	1.05	1.5	0.3%	99.7%
RSVPreF3 OA investigational vaccine Non-inferiority* (1-sided test with alpha = 2.5%)					
GMTs RSV-A neutralizing titer	0.45	1.05	1.5	4.6%	95.4%
GMTs RSV-B neutralizing titer	0.45	1.05	1.5	4.6%	95.4%
Global Power and Global Type II error				9.5%	90.5%

Abbreviations: Ab=antibody; ELISA=enzyme linked immunosorbent assay; gE=varicella zoster virus -glycoprotein

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E; GMC=geometric mean concentration; GMT=geometric mean titer; HZ/su=herpes zoster/subunit; RSV-A=respiratory syncytial virus subtype A; RSV-B=respiratory syncytial virus subtype B.
*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 RSVPreF3 OA investigational vaccine: non-inferiority limit = 1.5 (log10[1.5] = 0.176)
For HZ/su vaccine: non-inferiority limit = 1.5 (log10[1.5] = 0.176)
Reference Ratio= 1.05 (log10[1.05] = 0.021)

Considering a slight interference of 1.05 for the reference ratio in favor of the control group versus Co-Ad group with a common population standard deviation of 0.45 for the log10 transformed RSV-A/RSV-B neutralizing titer and 0.35 for the log10 transformed HZ/su anti-gE Ab GMC, the study has at least 90.5% power to meet the primary objectives.

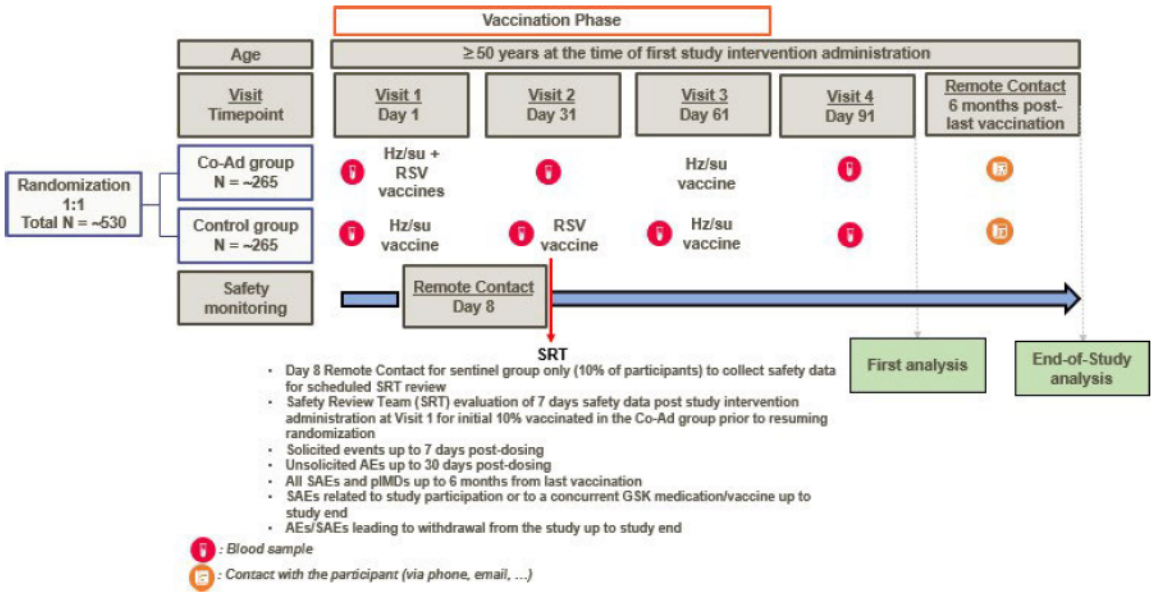
3. STUDY DESIGN

3.1. General Description

This is a phase III, open-label, randomized, controlled, multi-country study in medically stable older adults of ≥ 50 YOA with two parallel groups. Participants will be randomly assigned to 2 study groups at Visit 1 (Day 1):

- Co-administration (Co-Ad) group: Study interventions will be administered on Visit 1 (Day 1) in which participants will receive both HZ/su vaccine and RSVPreF3 OA investigational vaccine; and on Visit 3 (Day 61) in which the second dose of HZ/su vaccine will be administered. A total of four site visits (Visit 1 [Day 1], Visit 2 [Day 31], Visit 3 [Day 61] and Visit 4 [Day 91]) and a remote contact 6 months post-last vaccination are needed.
- Control group: Study interventions will be administered on Visit 1 (Day 1) in which participants will receive HZ/su vaccine, Visit 2 (Day 31) in which participants will receive RSVPreF3 OA investigational vaccine; and Visit 3 (Day 61) in which participants will receive the second dose of HZ/su vaccine. A total of four site visits (Visit 1 [Day 1], Visit 2 [Day 31], Visit 3 [Day 61] and Visit 4 [Day 91]) and a remote contact 6 months post-last vaccination are needed.

