ICOSAVAX

A Phase 2a Randomized, Observer-blind, Placebo-controlled, Dosage Optimization, Multi-center Clinical Trial to Evaluate the Safety and Immunogenicity of IVX-A12, a Respiratory Syncytial Virus and Human Metapneumovirus Bivalent Combination Virus-like Particle Protein Subunit Vaccine, in Adults 60 to 85 Years of Age

(Safety and Immunogenicity of IVX-A12 in Adults 60 to 85 Years of Age)

Sponsor:	Icosavax Inc. 1930 Boren Avenue, Suite 1000 Seattle, WA 98101 USA
Protocol Number:	ICVX-12-201
IND Number:	28672
Investigational Medicinal Products:	• IVX-A12 (a bivalent vaccine comprised of IVX-121 [respiratory syncytial virus-like particle protein subunit vaccine] and IVX-241 [human metapneumovirus virus-like particle protein subunit vaccine]) • Placebo
Synopsis Date:	02 April 2024
Version:	5.0

1.0 ADMINISTRATIVE INFORMATION

1.1 Safety Contact Information

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Fax: 1-877-464-7787

1.2 Approval

REPRESENTATIVES OF ICOSAVAX

This trial will be conducted in accordance with this clinical trial protocol and with the following:

- The Declaration of Helsinki [1].
- International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use E6 (R2) Good Clinical Practice (GCP): Consolidated Guideline [2].
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.

APPROVAL

PPD [redacted]

Date

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the ʅ q ˇ′o v brochure (IB), and any other product information provided by the sponsor. I agree to conduct this trial in accordance with the requirements of this protocol and protect the rights, safety, privacy, and well-being of trial subjects in accordance with the following:

- The Declaration of Helsinki [1].
- ICH, E6 (R2) GCP: Consolidated Guideline [2].
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.4.4 of this protocol.
- Terms outlined in the clinical trial site agreement.
- Appendix A Responsibilities of the investigator.

Signature of Investigator | Date

Investigator Name (print or type)

4L q ˇ′o Title

Location of the Site (City, Country)

1.3 Protocol Version History

Changes from Version 4.0 dated 03 November 2023 to Version 5.0 dated 02 April 2024

Rationale:	
Section	**Description**
Protocol synopsis	Modifications were made consistent with the protocol body
Section 2.2	Removal of time and events schedule for Part 2 replaced with time and events schedule for the extension
Section 2.3	Update of trial schematic to remove Part 2 and instead include the trial extension
Section 4.4	Rationale of the trial updated to reflect the inclusion of the extension
Section 5.0	Objectives and endpoints added for the observational extension
Section 6.1	Trial design updated to remove Part 2 and instead include the observational extension
Section 6.3	Planned duration updated to reflect the additional time for those subjects included in the extension
Section 7.1 and Section 7.2	Inclusion / exclusion criteria related to Part 2 removed.
Section 7.3	New section: Trial Observational Extension
Section 8.1, 8.2, 8.4	Investigational medicinal products sections updated to remove references to Part 2
Section 8.5	Inclusion of unblinding at Day 365 visit, prior to extension
Section 9.1, 9.1.1	Trial procedures and informed consent updated to reflect trial extension instead of Part 2.
Section 9.1.5	Vital signs updated to confirm that SpO_2 will not be performed during trial extension unless clinically indicated.
Section 9.1.6	Immunogenicity assessments updated to reflect removal of Part 2 and inclusion of trial observational extension
Section 9.1.8	Safety assessments updated to reflect removal of Part 2 and inclusion of trial observational extension
Section 9.1.10	Processing, labeling and storage of biological samples updated to reflect removal of Part 2 and inclusion of trial observational extension
Section 9.2	Time and events schedule updated to reflect removal of Part 2 and inclusion of trial observational extension
Section 10.4.3	Updated to reflect collection of MAAEs through to Day 730

Section 10.4.4	Updated to reflect collection of SAEs through to Day 730
Section 11.2	Remove SMC review prior to initiation of Part 2
Section 13.1.1	Update to definition of the Per Protocol Set and the addition of the Extension Enrolled Set
Section 13.1.3	Update to immunogenicity analyses section to reflect the removal of Part 2 but the inclusion of the observational trial extension
Section 13.1.4	Update to efficacy analyses section to reflect the removal of Part 2 but the inclusion of the observational trial extension
Section 13.1.5	Update to safety analyses section to reflect the removal of Part 2 but the inclusion of the observational trial extension
Section 13.2	Update to Interim Analysis / Data Reviews section to reflect the removal of Part 2 but the inclusion of the observational trial extension
Section 13.3	Update to Primary / Secondary Analyses for the CSR section to reflect the removal of Part 2 but the inclusion of the observational trial extension

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2.0 SUMMARY

Name of Sponsor: Icosavax Inc. 1930 Boren Avenue, Suite 1000 Seattle, WA 98101 USA	**Protocol Number:** ICVX-12-201	**Generic Name of Trial Vaccine:** IVX-A12 (respiratory syncytial virus and human metapneumovirus bivalent combination virus-like particle protein subunit vaccine)
Title of the Trial: A Phase 2a Randomized, Observer-blind, Placebo-controlled, Dosage Optimization, Multi-center Clinical Trial to Evaluate the Safety and Immunogenicity of IVX-A12, a Respiratory Syncytial Virus and Human Metapneumovirus Bivalent Combination Virus-like Particle Protein Subunit Vaccine, in Adults 60 to 85 Years of Age.		
Trial Period: Approximately 12 months; extended to 24 months in a subset of subjects.		**Clinical Phase:** Phase 2a
IND No.: 28672		**EudraCT No.:** Not applicable.
Indication: Active immunization for the prevention of acute illness (ARI) and lower respiratory tract illness (LRTI) caused by respiratory syncytial virus (RSV) and human U q º Lq U ˇ v ć x G ♯ v Ľ v *.q v º … * v Pc v q º v B º ´ q b		

Background and Rationale:

RSV is a single-strand, negative sense ribonucleic acid (RNA) virus belonging to the Orthopneumovirus genus of the family *Pneumoviridae* (Rima et al., 2017). There are two major genetic lineages, A and B (subgroups A and B, respectively), which are antigenically related, and cross-neutralizing antibodies are induced upon infection with either subgroup. RSV is a major cause of LRTI worldwide in all age groups. Epidemiological data suggest that in the USA alone, RSV may cause >170,000 hospitalizations and ~14,000 deaths annually (Colosia et al., 2017). RSV is also an important cause of respiratory disease in Europe, South Africa, and Australia (Falsey and Walsh, 2000; Htar et al., 2019; Cattoir et al., 2019; Langedijk et al., 2020; Broberg et al., 2018). Clinical data has identified a substantial disease burden in adults comparable to influenza, with most of the hospitalization and mortality occurring in older adults over 65 years of age (Fleming et al., 2015). The incidence and severity of RSV disease is particularly high in the frail elderly and in adults with cardiopulmonary conditions, who are considered at high risk for complications and hospitalization due to RSV (Falsey et al., 2005).

RSV infections are ubiquitous with lifelong reinfections in all age groups indicating that immunity is neither sustained nor complete (Karron, 2008; Hall et al., 1991; Bergeron and Tripp, 2021). RSV spreads by respiratory droplets and close contact with infected persons or fomites. In temperate climates there is an annual winter epidemic (Brandt et al., 1973), whereas in tropical areas seasonality is less distinct, but infection is most common during the rainy season (Weber et al., 1998). The severity of RSV disease is largely determined by the extent of viral replication following infection (Graham, 2011). The production of neutralizing antibodies (NAbs) should be the goal of vaccination as it is associated with protection against disease. However, seropositivity only confers partial protection against infection (Graham, 2011).

hMPV is a single-strand, negative sense RNA virus of the Metapneumovirus genus in the *Pneumoviridae* family (Rima et al., 2017), and was first described in 2001 when it was isolated from children with respiratory disease (van den Hoogen et al., 2001). The most

closely related human pathogen is RSV. As with RSV, there are two major genetic lineages of hMPV, A and B (subgroups A and B, respectively), which are antigenically related and cross-neutralizing antibodies are induced upon infection with either subgroup (van den Hoogen, 2004; Skiadopoulos, 2004). hMPV represents one of the leading causes of acute respiratory tract infections in infants, children, immunosuppressed patients, and the elderly (Jagusic et al., 2019; Gálvez et al., 2021). Several studies have shown that hMPV is highly prevalent worldwide, and in the USA alone, approximately 20,000 hospitalizations are registered every year due to this virus (Divarathna et al., 2019; Williams et al., 2010). In older adults, hMPV is responsible for a significant proportion of serious respiratory infections, with similar rates of infection as RSV. In the Etiology of Pneumonia in the Community (EPIC) trial, hMPV was confirmed in 4% of adults hospitalized with community-acquired pneumonia whereas RSV was confirmed in 3% of adults (Jain et al., 2014). Similar to RSV, NAbs alone can protect against hMPV infection (Williams, 2007; Hamelin, 2008). In mouse models, infection with hMPV protects against near term re-infection (MacPhail, 2004); macaques infected with hMPV demonstrated seroconversion and temporary protection from subsequent infection that waned over several months (van den Hoogen, 2007). As with RSV, in the presence of positive hMPV antibody titers, reinfections may occur in both healthy and immunocompromised adults (Madhi et al., 2007; Williams et al., 2006).

In May 2023, the US Food and Drug Administration (FDA) approved the first RSV vaccine (Valero, 2023) with a second vaccine approved shortly thereafter (Walsh, 2023). . Currently, there are no approved vaccines for hMPV. The Icosavax candidate vaccine, IVX-A12, is a bivalent combination formulation containing IVX-121 and IVX-241 virus-like particles (VLPs), computationally designed recombinant protein subunit vaccines for RSV and hMPV, respectively. Each VLP is composed of two recombinant proteins, Component A (CompA) and Component B (CompB-01), which have been designed to cooperatively assemble to form an icosahedral virus-like structure. Component A is a fusion protein-specific for each vaccine candidate (either CompA-RSV-02 or CompA-hMPV-01 for RSV and hMPV, respectively) and is expressed with the prefusion F (Pre F) protein from the respective virus, which has been shown to induce robust NAb responses in nonclinical models. The IVX-121 and IVX-241 VLPs display 20 copies of the respective Pre F protein trimers on their surface. CompB-01 is a common component across both VLPs and provides the structural element that supports the multimeric display of CompA-RSV-02 or CompA-hMPV-01. When combined, the two components self-assemble into VLPs that show enhanced immunogenicity compared with either soluble RSV (DS-Cav1) or hMPV prefusion antigen trimers. The soluble DS-Cav1 RSV Pre F protein was recently tested clinically and shown to be tolerable and immunogenic (Ruckwardt et al., 2021).

