Statistical Analysis Plan

Text

SAP Text Version Number: 3.0
SAP Text Date: (DD-Mmm-YYYY): 25-Nov-2024

Sponsor Name: Icosavax Inc.

Protocol Number: ICVX-12-201
Protocol Title: A Phase 2a Randomized, Observer-blind, Placebo-controlled, Dosage Optimization, Multi-Center Clinical Trial to Evaluate the Safety and Immunogenicity of IVX-A12, a Respiratory Syncytial Virus and Human Metapneumovirus Bivalent Combination Virus-like Particle Protein Subunit Vaccine in Adults 60 to 85 Years of Age
(Safety and Immunogenicity of IVX-A12 in Adults 60 to 85 Years of Age)

Protocol Version and Date: (DD-Mmm-YYYY): 5.0 (02-Apr-2024)

Syneos Health Project Code: 7046828

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	17-Aug-2023	PPD	Initial Version
2.0	19-Sep-2024	PPD	Added definition to Section 7.3.2 that if a immunogenicity result is less than LLOQ or greater than ULOQ, the respective LLOQ or ULOQ will be used. Updates for Protocol Version 5.0. Minor Grammatical Updates Incorporated comments from Icosavax/AstraZeneca Removed urinalysis summary tables Added requested urinalysis listing for abnormalities Added incorrectly reported listing for adverse reactions Added durability outlier text for boxplots and listings
3.0	25-Nov-2024	PPD	Removed the Observational Extension Analysis information from Sections 2.2, 4.1.2, 4.6.2, 5.2, 6.2.2, 7.1.1, 7.5, 8.2, 9.2, 10.2, 12. Added LRTI analysis of non-RSV/hMPV events for Main Trial in Section 10.1.1 and 10.1.1.7. Revised Section 12 to include post hoc analysis. Minor grammatical fixes

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

PPD [redacted] Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
PPD [redacted] Senior Reviewing Biostatistician	Signature	Date (DD-Mmm-YYYY)

Icosavax Inc. Approval

PPD [redacted] Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
ARI	Acute Respiratory Illness
ATC	Anatomical Therapeutic Chemical
ARI	Acute respiratory illness
BDRM	Blinded Data Review Meeting
BMI	Body Mass index
CESI	Clinical Event of Special Interest
CI	Confidence Interval
CRF	Case Report Form
CTMS	Clinical Trial Management System
EES	Extension Enrolled Set
ELISA	Enzyme-linked Immunosorbent Assay
EPPS	Extension Per Protocol Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMFR	Geometric Mean Fold Rise
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
hMPV	Human Metapneumovirus
IA	Interim Analysis
ICF	Informed Consent Form
IgG	Immunoglobulin G
IVX-A12a	IVX-A12 unadjuvanted
IVX-A12d	IVX-A12 adjuvanted
IWRS	Interactive Web Randomization System

Abbreviation	Description
ICH	International Conference on Harmonization
LLOQ	Lower Limit of Quantification
LRTI	Lower respiratory tract illness
MAAE	Medically-Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NAb	Neutralizing Antibody
pIMC	Potential Immune-Mediated Condition
PPS	Per Protocol Set
PT	Preferred Term
RCD	Reverse Cumulative Distribution
RCDC	Reverse Cumulative Distribution Curve
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMC	Safety Monitoring Committee
SNA	Serum Neutralization Assay
SRR	Seroresponse Rate
SOC	System Organ Class
SOP	Standard Operating Procedure
TFL	Table, Figure and Listing
VLP	Virus-like Particle

2. Purpose

The statistical analysis plan (SAP) is developed under the protocol version 5.0 dated 02 April 2024 in concert with subsequent notification that the open label extension of the trial (in protocol version 5.0) was discontinued by the Sponsor (October 2024). The purpose of this SAP is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all derived datasets, and tables, figures and listings.

2.2. Timings of Analyses

An independent safety monitoring committee (SMC) will be constituted to monitor the safety of all subjects enrolled in the trial, including solicited local adverse reactions (ARs), solicited systemic ARs, unsolicited adverse events (AEs), and clinical laboratory data. The SMC will review safety data collected during the 7 consecutive days following vaccination for all subjects, focusing on the interpretation of solicited local ARs and solicited systemic ARs, unsolicited AEs and clinical laboratory data in the first week after dosing when most reactogenicity is expected to occur. Details of the membership, roles and functioning of the committee will be available in the SMC charter.

Further description of the SMC analyses can be found in the SMC charter. The SMC charter was authored by Icosavax Inc. For the closed SMC session, an unblinded team from Syneos Health Biostatistics will perform the analyses as described in Section 4.4 of this SAP to maintain the blinding of the trial.

Two interim analyses (IA) will be performed: the first when all subjects have completed the Day-28 safety assessments and all Day-28 immunogenicity data are available; the second when all subjects have completed the Day-180 safety assessments and all Day-180 secondary immunogenicity data are available. These analyses will support further evaluation of safety and immunogenicity of IVX-A12 in older adults. The purpose of the interim analyses will be used for confirmation of dosage level and formulation selected for further evaluation in older adults 60 years of age or older. For each of the interim analyses, a data-cut will be performed. For the Day-28 interim analysis, all data through day 28 will be included. For the Day-180 interim analysis, all data through day 180 will be included. Additional details regarding the data cut will be found in the *Data Cut-Off Guidance* document.

A primary analysis is planned after all subjects complete the final trial visit, Day 365, or terminate early from the trial and all data is available. The open label extension of the trial starting after Visit Day 365 was discontinued early, prior to the subjects completing Day 545. The limited amount of data from the extension will be reported once all data are available.

3. Study Objectives

3.1. Main Trial Objectives

3.1.1. Primary Safety Objective

The primary safety objective is to assess the safety and tolerability of IVX-A12 bivalent candidate vaccine with or without MF59 adjuvant compared to placebo up to 1 year following a single IVX-A12 vaccination when administered as a single-dose regimen in healthy older adults 60 to 85 years of age.

3.1.2. Primary Immunogenicity Objectives

The primary immunogenicity objectives are as follows:

- To evaluate the serum Neutralizing Antibody (NAb) responses to IVX-A12 +/- MF59 or placebo, measured by live virus serum neutralization assays (SNA), at Day 28.
- To evaluable the serum immunoglobulin G (IgG) binding antibody response to IVX-A12 or placebo, measured by enzyme-linked immunosorbent assays (ELISA), at Day 28.
- To evaluate the proportion of subjects with a ≥4-fold increase in serum NAb and serum IgG binding antibody titers to IVX-A12 from prevaccination/baseline (Day 0) to Day 28.

3.1.3. Secondary Safety Objective

The secondary safety objective is to assess the safety of IVX-A12 compared to placebo by the incidence of serious adverse events (SAEs), adverse events of special interest (AESIs) (which were defined as potential immune-mediated conditions (pIMCs)), medically-attended adverse events (MAAEs), clinical event of special interest (CESIs) (which were defined as lower respiratory tract illness (LRTI) cases of any severity (mild, moderate, severe) caused by RSV and/or hMPV), LRTI cases of any severity (mild, moderate, severe) not caused by RSV or hMPV, and AEs leading to trial withdrawal up to Day 365 (end of the main trial).

3.1.4. Secondary Immunogenicity Objectives

The secondary immunogenicity objectives are as follows:

- To evaluate the serum NAb response to IVX-A12 or placebo at Day 0, Day 180, and Day 365
- To evaluate the serum IgG binding antibody response to IVX-A12 or placebo at Day 0, Day 180, and Day 365 after vaccination.
- To evaluate the proportion of subjects with a ≥4-fold increase in serum NAb and serum IgG binding antibody titers at Day 180 and 365 compared to baseline (Day 0).
- To evaluate the proportion of subjects with an ≥8-fold increase in serum NAb and serum IgG binding antibody titers are Day 28, Day 180 and Day 365 compared to baseline (Day 0).

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3.2. Observational Extension Objectives

3.2.1. Primary Objective

There are no primary objectives for the observational extension portion of the trial.

3.2.2. Secondary Safety Objective

The secondary safety objective, for the observational extension trial, is to describe the incidence of SAEs, AESIs, and MAAEs in consenting IVX-A12a vacinees and placebo recipients through an additional 12 months (Day 730).

Note: given the observational extension portion of the trial was discontinued, these data will only be included in a listing through time of subject discontinuation.

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4. Study Details/Design

4.1. Brief Description

4.1.1. Main Trial Brief Description

The Phase 2a clinical trial of IVX-A12 is a randomized, observer-blind, placebo-controlled, dosage optimization, multi-center trial to evaluate the safety and immunogenicity of a single IM dose of two different formulations of IVX-A12 (IVX-A12a with diluent alone and IVX-A12d with MF59®) compared to placebo (diluent) in adults 60 to 85 years of age. The dosage level and formulation were selected based on the totality of the IVX-A12 nonclinical data and the interim safety and immunogenicity clinical data from the ongoing IVX-A12 Phase 1 clinical trial.

