Clinical Study Protocol	
Study Intervention	IVX-A12
Study Code	ICVX-12-202
Version	3.0
Date	06 June 2024

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

Sponsor Name: Icosavax, a member of the AstraZeneca Group

Legal Registered Address: 1930 Boren Ave suite 1000, Seattle, WA 98101, USA

Regulatory Agency Identifier Number(s): IND 28672

This protocol has been subject to a peer review according to AstraZeneca standard procedures. The protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Standard - Bioethics and in compliance with prevailing laws and regulations.

Version Scope: Global

Brief Title: A study to characterize the safety and immunogenicity of IVX-A12 in adult participants 60 years of age and older

Study Phase: II

Study Clinical Lead Name and Contact Information will be provided separately.

Study Clinical Lead is responsible for the clinical integrity of the study.

SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP Version 3	06 June 2024
CSP Version 2	11 April 2024
CSP Version 1	25 March 2024

CSP Version 3.0, 06 June 2024

Overall Rationale for the Modification:

The purpose of this protocol modification is the addition of safety rules for halting enrollment of the study.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 5.5	Addition of safety rules for halting enrollment of the study	To provide safety rules for halting enrollment in the study as per FDA request

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AR	Adverse reaction
ARI	Acute respiratory illness
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
CI	Confidence interval
CMI	Cell-mediated immunity
CRO	Contract Research Organization
CSR	Clinical Study Report
CTIS	Clinical Trials Information System
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFP	Green fluorescence protein
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GSK	GlaxoSmithKline
HBS	Human Biological Sample(s)
hMPV	Human metapneumovirus
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
LRTD	Lower respiratory tract disease
MAAE	Medically-attended adverse event

Abbreviation or special term	Explanation
µg	microgram
mL	milliliter
MMRM	Mixed model for repeated measures
N/A	Not applicable
nAb	Neutralizing antibody
NIMP	Non-investigational Medicinal Product
PBMC	Peripheral blood mononuclear cells
preF	Prefusion F
RTSM	Randomization and Trial Supply Management
RSV	Respiratory syncytial virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reactions
US	United States
USPI	United States Prescribing Information
VLP	Virus-like Particle

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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

Rationale:

The following table lists the estimands for the primary objectives:

Objectives	Estimand Description/Endpoints
Primary Immunogenicity	
To characterize the nAb responses to RSV in serum following vaccination with IVX-A12 or licensed RSV vaccine	**Population**: Immunogenicity analysis set **Endpoints**: RSV A nAb titers at Day 29 **Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response will be censored at the date of the intercurrent event. **Summary measures**: • GMTs by vaccination group • GMFRs from baseline by vaccination group
Primary Safety	
To assess the safety of single IM vaccination with IVX-A12 or licensed RSV vaccine	**Population**: Safety analysis set • Incidence of immediate unsolicited AEs within 30 minutes of dosing • Incidence of injection site and systemic solicited ARs through 7 days post-vaccination • Incidence of unsolicited AEs through 28 days post-vaccination • Incidence of SAEs, MAAEs, and AESIs through 6 months post-vaccination

For exploratory objectives, see Section 3 of the protocol.

Overall Design Synopsis:

This Phase 2 study will be a randomized, modified double-blind, active controlled study to characterize the safety and immunogenicity of IVX-A12 in adults ≥60 years of age.

Brief Summary:

The primary purpose of this study will be to characterize the safety and immunogenicity of IVX-A12 in adults ≥60 years of age.

The study duration for each participant will be approximately 6 months following administration of the study intervention.

Disclosure Statement:

This is a parallel group, single-dose, modified double-blind, safety and immunogenicity study.

Number of Participants:

Approximately 140 participants ≥60 years of age will be randomized 1:1 in the study to receive IVX-A12 or licensed RSV vaccine, AREXVY® (GSK Biologicals, Rixensart, Belgium).

Intervention groups and Duration:

One dose of IVX-A12 300 µg IM injection or one dose of AREXVY IM injection.

The study duration for each participant will be approximately 6 months following administration of the study intervention.

Data Monitoring / Other Committee:

Not Applicable.

Statistical Methods:

Only descriptive statistics will be used to summarize the immunogenicity and safety endpoints. There will be no formal hypothesis testing.

The immunogenicity analysis set will include all randomized and dosed participants in the safety analysis set who had no protocol deviations judged to potentially interfere with the generation or interpretation of an immune response. The safety analysis set will include all randomized and dosed participants. Analyses conducted using these analysis sets will be based on the actual study intervention received.

The sample size of 140 participants is based on having sufficient precision for a descriptive assessment of immunogenicity and safety.

The Day 29 primary analysis will be conducted when all participants have completed their Day 29 visit. Subsequently, the final analysis will be performed when all participants complete the study. For the Day 29 primary analysis, adjusted GMTs and GMT ratios, along with their corresponding 95% CIs, will be estimated using an ANCOVA model that includes a dependent variable of log titers, study arm as a fixed effect, and log baseline titer and age group as covariates. For the final analysis, model-adjusted GMTs and GMT ratios at Days 29 and 181, along with their corresponding 95% CIs, will be estimated using an MMRM that includes a dependent variable of log titers, study arm as a fixed effect, log baseline titer, age group (60 to 69, 70 to 79, and ≥80 years of age), visit indicators (Days 29 and 181) as covariates, and a study arm by visit interaction term.

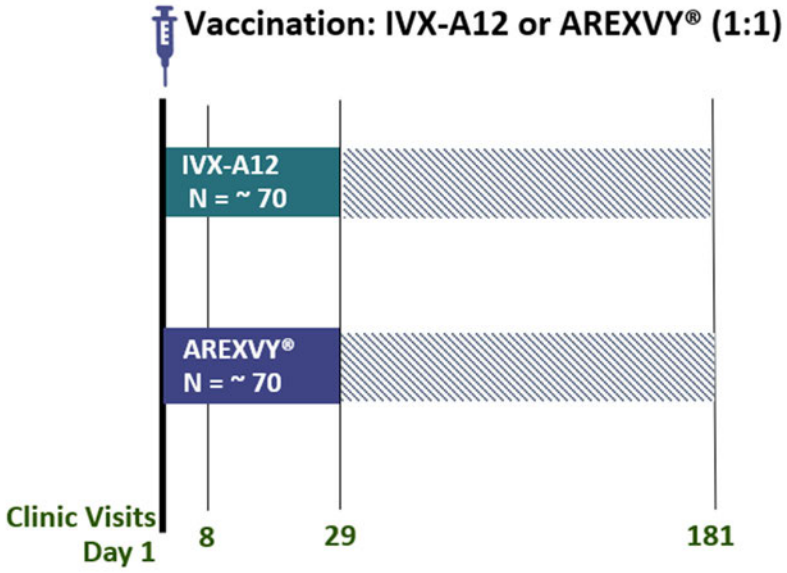
Model-adjusted GMT and GMT ratios will be used for analyses of the nAb response endpoints. Geometric mean fold rises and seroresponse (defined as a GMFR ≥4) will be unadjusted.

