STATISTICAL ANALYSIS PLAN	
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A Phase 2, Randomized, Modified Double-Blind, Active Controlled Study to Characterize the Safety and Immunogenicity of IVX-A12 in Adults 60 Years of Age and Older

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LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units. Examples are provided below. These can be modified at study level.

Abbreviation or Specialized Term	Definition
AE	Adverse event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
CDL	Clinical Database Lock
CI	Confidence Interval
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
ECG	Electrocardiogram
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
hMPV	Human Metapneumovirus
IAS	Immunogenicity Analysis Set
IP	Investigational Product
IPD	Important Protocol Deviation
IRT	Interactive Response Technology
IV	Intravenous
LLoQ	Lower Limit of Quantification
MAAE	Medically-attended Adverse Events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measurements
nAb	Neutralizing Antibody
PD	Protocol Deviation
PDNC	Protocol Deviation and Non-compliance
PT	Preferred Term

Abbreviation or Specialized Term	Definition
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SIP	Study Integrity Plan
SOC	System Organ Class
ULoQ	Upper Limit of Quantification
VLP	Virus-like Particle

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	26 June 2024	Initial approved SAP	N/A	N/A
First amendment to SAP	27 Aug 2024	1 General update: "Arm" changed to "group" 2 Table 2 and Section 2: clarified description of Immunogenicity analysis set in Table 2 and added note in Section 2 regarding this change 3 Sections 3.2, Section 4.2.1.7, and Table 5: removed MN RSV A assay from primary analysis 4 Section 3.4: added language for presentation of CIs for subgroup analyses with small sample size 5 Sections 3.4.1 and 4.2.1.8: added definition of Baseline Tertiles to Sections 3.4.1 and 4.2.1.8 6 Section 4.1.11.1: further divided partially compliant (1-7 days completed) into partially compliant (6-7 days completed) and poorly compliant (1-5 days completed) 7 Section 4.6.2.1: removed language related to imputation of missing AE severity or AE relationship, and updated rules for summarizing AEs with missing intensity or missing relationship 8 Section 4.6.2.1: clarified calculation of duration for solicited ARs with missing stop dates 9 Section 4.6.2.2: changed threshold of duration for presenting number and percentage of participants who experience an AR from <=3 days to <=4 days 10 Section 4.6.2.2: removed statement related to presentation of unsolicited AEs by maximum severity. 11 Section 4.6.2.2: included a statement for presentation of unsolicited AEs by decreasing frequency on PT 12 Appendix A: added PT codes 13 Appendix B: for imputation of missing start day, removed statement related to "AE onset status on day of IP administration field"	Yes	1 Editorial update 2 Clarification on the immunogenicity analysis set definition 3 Clarification of assays used in primary analyses 4 Clarified presentation of CIs in analyses 5 Clarification on the calculation of tertiles 6 To align with definition of important PD for eDiary completion (i.e. >=3 is an IPD) 7 To minimize bias, missing AE severity or missing AE relationship will not be imputed 8 Clarification of calculation of duration 9 To align with competitor studies 10 Summary not needed for interpretation 11 Summary needed for interpretation of safety through Day 29 12 Updated to include additional potential intercurrent events 13 Removed as field is not collected in the eCRF

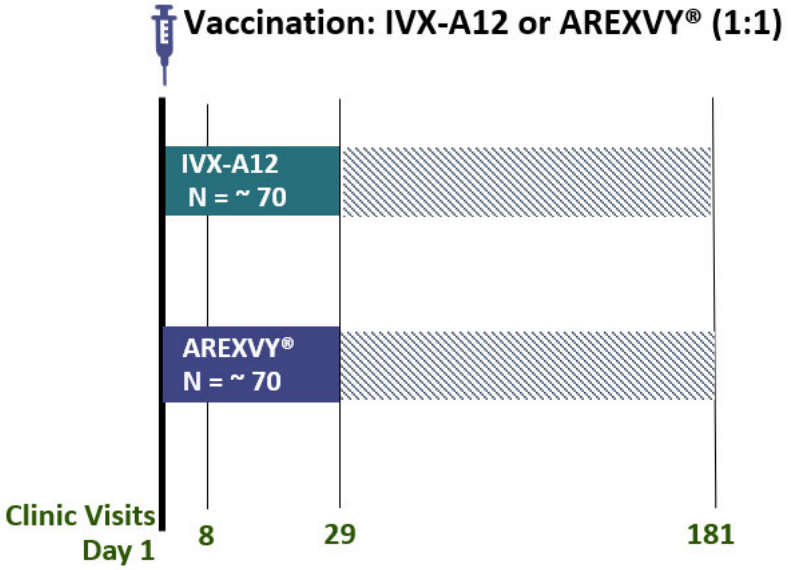
1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study ICVX-12-202, a Phase 2, Randomized, Modified Double-Blind, Active Controlled Study to Characterize the Safety and Immunogenicity of IVX-A12, a RSV and hMPV VLP vaccine, in Adults 60 Years of Age and Older, supporting the clinical study report. The reader is referred to the CSP, CRF, and SIP for details of study conduct, data collection, and study integrity, respectively.