Figure A: Study Schema



Abbreviations: AE=Adverse Event; Co-Ad group=Co-Administration group; D=Day; Hz/su=herpes zoster recombinant subunit; GSK=GlaxoSmithKline; N=Number of participants; pIMD=potential Immune-Mediated Disease; RSV=RSVPreF3 OA investigational vaccine; SAE=Serious Adverse Event.

Medically stable older adults ≥ 50 YOA will be enrolled in this study according the inclusion and exclusion crtieria (see protocol Section 5.0). Approximately 530 participants will be randomly assigned to the 2 study intervention groups in a 1:1 ratio prior to intervention to provide approximately 265 enrolled participants in each study intervention group.

The randomization algorithm will use a minimization procedure accounting for age (50-59, 60-69, or ≥ 70 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 30% of participants 50 to 59 YOA, approximately 30% of participants 60 to 69 YOA, and approximately 25% of participants ≥ 70 YOA. The remaining 15% will be distributed freely across the three age categories.
- Approximately 40% of participants from each sex. The remaining 20% can be distributed freely between the 2 sexes.

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Table B: Study Groups

Study groups	Number of participants	Age (min)	Study interventions
Co-Ad	265	≥ 50 years	RSVPreF3 OA and first of two doses of HZ/su vaccine co-administered, second dose of HZ/su administered separately
Control	265	≥ 50 years	One dose of RSVPreF3 OA investigational vaccine and two doses of HZ/su vaccine all administered separately

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

- Co-Ad study intervention group: Total duration is approximately 8 months. There will be 4 study visits on site: Visit 1 on Day 1, when the participants receive study intervention (both RSVPreF3 OA and HZ/su as co-administered), Visit 2 on Day 31 when blood sampling for RSVPreF3 OA vaccine antibody testing will be performed, Visit 3 (Day 61) in which the second dose of HZ/su vaccine will be administered, and Visit 4 (Day 91) when blood sampling for HZ/su vaccine antibody testing will be performed. A safety follow-up visit will be made to the participant on Day 243 (i.e., 6 months after last vaccine is received) via telephone or by any other convenient means of communication.
- Control study intervention group: Total duration is approximately 8 months. There will be 4 study visits on site: Visit 1 on Day 1, when the participants receive HZ/su vaccine, Visit 2 on Day 31 when the participants receive RSVPreF3 OA vaccine, Visit 3 on Day 61 when HZ/su vaccine will be administered and blood sampling for RSVPreF3 OA vaccine antibody testing will be performed, and Visit 4 (Day 91) when blood sampling for HZ/su vaccine antibody testing will be performed. A safety follow-up visit will be made to the participant on Day 243 (i.e., 6 months after last vaccine is received) via telephone or by any other convenient means of communication.

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

The following analyses will be performed for this study:

- First Analysis
- End of Study (EOS) Analysis

All planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this SAP, Database Lock and Sponsor Authorization of Analysis Sets.

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

The first analysis, including reactogenicity, safety, and final immunogenicity data, is planned when data for at least primary and secondary endpoints up to and including Visit 4 (Day 91) for the Co-Ad and the control group, are available for all participants.

4.3. EOS Analysis

The EOS analysis includes all data obtained until 6 months post-last dose.

This SAP is focused / limited to planned first and EOS analyses. Outputs required for the first analyses will be flagged in the tables, figures and listings (TFL) mock shells document.

5. ANALYSIS SETS

Agreement and authorization of participants included / excluded from each analysis set will be conducted prior to production for the first 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.
- 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 entered the study who were randomized or received study intervention or underwent a post-screening study 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 at least one study intervention. Analysis per group is based on the study intervention administered (i.e., study intervention actually received).