The candidate IVX-121 and IVX-241 VLPs are manufactured as separate drug substances and combined to create the IVX-A12 bivalent formulation containing both VLPs. The proposed mechanism of action of IVX-A12 is to increase the proportion of RSV- and hMPV-specific NAbs that are associated with protection, compared to non-neutralizing antibodies (Ngwuta et al., 2015; Falloon et al., 2017). IVX-A12 is intended for active immunization of the target population of older adults who are most at risk for disease following infection with RSV and hMPV.

The candidate vaccine, IVX-A12, is a single-dose liquid formulation (0.5 mL) for intramuscular (IM) injection in adults 60 to 85 years of age, the target population.

Nonclinical studies of IVX-A12 bivalent combinations of the IVX-121 and IVX-241 VLPs demonstrated the ability of both Pre F protein antigens on the Icosavax VLP platform to

induce strong NAb responses. In addition, preclinical experiments showed the effects of IVX-A12 dosage levels, number of doses, and need for adjuvant vary with RSV exposure history (either naïve or primed by infection) of the animals. The recent Phase 1/1b clinical trial (IVX-121-01) with the RSV monovalent IVX-121 VLP subunit vaccine also helped guide selection of IVX-A12 dosage levels formulated as either (i) aqueous vaccine or (ii) as adjuvanted vaccine with MF59® for the first-in-human evaluation of IVX-A12 vaccine. MF59 is a nanoemulsion adjuvant composed of squalene, polysorbate 80, sorbitan trioleate, and citrate. MF59 is widely used in the subunit influenza vaccine FLUAD® that is licensed in the USA, European countries, and other countries (FLUAD Quadrivalent, Product Insert, 2021). In total, approximately 150 million doses of vaccines with MF59 have been distributed and no safety concerns have been observed related to MF59 (; wº´ºLvq v*tSpcm( ). No safety concerns have been observed related to MF59 (; wº´ºL et al., 2013). Furthermore, increased dosage levels of MF59 (19.5 mg and 29.75 mg of squalene, up to 3 times the normal amount contained in licensed vaccines containing MF59) have shown to be well tolerated in º… * v PM years of age in a recent Phase 1 clinical trial (Otten, et al., 2020).

Boosting immunity in RSV-and hMPV-seropositive individuals with IVX-A12, a combination bivalent vaccine, may be challenging if one antigen interferes with the immune response to the other antigen. Imbalanced immune responses may require use of adjuvant in that scenario. However, studies in RSV- and hMPV-naïve mice and cotton rats did not demonstrate significant immune interference after vaccination when RSV and hMPV VLPs were administered in varying concentration ratios.

This Phase 2a clinical trial is evaluating the safety and immunogenicity of an unadjuvanted dosage level of 150 µg RSV/ 150 µg hMPV of IVX-A12 (IVX-A12a) and a dosage level of 150 µg RSV/150 µg hMPV of IVX-A12 adjuvanted with MF59 (IVX-A12d) compared to placebo in adults 60 to 85 years of age. Safety and immunogenicity data from this proposed Phase 2a clinical trial will allow the selection of an optimal dosage level and formulation of IVX-A12 for adults 60 to 85 years of age in future clinical trials.

The dosage level and formulations of IVX-A12 for this Phase 2a clinical trial were selected based on the totality of the IVX-A12 nonclinical data and the interim safety and immunogenicity clinical data from the ongoing IVX-A12 Phase 1 clinical trial. Two different IVX-A12 formulations, IVX-A12a and IVX-A12d, or placebo were administered as a single IM dose to older adult subjects enrolled into two age strata (adults 60 to 69 years of age and elderly adults 70 to 85 years of age). Eligible older adult subjects were randomized to different trial groups to ensure balance among the groups. This Phase 2a clinical trial included a sentinel group of 40 subjects (16 subjects per active treatment group [n=32]; 8 subjects in the placebo group) to conservatively assess the 150 µg RSV/150 µg hMPV dosage level in combination with MF59**.**

Based on the interim analysis (IA) of Day 28 data from this ongoing trial and data from the Phase 1 (ICVX-12-101) trial, the sponsor has determined the trial subjects will be unblinded at Day 365. IVX-A12a and placebo recipients will be asked to be followed for an additional 12 months for safety and to return to the clinic on visit Day 730 for one immunogenicity blood draw (observational extension).

The Day 28 IA data from this Phase 2 trial demonstrated the following:

- Slightly more reactogenicity was observed in subjects who received IVX-A12 with MF59 compared to those who received IVX-A12 without MF59;

- The inclusion of MF59 did not improve the immunogenicity of 150 µg RSV / 150 µg hMPV in this older, Phase 2 population relative to the Phase 1 population; and
- The overall safety data (i.e., unsolicited adverse events [AEs], and adverse reactions [ARs]) between Phase 1 and Phase 2 were similar even with the doubling of the IVX-A12 RSV dosage level in the Phase 2 trial compared to dosage levels evaluated in the Phase 1.

IVX-A12a induced neutralizing and binding antibody responses to RSV and hMPV, which supports the selection of the unadjuvanted dosage level of 150 µg RSV/150 µg hMPV for further clinical evaluation.

The trial will be conducted in accordance with the protocol, ICH of Technical Requirements for Pharmaceuticals for Human Use, GCP Guidelines, Declaration of Helsinki, and applicable regulatory requirements.

Objectives and Endpoints:

Main Trial

Primary Safety

Objective	Endpoints
To assess the safety and tolerability of the IVX-A12 bivalent candidate vaccine compared to placebo up to 1 year following a single IVX-A12 vaccination.	- Solicited local (injection site) reactions and systemic ARs for 7 consecutive days starting from Day 0 to Day 6 after vaccination. - Unsolicited AEs from Day 0 to Day 28.

Primary Immunogenicity

Objectives	Endpoints
- To evaluate the serum NAb response to IVX-A12 or placebo, measured by live virus serum neutralization assays (SNA), at Day 28. - To evaluate the serum immunoglobulin G (IgG) binding antibody response to IVX-A12 or placebo, measured by enzyme-linked immunosorbent assays (ELISA), at Day 28. - To evaluate the proportion of subjects ˇćvºv h-fold increase in serum NAb and serum IgG binding antibody titers to IVX-A12 from prevaccination/baseline (Day 0) to Day 28.	- Geometric mean titers (GMT) of RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb at Day 28. - GMT of RSV and hMPV Pre F protein-specific IgG antibody titers at Day 28. - Proportion of subjects with a h-fold increase in serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb from prevaccination/baseline (Day 0) to Day 28 after vaccination (defined as seroresponse rate [SRR]). - Proportion of subjects with h-fold increase (SRR) in RSV- and hMPV-specific IgG antibody titers from prevaccination/baseline (Day 0) to Day 28. - Geometric mean fold rise (GMFR) at Day 28 versus Day 0 in serum anti

	RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific Nabs and RSV and hMPV Pre F protein-specific IgG antibody titers.
Secondary Safety	
Objective	Endpoints
To assess the safety of IVX-A12 compared to placebo by describing the incidence of serious adverse events (SAEs), adverse events of special interest ([AESI],which are potential immune-mediated conditions [pIMCs]), medically-attended adverse events (MAAEs), LRTI cases of any severity (mild, moderate, severe) caused by RSV and/or hMPV (clinical event of special interest [CESI]), LRTI cases of any severity (mild, moderate, severe) not caused by RSV or hMPV, and adverse events (AEs) leading to trial withdrawal up to Day 365.	- SAEs, AESIs (which are pIMCs), MAAEs, and AEs leading to trial withdrawal up to Day 365 (end of main trial). - Mild, moderate, or severe LRTI cases caused by RSV or hMPV (CESI) up to Day 365. - Clinical safety laboratory parameters at screening, and Days 0, 7, and 28; - Mild, moderate, or severe LRTI cases not caused by RSV or hMPV up to Day 365.
Secondary Immunogenicity	
Objectives	Endpoints
- To evaluate the serum NAb response to IVX-A12 or placebo at Day 0, Day 180, and Day 365. - To evaluate the serum IgG binding antibody response to IVX-A12 or placebo at Day 0, Day 180, and Day 365 after vaccination. - To evaluate the proportion of subjects ˇćvºv h-fold increase in serum NAb and serum IgG binding antibody titers at Days 180 and 365 compared to baseline (Day 0). - To evaluate the proportion of subjects with an)-fold increase in serum NAb and serum IgG binding antibody titers at Days 28, 180 and 365 compared to baseline (Day 0).	- GMT of RSV/A , RSV/B-, hMPV/A-, and hMPV/B-specific NAb at Days 0, 180, and 365. - GMTs of RSV and hMPV prefusion F protein-specific IgG antibody titers at Days 0, 180, and 365. - G ˇ Lv Bv YĞqN v ˇćvºv h-fold increase (SRR) in serum anti-RSV/A-, RSV/B- hMPV/A-, and hMPV/B-specific NAb from prevaccination/baseline (Day 0) to Days 180, and 365 after vaccination. - Proportion of subjects with an)-fold increase in serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb from prevaccination/baseline (Day 0) to Days 28, 180, and 365 after vaccination. - Proportion of subjects with h-fold increase (SRR) in RSV- and hMPV prefusion F protein-specific IgG antibody titers from

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

CCI [redacted]

Observational Extension	
Secondary Safety	
Objective	Endpoints
To describe the incidence of SAEs, AESI, and MAAEs in consenting IVX-A12a vaccinees and placebo recipients through an additional 12 months (Visit Day 730).	SAEs, AESIs, and MAAEs from Day 365 through Day 545 and up to Day 730.