The terms study intervention, study vaccination, and study group are used throughout this SAP and refer to IVX-A12 and/or licensed RSV vaccine, AREXVY® (GSK Biologicals, Rixensart, Belgium).

The study groups and overall study design are described in Figure 1.

Figure 1 Study Design



2 CHANGES TO PROTOCOL PLANNED ANALYSES

The description for the Immunogenicity analysis set is further specified to target the intended study population.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Sample Size Determination

Approximately 140 participants will be randomized 1:1 to IVX-A12 or AREXVY. Because all analyses will be descriptive in nature and no hypothesis is being tested statistically, no formal sample size calculations were performed. The sample size is considered sufficient for an assessment of immunogenicity and safety. For RSV A, an exploratory GMC ratio of 0.9, the 95% CI will be 0.57 to 1.42. A [redacted] standard deviation (SD) of [redacted] was assumed for RSV A, based on data reported by previous IVX-A12 Phase 1 and 2 studies. No replacement will be made for participants who withdraw from the study.

Table 1 Confidence intervals for assumed sample sizes and GMC ratios

NI Margin: 0.67	**GMC ratio = 0.9**		**GMC ratio = 1.0**	
Total N	**95% CI**	**80% CI**	**95% CI**	**80% CI**
100	0.52, 1.55	0.63, 1.28	0.58, 1.72	0.70, 1.42
140	0.57, 1.42	0.67, 1.21	0.63, 1.58	0.74, 1.35
180	0.60, 1.34	0.69, 1.17	0.67, 1.50	0.77, 1.30

3.2 Timing of Analyses

- The Primary Analysis will be performed after all participants have completed Day 29 (Visit 3) safety assessments and when all Day 29 primary immunogenicity data for RSV A (GFP RSV A MN Assay, [redacted]) are available. This analysis will support further evaluation of immunogenicity and safety of IVX-A12 in older adults. In addition, all available safety and immunogenicity data for RSV B (GFP RSV B MN Assay, [redacted]), RSV A and RSV B MN Assays ([redacted]), and hMPV A and hMPV B (hMPV MN Assays, [redacted]) at the time of the primary analysis will be summarized as exploratory analyses.

- The Final Analysis will be performed after all participants have completed Day 181 (Visit 4) or terminate early from the trial and all data are available.

3.3 Analysis Populations

The following populations are defined (Table 2):

Table 2 Populations for Analysis

Population/analysis set	**Description**
Safety analysis set (SAF)	All randomized participants who receive study intervention, irrespective of their protocol adherence and continued participation in the study.

Table 2 Populations for Analysis

Population/analysis set	Description
	Participants who withdraw consent to participate in the study will be included up to the date of their study withdrawal. Participants will be classified according to the study intervention they actually received. The SAF is to be used for safety analyses.
Immunogenicity analysis set (IAS)	All participants in the SAF who have no important protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response and have baseline and at least one post-baseline immunogenicity samples collected. Participants will be classified according to the study intervention they actually received. The IAS is to be used for the analysis of immunogenicity endpoints.

In addition to the analysis sets defined above, summaries of participant disposition and participants not randomized will be performed in a Screened set, including all participants who have provided informed consent.

3.4 General Considerations

Data will be provided in data listings sorted by vaccination group and participant number. Tabular summaries will be presented by vaccination group and overall. Vaccination group will be defined as the actual vaccination received by a randomized participant.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum, maximum, and quartiles where appropriate.

All point estimates will be presented with a two-sided 95% CI, unless otherwise stated. For subgroup analyses, CIs will be presented for subgroup categories which have at least 5 evaluable participants per vaccination group.

The RSV nAb responses are measured as concentrations in IU/mL and therefore the geometric mean responses will be referred to as GMCs while the hMPV nAb responses are measured as titers (1/dilution) and the geometric mean responses will be referred to as GMTs. The GMCs and GMTs are referred to generally as geometric mean responses.

Immunogenicity summaries involving the Day 29 endpoint will include participants in the immunogenicity analysis set with a non-missing baseline and a non-missing result at Day 29.

For immunogenicity summaries involving data through Day 181, evaluable participants will be those in the immunogenicity analysis set with non-missing baseline and at least one non-missing post-baseline (Day 29 or 181) result.

Immunogenicity results below the LLoQ will be imputed to half of the LLoQ and results above the ULoQ will be imputed to the ULoQ prior to computing geometric mean responses. Responses will be imputed before any model-adjustment is performed.

The data analyses will be conducted using the SAS® System version 9.4 or above (SAS Institute Inc., Cary, NC). All SAS® programs used to generate analytical results will be developed and validated according to AstraZeneca programming standards and validation procedures.

3.4.1 General Study Level Definitions

Baseline

Baseline for immunogenicity endpoints is defined as the last non-missing result on the day of receiving study vaccination. Samples taken on the day of vaccination will be considered as evaluable for baseline, regardless of whether samples were drawn post-vaccination. If there is no value prior to or on the day of study vaccination, the baseline value will not be imputed and will be set to missing.