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 all the 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 blood sample post HZ/su vaccine dose 2 vaccination for 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 blood sample post HZ/su vaccine dose 2 vaccination for Co-Ad group (i.e., control group subjects need to meet all above criteria at Visits 2 and 3; Co-Ad group subjects need to meet all above criteria at Visits 1, 2, 3 and 4).

HZ/su PPS:

All eligible participants in the ES:

- who received two doses of HZ/su vaccine as per protocol in the control group and received all the study interventions in the Co-Ad group
- who had immunogenicity results pre- and post-dose for anti-gE antibody concentrations
- who complied with blood draw interval for zoster samples
- without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination* up to blood sample post HZ/su vaccine dose 2 vaccination, and
- did not meet any of the criteria for elimination up to blood sample post HZ/su vaccine dose 2 vaccination (i.e., control group subjects need to meet all above criteria at Visits 1, 3 and 4; Co-Ad group subjects need

to meet all above criteria at Visits 1, 2, 3 and 4).

*Intercurrent medical conditions that may lead to elimination from the PPS are defined as confirmed immunodeficiency condition.

6. GENERAL CONSIDERATIONS

Data will be summarized descriptively.

For categorical data: N, percentage.

For continuous data: N, mean, SD, median, maximum, minimum.

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 SCR.

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 the day of the first dose of each study vaccination, which is Day 1 for all participants. 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. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

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) and window conventions are included in Table E (Co-Ad group and Control group).

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

Interval	Planned visit interval	Allowed interval range*
Visit 1 (Day 1) → Remote Contact (Day 8)*	8 days	-
Visit 1 (Day 1) → Visit 2 (Day 31)	30 days	30-42 days
Visit 1 (Day 1) → Visit 3 (Day 61)	60 days	60-84 days
Visit 3 (Day 61) → Visit 4 (Day 91)	30 days	30-42 days
Visit 3 → Phone contact	180 days	180-210 days

Note: Participants may not be eligible for the HZ/su and RSV Per Protocol Set (PPS) if the visits happen beyond this interval. Intervals between visits and phone contact do not affect HZ/su and RSV PPS eligibility.

*Day 8 Remote Contact is applicable to the sentinel group only.

Table D: Intervals between Study Visits (Control Group)

Interval	Planned visit interval	Allowed interval range*
Visit 1 (Day 1) → Remote Contact (Day 8)*	8 days	-
Visit 1 (Day 1) → Visit 2 (Day 31)	30 days	30-42 days
Visit 2 (Day 31) → Visit 3 (Day 61)	30 days	30-42 days
Visit 3 (Day 61) → Visit 4 (Day 91)	30 days	30-42 days
Visit 3 → Phone contact	180 days	180-210 days

Note: Participants may not be eligible for the HZ/su and RSV Per Protocol Set (PPS) if the visits happen beyond this interval. Intervals between visits and phone contact do not affect HZ/su and RSV PPS eligibility.

*Day 8 Remote Contact is applicable to the sentinel group only.

Table E: Window convention (Co-Ad Group and Control Group)

Assigned Study Day	Visit label as per protocol	Visit assigned
Day 1	Visit 1	Visit 1 (Day 1)
Day 31 (Day 1 + 30 to 42 days)	Visit 2	Visit 2 (Day 31)
Day 61 (Day 1 + 60 to 84 days)	Visit 3	Visit 3 (Day 61)
Day 91 (Day 1 + 90 to 126 days)	Visit 4	Visit 4 (Day 91)

[redacted]

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 least square point estimate and its 2-sided 95% CI will be derived from an ANCOVA model on log10 transformed concentration/titer. Covariate and factor included in the model are described in 7.1.

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 (mean geometric increase): The geometric mean of the within participant ratios of the post-dose concentration/titer over the pre-dose concentration/titer.

VRR for anti-gE post-second dose is defined as the percentage of participants who have at least:

A 4-fold increase post-vaccination anti-gE antibody concentration as compared to (over) the pre-vaccination anti-gE antibody concentration, for participants who are seropositive at pre-vaccination, or,

A 4-fold increase post-vaccination anti-gE antibody concentration as compared to (over) the anti-gE antibody cut-off value for seropositivity (97 mIU/mL), for participants who are seronegative at pre-vaccination.

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Seropositivity is defined as the percentage of participants whose concentration is greater than or equal to the assay cut-off value (97 mIU/mL).

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/LLOQ values but the exact value if the exact value is greater than ULOQ or below the LLOQ.