CCI [redacted]

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Clinical Trial Design:

This Phase 2a clinical trial of IVX-A12 is a randomized, observer-blind, placebo -controlled, dosage optimization, multi-center trial to evaluate the safety and immunogenicity of two formulations of IVX-A12: an unadjuvanted dosage level of 150 µg RSV/150 µg hMPV of IVX-A12 (IVX-A12a) and a dosage level of 150 µg RSV/150 µg hMPV of IVX-A12 adjuvanted with MF59 (IVX-A12d) compared to placebo (diluent) in adults 60 to 85 years of age. The dosage level and formulations (either aqueous [IVX-A12a] or adjuvanted with MF59 [IVX-A12d]) were determined based on the totality of the IVX-A12 nonclinical data and the interim safety and immunogenicity clinical data from the ongoing IVX-A12 Phase 1 clinical trial. A total of 300 µg IVX-A12 (75µg RSV/225µg hMPV) has been evaluated with MF59 in the IVX-A12 Good Laboratory Practice (GLP) toxicology study and up to 225 µg of IVX-A12 (75 µg RSV/150 µg hMPV) has been evaluated with MF59 in the Phase 1 clinical trial [ICVX-12-101]).

This Phase 2a clinical trial has three treatment groups: Two IVX-A12 groups and one placebo group. The total amount of VLP in the two IVX-A12 groups will not exceed 300 µg of VLPs.

Group A: IVX-A12a, the unadjuvanted dosage level of 150 µg RSV/ 150 µg hMPV.

Group B: IVX-A12d, the dosage level of 150 µg RSV/ 150 µg hMPV adjuvanted with MF59.

Group C: placebo.

Approximately 250 subjects were randomly allocated at a ratio of 2:2:1 to receive one of the two IVX-A12 formulations (IVX-A12a [N=100] or IVX-A12d [N=100]) or placebo (N=50), respectively. Subjects were also stratified by age group (60 to 69 years of age and 70 to 85 years of age). Dosing of the two IVX-A12 groups and placebo groups started in parallel. Age-stratified randomization should balance assignment between the two age groups. The planned subject allocation to trial groups is provided in Table S1.

The time and events schedules for the main study and for the observational extension are presented in Section 2.1 and Section 2.2, respectively. The trial design schematic is shown in Section 2.3.

Table S1 Clinical Trial Schema

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

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

Trial Procedures:

Approximately 250 adult subjects (60 to 85 years of age) were enrolled. A subject was considered to be enrolled upon having signed the informed consent form (ICF). Subjects were randomly allocated to receive either IVX-A12 or placebo at a ratio 2:2:1, resulting in approximately 100 subjects in each IVX-A12 group and 50 in the placebo group. In addition, subjects were stratified by age groups (60 to 69 years of age versus 70 to 85 years of age).

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

There are a total of seven scheduled clinic visits required for each subject (at screening, then Days 0, 7, 28, 90, 180, and 365), and five phone contacts (on Days 3, 14, 56, 135, and 270) for Subjects remaining in the main study which ends on Visit Day 365. At Visit Day 365, all trial subjects will be unblinded; IVX-A12a and placebo recipients will be invited to enroll into the extension, which includes a telephone call at Day 545 (approximately 6 months from Day 365) and a clinic visit at approximately 12 months (Day 730) after the Day 365 visit for a final blood draw.

Assessments:

Safety assessments: All solicited local (injection site) reactions and systemic ARs were collected for all subjects for 7 consecutive days, starting from the day of the single-dose administration (Day 0) through Day 6 (7 days total); unsolicited AEs through Day 28; and safety blood samples (clinical laboratory evaluation at screening, Day 0/baseline, Day 7, and Day 28). SAEs, AESIs, MAAEs, AEs leading to trial withdrawal, and CESI are captured from the time of randomization to the end of the trial evaluation on Day 365, approximately 12 months after vaccination. Clinic staff (a trained healthcare provider) contact the subject by phone call or using a digital application (e.g., SMS text) to facilitate the collection of relevant safety information such as concomitant medication use and occurrence of AEs/SAEs. Throughout the trial (until Day 365), all subjects

complete a respiratory symptom surveillance tool approximately twice a week (i.e., approximately twice within 7 -day intervals starting on Day 0 post-vaccination) to be monitored for the trial-defined CESI of mild, moderate, or severe LRTI caused by RSV and/or hMPV, using the established case definition and algorithm for evaluation of ARI and using nasopharyngeal (NP) swabs for the detection of RSV, hMPV, and other respiratory viruses. Subjects will be instructed to return to the clinic for assessment within 3 to 7 days of onset of ARI (ideally within 3 days) to maximize detection of virus.

After subjects are unblinded to their trial group assignment at Day 365, consenting IVX-A12a and placebo recipients will be contacted by clinic staff by phone call or with a digital application (e.g., SMS text) to facilitate the collection of MAAEs, AESIs, and SAEs, at Day 545; MAAEs, AESIs and SAEs will also be collected at the clinic visit on Day 730.

Immunogenicity assessments: Blood sampling for immunogenicity will be taken at Days 0, 28, 180, and 365. IVX-A12a and placebo subjects consenting to the extension portion of the trial will have a single blood sampling for immunogenicity at Day 730.

Stopping Rules:

Monitoring of safety signals will be performed throughout the trial by an independent Safety Monitoring Committee (SMC). The clinical trial will be halted if there is clear evidence of potential harm or harmful effects. Vaccine administration may be paused for further review and assessment if any of the following events occur:

- In any trial subject:
    - Any death that could be related to vaccine as per the investigator, sponsor, or SMC chair occurring during the trial;
    - Any vaccine-related SAE during the trial;
    - Any life-threatening (Grade 4) vaccine-related AE during the trial, which needs medical intervention including:
        - Ulceration, abscess or necrosis at the injection site;
        - Laryngospasm, bronchospasm or anaphylaxis within 24 hours after administration of vaccine.
    - An allergic or hypersensitivity reaction such as fever >40°C or generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of vaccine.
- If 2 or more subjects in a single trial group experience the same severe (Grade 3) AE/AR (Preferred Term [PT] in a given Medical Dictionary for Regulatory Activities [MedDRA] system organ class [SOC]) within the first 7 days following vaccination that persists for at least 48 hours and cannot be clearly attributed to another cause:
    - Severe (Grade 3) vaccine-related solicited local (injection site) reactions (excluding measured grades of erythema and swelling alone) or systemic ARs;
    - Severe (Grade 3) vaccine-related unsolicited AE during the trial;
    - Severe (Grade 3) vaccine-related vital sign(s) abnormality;
    - Severe (Grade 3) vaccine-related clinical laboratory abnormality.

In the case that a pre-defined safety signal is met in any trial group, subsequent dosing will be halted to permit a complete evaluation of the reported event(s), and to consult the SMC. Based on the review of the data, the SMC may recommend temporary or permanent stopping, or continuation of dosing. When dosing resumes after a halt, further measures for safety may be introduced.

Subject Population:

Subject Population (age range): Adults 60 to 85 years of age.

Planned Number of Subjects: Approximately 250 total; approximately 100 in each of the two IVX-A12 groups and 50 in the placebo group.

Planned Number of Groups: A total of three trial groups: two IVX-A12 groups and one placebo group.

From Day 365, IVX-A12a and placebo recipients who consent to follow-up for an additional 12 months are also defined as the trial q qL ˇ L population Y q b

Inclusion Criteria:

1. Male or female subjects, 60 to 85 years of age, who must be in stable health based on medical history, vital signs, physical examination, and laboratory evaluation prior to vaccination, in the ˙L q ˇ´º vN*L˙NP*vČ …´U qL ≥
2. Subjects may have ongoing chronic conditions (comorbidities such as hypertension, congestive heart failure, chronic obstructive pulmonary disease, type 2 diabetes mellitus, hyperlipoproteinemia, or hypothyroidism) who are, ˙Lvćqv˙L q ˇ´º v opinion, medically compensated and without recent exacerbation (for example, no emergency room [ER] visits and no change to medical treatments or medications to better control the condition) within the prior 3 months;
3. Subjects able to voluntarily give written informed consent and can comply with trial procedures including follow-up for approximately 12 months after vaccination;
4. Body mass index 17 to <40 kg/m^2 at screening;
5. Before randomization, female subjects must be unable to conceive (e.g., menopausal, i.e., 12 consecutive months without menstruation, hysterectomy, oophorectomy, etc.) and not intending to conceive by any method;
6. Subject must agree not to donate blood from the time of vaccination through 3 months after vaccination;
7. Subject must be willing to provide verifiable identification and have the means to be N L ºNq…vºL…v vN L ºNvćqv˙L q ˇ´º v vćqv ˇq v ºBv… ˙L´vćqvqL ˇqvN*L˙NP*v trial.

Exclusion Criteria:

1. Subjects with moderate or severe liver disease, metastatic solid tumor, and acquired immunodeficiency syndrome (AIDS) are to be excluded. In addition, subjects with underlying significant illness or condition(s) or ongoing treatment that, in the opinion of the investigator, could (i) interfere with the conduct of the trial, (ii) pose an unacceptable risk to the subject in this trial, (iii) interfere with the YČqN ability to comply with the trial procedures or abide by the trial restrictions, (iv) interfere with the ability to interpret safety data, or (v) prevent completion of the trial are to be excluded;
2. Older adults who meet frail elderly criteria (older persons with medical, nutritional, cognitive, emotional, or activity impairments, as defined by the Dalhousie Clinical Frailty / N qv hV Rockwood et al., 2005), See Appendix C;
3. Prior receipt of any licensed or investigational RSV or hMPV vaccine within the past 12 months;

4. Prior receipt of another investigational medicinal product (IMP; trial drug, biologic, or device) not authorized for use in the USA and European Union within the past 3 months;
5. Laboratory-confirmed RSV or hMPV infection within 12 months prior to enrollment;
6. Currently enrolled or plan to participate in another clinical trial with an investigational agent (including licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication) to be received during the trial period;
7. History of malignancy within 5 years before screening not in the following categories: (i) subjects with squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix may be enrolled at the discretion of the investigator, (ii) subjects with a history of malignancy within 5 years before screening, with minimal risk of recurrence per the investigator's judgment, can be enrolled;
8. Per medical history, subjects with chronic active hepatitis B or hepatitis C infection, human immunodeficiency viruses type 1 or type 2 infection, acute polyneuropathy (such as Guillain-Barré syndrome), or chronic idiopathic demyelinating polyneuropathy; subjects whose hepatitis C antibody test is positive but whose viral loads are negative may be enrolled;
9. Acute illness, with or without fever at the time of planned vaccination;
10. History of hypersensitivity or serious adverse reactions to vaccines, such as anaphylaxis or angioedema, or any known allergies to any component of the IVX-121 and/or IVX-241 vaccine, or hypersensitivity to latex;
11. Abnormal function of the immune system resulting from clinical conditions including chronic administration of systemic corticosteroids (oral/intravenous/IM at a daily dose equivalent of >20 mg prednisone in a period of more than 14 days), or administration of immunosuppressive chemotherapy, biologics, or radiotherapy within the past 3 months prior to planned vaccination;
12. Subjects who have received treatment with immunoglobulins or other biologics, such as immunosuppressive therapies expected to modify immune response to vaccination (including monoclonal antibodies [MAbs] for chronic underlying conditions) within the past 3 months prior to planned vaccination;
13. Trial personnel as an immediate family or household member;
14. For licensed vaccines:
    a) Receipt of licensed inactivated vaccines (including seasonal influenza vaccine) within 14 days prior to trial vaccine administration on Day 0, or licensed replicating vaccines such as RNA or live-attenuated virus vaccines within 30 days prior to Day 0.
    b) Receipt of licensed vaccines is permitted after completion of the Day 28 visit.
    c) Receipt of any licensed COVID-19 vaccines is permitted if dosing regimen completed within 21 days prior to Day 0 or after completion of the Day 28 visit.