The main portion of this Phase 2a clinical trial will have three vaccine groups: Two IVX-A12 groups and one placebo group. The total amount of VLP in the two IVX-A12 groups will not exceed 300 µg of VLPs. IVX-A12a, IVX-A12d, or placebo will be administered as a single IM dose to older adult subjects enrolled into two age strata (adults 60 to 69 years of age and elderly adults 70 to 85 years of age). Eligible older adults will be randomized simultaneously to the different trial groups to ensure balance among the groups. This Phase 2a clinical trial includes a sentinel group of 40 subjects (16 subjects per active treatment group [n=32]; 8 subjects in the placebo group) to conservatively assess the 150 µg RSV/150 µg hMPV dosage level in combination with MF59®. Sentinel subjects were closely monitored for a minimum of 48 hours and, if no stopping rules were triggered, the remaining subjects were enrolled.

Approximately 250 subjects will be randomly allocated at a ratio of 2:2:1 to receive one of the two IVX-A12 formulations (IVX-A12a [N=100] or IVX-A12d [N=100]) or placebo (N=50), respectively. Subjects were also be stratified by age group (60 to 69 years of age and 70 to 85 years of age). The planned subject allocation to trial groups is provided in Table 1.

Table 1

Group	Dosage Level	Total (N=250)*
A	IVX-A12a (unadjuvanted 150 µg RSV/ 150 µg hMPV)	100
B	IVX-A12d (150 µg RSV/ 150µg hMPV adjuvanted with MF59®)	100
C	Placebo†	50

† Placebo will be aqueous diluent
*Note: The stratified randomization will ensure balanced dosage level group assignment between the two age groups (60 to 69 years of age and 70 to 85 years of age, respectively).

4.1.2. Observational Extension Trial Brief Description

Eligible IVX-A12a and placebo recipients will be invited to enroll into the observational extension portion of the trial, which includes a telephone call at Day 545 (approximately 6 months from Day 365) and a clinic visit at approximately 12 months (Day 730) after the Day 365 visit for a final blood draw. The upper age limit of 85 years was removed.

The observational extension portion of the trial discontinued early, prior to the subjects completing Day 545.

4.2. Subject Selection

Adults 60-85 years of age will be enrolled. Inclusion and exclusion criteria are described in the protocol in Sections 7.1 and 7.2, respectively.

4.3. Determination of Sample Size

4.3.1. Main Trial Determination of Sample Size

Sample size for this trial is not based on any formal hypothesis testing. Analyses of safety and immunogenicity will be primarily descriptive in nature. An approximate total of 250 subjects (approximately 100 subjects in each of the IVX-A12 groups and 50 subjects in the placebo group) will be randomized. With 100 subjects in each IVX-A12, there is a 63.4% probability of observing at least 1 subject with an AE if the true incidence of the AE is 1% and 86.7% probability of observing at least 1 subject with an AE if the true incidence of the AE is 2%. The trial will have more than 90% power to detect a difference of 20% or more in seroresponse rate *(*SRR) or detect a 2-fold increase or more in GMT or GMFR (assuming standard deviation at 0.5 $\log_{10}$), between the two IVX-A12 groups (or between the IVX-A12 group and placebo group), with a two-sided type-1 error rate at 0.05.

4.3.2. Observational Extension Trial Determination of Sample Size

Enrollment is based on subject consent, interest, eligibility, and prior vaccination receipt (IVX-A12a or placebo) to continue in the observational extension trial. No sample size is calculated for the observational extension trial.

4.4. Vaccine Group Assignment and Blinding

Only subjects who have a signed informed consent form (ICF) and meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization and assignment to a vaccine group. The randomization specification will be approved by the sponsor's trial statistician, or designee. Subject randomization will be conducted using an interactive web randomization system (IWRS). The system will ensure proper distribution of subjects across trial groups at each strata.

The Syneos Health (SYNH) blinded team will include a Lead Biostatistician, SDTM programmers, ADaM/TFL programmers as well as a Senior Reviewing Statistician. A separate unblinded team will work independently of the blinded team to receive, review, and manage the unblinded data. The unblinded team--including unblinded statisticians and unblinded programmers--do not have any day-to-day roles in the conduct of the trial.

The IAs and any SMC will occur while the trial is still blinded. Unblinded outputs during the course of the trial will be presented to the SMC in a fully unblinded fashion for vaccine groups in summaries, and listings will be presented by vaccine group. A list of IA outputs is maintained in the document *ICVX-12-201 Interim Analysis Tables Listings Figures*.

The blinded team will develop and validate the SAS programs necessary for analysis on the blinded data. Once validated, the unblinded programming team members will run the SAS programs on the unblinded trial data in a secure, access-restricted area. The unblinded statistician will review the outputs produced by the unblinded team. For the SMC, unblinded outputs will be distributed via Cocinnity in an unblinded area for the SMC, where only unblinded members have access. Otherwise, unblinded outputs will be distributed via Egnyte in an unblinded area, where only unblinded members have access.

Data with the potential to unblind will be available to the blinded team only in a blinded fashion. Any potentially unblinding information would be masked prior to hand-off to the blinded team.

The main trial will remain blinded until database lock for the primary analysis at Day 365, except for subjects who will receive a letter with their treatment assignment at their Day 365 visit. Blinded Clinical Research Associates and the Blinded Clinical Lead will also be unblinded at the end of each Day 365 visit. The remaining team members will remain blinded until every subject has completed their Day 365 visit and the Day 365 database has been locked. At the time of primary analysis, the SYNH blinded biostatistics team will become unblinded. For further details, reference the Unblinded Team Management Plan.

4.5. Administration of Study Medication

In the main trial, IVX-A12 +/- MF59 or placebo will be administered intramuscularly as a single dose.

4.6. Trial Procedures

4.6.1. Main Trial Procedures

Randomization will occur simultaneously into all three vaccine trial groups (IVX-A12a, IVX-A12d, and placebo). Initial vaccinations will be performed in sentinel subjects and then expanded to the remaining subjects in each of the three trial groups. In total, there will be 40 sentinels. In each IVX-A12 group, 16 sentinel subjects will receive IVX-A12a (8 subjects from age stratum 60 to 69 years of age and 8 subjects from age stratum 70 to 85 years age); 16 sentinel subjects will receive IVX-A12d (8 subjects from age stratum 60 to 69 years of age and 8 subjects from age stratum 70 to 85 years age). In the placebo group, 8 sentinel subjects will receive placebo (4 subjects from age stratum 60 to 69 years of age and 4 subjects from age stratum 70 to 85 years of age). Sentinels will be closely monitored for a minimum of 48 hours. If no stopping rules are triggered, the remaining subjects in the IVX-A12 and placebo groups will be enrolled. The independent SMC will be responsible for the application of stopping rules, if achieved.

Trial subjects will receive a single dose on Day 0 (Study Day 1). The cohorts are shown in Table 1. The Time and Events Schedule is described in the protocol.

There will be a total of seven scheduled clinic visits required for each subject (at screening, then Days 0, 7, 28, 90, 180, and 365), and five phone contacts (on Days 3, 14, 56, 135, and 270) for all subjects.

4.6.2. Observational Extension Trial Procedures

There will be a total of two scheduled clinic visits required for each subject (Day 365 and Day 730) and one phone contact (on Day 545) for all subjects. Note: The Sponsor terminated the trial prior to Day 545.

5. Endpoints

The primary, secondary, and exploratory endpoints used to evaluate safety and immunogenicity are described in the following sections:

5.1. Main Trial Endpoints

5.1.1. Primary Endpoint(s)

5.1.1.1. Co-primary Endpoints (Safety)

- Solicited local (injection site) reactions and systemic ARs for 7 consecutive days starting from Day 0 to Day 6;
- Unsolicited AEs from Day 0 to Day 28.

5.1.1.2. Co-primary Endpoints (Immunogenicity)

- Geometric mean titers (GMT) of RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb at Day 28;
- GMT of RSV and hMPV prefusion F protein-specific IgG antibody titers at Day 28;
- Proportion of subjects with a ≥4-fold increase in serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb from prevaccination/baseline (Day 0) to Day 28 after vaccination (defined as SRR);
- Proportion of subjects with ≥4-fold increase (SRR) in RSV- and hMPV-specific IgG antibody titers from prevaccination/baseline (Day 0) to Day 28;
- Geometric mean fold rise (GMFR) at Day 28 versus Day 0 in serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb and RSV and hMPV prefusion F protein-specific IgG antibody titers.