Model-adjusted GMT and GMT ratios, along with their corresponding 95% CIs, will be calculated for each study arm and will be summarized by visit based on the immunogenicity analysis set. Unadjusted GMFR and seroresponse, along with their corresponding 95% CIs will be calculated for each study arm and summarized by visit.

1.2 Schema

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

Figure 1 Study Design



1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Vaccination and Follow-up Period				Details in Protocol Section or Appendix
Visit number	1	2	3	4	
Visit Day (window) days	1 (N/A)	8 (+2)	29 (+3)	181 (±14)	
Visit type	Clinic	Clinic	Clinic	Clinic	
Informed consent [a]	X (pre-dose)				Section 5.1
Demography and Medical history	X (pre-dose)				Sections 5.1 and 5.2
Targeted physical examination based on medical history	X (pre-dose)				Section 8.3.1
Height, Weight	X (pre-dose)				Section 8.3.2
Body temperature, Blood pressure	X (pre-dose)				Section 8.3.2
Verify eligibility criteria	X (pre-dose)				Sections 5.1 and 5.2
Randomization	X (pre-dose)				Section 6.3
Immunogenicity serum sample	X (pre-dose)		X	X	Section 8.9.1
Blood sample for cell-mediated immune responses	X (pre-dose)	X	X	X	Section 8.9.2
Vaccine administration	X				Sections 6.1 and 6.2
Immediate post-vaccination assessment [b]	X				Section 8.3.5.1
eDiary distribution and training for solicited ARs	X				Section 8.4.6
Solicited ARs [c]	X (ongoing through Day 8)				Section 8.4.6
eDiary collection		X			Section 8.4.6
Unsolicited AEs	X				Section 8.4.1 and 8.4.2
SAEs/AESIs/MAAEs	X				Section 8.4.1, 8.4.2, 8.4.7, 8.4.8, and 8.4.10
Concomitant medications [d]	X				Section 6.9

[a] Confirm consent form signed prior to any procedures.

[b] Immediate unsolicited AEs to be collected during the 30-minute observation period following vaccination.

[c] Predefined solicited ARs recorded by participant in eDiary to assess reactogenicity. Investigators are to follow-up on any solicited ARs that are ongoing at Day 8 through to their resolution (see Sections 8.4.6 and 9.4.3).

[d] All concomitant medications will be recorded in the source documents. Prohibited medications and any medications used to treat SAEs or AESIs will also be recorded in the eCRF.

2 INTRODUCTION

2.1 Study Rationale

The candidate vaccine, IVX-A12, is a single-dose liquid formulation for intramuscular (IM) injection (0.5 mL dose) in adults ≥60 years of age to prevent lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) and human metapneumovirus (hMPV). In IVX-12-202, the vaccine candidate will be evaluated at a dosage level of 150 µg RSV / 150 µg hMPV and will be mixed with an aqueous diluent. This Phase 2 clinical study, IVX-12-202, will expand the safety and immunogenicity database of the candidate vaccine, IVX-A12, in relation to a United States (US)-licensed RSV vaccine. The primary purpose of this trial will be to assess the immunogenicity and safety of IVX-A12 compared with a licensed RSV vaccine, AREXVY (GlaxoSmithKline [GSK] Biologicals, Rixensart, Belgium) in adults ≥60 years of age.

2.2 Background

2.2.1 Respiratory syncytial virus and human metapneumovirus

RSV and hMPV are two highly contagious and common causes of respiratory infection across all age groups. In older adults and other high-risk groups, such as infants and the immunocompromised, RSV and hMPV are a significant cause of morbidity and mortality.

In one study evaluating the infectious causes of hospitalized community-acquired pneumonia in adults in the US, hMPV and RSV were the third and fourth most common viral pathogens identified, respectively (Jain et al 2015). Globally in developed countries in 2019, there was an estimated 5.2 million RSV related acute respiratory illnesses (ARIs) in adults 65 years and older, with 9.67% hospitalized (Savic et al 2023). In the US, RSV infects approximately 3 to 7% of adults 65 years and older each year (Falsey et al 2005). The burden of disease for RSV among US adults 65 years of age and older has been estimated to be 60,000 to 160,000 hospitalizations (Branche et al 2022, McLaughlin et al 2022, Zheng et al 2022, US CDC 2023) and 6,000 to 10,000 deaths (Thompson et al 2003, Matias et al 2014) each year. RSV has been identified as the cause of medically-attended ARI in up to 12% of adults 50 years or age and older with a mortality rate of 6 to 8% in those hospitalized (Colosia et al 2017).

While the burden of disease for hMPV has been less studied, hMPV infections can similarly lead to severe disease in at-risk populations as shown recently in 2023 when hMPV infections in the US peaked in mid-March with 1 in 10 patients in intensive care beds testing positive for hMPV (Wise 2023). Furthermore, the average annual rates of hospitalization associated with RSV and hMPV in adults 65 years of age and older in the US have been reported to be similar to influenza (Widmer et al 2012).

In May 2023, two vaccines indicated for the prevention of LRTD caused by RSV in adults 60 years of age and older obtained approval in the US and other countries: AREXVY (GSK)

and ABRYSVO® (Pfizer). Both RSV vaccines are given intramuscularly in a 0.5 mL dose, manufactured in Chinese Hamster Ovary (CHO) cell lines, and contain 120 µg of recombinant RSV prefusion F (preF). AREXVY is adjuvanted (AS01E) while ABRYSVO does not contain an adjuvant. However, no vaccines against hMPV or a combination RSV and hMPV vaccine are currently licensed.

2.2.2 IVX-A12

Icosavax (a member of the AstraZeneca group of companies) is developing IVX-A12, an RSV/hMPV combination vaccine, to protect adults 60 years of age and older against RSV- and hMPV-associated respiratory disease. IVX-A12 utilizes a novel virus-like particle (VLP) vaccine platform, which presents a high-density, multivalent display of the respective viral antigen. The multi-antigen structural display is similar to F-protein arrangement presented to the immune system during viral infection and is hypothesized to elicit a stronger, more durable, and broader antibody response (Mohsen and Bachmann, 2022).

The VLP platform technology is composed of two components: Component A (a trimeric protein genetically fused to the target infectious disease antigen of interest and produced in CHO cells) and Component B (a common, computationally-designed, homopentamer component used across multiple vaccine candidates and produced in E. coli). When the two components are mixed, self-assembly of a VLP occurs with icosahedral symmetry and particle size to mimic a virion (each VLP has 12 copies of the Component B pentamer). The VLP Component A antigen for the RSV vaccine candidate (IVX-121) is using a similar RSV A preF antigen as in GSK's licensed RSV vaccine (DS-Cav1, licensed from the National Institutes of Health) (Ruckwardt et al 2021) and presents 60 copies of the RSV preF protein on the VLP surface. The VLP Component A antigen for the hMPV vaccine candidate (IVX-241) uses the hMPV A preF protein and presents 60 copies of the hMPV preF protein on the VLP surface.

Further description of the chemistry, pharmacology, efficacy, and safety of IVX-A12 is provided in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of IVX-A12 can be found in the IB and Development Safety Update Report.