Investigational Medicinal Products:

IVX-A12: The two investigational IVX-A12 formulations for testing will be composed of a constant IVX-121 RSV VLP dosage level (150 µg) with one constant IVX-241 hMPV VLP dosage level (150 µg).

The two formulations of IVX-A12 will be:

- An unadjuvanted dosage level of 150 µg RSV/150 µg hMPV of IVX-A12 (IVX-A12a); and
- A dosage level of 150 µg RSV/150 µg hMPV of IVX-A12 adjuvanted with MF59 (IVX-A12d)

These two formulations will be compared to placebo (diluent).

The final investigational IVX-A12 drug product will be administered either as an aqueous vaccine (IVX-A12a) or with MF59 to be mixed 1:1 in the clinic (IVX-A12d). The amount of MF59 (squalene) per dose will not exceed 9.75 mg. Specific instructions for preparation of vaccine will be provided in the pharmacy manual.

The intended volume for administration of IVX-A12 is 0.5 mL for IM administration.

Placebo: Sterile aqueous diluent, delivered as a 0.5 mL dose. The placebo does not contain preservatives.

Route of Administration: IM administration of a single IVX-A12 or placebo dose into the deltoid of the non-dominant arm.

Duration Subject Participation:

The duration of subject participation in the main trial will be approximately 12 months. The trial will be unblinded at Visit Day 365, where subjects who received IVX-A12a or placebo will be invited to consent to another 12 months of follow-up.

Statistical Considerations:

Analysis sets:

Safety Set: The safety set will consist of all subjects who received a dose of IVX-A12 or placebo. Subjects will be analyzed as treated.

Full Analysis Set (FAS): The FAS will include all randomized subjects who received a dose of IVX-A12 or placebo. Subjects will be analyzed as randomized.

Per-Protocol Set (PPS): The PPS will include all subjects in the FAS who received a dose of IVX-A12 or placebo and have no major protocol deviations that have a significant impact on immunogenicity results. ~~which may exclude subjects from the PPS~~. Subjects will be analyzed as randomized.

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

Analysis of Disposition, Demographics, Other Baseline Characteristics, Medical History, and Medications:

Age, gender, race, and other baseline characteristics (including baseline RSV and hMPV NAb titers) will be summarized descriptively by treatment group for all randomized subjects.

Immunogenicity Analyses:

Immunogenicity data will be summarized for each treatment group and strain (RSV/A, RSV/B, both RSV strains and either RSV strain; hMPV/A, hMPV/B, both hMPV strains and either hMPV strain). The GMT will be calculated for RSV/A, RSV/B, hMPV/A and hMPV/B titers separately along with their 95% confidence interval (CI). The adjusted GMT and corresponding 95% CI will be obtained from an analysis of covariance (ANCOVA) model, which will include log-transformed baseline titers, age group, and treatment group as

terms. Durability will be assessed at Days 180 and 365 by comparing to Day 28 data. The geometric mean of fold changes and corresponding 95% CI will be calculated.

G ˇ Lv Bv YǴqN v ˇćv h-fold increase (SRR), 8-fold increase, and GMFR from prevaccination/baseline (Day 0) will be summarized for Days 28, 180, and 365 after vaccination. RCD curves will be generated. Respective data will also be summarized for Day 730.

The VLP core-specific IgG titers will be summarized at Days 0, 28, 180, 365, and in the extension population subset at Day 730 with GMT and 95% CI.

Separate summaries will be provided for subjects that agreed to participate in the extension portion of the trial and will include these YǴqN data from the beginning of the trial through Day 730.

All immunogenicity data will be listed.

Efficacy analysis:

Cases of mild, moderate, or severe LRTI and any severity LRTI due to RSV and/or hMPV (CESIs), meeting the protocol-specified definitions, will be summarized by vaccine group and placebo group starting on Day 14 through the end of the trial (Day 365). Listings will be provided.

Safety Analyses:

Solicited local (injection site) reactions and solicited systemic ARs: Solicited ARs will be summarized for 7 days starting from the day of dosing (Day 0) through Day 6 (total of 7 days). The summary will be by day and overall, within 7 days. Solicited ARs by maximum severity will also be summarized.

Unsolicited AEs: Unsolicited AEs will be assessed from day of dosing (Day 0) through 28 days post-vaccination and coded according to MedDRA and summarized by SOC and PT. The summary tables will include the number and percentage of subjects reporting unsolicited AEs by SOC and PT, and by SOC, PT, and maximum severity. Subjects q ĽǴv 5 º…ǫv(vºL…v ºNNĽe-related unsolicited AEs will also be summarized.

SAEs, AESIs, MAAEs, AEs leading to withdrawal, CESI (mild, moderate, or severe LRTI caused by RSV and/or hMPV) and mild, moderate, or severe LRTI cases not caused by RSV or hMPV: Will be assessed throughout the trial (from randomization on Day 0) and coded using MedDRA and summarized by SOC and PT. Separate summaries will be provided for subjects that agreed to participate in the extension portion of the trial and ˇ*vĽN* ..ǫvćq qv YǴqN v..º ºvB U vthe beginning of the trial through Day 730.

All solicited local and systemic ARs and unsolicited AEs will be listed.

Clinical laboratory tests including hematology, chemistry, and urinalysis will be summarized by vaccine groups. For numeric laboratory parameters, the observed value and change from baseline will be summarized by visit. For categorical laboratory parameters, the number of subjects and percentages will be summarized by visit. Shift tables may be provided as well. All laboratory data will be listed.

All vital signs observed value and change from baseline will be summarized by vaccine groups. Listing will also be provided.

Physical examination results will be listed.

Sample Size Justification:

Sample size for this trial is not based on any formal hypothesis testing. Analyses of safety, efficacy, and immunogenicity will be primarily descriptive in nature. An approximate total of 250 subjects (approximately 100 subjects in each of the IVX-A12

groups and 50 subjects in the placebo group) will be randomized. With 100 subjects in each IVX-A12 group, there is an 63.4% probability of observing at least 1 subject with an AE if the true incidence of the AE is 1%, and 86.7% probability of observing at least 1 subject with an AE if the true incidence of the AE is 2%. The trial will have more than 90% power to detect a difference of 20% or more in SRR or detect a 2-fold increase or more in GMT or GMFR (assuming standard deviation at 0.5 $\log_{10}$), between the two IVX-A12 groups (or between the IVX-A12 group and placebo group), with two--sided type-1 error rate at 0.05.

Interim Analysis/Data Reviews:

Two interim analyses (IAs) will be performed: The first IA was performed after all subjects completed the Day 28 safety assessments and when all Day 28 immunogenicity data are available; the second IA was performed after all subjects completed the Day 180 safety assessments, and when all Day 180 secondary immunogenicity data were available. These analyses further support evaluation of safety and immunogenicity of IVX-A12 in older adults. These IA will be used for confirmation of dosage level and formulation selected for further evaluation in older adults 60 years of age or older.

A final analysis of main trial will be performed after Day 365, and an analysis of the observational extension will be performed after Day 730.

Clinical Study Report (CSR):

A CSR will be prepared when Day 365 analyses have been completed for the primary and secondary objectives of the trial. Additional analyses including safety and immunogenicity through Day 730 may be provided in a Clinical Study Addendum.

Safety Review and Safety Monitoring Committee:

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

ICVX-12-201 Version 5.0 **(02 April 2024)**

2.1 Time and Events Schedule for ICVX-12-201: Main Trial

Day	**Screen**	**0**	**3**	**7**	**14**	**28**	**56**	**90**	**135**	**180**	**270**	**Unsch [m]**	**365 [n]**
Window (Days)	**-28 to -1**	**n/a**	**±1**	**-2 to +2**	**±3**	**±5**	**±7**	**±10**	**±10**	**±14**	**±14**	**-**	**±21**
Clinic Visit (or home-health visit) [a]	**X**	**X**		**X**		**X**		**X**		**X**		**X**	**X**
SMS/Phone Call/Digital App			**X**		**X**		**X**		**X**		**X**		
Screening Informed consent [b]	X												
Main Study Informed consent [b]		X											
Eligibility criteria	X												
Demographics	X												
Medical history	X												
Medication history [c]	X												
Urinalysis [d]	X											X	
Physical examination [e]	X	X [g]		X		X		X		X		X	X
Vital signs[f]	X	X [g]		X		X		X		X		X	X
Safety blood draw	X	X [g]		X		X						X	
Testing for RSV/hMPV/other respiratory pathogens (NP swab/PCR)												X	
Serology blood draw for SNA, ELISA [h]		X [g]				X				X			X
Confirm Eligibility		X [g]											
Randomization		X [g]											
Vaccine administration		**X**											
Post-vaccination assessment [i]		X											
Diary distribution and training		X											
Solicited ARs/post-vaccination diary completion and review [j]		X	X	X									
Unsolicited AEs		X	X	X	X	X						X	
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
RSS tool completion [k]		X	X	X	X	X	X	X	X	X	X	X	X
AEs leading to withdrawal		X	X	X	X	X	X	X	X	X	X	X	X
Assess for SAE, AESIs (including pIMC), MAAE, and CESI [l]		X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; AR, adverse reaction; AESIs, adverse event of special interest; pIMC, potential immune-mediated condition; CESI, clinical event of special interest; ELISA, enzyme-linked immunosorbent assay; LRTI, lower respiratory tract illness; MAAE, medically-attended AE; NP, nasopharyngeal; PCR, polymerase chain reaction; RSS, respiratory symptom surveillance; RSV, respiratory syncytial virus; SAE, serious AE; SNA, serum neutralization assay (live virus neutralization assay); Unsch, unscheduled.