Baseline Tertiles

Baseline tertiles are defined as follows: first tertile is <=33.3rd percentile, second tertile is >33.3rd - <=66.7th percentile, and third tertile is >66.7th percentile. Tertiles will be derived for each neutralization assay, across both study groups.

Study Groups

For the primary and final analyses, the study groups will be displayed in summaries as follows:

- IVX-A12 (RSV + hMPV)
- AREXVY (RSV)

Study Day

Study Day is defined as (date of assessment – date of study vaccination) + 1. Thus, the day of study vaccination will be study Day 1. There is no study Day 0.

Geometric Mean Concentration/Titer

Geometric mean concentrations/titers (GMCs/GMTs) will be calculated as the anti-logarithm $\Sigma(\log_2$ transformed response/n), ie, as the anti-logarithm transformation of the mean of the

log_2-transformed response, where n is the number of participants with non-missing response information.

The CI for the GMC/GMT is calculated as the anti-logarithm transformation of the upper and lower limits of the two-sided 95% CI for the mean of the log_2-transformed responses.

Geometric Mean Concentration/Titer Ratio

The GMC/GMT ratio will be calculated as the geometric mean of the post-baseline response for IVX-A12 divided by the geometric mean of the post-baseline titer for AREXVY. The denominator for each geometric mean response is the number of participants with non-missing post-baseline response information.

The CI for the GMC/GMT ratio is calculated as the anti-logarithm transformation of the upper and lower limits of the two-sided 95% CI for the difference in means of the log_2-transformed responses.

Geometric Mean Fold Rise

The geometric mean fold rise (GMFR) is calculated as the geometric mean of the ratios of the individual post-baseline response value to the baseline response value (fold-rise). The GMFR will be calculated as the anti-logarithm of $\Sigma(log_2$ transformed (post-baseline response/baseline response)/n), where n is the number of participants with non-missing response information at baseline and at the post-baseline timepoint.

The CI for the GMFR will be calculated as described for the GMC/GMT.

Seroresponse

Seroresponse is a binary outcome where a success is defined as a fold-rise ≥4. The CI for the proportion of participants with a seroresponse is calculated using the Clopper-Pearson exact method. In the event of 0% or 100% seroresponse, a one-sided 97.5% CI will be reported.

3.4.2 Visit Window

A windowing convention will be used to determine the assignment of immunogenicity laboratory assessments to a nominal study visit for analyses summarized by visit. Samples collected outside of the analysis visit windows defined in Table 3 will be excluded from by-visit analyses.

Table 3 Analysis Visit Windows for Immunogenicity Data

Visit Description	Visit Number	CSP Visit Window		Analysis Visit Window	
		Days Relative to Visit	Study Day	Days Relative to Visit	Study Day
Baseline	1	≤1	1	≤1	1

Visit Description	Visit Number	CSP Visit Window		Analysis Visit Window	
		Days Relative to Visit	Study Day	Days Relative to Visit	Study Day
Day 29 post-vaccination	3	+3	29-32	±5	24-34
Day 181 post-vaccination	4	±14	167-195	Same as CSP Visit Window	

In the event of multiple assessments within a single analysis visit window, then the following rules will be applied:

- If there are two or more observations within the same visit window, then the non-missing observation closest to the scheduled visit will be used in the analysis;
- If two observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis;
- If two observations are collected on the same day, then the non-missing observation with the earlier collection time will be included in the analysis. If the collection time is not available, the scheduled assessment will be favored over the unscheduled assessment.

If a visit window does not contain any observations, then the data will remain missing.

3.4.3 Handling of Unscheduled Visits

Not applicable.

3.4.4 Multiplicity/Multiple Comparisons

There are no planned multiplicity adjustments for this descriptive study.

3.4.5 Handling of Protocol Deviations in Study Analysis

Only important protocol deviations (IPDs) will be extracted from the Clinical Trial Management System (CTMS) for inclusion in reporting datasets and PD summaries. The study team will identify and document a final list of IPDs prior to database lock. The process for identification and assessment of protocol deviations, including a full list of IPDs, is detailed in a separate protocol deviation management plan developed by Syneos Health. Participants who are identified as having experienced an IPD may be excluded from the analysis sets or may have their data following the IPD excluded from the analyses.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation, and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior and concomitant medication, eDiary compliance, and duration of follow-up.

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Disposition and completion status can be obtained directly from the eCRF.

4.1.1.2 Presentation

Disposition will be summarized by vaccination group and overall.

The disposition summary will include:

- Participants screened
- Participants not randomized (including reasons not randomized)
- Participants randomized
- Participants randomized, not vaccinated (including reasons not vaccinated)
- Participants who received study intervention
- Participants ongoing in study at data cut-off date (primary analysis)
- Participants who completed the study
- Participants withdrawn from the study (including reasons for early withdrawal)

Only counts will be presented for the number of participants screened, screen failures, participants randomized, and randomized, not vaccinated. For all other categories the denominator for percentages will be the number of participants who received study vaccine.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Analysis sets are defined in Section 3.3.