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 value for anti-gE antibody concentrations, and LLOQ and ULOQ values 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 (50 to 59, 60 to 69 or ≥ 70 YOA) and study intervention group (Co-Ad or Control). The following covariate will be used in the ANCOVA: pre-dose $\log_{10}$-transformed concentration/titer. 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 B in section 3.1) which will be performed in a 1:1 ratio prior to intervention to provide approximately 265 enrolled participants per study intervention group.

7.3. Missing Data

Missing data (missing, incomplete or partial dates, AE measurement [including missing AE severity and relationship], prior and concomitant medications and death date) will be handled as per 0 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:

First sequence:

- The upper limit (UL) of the 2-sided 95% CI of the GMC ratio between the Control group (at Day 91) versus Co-Ad group (at Day 91) for anti-gE Ab 1-month after the second HZ/su vaccine dose is ≤1.5.

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[redacted]

AND

- 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 titer one month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

Second sequence:

- 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 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 (50-59 YOA, 60-69 YOA, >= 70 YOA) will be performed for demography summaries based on ES and PPS. Subgroup analyses by age category, race, ethnicity and gender will be performed for secondary immunogenicity endpoints (anti-gE antibody concentrations, RSV-A and RSV-B titers only), solicited events within 7 days, unsolicited events and grade 3 unsolicited events within 30 days of each dose, serious AEs and pIMD up to study end (6 months after last dose) 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 will be accounted for in this study.

9.1. Disposition

Participant disposition for all analysis sets and both Per-protocol sets, withdrawals, and reasons for exclusion from each analysis set, including inclusion as well as exclusion criteria will be presented for the SCR, ENR and ES. Specifically, the number of participants, vaccinated, completed the study, discontinued from the study and the reason for discontinuation will be summarized by study intervention group and overall for the ES. Additionally, the number of participants returning for each visit for the ES will be presented.

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 First and EOS Analyses. A summary table presenting the number and percentage of participants with important PDs and most importantly those associated to elimination from PPS and the number and percentage of participants excluded from the PPS analyses will be presented for participants in the SCR by study intervention group and overall. A listing of all PDs including an indicator of those excluded from the PPS and an indicator of COVID-19 causality will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

- Age (years) – at the time of first study intervention
- Age category (50-59, 60-69, ≥70, ≥75 YOA)
- Sex
- Race (as per Clinical Data Interchange Standards Consortium [CDISC] categories)
- Ethnicity
- Country
- Center

For web posting purposes, the demographic characteristics will be presented for the enrolled set. In addition, the following age categories will be summarized: 18-64, 65-84, and >=85. If the summary of demographics meets the

[redacted]

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

Information both on Medical / Vaccination History will be summarized for the ES by group and will be reported, along with pregnancies, as tabular listing based on SCR respectively.

- 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.

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).

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.

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 summarized by group after each vaccine dose

[redacted]

and overall, with exact 95% CIs.

13. MEDICATIONS

The number and percentage of participants and doses using concomitant medication (any medication, any medical device, any antipyretic and any antipyretic taken prophylactically, respectively) during the 7-day follow-up period (i.e., on the day of last study intervention and 6 subsequent days) and during the 30-day follow-up period (i.e., on the day of last study intervention and 29 subsequent days), will be summarized by study intervention group for each study intervention administration and overall with exact 95% CIs for the ES. Concomitant medications will also be presented in listings.

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.

14. STUDY INTERVENTION EXPOSURE

Exposure to study intervention will be presented for the ES per study intervention group and overall. The date and time of study intervention administration will be taken from the eCRF "Study intervention administration" forms (separate forms for HZ/su and RSVPreF3 OA investigational vaccine). For dosing instructions and route, refer to Table 8 of the Protocol.

15. IMMUNOGENICITY OUTCOMES

The primary analysis will be based on the applicable PPS (i.e., RSV PPS or HZ/su PPS) for analysis of immunogenicity. If, in any study intervention group, the percentage of vaccinated participants with serological results excluded from the applicable 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:

- Anti-gE ELISA Ab concentrations (mIU/mL) expressed as between groups GMC ratio, 1-month after the second HZ/su dose (Day 91 for both Co-Ad group and Control group)
- RSV-A neutralizing titers (ED60) expressed as between groups GMT (ED60) ratio, 1 month after the RSVPreF3 OA investigational vaccine dose (Day 31 for Co-Ad group and at Day 61 for Control group)
- RSV-B neutralizing titers (ED60) expressed as between groups GMT (ED60), 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:

- Between groups GMC ratio for HZ/su vaccine between the Control group over Co-Ad group for gE Ab concentrations (IU/mL) at 1-month after the second HZ/su vaccination (i.e., at Day 91 for both Co-Ad and Control groups) and 2-sided 95% CI will be computed.
  - The least square point estimate and its 95% 2-sided CIs of the between group GMC ratio will be derived from an ANCOVA model on log10 transformed concentrations and presented alongside descriptive GMCs and 95% CIs. The ANCOVA model will include the treatment group and age category (age at vaccination: 50 to 69, 60 to 69, or ≥70 YOA) as fixed effects, and the pre-vaccination log10-transformed concentration as covariate. The results will be presented in tables as well as graphs using forest plots.
- Between group GMT ratio for RSV investigational vaccine between the Control group over Co-Ad group

for RSV-A neutralizing titers (ED60) at 1-month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for Co-Ad group, and at Day 61 for Control group) and 2-sided 95% CI will be computed.

  - The least square point estimate and its 95% 2-sided CIs will be derived from an ANCOVA model on log10 transformed titers and presented alongside descriptive GMTs and 95% CIs. The same ANCOVA model used for the HZ/su GMC ratio will be applied for this summary. The results will be presented in tables as well as graphs using forest plots.

- Between group GMT ratio for RSV investigational vaccine between the Control group over Co-Ad group for RSV-B neutralizing titers (ED60) at 1-month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for Co-Ad group, and at Day 61 for Control group) and 2-sided 95% CI will be computed.
  - The least square point estimate and its 95% 2-sided CIs will be derived from an ANCOVA model on log10 transformed titers and presented alongside descriptive GMTs and 95% CIs. The same ANCOVA model used for the HZ/su GMC ratio will be applied for this summary. The results will be presented in tables as well as graphs using forest plots.

A successful primary immunogenicity conclusion will require:

First sequence:

- The upper limit of the 2 sided 95% CI of the GMC ratio between the Control group (at Day 91) versus Co-ad group (at Day 91) for anti-gE Ab 1-month after the second HZ/su vaccine dose is ≤1.5.

AND

- The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-A neutralizing titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

Second sequence:

- The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-B neutralizing titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

Testing will progress in the second sequence only if the first sequence is a success, so that no further adjustment of alpha is required.

Note: For anti-gE antibody concentration summaries, pre-vaccination is at Visit 1 for Co-Ad group and for Control

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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.

15.1.4. Analysis for Primary Immunogenicity Variables

Sensitivity analysis will be performed on the primary immunogenicity endpoints using the same primary ANCOVA model with the treatment group and age category (age at vaccination: 50-59, 60-69 or ≥70 years) as fixed effects and the pre-vaccination log10-transformed concentration or titer as applicable, as regressors, and with the addition of center as a random effect.

A second sensitivity analysis for the primary immunogenicity endpoints for RSV-A/B will be performed as described in Section 15.1.3. on a modified PPS including participants who received only one dose of HZ/su vaccine in the Co-Ad group.

15.2. Secondary Immunogenicity

The primary analysis of secondary immunogenicity endpoints will be based on the applicable PPS (i.e., RSV PPS or HZ/su PPS) for analysis of immunogenicity. If, in any vaccine 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.

15.2.1. Secondary Immunogenicity Variables & Derivations

The secondary immunogenicity endpoints are:

- Anti-gE antibody concentrations expressed as seropositivity rate with exact 95% CI at pre-vaccination and at 1-month post-second dose of HZ/su vaccine
- Anti-gE antibody concentrations expressed as GMC with 95% CI at pre-vaccination and at 1-month post-second dose of HZ/su vaccine
- Anti-gE antibody concentrations expressed as MGI with 95% CI at pre-vaccination and at 1-month post-second dose of HZ/su vaccine.
- VRR with exact 95% CIs at 1-month post-second dose of HZ/su vaccine.
- RSV-A neutralizing titers expressed as GMT and RSV-A neutralizing concentrations expressed as GMC at

pre-vaccination and at 1-month after the RSVPreF3 OA investigational vaccine dose.