Notes on the next page.

Notes:
[a] Home-health visits may be performed in lieu of clinic visit if permissible by local regulations and/or institutional/clinic standard operating procedures.
[b] Confirm consent form signed prior to any procedures.
[c] Medication history includes prior vaccinations.
[d] Urine dipstick test at screening. An abnormal result for glucose, ketones, pH, protein, specific gravity, and/or urobilinogen will trigger urine microscopy.
[e] Full physical exam (PE) at screening; symptom-directed PE at subsequent visits.
[f] Collection of vital signs to include blood oxygen (SpO_2) measurement
[g] Procedure to be performed prior to dosing.
[h] Collection of blood for serology (SNA and ELISA): Day 0, 28, 180, and 365.
[i] Post-vaccination observation for 60 minutes.
[j] Post-vaccination diary entry ends on Day 6. Diary review done with site personnel occurs on Day 7.[k] Respiratory Symptom Surveillance (RSS) tool to be completed twice a week by subjects throughout the trial, starting on Day 0 post-vaccination.
[l] The trial-defined CESI is mild to severe LRTI caused by RSV or hMPV.
[m] Perform unscheduled visits and procedures as applicable.
[n] Trial termination visit; subjects who terminate the trial early are recommended to complete certain trial-related procedures..

2.2 Time and Events Schedule for ICVX-12-201: Extension

Day	**365**	**545**	**730**	**Unsch**
Window (Days)	**N/A**	**±28**	**±28**	**-**
Clinic Visit (or home-health visit) [a]	**X**		**X**	**X**
SMS/Phone Call/Digital App		**X**		
Unblinding of subjects [b]	X			
Informed consent for extension [c]	X			
Concomitant medications [d]		X	X	X
Assess for SAEs, AESIs, MAAEs [e]		X	X	X
Vital signs			X	X
Physical examination [f]			X	X
Safety blood draw			X	X
Serology blood draw for SNA / ELISA			X	

Abbreviations: AESIs, adverse event of special interest; ELISA, enzyme-linked immunosorbent assay; MAAE, medically-attended adverse event; N/A, not applicable; SAE, serious adverse event; SNA, serum neutralization assay (live virus neutralization assay); Unsch, unscheduled.

[a] Home-health visits may be performed in lieu of clinical visits if permissible by local regulations and/or institutional/clinic standard operating procedures.

[b] Unblinding of all subjects will occur after they have completed their Day 365 assessments.

[c] Informed Consent for extension applicable only for selected Subjects in trial groups IVX-A12a or placebo.

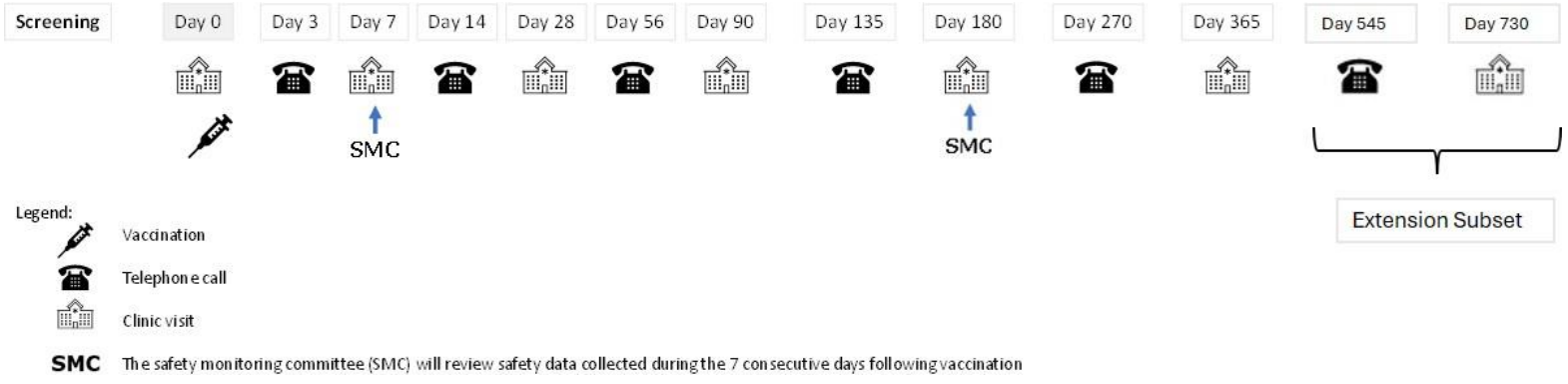
[d] For the trial extension, record concomitant medications and treatments only for self-reported SAEs and AESIs.

[e] For the trial extension, document self-reported SAEs, AESIs, and MAAEs.

[f] Symptom-directed physical examination, if needed.

2.3 Trial Design Schematic

[redacted]



3.0 TRIAL REFERENCE INFORMATION

3.1 Trial-related Responsibilities

The roles and responsibilities of all parties for trial-related activities are described in the project plan.

3.2 Principal Investigator

The sponsor will select a principal investigator from the investigators who participate in the trial. Selection criteria for this investigator will include significant knowledge of the protocol, the investigational vaccine, their expertise in the therapeutic area and the conduct of clinical research as well as participation. The principal investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the trial.

3.3 List of Abbreviations

Abbreviations used in the body of the protocol.

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANVOCA	analysis of covariance
ARI	acute respiratory illness
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CESI	clinical event of special interest
CI	confidence interval
CompA	component A
CompB-01	component B-01
CSR	clinical study report
CTM	clinical trial material
DS-Cav1	soluble RSV
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EPIC	Etiology of Pneumonia in the Community trial
ER	emergency room
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
hMPV	human metapneumovirus
IA	interim analysis
IB	ٰL q ˇ′o brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IgG	immunoglobulin G
IM	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IVX-A12a	unadjuvanted IVX-A12 formulation

IVX-A12d	IVX-A12 formulation adjuvanted with MF59®
IWRS	interactive web response system
LRTI	lower respiratory tract illness
MAAE	medically-attended adverse events
Mab	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NAb	neutralizing antibody
NP	nasopharyngeal
PCR	polymerase chain reaction
pIMC	potential immune-mediated condition
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per-protocol set
PT	preferred term
RBC	red blood cells
RCD	reverse cumulative distribution
RNA	ribonucleic acid
RSS	respiratory symptom surveillance
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SMC	safety monitoring committee
SNA	serum neutralization assay
SOC	system organ class
SpO_2	blood oxygen saturation
SRR	seroresponse rate
SUSAR	suspected unexpected serious adverse reaction
VLP	virus-like particle
WBC	white blood cells

Abbreviations used without expansion:

°C	degree Centigrade
Ig	immunoglobulin
mL	milliliter
USA	United States of America

3.4 Corporate Identification

ICVX	Icosavax, Inc.

4.0 INTRODUCTION

4.1 Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a single-strand, negative sense ribonucleic acid (RNA) virus belonging to the Orthopneumovirus genus of the family *Pneumoviridae* [3]. There are two major genetic lineages, A and B (subgroups A and B, respectively), which are antigenically related, and cross-neutralizing antibodies are induced upon infection with either subgroup. RSV is a major cause of lower respiratory tract illness (LRTI) worldwide in all age groups. Epidemiological data suggest that in the USA alone, RSV may cause >170,000 hospitalizations and ~14,000 deaths annually [4]. RSV is also an important cause of respiratory disease in Europe, South Africa, and Australia [5-9]. Clinical data has identified a substantial disease burden in adults comparable to influenza, with most of the hospitalization and mortality occurring in older adults over 65 years of age [10]. The incidence and severity of RSV disease is particularly high in the frail elderly and in adults with cardiopulmonary conditions, who are considered at high risk for complications and hospitalization due to RSV [11].

RSV infections are ubiquitous with lifelong reinfections in all age groups indicating that immunity is neither sustained nor complete [12-14]. RSV spreads by respiratory droplets and close contact with infected persons or fomites. In temperate climates there is an annual winter epidemic [15], whereas in tropical areas seasonality is less distinct, but infection is most common during the rainy season [16]. The severity of RSV disease is largely determined by the extent of viral replication following infection [17]. The production of neutralizing antibodies (NAbs) should be the goal of vaccination as it is associated with protection against disease. However, seropositivity only confers partial protection against infection [17].

4.2 Human Metapneumovirus

Human Metapneumovirus (hMPV) is a single-strand, negative sense RNA virus of the Metapneumovirus genus in the *Pneumoviridae* family [3], and was first described in 2001 when it was isolated from children with respiratory disease [18]. The most closely related human pathogen is RSV. As with RSV, there are two major genetic lineages of hMPV, A and B (subgroups A and B, respectively), which are antigenically related and cross-neutralizing antibodies are induced upon infection with either subgroup [19,20]. hMPV represents one of the leading causes of acute respiratory tract infections in infants, children, immunosuppressed patients, and the elderly [21,22]. Several studies have shown that hMPV is highly prevalent worldwide, and in the USA alone, approximately 20,000 hospitalizations are registered every year due to this virus [23,24]. In older adults, hMPV is responsible for a significant proportion of serious respiratory infections, with similar rates of

infection as RSV. In the Etiology of Pneumonia in the Community (EPIC) trial, hMPV was confirmed in 4% of adults hospitalized with community-acquired pneumonia whereas RSV was confirmed in 3% of adults [25]. Similar to RSV, NAbs alone can protect against hMPV infection [26,27]. In mouse models, infection with hMPV protects against near term re-infection [28]; macaques infected with hMPV demonstrated seroconversion and temporary protection from subsequent infection that waned over several months [29]. As with RSV, in the presence of positive hMPV antibody titers, reinfections may occur in both healthy and immunocompromised adults [30,31].

4.3 IVX-A12

The Icosavax candidate vaccine, IVX-A12, is a bivalent combination formulation containing IVX-121 and IVX-241 virus-like particles (VLPs), computationally designed recombinant protein subunit vaccines for RSV and hMPV, respectively. Each VLP is composed of two recombinant proteins, Component A (CompA) and Component B (CompB-01), which have been designed to cooperatively assemble to form an icosahedral virus-like structure. Component A is a fusion protein-specific for each vaccine candidate (either CompA-RSV-02 or CompA-hMPV-01 for RSV and hMPV, respectively) and is expressed with the Pre F protein from the respective virus, which has been shown to induce robust NAb responses in nonclinical models. The IVX-121 and IVX-241 VLPs display 20 copies of the respective Pre F protein trimers on their surface. CompB-01 is a common component across both VLPs and provides the structural element that supports the multimeric display of CompA-RSV-02 or CompA-hMPV-01. When combined, the two components self-assemble into VLPs that show enhanced immunogenicity compared with either soluble RSV (DS-Cav1) or hMPV prefusion antigen trimers. The soluble DS-Cav1 RSV Pre F protein was recently tested clinically and shown to be tolerable and immunogenic [32]. Based on nonclinical and early ongoing clinical trials, the Icosavax VLP high-density, multivalent design is hypothesized to provide immunologic advantages over simple subunit protein vaccines such as more breadth, magnitude, and persistence of vaccine induced NAb responses [43].