5.1.2. Secondary Endpoints

5.1.2.1. Safety Secondary Endpoints

- SAEs, MAAEs, AESIs (including pIMCs) and AEs leading to trial withdrawal up to Day 365 (end of the main trial);
- Mild, moderate, or severe LRTI caused by RSV and/or hMPV (CESI) up to Day 365;
- Clinical safety laboratory parameters at screening, and Days 0, 7, and 28;
- Mild, moderate, or severe LRTI cases not caused by RSV or hMPV up to Day 365.

5.1.2.2. Immunogenicity Secondary Endpoints

- GMT of RSV/A–, RSV/B-, hMPV/A-, and hMPV/B-specific NAb at Days 0, 180, and 365;
- GMTs of RSV and hMPV prefusion F protein-specific IgG antibody titers at Days 0, 180, and 365;
- Proportion of subjects with a ≥4-fold increase (SRR) in serum anti-RSV/A-, RSV/B- hMPV/A-, and hMPV/B-specific NAb from prevaccination/baseline (Day 0) to Days 180, and 365 after vaccination;
- Proportion of subjects with an ≥8-fold increase in serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb from prevaccination/baseline (Day 0) to Days 28, 180, and 365 after vaccination;
- Proportion of subjects with ≥4-fold increase (SRR) in RSV- and hMPV- prefusion F protein-specific IgG antibody titers from prevaccination/baseline (Day 0) to Days 180 and 365 after vaccination;

- GMFR at Days 180 and 365 versus Day 0 in serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb and RSV and hMPV prefusion F protein-specific IgG antibody titers;
- Reverse cumulative distribution (RCD) of serum NAb and IgG antibody titers at Days 0, 28, 180, and 365.

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6. Analysis Sets

This section will provide definitions of analysis sets to be analyzed.

6.1. Main Trial Analysis Sets

6.1.1. All Enrolled Set

The All Enrolled Set will include all screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and vaccine group allocation status in the trial. Unless specified otherwise, this set will be used for summaries of subject disposition and listings.

6.1.2. Randomized Set

The Randomized Set will include all enrolled subjects who have been randomized.

6.1.3. Safety Set

The Safety Set will consist of all subjects who received any amount of IVX-A12 or placebo. Subjects will be analyzed as "treated" (i.e., according to the vaccine a subject actually received, rather than the vaccine to which the subject may have been randomized). The set will be used for all analyses of safety endpoints.

6.1.4. Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects and received a dose of IVX-A12 or placebo. Subjects will be analyzed according to randomized group. This set will be used for analysis of demographics and other baseline characteristics and subject listings for immunogenicity.

6.1.5. Per Protocol Set

The Per Protocol Sets (PPS) will include all subjects in the FAS who received a dose of IVX-A12 or placebo and have no major protocol deviations, which may exclude subjects from PPS. Subjects will be analyzed according to randomized group. If a subject has a major protocol deviation or RSV/hMPV infection after Day 28, their post-Day 28 data point may be excluded. Blinded data review meeting (BDRM) will be conducted prior to each Interim Analysis and prior to data base lock and unblinding of the vaccine groups. During the BDRMs, a final decision (sponsor call) will be taken as to which subjects/visit will be excluded.

6.2. Observational Extension Trial Analysis Set

6.2.1. Extension Enrolled Set

The Extension Enrolled Set (EES) will consist of eligible subjects who consented to participate in the extension portion of the trial. Subjects will be analyzed as initially treated.

6.3. Protocol Deviations

Protocol deviations are defined as instances in which subjects or investigational site study personnel fail to adhere to the protocol requirements (e.g., eligibility criteria, addition or deletion of tests, dosing, duration of treatment, and/or any other aspect of the study design) and the deviation is considered major if the deviation has the potential to impact subject safety or the primary and secondary endpoints of the trial. Deviations are collected in Clinical Trial Management System (CTMS).

7. General Aspects for Statistical Analysis

7.1. General Methods

- No formal statistical hypotheses to be tested for the study. 95% confidence interval (CI) and p-value are presented for data nature.

- Unless otherwise specified, summaries will be presented by vaccine group, aggregate IVX-A12, and overall.

- Vaccine groups will be categorized as:
  - Main Trial:
    - 150 µg RSV/ 150 µg hMPV IVX-A12a (unadjuvanted)
    - 150 µg RSV/ 150 µg hMPV IVX-A12d (adjuvanted with MF59®)
    - Placebo

Aggregate IVX-A12 includes 150 µg RSV/ 150 µg hMPV IVX-A12a (unadjuvanted) and 150 µg RSV/ 150 µg hMPV IVX-A12d (adjuvanted with MF59®).

  - Observational Extension Trial:
    - 150 µg RSV/ 150 µg hMPV IVX-A12a (unadjuvanted)
    - Placebo

- All listings will display age, sex, and race.

- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Additionally, quartiles will be provided for continuous variables related to immunogenicity. The same number of decimal places as in the raw data will be presented when reporting minimum and maximum; 1 more decimal place than in the raw data will be presented when reporting mean, median, least squares, and quartiles; and 2 more decimal places than in the raw data will be presented when reporting SD. No more than 3 decimal places will be presented. For confidence intervals (CIs) for mean will be presented with the same decimal places as the mean. For p-values and correlations, 3 decimal places will be presented. P-values <0.001 and >0.999 with be presented as '<0.001' and '>0.999', respectively.

- Descriptive statistics for categorical/qualitative data will include frequency counts and percentages. The total number of subjects in each vaccine group and placebo will be used as the denominator for percentage calculations, unless stated otherwise in the table shell. All percentages will be presented with one decimal point, unless specified otherwise. For percentages equal to 100 will show as 100 rather than 100.0.

- For antibody titer and concentration, antibody concentrations above the lower limit of quantification (LLOQ) are considered accurate and their quantitated values will be reported. In computing geometric means (GM), a titer or concentration reported as < LLOQ will be converted to a value of ½ LLOQ. For calculating a fold-rise, < LLOQ will be converted to ½ LLOQ for a numerator, and < LLOQ will be converted to LLOQ for a denominator when only one of either the numerator or denominator is < LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way. If >Upper Limit, the upper value will be used to compute GM and fold-rise. Antibody titers and concentrations below the lower limit will be set to ½ LLOQ before performing GMT/GMFR calculations.

- For lab results with inexact values, <LLOQ will be converted to ½ LLOQ and >Upper limit will be analyzed as the upper value.
- All statistical analyses will be conducted with the SAS® software package version 9.4 or higher.
- Continuous immunogenicity endpoints will be logarithmically transformed with 2 as base for analysis.

7.1.1. Geometric Mean Titers (GMTs)

Unadjusted GMTs

Unadjusted GMTs and associated 2-sided 95% CI for PPS and EPPS will be calculated for each vaccine group. 95% CIs will be calculated by back transformation of the 95% CI for the mean of the log2 transformed assay results computed using Student's t distribution.

Adjusted GMTs

Adjusted GMTs and associated 2-sided 95% CIs will be obtained using an analysis of covariance (ANCOVA). Unless otherwise noted, for the ANCOVA, log2-transformed titers will be the outcome and vaccine group, age stratification category (age 60-69, age 70-85), and gender as factors and log2-transformed baseline titer as a continuous covariate. Least square means and 95% CIs will be back transformed to provide adjusted GMTs and confidence intervals for each grouping.

For the ANCOVA by age subgroup analyses category (as defined in Section 7.6), log2-transformed titers will be the outcome and vaccine group, age stratification category, and gender as factors and log2-transformed baseline titer as a continuous covariate. Least square means and 95% CIs will be back transformed to provide adjusted GMTs and confidence intervals for each grouping.

For tertile analyses (and by age subgroup analyses category and tertile), adjusted GMTs and associated 2-sided 95% CIs will be obtained using an analysis of variance (ANOVA). For the ANOVA, log2-transformed titers will be the outcome and vaccine group, age stratification category, and gender will be factors. Least square means and 95% CIs will be back transformed to provide adjusted GMTs and confidence intervals for each grouping.

Note: For the ANCOVA and ANOVA models, the factor of vaccine group consists of 150 µg RSV/ 150 µg hMPV IVX-A12a (unadjuvanted), 150 µg RSV/ 150 µg hMPV IVX-A12d (adjuvanted with MF59®), and Placebo for the PPS.

7.1.2. Geometric Mean Fold Rise (GMFR)

Unadjusted and adjusted GMFRs will be calculated similarly as the unadjusted and adjusted GMTs.