2.3.1 Risk Assessment

The safety precautions, eligibility, and study design are based on other RSV vaccines and emerging clinical data for IVX-A12. Anaphylaxis and other serious hypersensitivity reactions are important potential risks associated with administration of any vaccine. Hypersensitivity reactions, including anaphylaxis, are acute serious allergic reactions with multi-organ-system involvement that can present as, or rapidly progress to a severe life-threatening reaction

requiring immediate medical attention. Strategies used to mitigate the important potential risk of anaphylaxis and other serious hypersensitivity reactions are provided in the study exclusion criteria (Section 5.2).

Another risk very rarely observed with licensed RSV and influenza vaccines is Guillain-Barré Syndrome, which typically occurs within the first 3 weeks after vaccination. Monitoring will be conducted for Guillain-Barré Syndrome and other immune-mediated neurologic diseases, and atrial fibrillation, as they are considered adverse events of special interest (AESIs).

The safety database supporting IVX-A12 (all dosages evaluated with or without adjuvant (MF59®: oil-in-water emulsion) includes over 300 adults 60 years of age and older from two studies: the Phase 1 Study ICVX-12-101 (NCT05664334) and Phase 2a Study ICVX-12-201 (NCT05903183).

Available safety data from the Phase 1 and 2a studies show that, to date, IVX-A12 is well tolerated up to the maximum dose level tested of 300 µg. Reactogenicity events were monitored as solicited adverse reactions (ARs) and were consistent with reactions frequently observed following any vaccination. Solicited ARs were mostly mild or moderate in intensity and lasting less than 3 days post-vaccination. Across IVX-A12 groups, the most commonly reported solicited injection site ARs were tenderness and pain. The most commonly reported solicited systemic ARs were headache and myalgia in the Phase 1 Study ICVX-12-101, and myalgia and fatigue in the Phase 2a Study ICVX-12-201. There were no vaccine-related serious adverse events (SAEs), deaths, adverse events (AEs) leading to discontinuation, or vaccine-related medically-attended adverse events (MAAEs) reported up to Day 28 post-vaccination.

AEs, SAEs, MAAEs, and AESIs will be collected in this study (see Section 8.4.1). Participants will be provided an eDiary, which allows the investigator to review local reactions and systemic reactions post-vaccination.

For risks associated with AREXVY, please refer to the US Prescribing Information (USPI).

2.3.1.1 Study Procedures

Venipuncture will be performed during this study. Therefore, at the venipuncture site, there is a risk of bleeding, bruising, formation of a hematoma, and infection. In order to mitigate this, the blood draws in this study will only be conducted by appropriate site personnel.

2.3.2 Benefit Assessment

IVX-A12 is an investigational RSV/hMPV combination vaccine with the anticipated benefit to prevent LRTD caused by RSV and hMPV in adults 60 years of age and older.

Assessment of IVX-A12's clinical benefit is currently based on analysis of nAb levels

observed in the Phase 1 and 2a clinical studies assessing immunogenicity of IVX-A12. In the Phase 1 Study ICVX-12-101 and the Phase 2a Study ICVX-12-201, a rise in nAb titers for RSV and hMPV was observed in older adults ≥60 years and older up to 28 days following vaccination across all IVX-A12 dosage levels of up to 300 µg.

This study provides an opportunity for participants to receive either IVX-A12 or a licensed RSV vaccine. Furthermore, participants will also be contributing to the development of a vaccine which may have prophylactic benefits in an area of unmet medical need as there currently are no licensed hMPV vaccines. Additionally, combining RSV/hMPV into one vaccine could decrease morbidity and mortality of respiratory disease in the older adult population, while also improving vaccination coverage, and save preparation/administration time for providers.

Recipients of IVX-A12 do not have any guaranteed benefit. The information gained from this study will inform future decisions for the development of a safe and effective vaccine for the prevention of RSV and hMPV.

2.3.3 Overall Benefit/Risk Conclusion

For the safety of participants, this protocol has incorporated various risk mitigation measures including appropriate inclusion and exclusion criteria (see Sections 5.1 and 5.2) and close monitoring of participants to minimize known and potential risks.

Taking into account the measures to minimize risks to study participants, the known and potential risks identified in association with IVX-A12 are justified by the anticipated benefits of protection from RSV/hMPV for participants who receive IVX-A12.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 Objectives and Endpoints

Objectives	Estimand Description/Endpoints
Primary Immunogenicity	
To characterize the nAb responses to RSV A in serum following vaccination with IVX-A12 or licensed RSV vaccine	**Population**: Immunogenicity analysis set **Endpoints**: RSV A nAb titers at Day 29 **Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response will be censored at the date of the intercurrent event. **Summary measures**: • GMTs by vaccination group • GMFRs from baseline by vaccination group
Primary Safety	
To assess the safety of single IM vaccination with IVX-A12 or licensed RSV vaccine	**Population**: Safety analysis set **Summary measures**: • Incidence of immediate unsolicited AEs within 30 minutes of dosing • Incidence of injection site and systemic solicited ARs through 7 days post-vaccination • Incidence of unsolicited AEs through 28 days post-vaccination • Incidence of SAEs, MAAEs, and AESIs through 6 months post-vaccination
Exploratory	
To characterize the durability of the nAb responses to RSV A in serum following vaccination with IVX-A12 or licensed RSV vaccine	RSV A nAb titers through Day 181
To compare the nAb responses to RSV in serum following vaccination with IVX-A12 or licensed RSV vaccine	RSV A nAb and RSV B nAb titers through Day 181
To compare the nAb responses to hMPV in serum following vaccination with IVX-A12 or licensed RSV vaccine	hMPV A nAb and hMPV B nAb titers through Day 181
To evaluate CMI	Immune responses using functional and/or phenotypic profiling methods
To assess additional immune responses	Other exploratory assays for humoral or cellular immune responses may be performed based upon emerging safety, efficacy, immunobridging, and immunogenicity data

4 STUDY DESIGN

4.1 Overall Design

This Phase 2 clinical study is a randomized, modified double-blind, active controlled study to characterize the safety and immunogenicity of IVX-A12.

Approximately 140 participants will be randomized in a 1:1 ratio to receive IVX-A12 (approximately N=70) or licensed RSV vaccine, AREXVY (approximately N=70). Randomization will be centrally stratified by age (60 to 69, 70 to 79, and ≥80 years of age).

The Schedule of Activities (SoA) is presented in Section 1.3. Blood will be taken for immunological assessments as per the SoA. All participants will be given a thermometer, ruler, and a proprietary eDiary application designed for use with the participant's smart device or a provisioned eDiary device with instructions for use. Participants will be asked to report on solicited ARs in the eDiary beginning on the day of vaccination (Day 1) and for 7 days following the day of vaccination (up to Day 8). Unsolicited AEs will be collected by participants through Visit 3. SAEs, MAAEs, and AESIs will be recorded throughout the study.

The duration of each participant's involvement in the study will be approximately 6 months following administration of study vaccination.

The study is planned to be conducted at approximately 4-5 sites in the US.