4.1.2.2 Presentation

The number of participants included in each analysis set (by actual vaccination group) will be summarized. The number of participants excluded from each defined analysis set along with the reason for exclusion will also be summarized. A participant may be excluded from an analysis set for more than one reason. They will be counted once for the number of participants excluded from each set and once for each reason for exclusion.

The number and percentage of participants included in each analysis set by site will also be presented, with the denominator for calculation of percentages being the number of participants in the analysis set. No summaries will be presented by vaccination group using the Screened set.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Protocol deviations are defined as instances in which participants or investigational site study personnel fail to adhere to the protocol requirements. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. Deviations are collected in the CTMS. A detailed list of possible IPDs and the process for identifying and assessing them by the clinical study team will be outlined in the PDNC management plan developed by Syneos Health. The protocol deviation categories will be reviewed by the medical and statistical team members before the CDL and classified as non-important or important per the PDNC plan.

4.1.3.2 Presentation

All IPDs will be extracted from the CTMS for inclusion in reporting datasets and PD summaries, while non-IPDs will be available in the CTMS system but will be excluded from reporting in the CSR.

Important PDs will be summarized for participants in the safety set. The number and percentage of participants with at least one IPD, as well as the number and percentage by category will be presented by vaccination group. The total number of participants will be presented for each protocol deviation category. The same participant may have more than one IPD within a category and will be counted once in each category. The denominator for percentages will be the number of participants in the safety analysis set.

Deviations in the following categories will be reviewed on a regular basis (as outlined in the PDNC plan) for consideration as important for the evaluation and implementation of the study:

- Concomitant Medication
- Inclusion or exclusion criteria

- Informed consent
- Investigational product
- Met Withdrawal Criteria but was not Withdrawn
- Patient Privacy
- Randomization
- SAE not reported or reported late
- Study Procedure
- Visit Schedule

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic information will be directly obtained from the eCRF. Age and year of birth will be collected in the eCRF and integrated into the IRT system.. The denominator for calculation of percentages will be the number of participants in the analysis set. Participants will be excluded from the summary (eg, means) of an individual parameter if data are missing.

4.1.4.2 Presentation

Demography data will be summarized for the Safety and Immunogenicity analysis sets. Demographics will be summarized descriptively for the entire study population, by study group, and by age subgroup category. Demographic parameters will include:

- Age (years) at consent
- Gender at birth
- Race
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White or Caucasian
  - Japanese or Japanese descent
  - Other
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not reported/specified

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Height and weight will be taken directly from the eCRF. The BMI will be calculated as weight in kilograms divided by height in meters squared.

4.1.5.2 Presentation

Baseline characteristics will be presented along with demography and will be summarized for the Safety analysis sets. Participants will be excluded from the summary (eg, means) of an individual parameter if data are missing. Baseline characteristics will include:

- Height (m)
- Weight (kg)
- BMI (kg/m^2)

4.1.6 Disease Characteristics

This study includes normal healthy participants and therefore summaries of baseline disease characteristics are not applicable.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history can be obtained directly from the eCRF.

4.1.7.2 Presentation

The number and percentage of participants will be summarized for the safety set by MedDRA system organ class and preferred term. Medical history will be classified according to the MedDRA (initial version 27.0). Participants with multiple occurrences will be counted once per system organ class and preferred term regardless of the number of medical history occurrences. The denominator for calculation of percentages will be the number of participants in the safety set.

4.1.8 Concomitant Medications

4.1.8.1 Definitions and Derivations

A concomitant medication, which will be documented in the eCRF, is any medication that is taken on or after signed informed consent to treat an SAE or AESI, or if they are prohibited according to the CSP. Medications used to treat medical history conditions or other adverse events are otherwise recorded only in the source document.

4.1.8.2 Presentation

The number and percentage of participants who take concomitant medications will be summarized for the safety set by ATC classification and generic drug name. Concomitant medications will be classified according to the WHO-Drug Dictionary (initial version WHODrug Global B3 Mar 2024). Participants will be counted once per ATC classification and generic drug name regardless of the frequency of medication usage. The denominator for calculation of percentages will be the number of participants in the analysis set.

4.1.9 Study Drug Compliance

A single dose of study vaccine will be administered by study site staff and therefore study drug compliance issues are not foreseen for this study. Summaries of study drug compliance are not planned, however the number and percentage of participants who receive study vaccination will be included in the disposition summary described in Section 4.1.1.

4.1.10 Duration of Follow-up

4.1.10.1 Definitions and Derivations

Duration of follow-up will be calculated for the study periods, Day 1 to Day 29 and Day 1 to Day 181, as the number of days from vaccination to the end of the follow-up period or study discontinuation, whichever is earlier [eg minimum (Study Day 29 visit date, discontinuation date) – vaccination date + 1].

4.1.10.2 Presentation

The number of participants, mean, standard deviation, median, minimum, and maximum duration of follow-up (in days) will be summarized for participants in the Safety analysis set, for each study period.