7.1.3. Geometric Mean Ratio (GMR)

For each subject and visit, the ratio of serum anti-RSV/A versus RSV/B and serum anti-hMPV/A versus hMPV/B titers and fold-rises will be calculated to determine the GMR of titers and fold-rises.
The unadjusted geometric mean ratio (GMR) and 95% CIs of the titers and fold-rise for serum anti-RSV/A versus RSV/B and serum anti-hMPV/A versus hMPV/B will be calculated similarly to the unadjusted GMTs. The adjusted GMRs and 95% CIs will be calculated, similarly to the adjusted GMT models. The log2 transformed baseline titers will be included as the continuous covariates.

For each subject and visit, the ratio of fold-rise in IgG prefusion F protein-specific antibody titers versus the fold-rise in the corresponding Nab titers of serum anti-RSV/A or hMPV/A will be calculated to determine the GMR.

The unadjusted GMR and 95% CIs of the fold-rise in IgG prefusion F protein-specific antibody titers versus the fold-rise in the corresponding Nab titers of serum anti-RSV/A or hMPV/A will be calculated similarly to the unadjusted GMTs. The adjusted GMRs and 95% CIs will be calculated, similarly to the adjusted GMT models. The log2 transformed baseline titers will be included as the continuous covariates.

7.1.4. 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.

When summarizing by age subgroup category, 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 by total arm within each age subgroup category.

7.1.5. Reverse Cumulative Distribution Curves (RCDCs)

Reverse cumulative distribution curves (RCDCs) for assays (on a log scale for x-axis) for a combination of available time points and vaccine groups will be generated.

7.1.6. Tukey Method for Outlier Detection

Tukey's method for outlier detection will be implemented whereby datapoints either below Q1 − 1.5IQR or above Q3 + 1.5IQR are flagged. (Q1 and Q3 represent the 25th and 75th percentile of the data, respectively. IQR represents the width of the interquartile range). When utilizing the Tukey Method, the datapoints, including the boundaries, will be calculated using the log2 transformed values. The outliers and boundaries will be back-transformed for presentation.

7.1.7. Immunogenicity Titers and Concentrations below LLOQ or above ULOQ

Antibody titers and concentrations below the LLOQ will be set to LLOQ before performing the conversion, as described in section 7.1, for GMT/GMFR calculations. Antibody titers and concentrations above the ULOQ will be set to ULOQ before performing GMT/GMFR calculations. Methods of computation involving LLOQ and ULOQ are described in section 7.1.

7.2. Key Definitions

Baseline

Unless otherwise specified, Baseline is defined as the last available value prior to the first administration of IVX-A12 vaccine (or placebo) and includes assessments taken on Day 0 (Study Day 1).

Change from baseline

The change from baseline will be calculated for each post-baseline assessment as:

Change from Baseline = Post-baseline value - Baseline value

Fold Change from baseline

The fold change from baseline will be calculated for each post-baseline assessment as:

Fold change from Baseline = Post-baseline value / Baseline value

Study Day

Study day is calculated as (event date – vaccination date + 1) if event date >= vaccination date; and (event date – vaccination date) if event date < vaccination date.

7.3. Missing Data

This section will describe the handling of missing data and partial/missing dates.

7.3.1. Safety Data

Missing date imputation will be applied to prior and concomitant medications and adverse events as described in Table 2.

Table 2: Imputation Rules for Missing Start/Stop Dates

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Date is completely missing	Impute the date as dose date	If the status is ongoing then do not impute, i.e., leave the end date missing; if the status is not ongoing, then impute the date as the study end reference date
Missing month and day, and the year is present	If the year is the same as the year of dose date, then impute day and month same as dose day and month; If the year is different with dose year, then use January 1	If the year is the same as the year of the study end reference date, then impute the day and month same as the day and month of the study end reference date; If the year is different from the year of study end reference date, then use December 31
Missing day, but year and month are present	If the year and month are the same as the year and month of dose date, then impute the date same as dose date; If Year or month are different with than dose year or month, then impute the date as first day of that month	If the year and month are the same as the year and month of the study end reference date, then impute the day same as the day of the study end reference date; If the year or month is different from the year or month of the study end reference date, use the last day of the month.

Missing month, but year and day are present	If year is the same as dose year than then impute the month same as dose; If Year is different with dose year, than then impute the month as January	If the year is the same as the year of study end reference date, then impute the month same as the month of study end reference date; If the year is different from the year of study end reference date, then impute the month as December.

7.3.2. Immunogenicity

Missing immunogenicity data will be retained as missing.

7.4. Visit Windows

There will be no derivation for visit windows in terms of summary of assessments. Nominal visits will be used for listings and tables.

7.5. Analysis Windows for Immunogenicity

Immunogenicity results will be excluded if the study day collected occurs outside of the analysis windows, as indicated in Table 3.

Table 3: Immunogenicity Analysis Windows

Scheduled Visit	Analysis Target Study Day	Analysis Window	Analysis Window	
			Lower Bound	Upper Bound
Day 28	29	± 5 days	24	34
Day 180	181	± 14 days	167	195
Day 365	366	± 21 days	345	387

7.6. Unscheduled Visits

Data collected at unscheduled visits will be included in listings but not included in summaries. Unscheduled visits may be included in shift tables when specified.

7.7. Subgroups

Subgroup analysis will be completed by age subgroup analyses category (age 60-69, age 70-85, age 70-79, age 80-85, and age 60-75 [at randomization]) and baseline tertiles (RSV-A, RSV-B, hMPV-A and hMPV-B NAbs and RSV and hMPV IgG prefusion F protein-specific antibody titers), where specified.

Additional subgroup analyses may be requested on an as-needed basis.

8. Demographics, Other Baseline Characteristics and Medication

Demographics, Other Baseline Characteristics and Medication will be presented separately for the main trial and observational extension trial.

8.1. Main Trial Demographics, Other Baseline Characteristics and Medication

8.1.1. Subject Disposition and Withdrawals

Subject disposition will be presented for all enrolled subjects, which will include the following:

- The number of subjects enrolled (i.e., provided informed consent and provided demographic and/or baseline screening assessments);
- The number of subjects resulting in screen failure;
- The number of subjects screened but not randomized;
- The number of subjects randomized.

Among the randomized subjects, the following will be summarized by vaccine groups and aggregate IVX-A12 and Overall:

- The number of subjects randomized by age stratification category
- The number (%) of subjects in Safety Set;
- The number (%) of subjects in Full Analysis Set and Per Protocol Set;
- The number (%) of subjects who completed the main trial;
- The number (%) of subjects who continue to observational extension trial;
- The number (%) of subjects who prematurely discontinued from the trial and the associated reasons.

All disposition will also be listed. Listings of inclusion in analysis sets and exclusion reasons will also be presented.

A summary of screen failures will be presented, which will include the number (%) of subjects resulting in screen failure and their reason for not being eligible. Also, for the screen failures who do not meet eligibility criteria, the inclusion or exclusion criteria not being met will be presented.

A list of protocol deviations will be provided with the date the deviation occurs, the category (eg, inclusion/exclusion criteria, informed consent (ICF)/subject privacy, etc.), severity (major/minor) and the description of the deviation. Major and minor protocol deviations will be summarized separately in the same table by vaccine group, IVX-A12 aggregate, and overall for the Randomized Set.

8.1.2. Demographic and Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the Full Analysis Set by vaccine group, IVX-A12 aggregate, and overall. Descriptive statistics for height, weight, and body mass index (BMI) will be presented including n, mean, SD, median, minimum, and maximum for numeric variables and frequency and percentage for categorical variables.

Demographics and baseline characteristics will include age (descriptive statistics and categorically by age subgroup analyses categories: 60 to 69 years, 70 to 85 years, 70-79 years, 80-85 years, 60-75 years, gender, race, ethnicity, Dalhousie Clinical Frailty Score, height, weight, body mass index). Collected age (at time of randomization) will be used in table.

Height (in cm) at baseline = height (in inches) * 2.54

Weight (in kg) at baseline = weight (in lbs) * 0.4536

BMI (kg/m^2) at baseline = $Weight(kg)/[Height(cm)*0.01]^2$

Baseline RSV-A (IU/mL, MN50 titer), RSV-B (IU/mL, MN50 titer), hMPV-A, hMPV-B titers, and their corresponding tertiles will be presented including n, geometric mean, median, minimum and maximum.

Demographics and baseline characteristics will be repeated for the Safety Set and Per Protocol Set.

Demographics and baseline characteristics will also be repeated by age subgroup analyses categories for the Safety Set and Per Protocol Set.

Eligibility, including Inclusion/exclusion criteria, demography, baseline characteristics, smoking and alcohol use history, household information will be listed.