4.2 Scientific Rationale for Study Design

The overall study design is similar to other vaccine studies evaluating immunogenicity and safety of an investigational product to a licensed vaccine (NCT06147063, NCT04583618, NCT03698279, NCT05245838). The primary endpoints are standard immunogenicity and safety assessments. The study will assess immunogenicity descriptively to help refine assumptions for potential Phase 3 endpoints.

4.2.1 Rationale for Study Population

This study will be conducted in the intended initial target population for IVX-A12, adults 60 years and older, who are the recommended population for receiving a licensed RSV vaccine ahead of the winter season.

4.3 Justification for Dose of IVX-A12

The dose of IVX-A12 for this protocol is 300 µg (150 µg RSV and 150 µg hMPV), as a non-adjuvanted dose. This dose was selected based on pre-clinical data of IVX-A12 and clinical data generated from the Phase 1 (ICVX-12-101) and Phase 2a (ICVX-12-201) studies.

4.4 End-of-study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under Food and Drug Administration (FDA) and European Union (EU) regulatory requirements:

EU requirements define study completion as the last visit of the last participant for any protocol- related activity.

FDA requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last scheduled procedure shown in the SoA.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Adults ≥60 years of age at the time of signing informed consent.

Type of Participant and Disease Characteristics

2. Participants who are medically stable such that, according to the judgment of the Investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up.

- A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months prior to enrollment.

3. Able to understand and comply with study requirements/procedures including attending all scheduled study visits (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

Informed Consent

Capable of giving signed informed consent as described in Appendix A. Consenting to study participation includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol and also agreeing to any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US). Consent must be obtained from the participant prior to performing any protocol -related procedures, including screening evaluations.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Acute (time-limited) or febrile (temperature ≥38.0 °C [100.4 ºF]) illness/infection within 3 days of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves.
2. History of a clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.
3. History of hypersensitivity to any component of the study vaccination.
4. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis).
5. Known or suspected congenital or acquired immunodeficiency.
6. Known or suspected autoimmune condition as determined by history and/or physical examination.
7. History of Guillain-Barré syndrome or any other demyelinating condition.
8. History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.
9. Any condition that may significantly increase the risk to the participant because of participation in the study, impact the participant's ability to participate in the study, or impair the interpretation of the study data.

Prior/Concomitant Therapy

10. Receipt of any licensed or investigational RSV and/or hMPV vaccine any time prior to administration of study intervention.
11. Receipt of any licensed vaccine (other than licensed influenza or COVID-19 vaccines) within 28 days prior to or expected receipt within 28 days after administration of study intervention. Licensed influenza or COVID-19 vaccines are permitted beginning >14 days prior to and >14 days after administration of study intervention
12. Receipt of immunoglobulin or blood products within 3 months prior to administration of study intervention or expected receipt during the study.
13. Receipt of immune-modifying drugs or immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy within 6 months prior to enrollment (or expected receipt during study), or long-term systemic corticosteroid therapy (prednisolone or equivalent at a dose of ≥20 mg daily or every other day for more than 2 consecutive weeks) within 6 months prior to study intervention or anticipated receipt during study. Topical/inhaled steroids or short-term oral steroids are permitted.

Prior/Concurrent Clinical Study Experience

14. Participation in another study or receiving interventional study investigational medicinal product (IMP), in the preceding 28 days or expected receipt of another study intervention (or participation in another study) during the period of study follow-up.

Other Exclusions

15. Employees of the Sponsor involved in planning, executing, supervising, or reviewing the IVX-A12 program, clinical study site staff, or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
16. Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the study conduct or completion.
17. Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.
18. Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

5.3 Lifestyle Considerations

Restrictions relating to concomitant medications are described in Section 6.9.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only a single rescreening is allowed in the study. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 Criteria for Temporarily Delaying Enrollment, Randomization, or Administration of Study Intervention

The clinical trial enrollment will be halted if there is clear evidence of potential harm or harmful effects. Vaccine administration will be paused for further review and assessment if any of the following events occur:

- Any SAE (including death and serious allergic or hypersensitivity reaction) or AESI (see Section 8.4.7) that could be related to vaccine as per the Investigator or Sponsor.
- ≥ 3 participants per group experiencing ≥ Grade 3 unsolicited non-serious reaction of the same or similar type (not explained by any other possible etiology) assessed as related to study vaccine.

If any of the above criteria are met, a decision will be made as to whether dosing in the study will be allowed to resume.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, IMPs and non-investigational medicinal product (NIMPs), medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

Participants will be randomized in a 1:1 ratio to receive either IVX-A12 or AREXVY on Visit 1. Details of these study interventions are presented in Table 3.

It is recommended that the study interventions be administered as an IM injection into the deltoid of the non-dominant arm.

All study participants will be observed in the clinic for at least 30 minutes after administration of study intervention (see Section 8.3.5.1). Allergic reactions to vaccines are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Table 3 Study Interventions

Intervention name	IVX-A12	AREXVY
Type	Vaccine	Vaccine
Dose formulation	0.6 mg/mL IVX-121 and 0.6 mg/mL of IVX-241 in aqueous buffer (20 mM Tris, 100 mM NaCl, 4% (w/v) Trehalose, 0.05% (v/v) PS-20, pH 7.4).	Solid concentrate for suspension for injection supplied as a single-dose vial of lyophilized antigen component to be reconstituted with the accompanying vial of adjuvant suspension component
Unit dose strength(s)	0.5 mL	0.5 mL
Dosage level(s)	Single IM dose of 300 µg (150 µg RSV / 150 µg hMPV)	Single IM dose of 120 µg RSVPreF3 antigen
Route of administration	IM injection	IM injection
Use	Investigational	Active Comparator
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Icosavax	Icosavax
Packaging and labelling	Study intervention will be provided in a glass vial. Each glass vial will be labelled as required per country requirement.	AREXVY will be packaged and labelled as required per country requirement.

6.2 Preparation, Handling, Storage, and Accountability

- The Investigator or designee (eg, unblinded pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorization is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying the Sponsor (or designated party); release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by the Sponsor (or designated party).
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

- The Investigator, institution, and the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual or specific handling instructions.

6.2.1 Dose Preparation

The dose of IVX-A12 and AREXVY for administration must be prepared by the unblinded pharmacy staff members (or an appropriate designee trained in study drug preparation), using aseptic technique in compliance with local regulations and site requirements.

Doses of AREXVY vaccine administered as part of this study will be prepared in accordance with current local pharmacy or clinic guidelines per the USPI.

Refer to the Pharmacy Manual for detailed information on dose preparation and handling procedures for IVX-A12 and AREXVY.

6.2.2 Dose Administration

IVX-A12 must reach room temperature prior to administration. Once the IVX-A12 vial is punctured to perform dilution and drawn into a syringe for administration, the dose must be administered within 4 hours of vial puncture. The study intervention will be administered as a single IM injection, according to standard procedures for IM injections.

Doses of AREXVY vaccine administered as part of this study will be administered in accordance with current local pharmacy or clinic guidelines per the USPI.

The dose of IVX-A12 and AREXVY may be administered by an unblinded pharmacy staff member (or an appropriate designee in accordance with local and institutional regulations) who is independent of safety and other trial evaluations.