The candidate IVX-121 and IVX-241 VLPs are manufactured as separate drug substances and are combined to create the IVX-A12 bivalent formulation containing both VLPs. The proposed mechanism of action of IVX-A12 is to increase the proportion of RSV- and hMPV-specific NAbs that are associated with protection, compared to non-neutralizing antibodies [33,34]. IVX-A12 is intended for active immunization of the target population of older adults who are most at risk for disease following infection with RSV and hMPV.

The candidate vaccine, IVX-A12, is a single-dose liquid formulation (0.5 mL) for intramuscular (IM) injection in adults 60 to 85 years of age, the target population. The IVX-A12 candidate vaccine will be formulated as an aqueous vaccine, to be

diluted 1:1 (V/V) with diluent. The IVX-A12 candidate vaccine was also formulated as an adjuvanted vaccine with MF59, an oil-in-water emulsion for further evaluation in this Phase 2 trial, based on interim analysis (IA) of data from the ongoing Phase 1 clinical trial (ICVX-12-101) of IVX-A12 (see below).

Nonclinical studies of IVX-A12 bivalent combinations of the IVX-121 and IVX-241 VLPs demonstrated the ability of both Pre F protein antigens on the Icosavax VLP platform to induce strong NAb responses. In addition, preclinical experiments showed the effects of IVX-A12 dosage levels, number of doses, and need for adjuvant vary with RSV exposure history (either naïve or primed by infection) of the animals. The recent Phase 1/1b clinical trial (IVX-121-01) with the RSV monovalent IVX-121 VLP subunit vaccine also helped guide selection of IVX-A12 dosage levels formulated as either (i) aqueous vaccine or (ii) as adjuvanted vaccine with MF59 for the first-in-human evaluation of IVX-A12 vaccine. MF59 is a nanoemulsion adjuvant composed of squalene, polysorbate 80, sorbitan trioleate, and citrate. MF59 is widely used in the subunit influenza vaccine FLUAD that is licensed in the USA, European countries, and other countries [35]. In total, approximately 150 million doses of vaccines with MF59 have been distributed and no safety concerns have been observed related to MF59 [36]. Furthermore, increased dosage levels of MF59 (19.5 mg and 29.75 mg of squalene, up to 3 times the normal amount contained in licensed vaccines containing MF59) have shown to Yqv q*v *q º q…vLvº… * v PMv qº v Bº´qvLvºvqNqL vGćº qvmN*LNº*trial [40].

Boosting immunity in RSV-and hMPV-seropositive individuals with IVX-A12, a combination bivalent vaccine, may be challenging if one antigen interferes with the immune response to the other antigen. Imbalanced immune responses may require use of adjuvant in that scenario. However, studies in RSV- and hMPV-naïve mice and cotton rats did not demonstrate significant immune interference after vaccination when RSV and hMPV VLPs were administered in varying concentration ratios.

4.4 Rationale for the Proposed Trial

Elderly adults, especially those with underlying chronic diseases, are highly susceptible to viral causes of community-acquired pneumonia caused by influenza virus, RSV, and hMPV [25; 11; 31; 40]. Although the US FDA recently approved the first two RSV vaccines to prevent RSV disease [41], this proposed trial evaluating IVX-A12 remains relevant for the following reasons: to assess immune responses induced by A12a to hMPV in addition to RSV, and to describe the persistence of those induced immune responses over time. This Phase 2a clinical trial is evaluating the safety and immunogenicity of an unadjuvanted dosage level of 150 µg RSV/ 150 µg hMPV of IVX-A12 (IVX-A12a) and a dosage level of 150 µg RSV/150 µg hMPV of IVX-A12 adjuvanted with MF59 (IVX-A12d) compared to placebo in adults 60 to 85 years of age. Safety and immunogenicity data from this proposed Phase2a

clinical trial will allow the selection of an optimal dosage level and formulation of IVX-A12 for adults 60 to 85 years of age in future clinical trials.

The dosage level and formulations of IVX-A12 for this Phase 2a clinical trial have been selected based on the totality of the IVX-A12 nonclinical data and the interim safety and immunogenicity clinical data from the ongoing IVX-A12 Phase 1 clinical trial. Either of the two different IVX-A12 formulations, IVX-A12a and IVX-A12d, or placebo will be administered as a single IM dose to older adult subjects enrolled into two age strata (adults 60 to 69 years of age and elderly adults 70 to 85 years of age). Eligible older adult subjects were randomized to the different trial groups to ensure balance among the groups.

This Phase 2a clinical trial includes a sentinel group of 40 subjects (16 subjects per active treatment group [n=32]; 8 subjects in the placebo group) to conservatively assess the 150 µg RSV/150 µg hMPV dosage level in combination with MF59**.**

Subsequently, based on IA from Day 28 of this trial and from emerging data of the IVX-A12 Phase 1 trial (ICVX-12-101), the trial Sponsor has determined that the dosage level and formulation of IVX-A12 to be carried forward for further evaluation will be IVX-A12a [150 µg RSV/150 µg hMPV with no adjuvant]. Therefore, to evaluate the persistence of RSV and hMPV antibodies long term follow-up will be offered to the IVX-A12a vaccinees and contemporaneous placebo recipients.

More specifically, data from the first IA of this Phase 2 trial at Day 28 demonstrated that the safety and reactogenicity between Phase 1 and Phase 2 data were similar even with the doubling of the IVX-A12 RSV dosage level in the Phase 2 trial. The Phase 2 trial data showed that local and systemic reactions were mostly mild with a few moderate reactions, and no serious or severe AEs, and no AEs leading to trial discontinuation were observed. There were no LRTI cases of any severity (mild, moderate, severe) caused by RSV and/or hMPV (CESIs) through Day 28. The inclusion of MF59 did not improve the immunogenicity of 150 µg RSV/150 µg hMPV in this older Phase 2 population relative to the Phase 1 population, and slightly more reactogenicity was observed with the addition of MF59 than with IVX-A12a alone.

In addition, IVX-A12a appeared to generate similar neutralizing and binding antibody responses to RSV when compared to those induced by already licensed RSV vaccines, which supports the selection of this unadjuvanted dosage level of 150 µg RSV/150 µg hMPV as the appropriate dosage level and formulation composition for further development.

5.0 OBJECTIVES AND ENDPOINTS

Main Trial	
Primary Safety	
Objective	Endpoints
To assess the safety and tolerability of the IVX-A12 bivalent candidate vaccine compared to placebo up to 1 year following a single IVX-A12 vaccination.	- Solicited local (injection site) reactions and systemic ARs for 7 consecutive days starting from Day 0 to Day 6 after vaccination. - Unsolicited AEs from Day 0 to Day 28.
Primary Immunogenicity	
Objectives	Endpoints
- To evaluate the serum NAb response to IVX-A12 or placebo, measured by live virus serum neutralization assays (SNA), at Day 28. - To evaluate the serum immunoglobulin G (IgG) binding antibody response to IVX-A12 or placebo, measured by enzyme-linked immunosorbent assays (ELISA), at Day 28. - To evaluate the proportion of subjects ˇćvpv h-fold increase in serum NAb and serum IgG binding antibody titers to IVX-A12 from prevaccination/baseline (Day 0) to Day 28.	- Geometric mean titers (GMT) of RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb at Day 28. - GMT of RSV and hMPV Pre F protein-specific IgG antibody titers at Day 28. - Proportion of subjects with a h-fold increase in serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb from prevaccination/baseline (Day 0) to Day 28 after vaccination (defined as seroresponse rate [SRR]). - Proportion of subjects with h-fold increase (SRR) in RSV- and hMPV-specific IgG antibody titers from prevaccination/baseline (Day 0) to Day 28. - Geometric mean fold rise (GMFR) at Day 28 versus Day 0 in serum anti RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific Nabs and RSV and hMPV Pre F protein-specific IgG antibody titers.
Secondary Safety	
Objective	Endpoints
To assess the safety of IVX-A12 compared to placebo by describing the incidence of serious adverse events	- SAEs, AESIs (which are pIMCs), MAAEs, and AEs leading to trial

(SAEs), adverse events of special interest ([AESI],which are potential immune-mediated conditions [pIMCs]), medically-attended adverse events (MAAEs), LRTI cases of any severity (mild, moderate, severe) caused by RSV and/or hMPV (clinical event of special interest [CESI]), LRTI cases of any severity (mild, moderate, severe) not caused by RSV or hMPV, and adverse events (AEs) leading to trial withdrawal up to Day 365.	withdrawal up to Day 365 (end of main trial). - Mild, moderate, or severe LRTI cases caused by RSV or hMPV (CESI) up to Day 365. - Clinical safety laboratory parameters at screening, and Days 0, 7, and 28; - Mild, moderate, or severe LRTI cases not caused by RSV or hMPV up to Day 365.
Secondary Immunogenicity	
Objectives	Endpoints
- To evaluate the serum NAb response to IVX-A12 or placebo at Day 0, Day 180, and Day 365. - To evaluate the serum IgG binding antibody response to IVX-A12 or placebo at Day 0, Day 180, and Day 365 after vaccination. - To evaluate the proportion of subjects ˇćvºv h-fold increase in serum NAb and serum IgG binding antibody titers at Days 180 and 365 compared to baseline (Day 0). - To evaluate the proportion of subjects with an)-fold increase in serum NAb and serum IgG binding antibody titers at Days 28, 180 and 365 compared to baseline (Day 0).	- GMT of RSV/A , RSV/B-, hMPV/A-, and hMPV/B-specific NAb at Days 0, 180, and 365. - GMTs of RSV and hMPV Pre F protein-specific IgG antibody titers at Days 0, 180, and 365. - G ˇLv Bv YĞqN v ˇćvºv h-fold increase (SRR) in serum anti-RSV/A-, RSV/B- hMPV/A-, and hMPV/B-specific NAb from prevaccination/baseline (Day 0) to Days 180, and 365 after vaccination. - Proportion of subjects with an)-fold increase in serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb from prevaccination/baseline (Day 0) to Days 28, 180, and 365 after vaccination. - Proportion of subjects with h-fold increase (SRR) in RSV- and hMPV Pre F protein-specific IgG antibody titers from prevaccination/baseline (Day 0) to Days 180 and 365 after vaccination. - GMFR at Days 180 and 365 versus Day 0 in serum anti-RSV/A-, RSV/B-, hMPV/A-, and hMPV/B-specific NAb

	and RSV and hMPV Pre F protein-specific IgG antibody titers. - Reverse cumulative distribution (RCD) of serum NAb and IgG antibody titers at Days 0, 28, 180, and 365.
CCI [redacted]	
Observational Extension	
Secondary Safety	
Objective	Endpoints
To describe the incidence of SAEs, AESI, and MAAEs in consenting IVX-A12a vaccinees and placebo recipients through an additional 12 months (Visit Day 730).	SAEs, AESIs, and MAAEs from Day 365 through Day 545 and up to Day 730.
CCI [redacted]	