8.1.3. Medical History and Concomitant Diseases

Medical and surgical history will be summarized by primary System Organ Class (SOC) and Preferred Term (PT) coded via Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or greater. The number and percentage of subjects will be displayed for each SOC and PT for the Safety Set by vaccine group, IVX-A12 aggregate, and overall. Summaries will be ordered by descending frequency of SOC, and then within a SOC, by overall descending frequency of PT in the total column. If a subject has one or more history events more than once, the subject is counted only once under any given SOC or PT.

All medical history data of subjects will be listed for the Safety Set.

8.1.4. Vaccine History

All non-trial vaccines that were received within the past one year will be summarized by vaccine names. The number and percentage of subjects will be displayed for each vaccine name for the Safety Set by vaccine group, overall IVX-A12 aggregate, and overall. Number of subjects with at least one vaccine received within the past one year resulting in a reaction will also be summarized.

All vaccine history data of subjects will be listed for the Safety Set.

8.1.5. Medication

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) Format B3 Version March 2023.

Prior medications are defined as any medications taken before trial dose administration, regardless of whether it was stopped prior to the trial dose administration. Concomitant medications are defined as any medications with start date or stop date on or after the trial dose administration until the end of the main trial. The prior and concomitant medications will be summarized separately.

For the purposes of classifying medications into prior/concomitant, the algorithms in section 7.3.1 will be used for imputing missing dates.

Medications will be summarized by Anatomical Therapeutic Chemical (ATC) Level 4 and PT. If ATC Level 4 is missing, the next higher non-missing ATC Level will be used. For each medication, the number and percentage of subjects will be displayed for the Safety Set by vaccine group, IVX-A12 aggregate, and overall. The tables will be sorted by overall descending frequency of ATC Level 4 and then, within an ATC Level, by overall descending frequency of PT in the total column. If a subject has one or more medications more than once, the subject is counted only once under any given ATC Level 4 or PT.

All prior and concomitant medications, up to the end of the main trial, will be listed for the Safety Set.

8.1.6. Extent of Exposure

All subjects are planned to receive either a) 1 dose of IVX-A12 at two dose levels, with or without MF59® adjuvant, or b) 1 dose of placebo. The doses are administered at Day 0 (Study Day 1). Dose administration data will be summarized and analyzed for the Safety Set, by vaccine group, IVX-A12 aggregate, and overall.

The number and percentage of subjects who received vaccination will be summarized. The frequency and percentage of administration route, body location, and laterality for each vaccination will be displayed as well.

A listing will be provided for the Safety Set.

8.2. Observational Extension Trial Demographics, Other Baseline Characteristics and Medication

A listing of subject disposition, including study discontinuation reason, will be provided for all subjects who continue into the observational extension trial (EES).

No baseline characteristics, protocol deviations, medical history or medication data will be provided.

9. Immunogenicity

9.1. Main Trial Immunogenicity

The immunogenicity analyses will be performed on the PPS, unless otherwise stated. Immunogenicity results will be excluded if the study day collected occurs outside of the analysis windows as indicated in Table 3.

All data will be listed, for the FAS, until the end of the main trial.

9.1.1. Primary Immunogenicity Endpoints and Analyses

The primary immunogenicity endpoints are listed in section 5.1.1.2. The definition of geometric mean titer (GMT) and geometric mean fold rise (GMFR) are provided in section 7.1.

9.1.1.1. Analysis for Primary Immunogenicity Endpoint

The unadjusted GMT of RSV/A RSV/B-, hMPV/A-, and hMPV/B-specific NAb (live-virus assays) at Day 28 will be calculated with their 95% CIs (unadjusted) by vaccine group, aggregate IVX-A12, and overall. The GMT of RSV and hMPV IgG prefusion F protein-specific antibody titers (ELISAs) at Day 28 will also be provided. Quartiles, minimum and maximum of the NAbs will also be displayed.

The unadjusted geometric mean fold rise (GMFR) at Day 28 versus baseline (Day 0) of (in serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb ([live-virus assays]) and RSV and hMPV IgG prefusion F protein-specific antibody titers ([ELISAs]), and the ratios will be calculated at Day 28 with their 95% CI for PPS by vaccine group, aggregate IVX-A12, and overall. A complete case analysis will be performed whereby those subjects in the PPS with Day 28 data are included. 95% CIs (unadjusted) will be calculated by back transformation of the 95% CI for the mean of the log2 transformed individual fold rise computed using Student's t distribution. Quartiles, minimum and maximum of the fold-rise in antibody titer from baseline (Day 0) to Day 28 will also be displayed.

Using an ANCOVA, the adjusted GMTs and GMFRs at Day 28 and its 95% CI will be calculated. The outcome variable is Day 28 log2 transformed titers. The factors will include vaccine group, age stratification category, and gender and the covariates will include, log2 transformed baseline titers. Least square means and 95% CIs are back transformed to provide geometric means. To assess whether an adjuvant is required in the formulation to enhance immune responses to IVX-A12, pairwise comparison of the GMT and GMFR least square means from this modeling between non-adjuvant and adjuvant groups will also be displayed. Also, to assess an improvement between the active treatments (IVX-A12a and IVX-A12d) versus placebo, pairwise comparison of the GMT and GMFR least square means from this modeling between IVX-A12a and Placebo and IVX-A12d and Placebo will be displayed. No adjustments for multiplicity will be performed. Data displays will also include boxplots of titers for anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B specific NAb ([live-virus assays]) and RSV and hMPV IgG prefusion F protein-specific antibody titers ([ELISAs] at Day 28 for all ages. Log2 transformed titers will be used to create boxplots and back-transformed. The y-axis will be on a log scale. For anti-RSV/A- and RSV/B, the y-axis will display both sets of units.

The above analysis will be repeated as follows:

- By age subgroup analyses category. When using an ANCOVA, the outcome variable is Day 28 log2 transformed titers. The factors will include vaccine group, age stratification category and gender and the covariate is log2 transformed baseline titers;

- By baseline tertile; When using an ANOVA, the outcome variable is Day 28 log2 transformed titers. The factors will include vaccine group, age stratification category and gender;
- By age subgroup analyses category and baseline tertile. When using the ANOVA, the factors will include vaccine group, age stratification category, and gender.

9.1.1.2. Analysis of Subjects with a ≥4-Fold Increase

The proportion of subjects with a ≥4-fold increase in serum anti-RSV/A-, RSV/B-, hMPV/A-, hMPV/B-specific NAb (live-virus assays), RSV and hMPV IgG prefusion F protein-specific antibody titers will be calculated at Day 28 and summarized by vaccine group for each of the following: RSV-A, RSV-B, both RSV strains, either RSV strains, hMPV-A, hMPV-B, both hMPV strains, either hMPV strains, RSV and hMPV IgG prefusion F protein-specific antibody titers. The 95% CI of the difference in proportion of subjects with a ≥4-fold increase in serum anti-RSV/A-, RSV/B-, hMPV/A-, hMPV/B-specific NAb (live-virus assays), RSV and hMPV IgG prefusion F protein-specific antibody titers between vaccine groups with and without adjuvant and IVX-A12a versus Placebo and IVX-A12d versus Placebo will be computed using Wilson's score method. Logistic regression models will be used to further describe the IVX-A12d response to vaccination when compared to IVX-A12a. Also, logistic regression models will be used to describe the response of IVX-A12a versus Placebo and the response of IVX-A12d versus Placebo. The outcome variable is binary (≥4-fold increase or no ≥4-fold increase). Vaccine group, log2 transformed baseline NAbs titer, age stratification category, and gender are included as explanatory variables.

The ≥4-fold increase analyses will be repeated for the following:

- By vaccine group and age subgroup analyses category. For the logistic regression models, vaccine group, log2 transformed baseline titer, age stratification category and gender are included as the explanatory variables;
- By vaccine group and baseline tertile; For the logistic regression models, vaccine group, age stratification category and gender are included as the explanatory variables;
- By vaccine group and age subgroup analyses and baseline tertile. For the logistic regression models, vaccine group, age stratification category and gender are included as the explanatory variables.

9.1.1.3. Analysis of Correlation

Spearman rank correlation coefficient will be calculated to determine correlation between RSV/A, RSV/B, hMPV/A, and hMPV/B, RSV IgG prefusion F protein-specific antibody titers, hMPV IgG prefusion F protein-specific antibody titers, and VLP core IgG specific titers at Day 0, Day 28, Day 180 and Day 365 across all vaccine groups.

9.1.1.4. Outlier Detection

All titer outliers, for the PPS, will be listed using Tukey's method as described in section 7.1.6 for Day 0 and Day 28 for serum anti-RSV/A–, RSV/B-, hMPV/A-, hMPV/B–specific NAbs, and RSV and hMPV IgG prefusion F protein-specific antibody titers.

9.1.2. Secondary Immunogenicity Endpoint(s) and Analyses

The secondary immunogenicity endpoints are defined in section 5.1.2.2. The definition of geometric mean fold rise (GMFR) is provided in section 7.1.