Once the IMP administration is completed, the syringe must be discarded with the blinding cover in place to ensure that the blind is maintained.

Refer to the Pharmacy Manual for detailed information on dose administration for IVX-A12 and AREXVY.

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using an Interactive Response Technology (IRT)/ Randomization and Trial Supply Management (RTSM). Randomization will be centrally stratified by age (60 to 69, 70 to 79, and ≥80 years

of age). Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site.

Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

6.4 Blinding

Neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since IVX-A12 and AREXVY are visually distinct prior to dose preparation (due to differences in packaging), the study intervention will be handled by an unblinded pharmacist and may be administered by an unblinded administrator (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations if another blinded study site member trained to give IMP injections is not available. Thus, personnel preparing and administering study intervention may be the same individual. Syringe masking will be required in order to maintain the blind. Refer to the Pharmacy Manual for detailed information on syringe masking procedures for IVX-A12 and AREXVY.

The following personnel will have access to the randomization list during the study, prior to clinical database lock:

- Those generating the randomization list and IRT/RTSM system

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The Investigator documents and reports the action to the Sponsor, without revealing the treatment given to participant to the Sponsor staff.

The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition, the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first

consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to the Sponsor, without revealing the treatment given to participant to the Sponsor staff.

6.5 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention(s) directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6 Dose Modification

Study intervention will be administered as described in Section 6.1 and Section 6.2 and per the schedule in the SoA (Section 1.3). Dose modification is not permitted.

6.7 Continued Access to Study Intervention After the End of the Study

There is no intervention after the end of the study (see definition in Section 4.4).

6.8 Treatment of Overdose

For this study, any dose of study intervention exceeding that specified in the protocol will be considered an overdose.

There is no specific treatment for an overdose with vaccine study intervention. If overdose occurs, the participant should be treated supportively with appropriate monitoring as necessary.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in eCRF and on the Overdose CRF module. An overdose without associated symptoms is only reported on the Overdose CRF module. Refer to Section 8.4.13 for details of AE/SAE reporting related to overdose.

6.9 Prior and Concomitant Therapy

All concomitant medications will be recorded in the source documents. Prohibited medications will additionally be recorded in the eCRF.

For SAEs and AESIs, medications (over-the-counter and prescription) used to treat the SAE or AESI will also be recorded in the eCRF along with the information listed below. Vitamins

and/or herbal supplements should not be recorded.

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency, and route

The Study Clinical Lead should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Permitted Concomitant Medications

- Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance.
- Primary care providers or Investigators, where appropriate, should prescribe concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.
- Participants who develop adverse events after receiving study intervention should be treated with licensed medications and interventions according to standard of care.
- The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

  Note: Prophylactic use of these medications to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.
- All routine vaccinations other than influenza or COVID-19 vaccines are permitted >28 days prior to and >28 days after the last dose of study intervention. Licensed influenza or COVID-19 vaccines are permitted beginning >14 days before and >14 days after administration of study intervention.

6.9.2 Prohibited Concomitant Medications

The following are prohibited, and the Sponsor must be notified if a participant receives any of these prohibited medications. Any use of prohibited medications must be recorded in the eCRF and reported as a protocol deviation.

The use of prohibited medications and/or vaccines does not always require a withdrawal of the participant from the study but may determine a participant's evaluability in the immunogenicity analysis set.

- Receipt of any licensed or investigational RSV and/or hMPV vaccine prior to administration of study intervention and through to completion of Visit 4.

  - Participants choosing to receive a licensed and/or authorized RSV vaccine outside the study should inform the Investigator so it can be documented; all doses of RSV vaccine must be recorded.
  - Participants who receive a licensed and/or authorized RSV vaccine outside the study should be encouraged to continue study conduct to be followed for safety reporting and all assessments
- Receipt of any licensed or investigational vaccine (other than licensed influenza or COVID-19 vaccines) within 28 days prior to, or receipt within 28 days after, administration of study intervention
  - Licensed influenza or COVID-19 vaccines are permitted beginning >14 days before and >14 days after administration of study intervention.
- Investigational products indicated for the treatment of RSV/hMPV
  - Note: For participants who become hospitalized with RSV or hMPV, participation in investigational treatment studies is permitted.
- Glucocorticoids at a dose of ≥20 mg/day of prednisone or equivalent given daily for ≥14 consecutive days between randomization and the participant's scheduled final visit.
  - Topical/inhaled steroids or short-term oral steroids are permitted.
- Immunoglobulins and/or any blood product within 3 months prior to administration of study intervention and through the participant's scheduled final visit.
- Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, mycophenolate, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy, between randomization and the participant's scheduled final visit.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

7.1 Discontinuation of Study Intervention

Each participant will receive one dose of study intervention. An individual participant will not receive study intervention if any of the following occur in the participant in question:

- Participant withdraws consent after signing the ICF
- Participant meets any of the exclusion criteria or fails to meet all inclusion criteria for study participation (see Section 5.1 and 5.2)

Each participant who has received study intervention will be followed for the full study period unless consent is withdrawn specifically from further study participation, or the participant is lost to follow-up.

Note that discontinuation from study intervention is *not* the same thing as a discontinuation or withdrawal from the study (see Section 7.2).

7.2 Participant Discontinuation/Withdrawal From the Study

Discontinuation of the participant from the study by the Investigator:

- A participant may be discontinued from the study at any time at the discretion of the Investigator for behavioral, compliance, or administrative reasons.

Voluntary withdrawal from the study by the participant

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant who wishes to withdraw from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, the Sponsor may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the Investigator and the Investigator must inform the Sponsor. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counselled on the importance of maintaining the assigned visit schedule. At this time ascertain whether the participant should or wishes to or continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, texts,

emails, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have been lost to follow-up.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Section 1.3 SoA. Protocol waivers or exemptions are not allowed.

- Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to assess course of action.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Instructions for the collection and handling of human biological samples (HBS) will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of HBS see Appendix C.

The maximum amount of blood collected from each participant, including any extra assessments that may be required, will not exceed approximately 190 mL over the duration of the study (see Section 8.9.1 for collection of blood samples collected for immunogenicity assessment). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General/Baseline Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Procedures outlined in the SoA are described throughout Section 8.

8.2 Efficacy Assessments

Not applicable. Immunogenicity assessments are described in Section 8.9.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the Section 1.3 SoA.

8.3.1 Physical Examinations

A targeted physical examination will include areas suggested by medical history. Any clinically significant abnormal finding prior to vaccination should be reported as medical history in the CRF. Any clinically significant abnormal finding following vaccination will be recorded as an AE, if started before Day 29. The day of the AE resolution must also be recorded.

Physical examination will be performed at timepoints as specified in the Section 1.3 SoA.

8.3.2 Vital Signs

Body temperature, blood pressure, height, and weight measurements will be performed at timepoints as specified in the Section 1.3 SoA.

8.3.3 Electrocardiograms

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

8.3.4 Clinical Safety 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.

8.3.5 Other Safety Assessments

8.3.5.1 Immediate Post-vaccination Observation

Participants will be kept under observation for at least 30 minutes after vaccination and assessed for immediate unsolicited AEs. The post-vaccination observation should be documented in the eCRF.