4.1.11 eDiary Compliance

4.1.11.1 Definitions and Derivations

The eDiary compliance rate will be measured as the number and percentage of days where the eDiary was completed, for participants in the safety analysis set. Participants will be categorized as either 100% compliant (8 days completed), partially compliant (6-7 days completed), poorly compliant (1-5 days completed), or non-compliant (0 days completed).

4.1.11.2 Presentation

The number of participants, mean, standard deviation, minimum and maximum eDiary compliance rate will be summarized for participants in the safety analysis set. Number and percentage of participants by compliance category will also be presented. The denominator for the calculation of percentages will be the number of participants in the safety analysis set.

4.2 Endpoint Analyses

The following table section covers details related to the primary and exploratory endpoint analyses.

Table 4. Primary and exploratory estimands

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To characterize the nAb responses to RSV A in serum following vaccination with IVX-A12 or licensed RSV vaccine					
Primary Analysis of the Immunogenicity Endpoint	RSV A (GFP MN RSV A Assay, [redacted] nAb concentrations at Day 29	Immunogenicity analysis set	Participant follow-up will be censored at the date of intercurrent event (IPD that may impact immune response, infection with RSV/hMPV, early withdrawal, death)	Model-adjusted GMCs by vaccination group	4.2.1.5
				• Unadjusted GMCs/GMFRs from baseline by vaccination group • Proportion of participants with seroresponse (GMFR ≥4 from baseline) by vaccination group.	4.2.1.7
Objective 2: To assess the safety of single IM vaccination with IVX-A12 or licensed RSV vaccine					
Primary Analysis of the Safety Endpoint	Immediate unsolicited AEs within 30 minutes of dosing	Safety analysis set	N/A	Incidence by vaccination group (descriptive)	4.6
	Injection site and systemic solicited ARs through 7 days post-vaccination (Day 1 to Day 8)		N/A	Incidence by vaccination group (descriptive)	4.6
	Unsolicited AEs through 28 days post-vaccination (Day 1 to Day 29)		N/A	Incidence by vaccination group (descriptive)	4.6
	SAEs, MAAEs, and AESIs through 6 months post-vaccination (Day 1 to Day 181)		N/A	Incidence by vaccination group (descriptive)	4.6
Objective 3: To characterize the durability of the nAb responses to RSV A in serum following vaccination with IVX-A12 or licensed RSV vaccine					
Exploratory	RSV A nAb concentrations through Day 181	Immunogenicity analysis set	Participant follow-up will be censored at the date of intercurrent event (IPD	• Model-adjusted GMCs by vaccination group and visit	4.2.3

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
			that may impact immune response, infection with RSV/hMPV, early withdrawal, death)	• Unadjusted GMCs/GMFRs from baseline by vaccination group and visit • Seroresponse rate by vaccination group and visit	
Objective 4: To compare the nAb responses to RSV in serum following vaccination with IVX-A12 or licensed RSV vaccine					
Exploratory	RSV A nAb concentrations through Day 181	Immunogenicity analysis set	Participant follow-up will be censored at the date of intercurrent event (IPD that may impact immune response, infection with RSV/hMPV, early withdrawal, death)	• Model-adjusted GMCs by vaccination group and visit • Model-adjusted GMC ratios by visit • Unadjusted GMCs /GMFRs from baseline by vaccination group and visit • Seroresponse rate by vaccination group by post-baseline visit • Difference in seroresponse rate by post-baseline visit	4.2.3
Exploratory	RSV B nAb concentrations through Day 181				
Objective 5: To compare the nAb responses to hMPV in serum following vaccination with IVX-A12 or licensed RSV vaccine					
Exploratory	hMPV A nAb titers through Day 181	Immunogenicity analysis set	Participant follow-up will be censored at the date of intercurrent event (IPD that may impact immune response, infection with RSV/hMPV, early withdrawal, death)	• Model-adjusted GMTs by vaccination group and visit • Model-adjusted GMT ratios by visit • Unadjusted GMTs/GMFRs from baseline by vaccination group and visit • Seroresponse rate by vaccination group and post-baseline visit	4.2.3
Exploratory	hMPV B nAb titers through Day 181				

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
				• Difference in seroresponse rate by post-baseline visit	

4.2.1 Primary Immunogenicity Endpoint – RSV A Neutralizing Antibody Response at Day 29

The primary immunogenicity objective of the study is to characterize the nAb responses to RSV A in serum following vaccination with IVX-A12 or AREXVY.

4.2.1.1 Definition

The primary endpoint is the nAb concentration for RSV A at Day 29. The primary analyses will be conducted on data reported from samples analyzed by the GFP RSV A neutralization assay conducted at [redacted]. Planned supplementary analyses will be performed on results reported by other exploratory assays, as discussed below in Section 4.2.1.7. Evaluable participants will be those in the IAS with non-missing concentration value at both baseline and Day 29.

4.2.1.2 Derivations

Geometric mean concentration (GMC), geometric mean fold rise (GMFR) and their corresponding 95% CIs will be calculated, as defined in Section 3.4.1. A log base 2 transformation will be used for nAb response. Additionally, the seroresponse rate and corresponding 95% CI will be reported. Concentration values below LLoQ and above ULoQ will be imputed according to Section 3.4.