The GMTs and adjusted GMTs for serum anti-RSV/A–, RSV/B-, hMPV/A- and hMPV/B–specific NAbs by live-virus assays at Days 180, and 365 will be calculated as described in section 9.1.1.1. The RSV and hMPV prefusion F protein–specific IgG antibody titers by ELISA will also be calculated at Days 180 and 365 as described in section 9.1.1.1. The analyses will be performed for the following:

- By vaccine group;
- By vaccine group and age subgroup analyses category;
- By vaccine group and baseline tertile;
- By vaccine group, baseline tertile and age subgroup analyses category.

GMTs, descriptive statistics, and 95% CIs will be produced for Day 0 for RSV/A-, RSV/B-, hMPV/A-, and hMPV/B- specific NAbs, and RSV and hMPV prefusion F protein-specific IgG antibody titers.

The GMFRs and adjusted GMFRs using ANCOVA (or ANOVA) for serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B specific NAb ([live-virus assays]) and RSV and hMPV IgG prefusion F protein-specific antibody titers ([ELISAs] and the ratios at Days 180, and 365 will be analyzed similarly as described in section 9.1.1.1. The analyses will be performed for the following:

- By vaccine group;
- By vaccine group and age subgroup analyses category;
- By vaccine group and baseline tertile;
- By vaccine group, baseline tertile and age subgroup analyses category.

Data displays will also be produced for repeat titer and fold-rise box plots for Days 0, 180, and 365 as described in section 9.1.1.1.

To assess the durability of RSV/A-, RSV/B-, hMPV/A-, and hMPV/B NAbs, and RSV and hMPV IgG prefusion F protein-specific antibody titers, the geometric fold-rise (decay) from Day 28 to Day 180 and Day 28 to Day 365 will be calculated. 95% CIs will be calculated by back transformation of the 95% CI for the mean of the log2 transformed individual fold rise computed using Student's t distribution. Median and quartiles of the fold-rise in antibody titer from Day 28 to Day 180 and Day 28 to Day 365 will also be displayed. The analyses will be performed for the following:

- By vaccine group;
- By vaccine group and age subgroup analyses category;
- By vaccine group and baseline tertile;
- By vaccine group, baseline tertile and age subgroup analyses category.

The geometric mean ratio (GMR) of the titers and fold-rise for serum anti-RSV/A- versus RSV-B will be calculated as described in section 9.1.1.1 for all scheduled visits. Similarly, GMR will be produced for the ratio of serum anti-hMPV/A versus hMPV/B. This analysis will be performed for the following:

- By vaccine group;
- By vaccine group and age subgroup analyses category.

The GMR of the fold-rise in IgG prefusion F protein-specific antibody titer (ELISA) versus the fold rise in NAbs at all post-baseline visits for RSV and hMPV. This analysis will be performed for the following:

- By vaccine group;
- By vaccine group and age subgroup analyses category.

The proportion of subjects with ≥4-fold increase in serum anti-RSV/A-, RSV/B-, hMPV/A- and hMPV/B-specific NAb versus baseline for Days 180 and 365 will be analyzed similarly as describe in section 9.1.2 by vaccine group, by vaccine group and age subgroup analyses category, by vaccine group and baseline tertile, and by vaccine group, baseline tertile, and age subgroup analyses category.

A similar analysis will be repeated for the proportion of subjects with ≥8-fold increase for all post-baseline visits in serum anti-RSV/A-, RSV/B-, hMPV/A- and hMPV/B-specific NAbs, as described in section 9.1.1.2, for the following:

- By vaccine group;
- By vaccine group and age subgroup analyses category.

Tertile analyses will not be completed for ≥8-fold increase.

Reverse cumulative distribution (RCD) curves will be provided for baseline (Day 0) to Days 28, 180, and 365 for the following assays: RSV/A-, RSV/B-, hMPV/A-, hMPV/B-specific NAbs and RSV and hMPV prefusion F protein-specific IgG antibody titers. RCD curves will produced for the following:

- By vaccine group;
- By vaccine group and age subgroup analyses category.

Analysis of correlation will be repeated, as described in section 9.1.1.3, for Days 180 and 365.

Outliers will be listed, as described in section 9.1.1.4, for Days 180 and 365.

To identify unknown RSV or hMPV infections, boxplots will be produced for serum anti-RSV/A–, RSV/B-, hMPV/A- and hMPV/B–specific NAbs to display the fold-rise from Day 28 to Day 180, Day 28 to Day 365, and Day 180 to Day 365. The box plots will be produced for the PPS and will utilize log2 transformed fold-rise and back-transformed. Listings will also be generated for serum anti-RSV/A–, RSV/B-, hMPV/A- and hMPV/B–specific NAbs, where fold increase ≥ 8, from Day 28 to Day 180, Day 28 to Day 365, and Day 180 to Day 365. The listings will be produced for the FAS.

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9.2. Observational Extension Trial Immunogenicity

No immunogenicity analysis will be performed for the observational extension trial due to early termination of the extension.

10. Safety

Safety will be presented separately for the main trial and observational extension trial.

10.1. Main Trial Safety

The safety analyses will be performed on the Safety Set and will include all data up to the end of the main trial, unless noted otherwise.

10.1.1. Adverse Events

Adverse events are collected as solicited, unsolicited AEs, SAEs, CESIs, and MAAEs. Solicited ARs are recorded in the subject diary; unsolicited AEs are collected on AE page of case report forms (CRFs). Furthermore, a solicited ARs that is ongoing after the diary period, leads to trial discontinuation, or results in an MAAE or SAE, should be entered on the AE page of the CRF as an unsolicited AE. The following are primary endpoints: Solicited local reactions and systemic ARs from the day of dosing (Day 0) through Day 6 (Study Day 1 to Study Day 7); Unsolicited AEs from day of dosing (Day 0) through 28 days post-vaccination (Study Day 1 to Study Day 29). SAEs, MAAEs and AEs leading to trial withdrawal from day of dosing (Day 0; Study Day 1) up to the end of the main trial, CESIs (mild, moderate or severe lower respiratory tract infection (LRTI) caused by RSV and/or hMPV) from day of dosing (Day 0; Study Day 1) up to the end of the main trial, and AESIs (including anaphylaxis, thrombocytopenia, and pIMCs, including Guillain Barre's syndrome, as defined in section 16) are secondary safety endpoints. AE summaries will be performed on the Safety Set, unless otherwise stated.

An overall summary of the number and percentage of subjects reporting any solicited ARs, Grade 3 solicited ARs, Grade 4 solicited ARs, ≥Grade 3 solicited ARs any unsolicited AEs, trial vaccine-related unsolicited AEs, Grade 3 unsolicited AEs, Grade 3 trial vaccine-related AEs, Grade 4 unsolicited AEs, Grade 4 trial vaccine-related AEs, ≥Grade 3 unsolicited AEs, ≥Grade 3 unsolicited AEs, SAEs, trial vaccine-related SAEs, CESIs, trial vaccine-related CESIs, AESIs (including pIMCs), trial vaccine-related AESIs (including pIMCs), MAAEs, trial-vaccine related MAAEs, AEs leading to trial discontinuation and AEs leading to death will be provided. The summary will be repeated by vaccine group and age subgroup analyses category.

A separate summary of the number and percentage of subjects reporting any AEs leading to main trial discontinuation, trial vaccine-related AEs leading to main trial discontinuation, SAEs leading to main trial discontinuation, trial vaccine-related SAEs leading to main trial discontinuation, CESIs leading to main trial discontinuation, trial vaccine-related CESIs related to main trial discontinuation, AESIs leading to main trial discontinuation, trial vaccine-related AESIs leading to main trial discontinuation, and MAAEs leading to main trial discontinuation, trial vaccine-related MAAEs leading to main trial discontinuation will also be provided. The summary will be repeated by vaccine group and age subgroup analyses category.

Listings will be provided for solicited ARs, unsolicited AEs, SAEs, CESIs, AESIs, MAAEs, non-RSV/hMPV LRTIs and AEs leading to main trial discontinuation for all data up to the end of the main trial. The listings will display study day, which is calculated as (event date – vaccination date + 1) if event date >= vaccination date; and (event date – vaccination date) if event date < vaccination date. AEs starting prior to the vaccination will be listed only and not included in summaries. A listing of solicited ARs, possibly reported incorrectly as unsolicited ARs, will also be included. If the solicited AR, possibly reported as an unsolicited AR, has a severity that is discrepant from the pre-defined diary, the discrepancy will also be reported.

10.1.1.1. Solicited Adverse Reactions within 7 Days of Trial Vaccine Administration

The occurrence of solicited ARs will be collected in the pre-defined diary by the subjects for 7 consecutive days following administration of vaccine dose (including the day of administration) and will be recorded on the CRF.