8.4 AEs, SAEs, and Other Safety Reporting

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorized representative) will notify the Investigator or designees of symptoms. These must then be assessed by the Investigator and if considered an AE it will be reported by the Investigator.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum severity or changes in severity
- Whether the AE is serious or not
- Investigator causality rating against the IMP(s) (yes or no)
- Action taken with regard to IMP(s)
- AE caused participant's withdrawal from the study (yes or no)
- Outcome

In addition, the following information will be collected for SAEs and, where applicable, AESIs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE description
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed

- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Medication given to treat SAE/AESI (Yes/No)

8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

Immediate unsolicited AEs (those that occur within the 30 minutes after each vaccine) will be recorded during the immediate post-vaccination observation period, per Section 8.3.5.1)

Unsolicited AEs will be collected from time administration of study intervention through Day 29.

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last study visit. MAAEs and AESIs will be recorded from time of administration of study intervention throughout the study, up to and including the last study visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a treated participant, the Investigator shall, without undue delay, report the Sponsor.

8.4.2 Follow-up of Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF.

The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/MAAE(s)/AESI(s)/SAE(s) at the end of the study, if judged necessary.

8.4.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.4.4 Adverse Events Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated vital signs should only be reported as AEs if they meet any of the following:

- Fulfill any of the SAE criteria
- Are clinically relevant as judged by the Investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required).

If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as additional information. In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE as per Section 8.4.1.

The results from the protocol-mandated vital signs will be summarized in the clinical study report (CSR).

8.4.5 Adverse Events Based on Signs and Symptoms

All signs or symptoms spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.6 Solicited Adverse Reactions (Reactogenicity)

Solicited injection site and systemic predefined ARs will be collected in a solicited AR reactogenicity eDiary for all participants for 7 days after study vaccination, from Day 1 (day of vaccination) through Day 8 (for a total of 8 days).

All participants will be given a standard digital thermometer for measuring daily temperatures, a ruler for measuring the size of injection site reactions if any, and an eDiary to capture reactogenicity. All participants will be asked to report on signs and symptoms of solicited ARs (Table 4) for 7 days following study vaccination and whether medication was taken to relieve the symptoms. Investigators will report on solicited ARs that are ongoing beyond the eDiary

reporting period (ie, 7 days following study vaccination) through to resolution. Solicited ARs should not be reported as unsolicited AEs during the 7 days following vaccination, unless they fulfill the criteria for SAEs or MAAEs. If a solicited AE has not resolved by Day 8, the solicited AE will be reported as "ongoing" in the eDiary and the investigator or designee must obtain the stop date from the participant to record in the eCRF.

Table 4 Predefined Solicited Adverse Reactions for Reactogenicity Assessment

Injection Site	Systemic
Injection site pain	Fever
Injection site erythema/redness	Chills
Injection site swelling	Headache
	Myalgia (muscle aches and pains)
	Fatigue (physical or mental tiredness)

Severity will be assessed for solicited ARs by the participant according to toxicity grading scales modified and abridged from the US FDA Guidance on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (US FDA 2007) as defined in Appendix B 4.

8.4.7 Adverse Events of Special Interest

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the investigational vaccine and requires close monitoring and rapid communication by the Investigators to the Sponsor. An AESI can be serious or non-serious. All AESIs will be collected from the time of administration of study intervention through completion of the study, up to and including the last study visit.

All AESIs will be collected in the eCRF through ongoing observation and questioning per Section 8.4.1. Serious AESIs will be recorded and reported per Section 8.4.10.

The AESIs for IVX-A12, which are based on adverse events reported with other RSV vaccines, are immune-mediated neurologic diseases (including Guillain-Barré syndrome) and atrial fibrillation.

8.4.8 Medically-attended Adverse Events

MAAEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.

MAAEs will be collected according to the timepoints specified in the SoA (Section 1.3). MAAEs will be collected from the time of administration of study intervention throughout the study, up to and including the last study visit.

Any AEs (including abnormal vital signs) identified on a routine study visit will not be considered MAAEs.

8.4.9 Hy's Law

Liver biochemistry are not required for routine safety monitoring as part of this study or for all participants in this study. However, the Investigator should be vigilant for Potential Hy's Law case from laboratory tests (performed for other reasons) or AEs or clinical signs and symptoms suggestive of liver injury. Such cases where a participant shows elevations in liver biochemistry may require further evaluation.

8.4.10 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, Investigators or other site personnel will inform the appropriate Sponsor representatives within 1 day, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated Sponsor representative will work with the Investigator to ensure that all the necessary information is provided to the Sponsor's Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when they become aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the Electronic Data Capture (EDC) system, an automated email alert is sent to the designated Sponsor representative.

If the EDC system is not available, then the Investigator or other study site staff reports the SAE via secure method to the appropriate Sponsor representative.

When the EDC is temporarily not accessible, the Sponsor Study Representative should confirm that the Investigator/site staff enters the SAE in the EDC when access resumes.

For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for IVX-A12 and the USPI for AREXVY.

8.4.11 Pregnancy

Not applicable for this population.

8.4.12 Medication Error and Study Intervention Misuse

8.4.12.1 Timelines

If an event of medication error **or** study intervention misuse occurs during the study, then the Investigator or other site personnel informs the appropriate Sponsor representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is completed within **1** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error or study intervention misuse (see Section 8.4.6) and **within 30 days** for all other events.

8.4.12.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or Sponsor NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.4.12.3 Study Intervention Misuse

Study intervention misuse is the **intentional** and inappropriate use (by a study participant) of IMP or Sponsor NIMP for medicinal purposes outside of the unauthorized product information, or for unauthorized IMPs or Sponsor NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of study intervention misuse can be found in Appendix B 4.

8.4.13 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP or Sponsor NIMP occurs in the course of the study, the Investigator or other site personnel inform appropriate Sponsor representatives immediately, but **no later**

than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.4.6) and **within 30 days** for all other overdoses.

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Optional Genomics Initiative

Optional Genomics Initiative research is not applicable in this study.

8.8 Biomarkers

Collected samples associated with cell-mediated immunity (CMI) and cellular biomarker analyses are described in Section 8.9.2.

8.9 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoA (Section 1.3). Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual. For storage, re-use, and destruction of samples see Appendix C.

The results from exploratory analyses may not be reported in the CSR.

8.9.1 Neutralizing Antibody Responses

Blood sampling for immunogenicity will be collected from all participants at Days 1, 29, and 181 (see Section 1.3). Neutralizing antibody responses to RSV A and RSV B will be measured using green fluorescence protein (GFP) neutralization assays at [redacted]. Additional exploratory assessment will be performed using RSV A and B microneutralization assay at Viroclinics Biosciences (Rotterdam, Netherlands). Neutralizing responses to hMPV A and hMPV B will also be evaluated. Collected samples may also be utilized to investigate additional humoral immune responses, as determined by the Sponsor based upon emerging safety, efficacy, immunobridging, and immunogenicity data.