4.2.1.3 Handling of Intercurrent Events

Results from samples collected after the date of an intercurrent event will be excluded from the analysis.

Intercurrent events for immunogenicity analyses include:

- Occurrence of a protocol deviation that can interfere with an immune response
- Infection with RSV/hMPV
- Early withdrawal from the study
- Death

An infection with RSV/hMPV will be identified using data collected in the AE eCRF. The list of PTs (MedDRA 27.0) used to select AEs pertaining to these infections are included in Appendix A. Partial or missing dates of an infection with RSV/hMPV will be imputed as described in the Appendix B.

4.2.1.4 Handling of Missing Data

No imputation is planned for missing endpoint values.

4.2.1.5 Primary Analysis of Primary Immunogenicity Endpoint

For the Day 29 primary analysis model-adjusted GMCs, along with their corresponding 95% CIs, will be estimated using an analysis of covariance (ANCOVA) model that includes a continuous dependent variable of log 2 response at Day 29, study group as a fixed effect (factor), and log 2 baseline response (continuous) and age group (categorical; 60 to 69, 70 to 79, and ≥80 years of age) as covariates.

Least square means and 95% CIs will be back-transformed to provide Day 29 model-adjusted GMCs and CIs for each study arm.

The following plots will be created for the Day 29 analysis:

- A bar plot by study group showing the GMCs and 95% CIs at baseline (raw values) and Day 29 (adjusted values)
- A line plot by study group showing the GMCs and 95% CIs at baseline (raw values) and Day 29 (adjusted values)
- A boxplot with scatterplot overlay by study group showing the distribution of the raw concentration data at Day 29
- A reverse cumulative distribution plot of the fold rise at Day 29, with fold rise values displayed on the x-axis and the percentage of participants with fold rise values greater than or equal to the corresponding fold rise displayed on the y-axis

4.2.1.6 Sensitivity Analyses of the Primary Immunogenicity Endpoint

Sensitivity analyses of the primary endpoint are not currently planned.

4.2.1.7 Supplementary Analyses of the Primary Immunogenicity Endpoint

4.2.1.8 Supplementary analyses of the primary endpoint are not currently planned. Subgroup Analyses

Descriptive summaries of GMCs, GMFRs, and seroresponse rate will be reported for the following subgroups:

- Age group categories (60 to 69, 70 to 79, and ≥80 years of age)
- Tertiles of baseline RSV A nAb concentration (≤33.3%, >33.3% to ≤66.7%, >66.7% across vaccination groups)

For each subgroup variable, if an adequate number of participants in each subgroup category is available to allow convergence of the model, model-adjusted GMCs will be derived for each subgroup category using the same ANCOVA and MMRM models as described above. Higher order interaction terms (ie study group*subgroup for ANCOVA model or visit*study group*subgroup for MMRM model) will be included in the model, using an appropriate

covariance matrix. If model convergence is not achieved, each subgroup level will be analyzed separately using a common, simpler model without the higher order interactions.

4.2.2 Primary Safety Endpoint

The primary safety objective is to assess the safety of single IM vaccination with IVX-A12 or AREXVY. All safety analyses are described in Section 4.6.

4.2.3 Exploratory Immunogenicity Endpoints: RSV A and RSV B nAb concentrations, and hMPV A and hMPV B nAb titers, through Day 181

4.2.3.1 Analysis considerations

The definition and derivation of summary quantities, as well as the handling intercurrent events, will be the same as the Primary Immunogenicity Endpoint described in Section 4.2.1. For summaries, evaluable participants will be those in the IAS with a non-missing value at both baseline and at least one non-missing post-baseline visit. Analyses below will be repeated for each of the four endpoints.

4.2.3.2 Exploratory analyses of the exploratory endpoints

To evaluate durability of nAb responses post-vaccination, model-adjusted GMCs/GMTs at Days 29 and 181, along with their corresponding 95% CIs, will be estimated using a mixed model for repeated measures (MMRM) that includes a dependent variable of log 2 responses, study group as a fixed effect, log 2 baseline response, age group, visit indicators (Days 29 and 181) as covariates, and a study group by visit interaction term. An appropriate covariance matrix structure will be selected to address repeated measurements. Least square means and 95% CIs will be back-transformed to provide model-adjusted GMC/GMTs and confidence intervals by study group, for each follow-up visit, Days 29 and 181. Unadjusted GMCs/GMTs, GMFRs from baseline, and seroresponse rate, with corresponding 95% CIs, will be estimated for each study group and summarized by post-baseline visit. Plots described in Section 4.2.1.5 may be repeated for these analyses.

Multiple imputation techniques will not be applied for any missing post-baseline immunogenicity measurement. This is because the MMRM inherently accounts for the missingness, under the assumption that the missing data are missing at random (MAR). Thus considering that missing data are MAR is a reasonable assumption for this descriptive clinical trial, then it is not necessary to perform MI.