- 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 having a fold increase in RSV-A neutralizing titers/concentrations ≥4 and their 2-sided 95% CIs will be tabulated.
- MGI for within participants ratios of the post-dose titer/concentration (at 1-month after the RSVPreF3 OA investigational vaccine dose) over the pre-dose titer/concentration (or baseline) for RSV-A neutralizing titers/concentrations
- Percentage of participants having a fold increase in RSV-A neutralizing titers/concentrations ≥4 and their 2-sided 95% CIs will be tabulated and presented graphically.
- MGI for within participants ratios of the post-dose titer/concentration (at 1-month after the RSVPreF3 OA investigational vaccine dose) over the pre-dose titer (at baseline) for RSV-A neutralizing titers/concentrations.
- RSV-B neutralizing titers expressed as GMT and RSV-B neutralizing concentrations expressed as GMC at pre-vaccination and at 1-month after the RSVPreF3 OA investigational vaccine dose.
- 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.
- Percentage of participants having a fold increase in RSV-B neutralizing titers/concentrations ≥4 and their 2-sided 95% CIs will be tabulated and presented graphically.
- MGI for within participants ratios of the post-dose titers/concentrations (at 1-month after the RSVPreF3 OA investigational vaccine dose) over the pre-dose titer (at baseline) for RSV-B neutralizing titers/concentrations

For the derivation of seropositivity, MGI, and VRR refer to 6.6.

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

Missing data will not be replaced.

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15.2.3. Analysis of Secondary Immunogenicity Variables

The secondary immunogenicity endpoints will be analyzed as follows:

- Seropositivity rate with exact 95% CI of the post-second dose concentration (at 1-month post-second dose of HZ/su vaccine) over the pre-vaccination for anti-gE antibody concentrations (IU/mL).
- GMC and 95% CI at pre-vaccination and at post-second dose concentration (at 1-month post-second dose of HZ/su vaccine) for anti-gE antibody concentrations (IU/mL).
- MGI and 95% CI for within participants ratios of the post-second dose concentration (at 1-month post-second dose of HZ/su vaccine) over the pre-vaccination for anti-gE antibody concentrations (IU/mL).
- VRR with exact 95% CI of the post-second dose concentration (at 1-month post-second dose of HZ/su vaccine) over the pre-vaccination for anti-gE antibody concentrations (IU/mL).
- GMT/GMC at pre-vaccination and at the post-dose titers and concentration (at 1-month post-dose of RSVPreF3 OA investigational vaccine) for RSV-A neutralizing titers and concentration (ED60 and IU/ml) will be tabulated and presented graphically.
- MGI for within participants ratios of the post-dose titers and concentration (at 1-month post-dose of RSVPreF3 OA investigational vaccine) over the pre-vaccination for RSV-A neutralizing titers and concentration (ED60 and IU/ml).
- Percentage of participants above pre-defined assay cut-off for RSV-A neutralizing titers (ED60) and concentration (IU/mL) and their exact 95% CI will be tabulated
- Percentage of participants having a fold increase in RSV-A neutralizing titers (ED60) and concentration (IU/mL) ≥4 and their 2-sided 95% CIs will be tabulated.
- RSV-A titers (ED60)/concentration (IU/mL) will be displayed using reverse cumulative curves
- Between group GMC ratio for RSV investigational vaccine between the Control group over Co-Ad group for RSV-A neutralizing concentration (IU/mL) at 1-month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for Co-Ad group, and at Day 61 for Control group) and 2-sided 95% CI will be computed as:
    - The least squares point estimate and its 95% 2-sided CIs will be derived from an ANCOVA model on log10 transformed titers and presented alongside descriptive GMCs and 95% CIs. The same ANCOVA model used for the primary analysis HZ/su GMC ratio will be applied for this summary. The results will be presented in tables as well as graphs using forest plots
- GMT/GMC at pre-vaccination and at the post-dose titers and concentration (at 1-month post-dose of

RSVPreF3 OA investigational vaccine) for RSV-B neutralizing titers and concentration (ED60 and IU/ml) will be tabulated and presented graphically