8.9.2 Cellular Mediated Immune Responses and Exploratory Analyses

Participants will have additional blood samples drawn on Days 1, 8, 29, and Day 181 for CMI and exploratory cellular biomarker analyses. Immune responses will be assessed by

characterizing peripheral blood mononuclear cells (PBMCs) using functional and phenotypic profiling methods that may include intracellular cytokine staining to evaluate Th1 and Th2 responses, activation induced marker assays, B-cell and innate immune cell phenotyping, single-cell RNA sequencing, and T and B-cell receptor sequencing.

8.10 Health Economics OR Medical Resource Utilization and Health Economics

Health economics / medical resource utilization and health economics parameters are not evaluated in this study.

8.11 Study Participant Feedback Questionnaire

This section is not applicable to this study.

9 STATISTICAL CONSIDERATIONS

The first version of the Statistical Analysis Plan (SAP) will be finalised prior to the earliest occurrence of the following milestones: 90 days after First Subject In or the first Dry Run; and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

There is no formal statistical hypothesis testing planned for this study. Descriptive analyses will support evaluation of immunogenicity and safety, and qualitative comparison between groups.

9.2 Sample Size Determination

Approximately 140 participants will be randomized 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.

9.3 Populations for Analyses

The following populations are defined (Table 5):

Table 5 Populations for Analysis

Population/analysis set	Description
Safety analysis set (SAF)	All randomized participants who receive one dose of study intervention, irrespective of their protocol adherence and continued participation in the study. Participants who withdraw consent to participate in the study will be included up to the date of their study withdrawal. For analyses and displays based on the SAF, 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 eligibility-related protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response. The IAS is to be used for the analysis of immunogenicity endpoints.

9.4 Statistical Analyses

9.4.1 General Considerations

Data will be provided in data listings sorted by vaccination group and participant number. Tabular summaries will be presented by vaccination group.

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 and maximum, and quartiles where more appropriate.

All point estimates will be presented with a two-sided 95% confidence interval (CI), unless otherwise stated.

Immunogenicity summaries for a specific endpoint will include participants in the immunogenicity analysis set with a baseline and at least one post-baseline quantifiable result for that endpoint.

9.4.2 Immunogenicity

9.4.2.1 Primary and Secondary Endpoint(s)

Geometric mean titer (GMT) will be calculated as the anti-logarithm $\Sigma(\log_2$ transformed titer)/n, ie, as the anti-logarithm transformation of the mean of the log-transformed titer, where n is the number of participants with titer information. The 95% CI about the GMT will be calculated as the anti-logarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log-transformed titers.

The fold rise is calculated as the ratio of the post-dose titer level to the pre-dose titer level.

Geometric mean fold rise (GMFR) will be calculated as anti-logarithm of Σ(log_2 transformed (post-dose titer/ pre-dose titer)/n. The 95% CIs for GMFR will be calculated similarly to those for GMT.

Seroresponse is a binary outcome where a success is when the fold rise in titers compared to baseline is ≥4. The number and percentage of participants with post-vaccination seroresponse, and 95% CIs, calculated using the Clopper-Pearson exact method, will be provided. In the event of a 0% or 100% seroresponse, a one-sided 97.5% CI will be reported.

For the Day 29 primary analysis, adjusted GMTs and GMT ratios, along with their corresponding 95% CIs, will be estimated using an analysis of covariance (ANCOVA) model that includes a dependent variable of log titers, study arm as a fixed effect, and log baseline titer and age group as covariates. For the final analysis, model-adjusted GMTs and GMT ratios at Days 29 and 181, along with their corresponding 95% CIs, will be estimated using an mixed model for repeated measures (MMRM) that includesa dependent variable of log titers,study arm as a fixed effect, log baseline titer, age group (60 to 69, 70 to 79, and ≥80 years of age), visit indicators (Days 29 and 181) as covariates, and a study arm by visit interaction term.

Model-adjusted GMTs and GMT ratios will be used for analyses of the nAb response endpoints, while raw unadjusted values will be summarized as supportive analyses. GMFR and seroresponse will be unadjusted.

The unadjusted and model-adjusted GMTs and GMT ratios, along with their corresponding 95% CIs will be calculated for each study arm and summarized by visit based on the immunogenicity analysis set. The unadjusted GMFR and seroreponse along with their corresponding 95% CIs, will be calculated for each study arm and summarized by visit. Descriptive statistics will include number of participants, geometric mean, 95% CI, minimum and maximum. Summaries may be repeated by pre-specified subgroups, including, but not limited to: age group. The final list of subgroup variables will be provided in the SAP.

Primary immunogenicity analyses will be conducted on data reported from samples analyzed by the GFP RSV A neutralization assay conducted at [redacted]. Supportive analyses will be performed on results reported by other exploratory assays, with more details provided in the SAP.

9.4.2.2 Exploratory Endpoint(s)

The analysis of exploratory endpoints will be described in the SAP.

9.4.3 Safety

Each solicited AR will be summarized overall and by study arm, study day, and severity grading. In addition, the number of days participants reported experiencing each event will be

presented. The duration of solicited ARs will be calculated as the last day of the AR – the first day of the AR + 1. If the event is ongoing on Day 8, the total number of days will include the days beyond Day 8 through the stop date for the event.

An overall summary of safety will be presented by study arm, including the number and percentage of participants who experience at least one AE (including immediate AEs), SAEs, AESIs and MAAEs. Summaries will present number and percentage of AEs in the categories listed that are related to study intervention as assessed by the Investigator, severe in intensity, serious, and resulting in death. A listing will cover details for each AE.

9.4.4 Other Analyses

Not applicable.

9.5 Planned Analyses

A 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 (measured in GFP RSV Neutralization Assay, [redacted]) are available. This analysis will support further evaluation of immunogenicity and safety of IVX-A12 in older adults.

A final analysis will be performed after all participants complete the study.

The SAP will describe the planned analyses in greater detail.

9.6 Data Monitoring Committee

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Sponsor will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organization (CRO), but the accountability remains with the Sponsor.

The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

Prompt notification by the Investigator to the Sponsor of any (potential) serious breach of the protocol or regulations is essential so that legal obligations and ethical obligations are met.

A "serious breach" means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

The Sponsor will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and Investigators.

Where the EU Clinical Trials Regulation 536/2014 applies, the Sponsor has in place processes to enter details of serious breaches into the European Medicines Agency Clinical Trials Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate Sponsor representatives immediately.

In certain regions/countries, the Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

The Investigator should have a process in place to ensure that:
The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach

A (potential) serious breach is promptly reported to the Sponsor or delegated party, through the contacts (email address or telephone number) provided by the Sponsor.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for one year after completion of the study.

A 3 Informed Consent Process

The Investigator or their representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study.

Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

A 4 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorized or does not have a business need to know the information.

The participant must be informed that in some cases their data may be pseudonymized. The General data Protection Regulation defines pseudonymization as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed.

In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (the Sponsor or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.

While the Sponsor has processes in place to deal with personal data breaches it is important that Investigators that work with the Sponsor have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

allow site staff or service providers delegated by the Investigator/institution to identify the occurrence of a (potential) personal data breaches.