To compare nAb response between IVX-A12 and the AREXVY, the GMC/GMT ratio and difference in seroresponse rate, along with corresponding 95% CIs, will be estimated and summarized at Day 29 and Day 181. The difference in seroresponse rate will be unadjusted and the 95% CIs calculated based on the Miettinen-Nurminen method (Miettinen and Nurminen 1985). Unadjusted and model-adjusted (from MMRM above) GMTRs with 95% CIs will be calculated.

4.2.3.3 Subgroup analyses of the exploratory endpoints

Subgroup analyses may be repeated as described in Section 4.2.1.8.

4.3 Pharmacodynamic Endpoint(s)

Not applicable.

4.4 Pharmacokinetics

Not applicable.

4.5 Other Exploratory Immunogenicity Endpoints

The following objectives of cellular-mediated and additional immune responses are exploratory and outside the scope of the CSR. Therefore, analyses of these data will not be described in this SAP.

4.5.1 Cellular Mediated Immune Responses

Participants are scheduled to have additional blood samples drawn on Days 1, 8, 29, and 181. The resulting data may be used to evaluate cell-mediated immunity and immune responses using functional/and or phenotypic profiling methods.

4.5.2 Additional Immune Responses

The immunogenicity serum samples taken on Days 1, 29, and 181 may be utilized in other exploratory assays to investigate additional humoral or cellular immune responses based upon emerging safety, efficacy, immunobridging, and immunogenicity data.

4.6 Safety Analyses

The domain safety covers exposure and adverse events.

Unless otherwise stated, the Safety analysis set will be used for this domain.

4.6.1 Exposure

This is a single dose vaccination study with dose administration performed by study site staff. Exposure summaries are not planned, however the number and percentage of participants who receive vaccination is included in the disposition summary described in Section 4.1.1. A listing of exposure details will be provided.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

Adverse events experienced by participants will be collected throughout the study as listed below:

- Immediate unsolicited AEs within 30 minutes of dosing
- Solicited injection site and systemic ARs for 7 days post-vaccination (Day 1 to Day 8)
- Unsolicited AEs for 28 days post-vaccination (Day 1 to Day 29)
- SAEs from date of ICF through 6 months post-vaccination (Day 1 to Day 181)
- MAAEs, AESIs, and deaths over the entire study period (Day 1 to Day 181)

Serious adverse events collected prior to vaccination from ICF will be included in the listings only.

Intensity of AEs is determined by the investigator as mild, moderate, or severe. If there are AEs with missing intensity, the category "Missing" will be summarized separately from the non-missing categories. The relationship of AE to study vaccination will be assessed by the investigator and recorded in the AE eCRF as "Yes" or "No" to the question "Is this event related to study medication?" If there are AEs with missing relationship, the category "Missing" will be summarized separately from the non-missing categories. Partial or missing dates for AEs, SAEs, AESIs, and MAAEs will be imputed as described in Appendix B. Duration of AEs will not be calculated using imputed dates and will instead be set to missing in the listings.

Solicited ARs that are present on the last eDiary completion date (Day 8) may not have resolved onDay 8. The solicited ARs which have not resolved at Day 8 will be marked as a continuing event and documented as an unsolicited AE in the AE eCRF in order to collect the stop date of the adverse reaction. However, the continuing event will not be summarized as an unsolicited AE to avoid duplication. The start date for the continuing event will be the first day the solicited AR was first recorded in the eDiary; the stop date will be recorded in the AE eCRF. The duration of solicited ARs will be calculated as the last day of the adverse reaction – the first day of the adverse reaction + 1. Participants with a missing stop date for a solicited AR will not be included in the calculation of duration and will instead be summarized as missing.

The severity of solicited ARs is collected directly in the eDiary except for fever, erythema/redness, and induration/swelling where the severity will be categorized programmatically as, mild (Grade 1), moderate (Grade 2), or severe (Grade 3) based on comparison of the temperature and diameter measurements recorded in the eDiary against the grade ranges provided in the appendix of the CSP. Measurements below the lower limit of the mild category will be categorized as "none" and will be excluded from duration summaries. A severity of potentially life-threatening is not collected in the eDiary and would instead be recorded as an SAE based on investigator assessment. For solicited ARs that are ongoing after Day 8, the maximum severity will be summarized over the entire duration of the event.

Adverse events of special interest are defined in the CSP and the data will be taken directly from the AE eCRF.

4.6.2.2 Presentations

All AEs will be listed for each participant.

An overall summary of safety will be presented, including the number and percentage of participants for each category, by study period. The denominator for calculation of percentages for adverse events will be the number of participants in the safety analysis set, who are still ongoing in the study at the beginning of the corresponding study period. The denominator for the calculation of percentages for solicited adverse reactions will be the number of participants who provided a response in the eDiary. Should a participant experience multiple events within a category, the participant will be counted only once for that category, in the category of their most severe or related event (where applicable). The overall summary of safety will be reproduced for each age subgroup category.