- MGI for within participants ratios of the post-dose titers and concentration (at 1-month post-dose of RSVPreF3 OA investigational vaccine) over the pre-vaccination for RSV-B neutralizing titers and concentration (ED60 and IU/ml).
- Percentage of participants above pre-defined assay cut-off for RSV-B neutralizing titers (ED60) and concentrations (IU/mL) and their exact 95% CI will be tabulated
- Percentage of participants having a fold increase in RSV-B neutralizing titers (ED60) and concentration (IU/mL) ≥4 and their 2-sided 95% CIs will be tabulated.
- RSV-B titers (ED60)/concentration (IU/mL) will be displayed using reverse cumulative curves
- Between groups GMC ratio for RSV investigational vaccine between the Control group over Co-Ad group for RSV-B neutralizing concentration (IU/mL) at 1-month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for Co-Ad group, and at Day 61 for Control group) and 2-sided 95% CI will be computed.
    - The least squares point estimate and its 95% 2-sided CIs will be derived from an ANCOVA model on log10 transformed titers and presented alongside descriptive GMTs and 95% CIs. The same ANCOVA model used for the HZ/su GMC ratio will be applied for this summary. The results will be presented in tables as well as graphs using forest plots.
- Note: For anti-gE antibody concentration 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.
- Subgroup tables will be created for the anti-gE antibody concentrations (IU/mL). RSV-A titers (ED60) and RSV-B titers (ED60) for seropositivity, GMC/GMT, MGI and VRR, split by age category, race, ethnicity and gender.

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.

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Secondary Safety Endpoints

- Solicited events
    - Percentage of participants reporting each solicited administration site event (pain, erythema / redness, swelling) with onset within 4 days and 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, shivering/chills and gastrointestinal symptoms [nausea, vomiting, diarrhea and or abdominal pain]) with onset within 4 days and 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 (all 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
    - Percentage of participants reporting all SAEs after vaccine administration (Day 1) up to End of Study (EoS) (6 months after last vaccination)
- pIMDs
    - Percentage of participants reporting all 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).

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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 group 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 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. Also, in the case of co-administered study interventions, an administration site event recorded for a participant following multiple study interventions will be counted as only one occurrence.

Causality, as indicated by the Investigator is classed as "related" and "not related" to RSVPreF3 vaccine and to HZ/su vaccine. A "related" AE is an AE with reasonable probability of being related to the medicinal products in the opinion of the investigator. If a participant reports multiple events with different severity within that SOC / PT, then the subject will be counted only once at the worst-case relationship to study intervention for the number of subjects.

See APPENDIX 2 for handling of partial dates for AEs.

Summaries of events causally related to study intervention will be reported separately for each study intervention (RSVPreF3 OA and HZ/su).

Some of the key safety analysis will be generated by age group at first vaccination: 50-59 YOA, 60-69 YOA, and ≥70 YOA.

For clinicaltrials.gov and EudraCT posting purposes, percentage of participants of combined solicited and unsolicited non-serious adverse events during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) will be produced by System Organ Class and preferred terms and according to occurrence of each event.

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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 Erythema / Redness at Injection Site Swelling at Injection Site	Fever Headache Fatigue Myalgia Arthralgia Shivering/Chills Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)

Table I: Intensity scales for solicited events – pain, headache, fatigue, myalgia, arthralgia, shivering/chills and gastrointestinal symptoms

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

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Event	Intensity grade	Parameter
	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
Shivering/Chills	0	None
	1	Mild: Shivering that is easily tolerated
	2	Moderate: Shivering that interferes with normal activity
	3	Severe: Shivering that prevents normal activity
Gastrointestinal symptoms	0	None
	1	Mild: Gastrointestinal symptom that is easily tolerated
	2	Moderate: Gastrointestinal symptom that interferes with normal activity
	3	Severe: Gastrointestinal symptom that prevents normal activity

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

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

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
Shivering/Chills	10008531	Chills
Diarrhoea	10012735	Diarrhoea
Abdominal pain	10000081	Abdominal pain
Nausea	10028813	Nausea
Vomiting	10047700	Vomiting

Solicited events will be summarized and listed as:

- 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 4-day follow-up 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 by visit. These summaries will be repeated by age group.

- The number and percentage of participants, with exact 95% CIs, reporting each solicited events (administration site and/or systemic) will be summarized separately for all 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 will be summarized separately for all 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, overall dose and overall participant. This summary will be repeated by age group.
- The number and percentage of participants, with exact 95% CIs, reporting systemic solicited events will be summarized separately for all 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 visit and overall visits and overall participant. This summary will be repeated by age group.
- Duration in days of solicited events will be summarized as follows:
  - Duration (days) of solicited administration site events will be summarized following each dose and overall,
  - Duration (days) of solicited systemic events will be summarized following each visit and overall,
  - where duration for the above solicited events summaries is defined as:
    - Duration = (End date – Start date) + 1, for AEs with Grade > 0
      - If a solicited AE is still Grade > 0 at Day 30, the end date will be considered equal to vaccination date + 29 days.
- Number of days with Grade 3 solicited events will be summarized as follows:
  - Number of days with Grade 3 solicited administration site events will be summarized following each dose and overall,
  - Number of days with Grade 3 solicited systemic events will be summarized following each visit and overall,
  - where number of days with Grade 3 events is derived as the sum of all post-vaccine days with known Grade 3 for the events category (administration site events or systemic events), recorded up to Day 30 post-vaccine.
- 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.