Any (potential) personal data breach is promptly reported to the Sponsor or delegated party, through the contacts (email address or telephone number) provided by the Sponsor.

The Sponsor and the site must demonstrate that they:

have taken all necessary steps to avoid personal data breaches and

have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).

where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.

where it has not been possible to develop an internal data breach reporting and investigation process, the site follows the Sponsor's instructions.

Notification of personal Data Breach to participants:

notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of the Sponsor as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

on behalf of the Sponsor, so that the Sponsor has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.

If a personal data breach occurs in a processor's systems, engaged by the Sponsor, the processor under contractual obligations with the Sponsor promptly and in due course after discovering the breach notifies the Sponsor and provides full cooperation with the investigation. In these cases, to the extent the Sponsor is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that the Sponsor has no access to the identifying personal information of the participants.

If a personal data breach involving a Sponsor's representative device (i.e. Study Monitor laptop), the Sponsor representative will provide the Sponsor with all of the information needed for notification of the breach, without disclosing data that allows the Sponsor directly or indirectly to identify the participants. The notification will be done by the Sponsor solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that the Sponsor has no access to the identifying personal information of the participants. The contract between the Sponsor and the Study Monitor shall expressly specify these conditions.

The contract between the site and the Sponsor for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

The safety of all Sponsor clinical studies is closely monitored on an ongoing basis by the Sponsor representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve members to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on www.astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites

according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.

The Sponsor or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the Sponsor’s Global retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in source data acknowledgment.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or the Investigator may include but are not limited to:

Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines

Inadequate recruitment of participants by the Investigator

Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before

submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AEs

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether it is considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of SAEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

Results in death.

Is immediately life-threatening.

Requires in-patient hospitalization or prolongation of existing hospitalization.

Results in persistent or significant disability or incapacity.

Is a congenital anomaly or birth defect.

Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-SAE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the medicinal product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Severity Rating Scale:

Mild (awareness of sign or symptom, but easily tolerated)

Moderate (discomfort sufficient to cause interference with normal activities

Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the medicinal product.

Time Course. Exposure to suspect drug. Has the participant received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host, or environmental factors.

Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? The Sponsor would not normally recommend or support a re-challenge.

Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

Is this a recognized feature of overdose of the drug?

Is there a known mechanism?

Causality of ‘related’ is made if following a review of the relevant data, there is evidence for a ‘reasonable possibility’ of a causal relationship for the individual case. The expression ‘reasonable possibility’ of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as ‘not related’.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as ‘no reasonable possibility’.

B 4 Toxicity Grading Scales for Solicited Adverse Events

The toxicity grading scales for the solicited AEs were modified and abridged from the US FDA Guidance on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA 2007).

- Table 6 Severity Grading for Solicited Injection Site Adverse Reactions
- Table 7: Severity Grading for Solicited Injection Site Adverse Reactions

Table 6 Severity Grading for Solicited Injection Site Adverse Reactions

	Solicited Injection Site Adverse Reaction Grade		
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	No interference with activity	Some interference with activity	Prevents daily activity
Erythema/redness [a, b]	25 to 50 mm	51 to 100 mm	> 100 mm
Swelling [a, b]	25 to 50 mm	51 to 100 mm	> 100 mm

[a] In addition to grading the measured injection site reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Any cases of necrosis and exfoliative dermatitis will be reported as SAEs

Table 7 Severity Grading for Solicited Systemic Adverse Reactions

	Solicited Systemic Adverse Reaction Grade		
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**
Fever (°F) [a]	≥ 100.4 to ≤ 101.1	≥ 101.2 to ≤ 102.0	≥ 102.1
Chills	No interference with activity	Some interference with activity	Prevents daily activity
Headache	No interference with activity	Some interference with activity	Prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Prevents daily activity

[a] Oral temperature; no recent hot or cold beverages or smoking.

B 5 Medication Error and Study Intervention Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or Sponsor NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

Occurred

Was identified and intercepted before the participant received the drug

Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

Drug name confusion

Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant

Drug not administered as indicated, eg, wrong route or wrong site of administration

Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet

Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature

Wrong participant received the medication (excluding IRT/RTSM errors)

Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error

Participant accidentally missed drug dose(s), eg, forgot to take medication

Accidental overdose (will be captured as an overdose)

Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Study Intervention Misuse

Study intervention misuse is the intentional and inappropriate use (by a study participant) of IMP or Sponsor NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Sponsor NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of study intervention misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Study Intervention Misuse Report Form. This form should be used both if the study intervention misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of study intervention misuse include but are not limited to:

- The study intervention is used with the intention to cause an effect in another person
- The study intervention is sold to other people for recreational purposes
- The study intervention is used to facilitate assault in another person
- The study intervention is deliberately administered by the wrong route
- Someone who is not enrolled in the study intentionally takes the study intervention

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each site keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment, and keeps record of receipt of arrival and onward shipment or disposal.

The Sponsor or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the Sponsor-assigned biobanks or other sample archive facilities and will be tracked by the appropriate Sponsor team for the remainder of the sample life cycle.

All appropriately consented samples will be retained for maximum 15 years from last subject last visit.

If required, the Sponsor will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

The Sponsor ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, the Sponsor is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

Ensures the participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to the Sponsor or delegate.

Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

Ensures that the participant and the Sponsor are informed about the sample disposal.

The Sponsor ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

C 3 International Air Transport Association Guidance Document 62nd edition

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

The International Air Transport Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into three categories: Category A, Category B, or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

UN 3373 – Biological Substance, Category B

Are to be packed in accordance with UN 3373 and IATA 650

Exempt Substances are substances which do not contain infectious substances, or substances which are unlikely to cause disease in humans or animals, are not subject to these regulations unless they meet the criteria for inclusion in another class.

Clinical study samples will fall into Category B or exempt under IATA regulations.

Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-62-en-pi650.pdf).

Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

Appendix D Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

CSP Version 2.0: (11 April 2024)

Overall Rationale for the Modification

The main purpose of this protocol modification is to expand on the AESI definition for RSV vaccines and to clarify the collection of prohibited medications and vaccinations.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 8.4.7 (Adverse Events of Special Interest)	Updated to specify that AESIs will include additional immune-mediated neurological disease and atrial fibrillation	To ensure robust assessment of safety

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 1.3 (Schedule of Activities)	Inclusion of height and weight measurement at Visit 1 (pre-dose)	To calculate BMI
	Footnote d updated to indicate that prohibited medications will be recorded in the eCRF	Minor update to align more closely with the ICF – clarification that prohibited medications will be recorded in the eCRF and not just in the source documents
Section 6.9 (Prior and Concomitant Medications)	Restricted medications' changed to 'prohibited medications'	Updated for clarity
Section 8.3.2 (Vital Signs)	Height and weight measurements added to the list of parameters assessed as part of vital signs	To calculate BMI
Section 8.4.12 (Medication Error and Study Intervention Misuse)	Title updated from 'Drug Abuse and Drug Misuse' to 'Study Intervention Misuse'	Updated for clarity
Appendix D (Protocol Version History)	Added	Added to reflect this amendment to the protocol

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