In this trial, solicited local ARs including pain, tenderness, erythema, and swelling. Solicited systemic ARs including headache, chills, fatigue, myalgia, arthralgia, vomiting, diarrhea, and fever occurring from the day of vaccination to 7 days post-vaccination. Solicited local and systemic ARs will be assessed as 'None', 'Mild', 'Moderate', 'Severe' or 'Potentially Life-threatening' according to defined severity grading scales as provided in protocol Table 7 and 8. Any solicited AR reported incorrectly as an unsolicited AE, as determined by the Icosavax medical lead, will be included in the solicited AR summaries, figures, and listings.

Solicited local and systemic ARs will summarized as below by vaccine group, aggregate IVX-A12, and overall:

- The number and percentage of subjects who experienced solicited ARs on each day within 7 days after the vaccine administration. The summary will be by day and overall within 7 days.
- The number and percentage of subjects who experienced solicited ARs by maximum severity.
- The number and percentage of subjects who experienced solicited ARs by number of days of occurrence (1-2 days, 3-5 days, 6+ days) and their corresponding 95% CIs.
    - Ongoing solicited ARs that become unsolicited adverse events will be included.

The above summaries will be repeated by age subgroup analyses category.

Stacked bar chart of solicited local and systemic ARs by maximum severity, and by maximum severity and age subgroup analyses category will also be provided.

10.1.1.2. Unsolicited Adverse Events

An unsolicited AE is an AE that was not solicited using the post-vaccination diary and that was spontaneously communicated by a subject. Unsolicited AEs will be collected for 28 days following the administration of the vaccination. Any solicited AR observed as continuing Day 7 following trial vaccination will be additionally recorded as an unsolicited AE.

Unsolicited AEs will be classified by system organ class (SOC) and preferred term (PT) according to MedDRA version 26.0 or greater.

The severity of AEs is determined by the investigator as Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3), and Potentially Life-threatening (Grade 4). If there are events with missing severity, the category 'Missing' will be summarized separately from the non-missing categories.

The relationship (causality) of AE to the vaccine will be assessed by the investigator as Related and Not Related. If there are events with missing relationship, the category 'Missing' will be summarized separately from the non-missing categories.

Any solicited AR reported incorrectly as an unsolicited AE, as determined by the Icosavax medical lead, will be included in the unsolicited adverse event summaries and listings.

Unsolicited AEs will be summarized as below by vaccine group, aggregate IVX-A12, and overall:

- The number and percentage of subjects reporting unsolicited AEs by SOC and PT.
- The number and percentage of subjects reporting unsolicited AEs by SOC, PT and maximum severity.
- The number and percentage of subjects reporting >=Grade 3 unsolicited AEs by SOC and PT.
- The number and percentage of subjects reporting vaccine-related unsolicited AEs by SOC and PT.
- The number and percentage of subjects reporting >=Grade 3 and vaccine-related unsolicited AEs by SOC and PT.

All above summaries will be repeated by age subgroup analyses category.

Summaries will be ordered by descending frequency of SOC, and then within each SOC, by overall descending frequency of PT in the total column. If a subject has one or more unsolicited AEs more than once, the subject is counted only once under any given SOC or PT.

A figure will be produced for unsolicited adverse events with a ≥2% total frequency by vaccine group. The percentage of subjects for each vaccine group will be displayed. Also, the risk difference (the difference in percentage of subjects that experience an unsolicited AE) and corresponding 95% CI will be displayed for IVX-A12a versus Placebo and IVX-A12d versus Placebo within figure.

10.1.1.3. Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Results in death;
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions);
- Congenital anomaly or birth defect in the offspring of a subject;
- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject, or may require intervention to prevent one of the other outcomes listed above.

All CESIs, AESIs and pIMCs occurring during the trial will also be reported as an SAE.

SAEs, up to end of the main trial, will be summarized as below by vaccine group, aggregate IVX-A12, and overall:

- The number and percentage of subjects reporting SAEs by SOC and PT.
- The number and percentage of subjects reporting SAEs by SOC and PT will be repeated by age subgroup analyses category.
- The number and percentage of subjects reporting vaccine-related SAEs by SOC and PT.
- The number and percentage of subjects reporting vaccine-related SAEs by SOC and PT by age subgroup analyses category.

All AEs leading to Death will be listed.

10.1.1.4. Medically-Attended Adverse Event (MAAE)

MAAEs are defined as AEs leading to an unscheduled visit to or by a healthcare professional, including visits to an emergency department, but not fulfilling seriousness criteria.

MAAEs, up to end of the main trial, will be summarized as below by vaccine group, aggregate IVX-A12, and overall:

- The number and percentage of subjects reporting MAAEs by SOC and PT.
- The number and percentage of subjects reporting MAAEs by SOC and PT will be repeated by age subgroup analyses category.
- The number and percentage of subjects who received concomitant medication treatment for the MAAEs by ATC Level 4 and PT.

10.1.1.5. Clinical Event of Special Interest (CESI)

CESIs are defined as AEs that will be specifically highlighted to the investigator. The single CESI for this trial is a CESI of mild (Grade1) moderate (Grade 2) to severe (Grade 3) lower respiratory tract illness (mild, moderate, or severe LRTI) caused by RSV and/or hMPV occurring in the subjects after vaccination.

CESIs. up to end of the main trial, are programmatically derived as defined in Protocol Section 10.1.3, and will be summarized as below by vaccine group, aggregate IVX-A12, and overall:

- The number and percentage of subjects reporting CESIs by SOC and PT.
- The number and percentage of subjects reporting vaccine-related CESIs by SOC and PT.

10.1.1.6. Adverse Events of Special Interest (AESI) and Potentially Immune-Mediated Disorders (pIMCs)

AESIs and pIMCs are AEs described by MedDRA preferred terms as defined in the protocol sections 10.4.4.1 and section 16 of the SAP.

AESIs, up to end of the main trial, will be summarized by vaccine group, aggregate IVX-A12, and overall as follows:

- The number and percentage of subjects reporting AESIs by SOC and PT.
- The number and percentage of subjects reporting vaccine-related AESIs by SOC and PT

10.1.1.7. LRTI Events Not Caused by RSV/hMPV

LRTIs not caused by RSV or hMPV, up to end of the main trial, will be summarized by vaccine group, aggregate IVX-A12, and overall, by reporting the number and percentage of subjects by SOC and PT.

10.1.2. Laboratory Evaluations

Clinical laboratory tests including hematology, clinical chemistry, and urinalysis will be collected at screening, Days 0, 7, and 28.

Hematology and clinical chemistry, up to end of the main trial, will be summarized as below by vaccine group, aggregate IVX-A12, and overall:

Numeric laboratory parameters: Actual values and change from baseline will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) by visit.

Shift tables for each hematology and chemistry laboratory parameters will summarize the change in the Federal Drug Administration (FDA) toxicity grades from baseline to the maximum post-baseline up to end of the main trial and for 'all visits up to Day 28' by vaccine group, aggregate IVX-A12, and overall. Unscheduled visits will be included. The denominator for percentages is the number of subjects assessed at each parameter and visit per baseline grade and with a post-baseline assessment.

For uni-directional parameters, i.e., parameters having only low grades or only high grades, a laboratory grade of 0 will be assigned to values within the normal range. Laboratory parameters having bi-directional FDA toxicity grading will have separate shift tables for each direction. For example, white blood cells will have a separate table for shift to low grade and shift to high grade. For each bi-directional parameter, a summary of shift to low grade will assign a toxicity grade of 0 to values within or above the normal range. Similarly, a summary of shift to high grade will assign a toxicity grade of 0 to values within or below the normal range.

All laboratory summaries will be repeated by age subgroup analyses category.

Data listings, up to end of the main trial, for laboratory test results will be provided, with an indicator for values that are outside the normal range. A listing including a subset of Grade 3 and Grade 4 toxicity hematology, chemistry, and urinalysis results will be provided.

A listing will also be provided for all abnormal urinalysis results of glucose, protein, white blood cells, and red blood cells. The listing will include all adverse events within 28 days of the abnormal assessment, including if the adverse event is considered an MAAE.

10.1.3. Vital Signs

Vital sign measurements include heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, pulse oximetry and temperature, and will be collected at screening, Days 0, 7, 28, 90, 180, and 365. Actual values and changes from baseline will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) by visit. Height, weight, BMI, and Dalhousie Frailty score are only required to be collected at the screening visit and summarized in the demographic and baseline characteristics table.

Vital sign abnormalities are assessed according to the FDA Toxicity Grading Scale (Grade 1, 2, 3, and 4).