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- 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.
- Subgroup analysis will be created for the solicited administration site events and the solicited systemic events within 7 days of each dose split by age category, race, ethnicity and gender.

16.1.2. 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 visit, 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 previous days) and the numerator will be the number of participants with eDiaries completed among the participants contributing to the denominator.

16.1.3. Unsolicited Adverse Events

All unsolicited adverse events summaries will be reported by MedDRA SOC, HLT, 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.

Unsolicited events will be summarized and listed as:

- The number and percentage of participants, with exact 95% CIs, with any unsolicited AEs during the 30-day follow-up period (i.e., the day of vaccination [per vaccination type, RSVPreF3 OA, or HZ/su] and 29 subsequent days) will be tabulated following each dose and overall. This summary will be repeated by age group.
  - This summary will be repeated for:

- Grade 3 unsolicited AEs
- Grade 3 non-serious unsolicited AEs
- Causally related unsolicited AEs
- Causally related, Grade 3 unsolicited AEs
- Unsolicited AEs resulting in a medically attended visit

The above analysis by visit will also be performed.

- The number and percentage of participants, with exact 95% CIs, with any non-serious unsolicited AEs during the 30-day follow-up period (i.e., the day of vaccination and 29 subsequent days) will be tabulated by group and by MedDRA SOC, HLT and PT, following each visit.
  - This summary will be repeated for:
    - Grade 3 non-serious AEs (this summary will be repeated by age group)
    - Causally related non-serious unsolicited AEs
    - Causally related, 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 unsolicited AEs.
- Subgroup analysis will be created for the unsolicited events and grade 3 unsolicited events within 30 days of each dose split by age category, race, ethnicity and gender.

All 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.

All unsolicited AEs will be included in a listing. All solicited (administration site and/or systemic AEs) and unsolicited AEs leading to study discontinuation or vaccine discontinuation will be included in a listing.

All atrial fibrillation events will be included in a listing.

16.1.4. Solicited and Unsolicited Adverse Events

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

16.1.5. 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 (i.e., day of last vaccination+[180-210]).

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:
  - Causally related 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.
- For web posting purposes, the number of occurrences and the number and percentage of participants with at least one SAE with onset after each vaccine administration up to study end (i.e, 6 months post-last vaccination) will be produced by SOC and PT. The same table will be produced for related SAE, fatal SAE and related fatal SAE.

Subgroup analysis will be created for the serious events up to study end (6 months after last dose) split by age category, race, ethnicity and gender.

16.1.6. pIMDs

For analysis of pIMDs, the reporting period will start at vaccination and will end at approximately 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:

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- The number and percentage of participants, with exact 95% CIs, with at least one report of pIMD (all pIMDs, causally related 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 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 pIMD with onset within 30 days of any dose will be summarized. This summary will be repeated for serious neurological demyelinating pIMDs with onset after each vaccine administration up to study end.

- Subgroup analysis will be created for the serious events up to study end (6 months after last dose) split by age category, race, ethnicity and gender.

16.1.7. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complications will be classed as AE or SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]). Pregnancies will also be listed.

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.

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-020)
Study 219331 – 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 and Control group visits will be represented as follows and in that order:

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

[redacted]

Long Name (default)	**Short Name**
Visit 2 (Day 31)	Day 31
Visit 3 (Day 61)	Day 61
Visit 4 (Day 91)	Day 91

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. HANDLING OF MISSING/PARTIAL DATA

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:

- 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 VALUE FOR ANTI-GE ANTIBODY CONCENTRATIONS, AND LLOQ AND ULOQ VALUES FOR RSV-A AND RSV-B TITERS AND CONCENTRATIONS

LLOQ value for Anti-GE Antibody Concentrations

	LLOQ value (unit)	ULOQ value (unit)
Anti-GE antibody concentrations	97 (mIU/mL)	

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

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