Event categories included in the overall summary are as follows:

- Study period: Day 1 to Day 29:
  - Unsolicited Immediate AE
    - Unsolicited immediate related AE
    - Unsolicited immediate severe AE
    - Unsolicited immediate related severe AE
  - Solicited AR
    - Solicited injection site AR
    - Solicited systemic AR
  - Unsolicited AE
    - Unsolicited related AE
    - Unsolicited severe AE
    - Unsolicited severe related AE
  - Unsolicited non-serious AE
    - Unsolicited related non-serious AE
  - SAE
    - Related SAE
  - Death
  - AE leading to study discontinuation
  - MAAE

    - Related MAAE
  - AESI
    - Related AESI
- Study period: From Day 30 to Day 181
  - SAE
    - Related SAE
  - Death
  - AE leading to study discontinuation
  - MAAE
    - Related MAAE
  - AESI
    - Related AESI
- Study period: From Day 1 to Day 181
  - SAE
    - Related SAE
  - Death
  - AE leading to study discontinuation
  - MAAE
    - Related MAAE
  - AESI
    - Related AESI

If there are at least 10 total events in an AE category (excluding ARs), that category will be presented in a summary by SOC and PT. Summaries by SOC and PT will be based on the study period used for reporting of the AE category. For example, unsolicited AEs would be summarized from Day 1 to Day 29, while SAEs would be summarized from Day 1 to Day 181. Participants with multiple occurrences are counted once per SOC and PT regardless of the number of occurrences. Unsolicited AEs by decreasing frequency on PT, based on the total across vaccine groups, will also be summarized from Day 1 to Day 29.

In separate tables, the number and percentage of participants reporting solicited adverse reactions will be summarized overall and by study day (Day 1 to Day 8), and by maximum severity. In addition, the time to onset and duration of each solicited AR, in days, will be summarized descriptively, including the number and percentage of participants who experience an AR with duration ≤4 days. The denominator for the percentage of participants who experience an AR with duration ≤4 days will be the number of participants reporting the

associated AR. Injection site and systemic solicited ARs will be reported along with the overall solicited AR summary by maximum severity.

4.6.3 Clinical Laboratory Tests

There are no scheduled clinical chemistry and hematology tests in this study. Such tests may be performed as clinically indicated based on participant health, medical history, and ongoing AEs.

4.6.4 Vital Signs

Body temperature and blood pressure will be captured in source documents, not the eCRF. Therefore, no summaries or listings will be created for these parameters.

4.6.5 Electrocardiogram

There are no scheduled ECGs in this study. Electrocardiograms may be performed as clinically indicated based on participant health, medical history, and ongoing AEs.

5 REFERENCES

Miettinen and Nurminen 1985
Miettinen O., Nurminen M. (1985), Comparative analysis of two rates. Stat. Med, 4: 213-226. https://doi.org/10.1002/sim.4780040211

Appendix A Preferred Terms for RSV/hMPV Infection

Infection	MedDRA 27.0 Preferred Terms	Preferred Term Code
RSV	Pneumonia respiratory syncytial viral	10035732
	Respiratory syncytial virus bronchiolitis	10038718
	Respiratory syncytial virus bronchitis	10069811
	Respiratory syncytial virus infection	10061603
	Respiratory syncytial virus test positive	10068563
hMPV	Human metapneumovirus test positive	10072859
	Metapneumovirus bronchiolitis	10085548
	Metapneumovirus infection	10066226
	Metapneumovirus pneumonia	10085550

Appendix B Missing and Partial Dates for Adverse Events and Concomitant Medications

If an AE onset date is completely missing, then the AE will be assumed to be post-vaccination and will be included in all applicable summaries, unless the stop date indicates otherwise. If the AE onset date is partially missing, AE dates will be handled using the following imputation rules:

The missing start day will be set to:

- First day of the month of occurrence if the start YYYY-MM is after the YYYY-MM of study vaccination.
- The day of study vaccination, if the start YYYY-MM is the same as the YYYY-MM of study vaccination
- The date of informed consent, if the YYYY-MM is before the YYYY-MM of the study vaccination.

If the start date is missing both the day and month, the start date will be set to:

- The date of the study vaccination, if the start year is the same as the year of study vaccination.
- January 1 of the year of occurrence.

The missing end day will be set to:

- The last day of the month of the occurrence, if the YYYY-MM is after the YYYY-MM of the study vaccination.
- The day of data cutoff date, early study withdrawal date, death date or end of study date if the earliest of these occurred in the same YYYY-MM as the partial end date.

If the end date is missing both the day and month, the end date will be set to:

- The data cutoff date, early study withdrawal date, death date or end of study date if the earliest of these occurred in the same year as the AE onset
- December 31 of the year of occurrence

If the start date is null, the date will be set to:

- The date of study vaccination
- Date of informed consent if the end date is on or prior to the date of vaccination.

If the end date is null and the AE outcome indicates that the event is recovered, the end date will be set to:

- The date of study vaccination, if the start date is prior to the date of study vaccination.
- The earliest of the data cutoff date, early study withdrawal date, death date or end of study date.

If the end date is null and the AE outcome indicates that the event is not recovered, the end date will not be imputed.

The same method will be used for missing and partial start and end dates for concomitant medications.