Shift tables for each vital sign parameter will summarize the change in the FDA toxicity grades from baseline to the maximum post-baseline (up to end of the main trial) and all visits up to Day 28 by vaccine group, aggregate IVX-A12, and overall. Unscheduled visits will be included. The denominator for percentages is the number of subjects assessed at each parameter and category with a baseline assessment.

All vital sign summaries will be repeated by age subgroup analyses category.

Box plots will be produced for systolic blood pressure and diastolic blood pressure for all ages and timepoints. The y-axis will include the vital sign parameter and unit. The x-axis will include the visit.

All vital sign results will be listed up to end of the main trial, including toxicity grade. A listing including a subset of Grade 3 and Grade 4 results will be provided.

10.1.4. Physical Examination

A full physical examination is performed at screening according to the investigator's standard practice. Additional physical examinations may be performed if indicated by review of the subject's medical history. Symptom-directed physical examinations are performed at subsequent visits if deemed necessary, including Days 0, 7, 28, 90, 180 and 365.

Any abnormal findings will be recorded. The clinical significance assessment of each body system ('Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant') will be tabulated.

All physical examination results, up to end of the main trial, will be listed, including details of abnormalities.

10.1.5. ARI Clinical Assessment and Respiratory Diagnostic Testing

ARI Clinical assessment and respiratory diagnostic testing will be listed.

10.2. Observational Extension Trial Safety

The safety analyses will be performed on the EES and will include data during observational extension trial (Visit Day 365 serology date + 1) to end of trial, unless otherwise stated.

10.2.1. Adverse Events

For the observational extension trial, adverse events are collected as SAEs, AESIs, and MAAEs. SAEs, MAAEs and AESIs (including anaphylaxis, thrombocytopenia, and pIMCs, including Guillain Barre's syndrome, as defined in section 16) from Visit Day 365 of observational extension to end of trial..

AEs resolving during the observational extension trial or start from Visit Day 365 + 1 will be listed.

11. Efficacy

11.1. Main Trial Efficacy

The efficacy analyses will be performed on the PPS, unless otherwise stated.

11.1.1. Exploratory Efficacy Analysis

The exploratory endpoint for efficacy is to enumerate the RSV or hMPV cases of mild, moderate, or severe LRTI (CESI) and any severity LRTI by vaccine group from Day 14 (study day 15) post-vaccination up to Day 365 (or end of the Main Trial).

Vaccine efficacy will be calculated as 100 x (1 – incidence rate ratio). The incidence rate for a vaccine group is the number of subjects with a mild, moderate, or severe LRTI due to RSV and/or hMPV divided by cumulative follow-up person time (in years) among all subjects at risk in vaccine group. A subject is considered at risk (and censored) up to the last day of contact while on study or 1st assessment of LRTI (CESI), whichever happens first. The incidence ratio is the ratio between the incidence rates of IVX-A12a to Placebo and IVX-A12d to Placebo. Vaccine efficacy will also be summarized by each severity (mild, moderate, and severe).

11.2. Observational Extension Trial Efficacy

There are no efficacy endpoints or analyses for the observational extension trial.

12. Changes from Analysis Planned in Protocol

- For the ANCOVA models, gender is included as factor. Gender is not listed as a factor in the protocol.
- Analyses will be repeated for age subgroup analyses category where indicated.
- Observational extension analysis is removed due to early termination of the study.
- A table and listing for the mild, moderate, or severe LRTI cases not caused by RSV or hMPV up to Day 365 was added after the tables, listings and graphs were completed to support the secondary endpoint.

13. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

13.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output
- One output file can contain several outputs or each output will be stored in a separate file
- Output files will be delivered in Word format or portable document format pdf
- Numbering of TFLs will follow International Conference on Harmonization (ICH) E3 guidance

13.2. Table, Figure, and Listing Format

13.2.1. General

- All TFLs will be produced in landscape format on *American letter size / A4 paper size*, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- Legends will be used for all figures with more than one variable, group, or item displayed
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below)
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate
- If footnotes are longer than 8 lines, footnotes will be displayed on first page, as a cover page. The table number, title, and population will also be included prior to the footnotes. Prior to the footnotes,

'Footnote Cover Page: ' will be displayed. On all subsequent pages, abbreviations will be listed and a footer will be included that states the following: See Page 1 for footnotes.

13.2.2. Headers

- All output will have the following header at the top left of each page:

  Sponsor: Icosavax, Inc.
  Protocol No.: ICVX-12-201

- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)

- The date the output was generated will appear along with the program name as a footer on each page

13.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

  Table x.y.z
  First Line of Title
  Second Line of Title if Needed
  XXX Analysis Set

13.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment

- For numeric variables, include 'unit' in column or row heading when appropriate

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set

- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable)

13.2.5. Body of the Data Display

13.2.5.1. General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

13.2.5.2. Table Conventions

- Units will be included where available
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.001, then present as <0.001. If the p-value is returned as >0.999, then present as >0.999

- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8), 13 (5.4)). For values that round down to 0.0, a common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the vaccine group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100, without decimal places

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'

- The percentage of subjects will normally be calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Details will be described in footnotes or programming notes, as necessary

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will be added describing whether the subject is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

13.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time

- Missing data will be represented on subject listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as 'N/A', unless otherwise specified

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study

- Units will be included where available

13.2.5.4. Figure Conventions

N/A

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display
- Footnotes will always begin with 'Note:' if an informational footnote, or [a], [b] etc. if a reference footnote. Each new footnote will start on a new line, where possible
- Subject specific footnotes are avoided, where possible
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Table Generation: ddmmmyyyy hh:mm')
- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed
  Example
  Cross references: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. An overview of the development of programs is detailed in Syneos Health End-to-End Process of the Production of Analysis Datasets (ADs) and Tables, Figures and Listings (TFLs) SOP (3922).

Syneos Health End-to-End Process of the Production of Analysis Datasets (ADs) and Tables, Figures and Listings(TFLs) SOP (3922) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

15. Index of Tables/Listings/Figures

Separate mock shell will be provided with all details.

16. Adverse Events of Special Interest (AESIs) and Potential Immune-mediated Conditions (pIMCs)

Gastrointestinal conditions	• Autoimmune pancreatitis • Celiac disease • Crohn's disease • Microscopic colitis • Ulcerative colitis • Ulcerative proctitis
Liver conditions	• Autoimmune cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis
Metabolic & endocrine conditions	• Addison's disease • Autoimmune hypophysitis • Autoimmune thyroiditis (including Hashimoto thyroiditis) • Diabetes mellitus type I • Grave's or Basedow's disease
Musculoskeletal and connective tissue conditions	• Ankylosing spondylitis • Antisynthetase syndrome • Cutaneous lupus • Dermatomyositis • Juvenile chronic arthritis (including Still’s disease) • Juvenile rheumatoid arthritis • Mixed connective tissue disorder • Polymyalgia rheumatica • Polymyositis • Psoriatic arthropathy • Reactive arthritis • Relapsing polychondritis • Rheumatoid arthritis • Scleroderma, including diffuse systemic form and CREST syndrome • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Systemic lupus erythematosus • Systemic sclerosis (with limited or diffuse cutaneous involvement)
Neuroinflammatory conditions	• Acute disseminated encephalomyelitis, including site specific variants (e.g., noninfectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis) • Cranial nerve inflammatory disorders, including paralyses/paresis (e.g., Bell's palsy) • Demyelinating disease • Encephalitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy • Multiple sclerosis • Myasthenia gravis (including Lambert-Eaton myasthenic syndrome) • Narcolepsy • Neuritis • Optic neuritis • Transverse myelitis

Skin conditions	• Alopecia areata • Autoimmune bullous skin diseases (including pemphigus, pemphigoid & dermatitis herpetiformis) • Cutaneous lupus erythematosus • Erythema nodosum • Lichen planus • Morphoea • Psoriasis • Sweet's syndrome • Vitiligo
Vasculitides	• Large vessels vasculitis, including giant cell arteritis such as Takayasu's arteritis & temporal arteritis • Medium sized and/or small vessels vasculitis including the following: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease thromboangiitis obliterans, necrotizing vasculitis and antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis
Others	• Antiphospholipid syndrome • Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, & mesangioproliferative glomerulonephritis) • Autoimmune hemolytic anemia • Autoimmune myocarditis/cardiomyopathy • Autoimmune neutropenia • Autoimmune pancytopenia • Autoimmune thrombocytopenia • Goodpasture syndrome • Idiopathic pulmonary fibrosis • Pernicious anemia • Polyglandular autoimmune syndrome • Raynaud's phenomenon • Sarcoidosis • Sjögren's syndrome • Stevens-Johnson syndrome • Uveitis

Adapted from Tavares Da Silva (2013)