CCI

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Clinical Trial Design

The IVX-A12 Phase 2a clinical trial is a randomized, observer-blind, placebo-controlled, dosage optimization, multi-center trial to evaluate the safety and immunogenicity two formulations of IVX-A12: an unadjuvanted dosage level of mMcv ´vR/ ‡jmMcv ´vćx G‡v B4‡D-A12 (IVA-OmpO vºL…vºv… º´qv*q q*v BvmMcv ´v RSV/150 ´ hMPV adjuvanted with MF59 (IVX-A12d) compared to placebo (diluent) in adults 60 to 85 years of age. The dosage level and formulations (either aqueous [IVX-A12a] or adjuvanted with MF59 [IVX-A12d]) were determined based on the totality of the iVX-A12 nonclinical data and the interim safety and immunogenicity clinical data from the ongoing IVX-OmpvGćº qvmN*L ˇNp*v ˇº*bvOv º*v B(ccv ´ IVX-A12 (75 ´ RSV/225 ´ hMPV) has been evaluated with MF59 in the IVX-A12 Good Laboratory Practice (GLP) toxicology study and v vppMv ´v B4‡D-A12 (75 ´ RSV/150 ´ hMPV) has been evaluated with MF59 in the Phase 1 clinical trial ICVX-12-101.

This Phase 2a clinical trial has treatment groups: Two IVX-A12 groups and one placebo group. The total amount of VLP in the two IVX-A12 groups will not exceed 300 µg of VLPs.

- **Group A:** IVX-A12a, the unadjuvanted dosage level of 150 µg RSV/150 ´v hMPV.
- **Group B:** IVX-A12d, the dosage level of 150 ´ RSV/150 ´ hMPV adjuvanted with MF59.
- **Group C:** placebo.

Approximately 250 subjects were randomly allocated at a ratio of 2:2:1 to receive one of the two IVX-A12 formulations (IVX-A12a or IVX-A12d) placebo, respectively. Subjects were stratified by age group (60 to 69 years of age and 70 to 85 years of age). Dosing of the two IVX-A12 groups and placebo groups started in parallel. Age-stratified randomization balanced assignment between the two age groups.

Subjects were considered randomized when they were assigned to a treatment group. The planned subject allocation to trial groups is provided in Table 1.

Table 1 Clinical Trial Schema

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

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

The time and events schedules for the main trial and for the observational extension are presented in Section 2.1 and Section 2.2, respectively. The trial design schematic is shown in Section 2.3.

Trial Procedures:

Approximately 250 adult subjects (60 to 85 years of age) were enrolled. A subject was considered enrolled upon having signed the informed consent form (ICF). Subjects were randomly allocated to receive either IVX-A12 or placebo at a ratio 2:2:1, resulting in approximately 100 subjects in each IVX-A12 group and 50 in the placebo group. In addition, subjects were stratified by age groups (60 to 69 years of age versus 70 to 85 years of age).

Randomization occurred simultaneously into all three trial groups (IVX-A12a, IVX-A12d, and placebo). Initial vaccinations were performed in sentinel subjects and then expanded to the remaining subjects in each of the three trial groups. In total, there were 40 sentinel subjects. In each IVX-A12 group, 16 sentinel subjects received IVX-A12a (8 subjects from age stratum 60 to 69 years of age and 8 subjects from age stratum 70 to 85 years of age); 16 sentinel subjects received IVX-A12d (8 subjects from age stratum 60 to 69 years of age and 8 subjects from age stratum 70 to 85 years of age). In the placebo group, 8 sentinel subjects received placebo (4 subjects from age stratum 60 to 69 years of age and 4 subjects from age stratum 70 to 85 years of age). Sentinels were closely monitored for a minimum of 48 hours. If no stopping rules were triggered, the remaining subjects in the IVX-A12 and placebo groups were enrolled.

There are a total of seven scheduled clinic visits required for each subject (at screening, then Days 0, 7, 28, 90, 180, and 365), and five phone contacts (on Days 3, 14, 56, 135, and 270) for all subjects in the main part of the trial. IVX-A12a and placebo subjects consenting to the extension portion of the trial will have a phone contact at Day 545 for safety assessments and a clinic visit at Day 730 for safety assessments and blood sampling for immunogenicity.

The time and events schedules for the main study and for the extension are presented in Section 2.1 and Section 2.2, respectively.

6.2 Justification for Trial Design, Dosage Level, and Endpoints

The interim safety and immunogenicity data from the Phase 1 clinical trial ICVX-12-mtmvqL ˇ*q..Sv GćºqvmvRºL… Uˇq..Sv, Y q q -blind, Placebo-controlled, Multi-center Trial to Evaluate the Safety and Immunogenicity of IVX-A12, a Respiratory Syncytial Virus and human Metapneumovirus Bivalent Combination Virus-like Particle Protein Subunit Vaccine, in Healthy Adults, 60 to 75 Years of O´q v demonstrated that IVX-A12 was well tolerated and immunogenic up to 28 days post single-dose vaccination in adults 60 to 75 years of age. The trial evaluated five dosage levels/formulations (low dosage level, 75 µg RSV/75µg hMPV ± MF59; medium dosage level,75 µg RSV/150 µg hMPV ± MF59; and high dosage level, 75 µg RSV/225 µg hMPV with no adjuvant) and met primary safety and immunogenicity endpoints.

Based on the totality of nonclinical and clinical data on IVX-A12, including these interim Phase 1 safety and immunogenicity data, the following two IVX-A12 dosage level and formulations were selected for evaluation in the proposed Phase 2a clinical trial: (1) 150 µg RSV/150 µg hMPV unadjuvanted; and (2) 150 µg RSV/150µg hMPV adjuvanted with MF59.

The intent of the selected formulations is to augment RSV-A and RSV-B immune responses, while preserving hMPV immune responses. In addition, IVX-121, the RSV component of the IVX-A12 RSV/hMPV bivalent vaccine candidate has been evaluated in a Phase 1/1b clinical trial in dosage levels up to 250 µg without adjuvant with no safety concerns noted up to 180 days post-vaccination. A total of 300 µg IVX-A12 (75 µg RSV/225 µg hMPV formulation) has been evaluated with MF59 in the IVX-A12 GLP toxicology study, and up to 225 µg of IVX-A12 (75 µg RSV/150 µg hMPV formulation) was clinically evaluated with MF59 in the ICVX-12-101 Phase 1 trial.

The sample size calculation is provided in Section 13.4.

6.3 Planned Duration of Subject's Participation in the Trial

The duration of subject participation in the main section of the trial will be approximately 12 months. At visit Day 365, after subjects are unblinded, IVX-A12a and placebo subjects (who were in the per protocol immunogenicity analysis set) will be invited to consent to longer term follow-up for approximately an additional 12 months.

6.4 Premature Termination or Suspension of Trial or Trial Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

The trial will be completed as planned unless one or more of the following criteria that require temporary suspension or early termination of the trial are satisfied.

- New information or other evaluation regarding the safety or efficacy of the investigational vaccine that indicates a change in the known risk/benefit profile, such that the risk/benefit is no longer acceptable for subjects participating in the trial.
- The SMC recommends that the trial should be suspended or terminated.
- Significant deviation from GCP that compromises the ability to achieve the primary trial objectives or compromises subject safety.
- The sponsor decides to terminate or suspend the trial.

6.4.2 Criteria for Premature Termination or Suspension of Trial Sites

A trial site may be terminated prematurely or suspended if the site (including the investigator) is found to be in significant deviation from GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the trial, or as otherwise permitted by the contractual agreement.

6.4.3 Procedures for Premature Termination or Suspension of the Trial or the Participation of Trial Sites

In the event that the sponsor, an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) or regulatory authority elects to terminate or suspend the trial or the participation of a trial site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable trial sites during the course of termination or trial suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All eligibility criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1) Male or female subjects, 60 to 85 years of age, who must be in stable health based on medical history, vital signs, physical examination, and laboratory q º*º ˇ Lv ˇ v v ºNNĽº ˇ LSvĽvćqvĽ q ˇ˝º vN*Ľ ĽºP*vČ …´U qL ≥
2) Subjects may have ongoing chronic conditions (comorbidities such as hypertension, congestive heart failure, chronic obstructive pulmonary disease, type 2 diabetes mellitus, hyperlipoproteinemia, or hypothyroidism) who are, in ćqvĽ q ˇ˝º v ĽˇLSvU q…Ľº** vN U qL º q…vºL…v ˇć v qNqL v exacerbation (for example, no emergency room [ER] visits and no change to medical treatments or medications to better control the condition) within the prior 3 months;
3) Subjects able to voluntarily give written informed consent and can comply with trial procedures including follow-up for approximately 12 months after vaccination;
4) Body mass index 17 to <40 kg/m^2 at screening;
5) Before randomization, female subjects must be unable to conceive (e.g., menopausal, i.e., 12 consecutive months without menstruation, hysterectomy, oophorectomy, etc.) and not intending to conceive by any method;
6) Subject must agree not to donate blood from the time of vaccination through 3 months after vaccination;
7) Subject must be willing to provide verifiable identification and have the means vYqvN L ºNq…vºL…v vN L ºNvćqvĽ q ˇ˝º v vćqv ˇq v ºBv… Ľ´vćqv entire clinical trial.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the trial:

1) Subjects with moderate or severe liver disease, metastatic solid tumor, and acquired immunodeficiency syndrome (AIDS) are to be excluded. In addition, subjects with underlying significant illness or condition(s) or ongoing treatment that, in the opinion of the investigator, could (i) interfere with the conduct of the trial, (ii) pose an unacceptable risk to the subject in this trial, (iii) interfere ˇćvćqv YĞqN vºY*˝ v vN U *vwith the trial procedures or abide by the

trial restrictions, (iv) interfere with the ability to interpret safety data, or (v) prevent completion of the trial are to be excluded;

2) Older adults who meet frail elderly criteria (older persons with medical, nutritional, cognitive, emotional, or activity impairments, as defined by the 2º€ ˇqv, *Ł ˇNp*ƶ3 º˘* v/ N qv hv[37] See Appendix C;

3) Prior receipt of any licensed or investigational RSV or hMPV vaccine within the past 12 months;

4) Prior receipt of another investigational medicinal product ([IMP]; trial drug, biologic, or device) not authorized for use in the USA and European Union within the past 3 months;

5) Laboratory-confirmed RSV or hMPV infection within the 12 months prior to enrollment;

6) Currently enrolled or plan to participate in another clinical trial with an investigational agent (including licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication) to be received during the trial period;

7) History of malignancy within 5 years before screening not in the following categories:(i) subjects with squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix may be enrolled at the discretion of the investigator, (ii) subjects with a history of malignancy within 5 years before screening, with minimal risk of recurrence per ˘Ł q ˇ˝º judgment, can be enrolled;

8) Per medical history, subjects with chronic active hepatitis B or hepatitis C infection, human immunodeficiency viruses type 1 or type 2 infection, acute polyneuropathy (such as Guillain-Barré syndrome), or chronic idiopathic demyelinating polyneuropathy; subjects whose hepatitis C antibody test is positive but whose viral loads are negative may be enrolled;

9) Acute illness, with or without fever at the time of planned vaccination;

10) History of hypersensitivity or serious adverse reactions to vaccines, such as anaphylaxis or angioedema, or any known allergies to any component of the IVX-121 and/or IVX-241 vaccine, or hypersensitivity to latex;

11) Abnormal function of the immune system resulting from clinical conditions including chronic administration of systemic corticosteroids (oral/intravenous/IM at a daily dose equivalent of >20 mg prednisone in a period of more than 14 days), or administration of immunosuppressive chemotherapy, biologics, or radiotherapy within the past 3 months prior to planned vaccination;

12) Subjects who have received treatment with immunoglobulins or other biologics, such as immunosuppressive therapies expected to modify immune responses to vaccination (including monoclonal antibodies [MAbs] for chronic underlying conditions) within the past 3 months prior to planned vaccination;
13) Trial Personnel as an immediate family or household member
14) For licensed vaccines:
    a) Receipt of licensed inactivated vaccines (including seasonal influenza vaccine) within 14 days prior to trial vaccine administration on Day 0, or licensed replicating vaccines such as RNA or live-attenuated virus vaccines within 30 days prior to Day 0.
    b) Receipt of licensed vaccines is permitted after completion of the Day 28 visit.
    c) Receipt of any licensed COVID-19 vaccines is permitted if dosing regimen completed within 21 days prior to Day 0 or after completion of the Day 28 visit.

There may be instances when individuals meet all eligibility criteria except one that relates to transient clinical circumstances (e.g., fever or recent use of excluded medication[s] or vaccine[s]). Under these circumstances, eligibility for enrollment may be considered if the appropriate window for delay has passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible (Section 7.4).

7.3 Trial Observational Extension

After approximately 12 months, trial subjects will be unblinded at their Day 365 visit. IVX-A12a and placebo subjects, whose data has not been excluded from immunogenicity analyses in the main part of the trial and who consent to be followed for safety and immunogenicity, will continue in the trial for an additional 12 months.

7.4 Criteria for Delay of Investigational Medicinal Product Administration and/or Blood Sampling

After enrollment, subjects may encounter clinical circumstances that warrant a delay in the administration of IMP. These situations are listed below:

1) Subjects with a clinically significant active infection (as assessed by the investigator) or body temperature >38.0°C (>100.4°F), within 3 days of planned IMP administration.
2) Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to vaccination. The reason for their use (prophylaxis versus

treatment) must be documented. IMP administration should be delayed to allow for a full 24 hours to have passed between having used antipyretics and/or analgesic medications and IMP administration.

In the event that a subject meets a criterion for delay of IMP administration, the subject may receive the IMP once the window for delay has passed as long as the subject is otherwise eligible for trial participation.

7.5 Criteria for Early Termination of a Subject’s Trial Participation

Under some circumstances, a YČqN trial participation may be terminated early. This means that no further trial procedures (including data collection) will be performed on that subject beyond the specific date of early termination of trial º N̆ˇ º ˇ LbvXćqv Ŭº vqº LvB vqº * v q U L̆º ˇ Lv Bvćqv YČqN v ˇº*v participation should be documented using the following categories:

1. **Adverse event**: The subject has experienced an AE/AR (irrespective of being related/unrelated to the IMP or trial-related procedures) that requires early termination because continued participation imposes an unacceptable risk to ćqv YČqN vćqº*ćvºL…j vćqv YČqN v ˇ v L ˇ**L ́v vN L L̆ qv º N̆ˇ º ˇ Lv because of the AE/AR. The subject will be encouraged to remain in the trial to be followed for safety observations; with no additional trial procedures conducted. If the subject is unwilling to continue because of the AE/AR, the primary reason for early termination of trial participation in this case will be ˇć… º º*v… qv vO1jOR vºL…vL v ˇć… º º*v BvN L qL Sv qqvYq* b
2. **Lost to follow-up**: The subject did not return to the clinic and at least three attempts to contact the subject were unsuccessful.
3. **Withdrawal of consent**: The subject wishes to withdraw from the trial. The Ŭº vqº LvB vqº * v q U L̆º ˇ Lv ˇ**vYqv ˇć… º º*v BvN L qL vBvćqv subject withdraws from participation due to a non-medical reason (i.e., reason other than AE/AR). While the subject has no obligation to provide a reason for withdrawing consent, attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be documented.
4. **Premature trial termination by the sponsor, a regulatory agency, the IEC/IRB, or any other authority**: If the clinical trial is prematurely terminated by the sponsor, the investigator is to promptly inform the trial subjects and local IEC/IRB and should assure appropriate follow-up for the YČqN bvXćqv Ŭº vqº LvB vqº * v q U L̆º ˇ LvL̆v ć ˇ vNº qv ˇ**vYqv ˇº*v q U L̆º ˇ L b
5. **Subject’s death** during trial participation.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding the IMP, placebo, and materials provided directly by the sponsor, and/or sourced by other means, that are required by the trial protocol, including important sections describing the management of clinical trial materials (CTM).

Details regarding the dosage form description and strengths, or composition for the extemporaneous preparation of the IMP can be found in the pharmacy manual.

8.1 Investigational Medicinal Products

8.1.1 IVX-A12

The two investigational IVX-A12 formulations for testing are composed of a constant IVX-121 RSV VLP dosage level (150 µg) with a constant IVX-241 hMPV VLP dosage level (150 µg).

The two formulations of IVX-A12 are:

- An unadjuvanted dosage level of 150 µg RSV/150 µg hMPV of IVX-A12 (IVX-A12a); and
- A dosage level of 150 µg RSV/150 µg hMPV of IVX-A12 adjuvanted with MF59 (IVX-A12d)

Both formulations will be compared to placebo (diluent).

The final investigational IVX-A12 drug product is administered either as an aqueous vaccine (IVX-A12a) or with MF59 to be mixed 1:1 in the clinic (IVX-A12d). The amount of MF59 (squalene) per dose will not exceed 9.75 mg. Specific instructions for preparation of vaccine are provided in the pharmacy manual.

The intended volume for administration of IVX-A12 is 0.5 mL for IM administration.

8.1.2 Placebo

Sterile aqueous diluent, delivered as a 0.5 mL dose. The placebo does not contain preservatives.

8.1.3 Labeling

A clinical label will be affixed to IMP containers in accordance with local regulatory requirements.

8.1.4 Inventory and Storage

Environmental storage conditions for sponsor-supplied IMPs and CTM used to administer the IMP (e.g., temperature, humidity, away from sunlight or heat) are described in the trial pharmacy manual. IVX-A12 formulations and placebo must be

stored at 2-8°C, and never frozen. Sponsor-supplied IMP should be stored under the specified conditions and remain in the original container until dispensed.

All CTM must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Receipt and dispensing of IMP must be recorded by authorized personnel at the trial site. A temperature log of the vaccine storage area must be maintained. Temperature excursions must be reported to the sponsor as soon as possible and use of these vaccines requires sponsor approval.

Additional details for inventory, storage and handling can be found in the pharmacy manual.

8.1.5 Dosage Level and Dosing Regimen

Subjects received a single IM dose of IMP Table 2 on Day 0. The criteria for dosage level escalation versus trial groups are described in Section 6.1 and the stopping rules are provided in Section 11.1.

Table 2 describes the doses that will be provided to each group.

Table 2 Sponsor-supplied IMP

Trial Group	Formulation				Route
	IVX-A12	VLP (µg)		MF59 (mg squalene)	
		RSV	hMPV		
A	IVX-A12a	150	150	0	IM
B	IVX-A12d	150	150	9.75	IM
C	Placebo	-	-	0	IM

Abbreviations: hMPV, human metapneumovirus; IM, intramuscular; RSV, respiratory syncytial virus; VLP, virus-like particle.

8.2 Investigational Medicinal Product Assignment and Dispensing Procedures

Subject randomization was conducted using an interactive web randomization system (IWRS). The system ensures proper distribution of subjects across trial groups at each stage.

Preparation and administration of the IMP and the placebo was performed by unblinded trial personnel/pharmacists/administrators. These people, identified prior to trial dosing on Day 0, do not perform any trial assessments for the duration of the trial.

If sponsor-supplied IMP is lost or damaged, the site can request a replacement. Expired IMP must not be administered.

8.2.1 Precautions to be Observed When Administering the Investigational Medicinal Product

Prior to IMP administration, a subject must be determined to be eligible to receive IMP (Sections 7.1 and 7.2), and it must be clinically appropriate in the judgment of the investigator to administer the IMP. IVX-A12 or placebo are injected by the IM route into the deltoid of the non-dominant arm. Standard immunization practices are to be observed and care should be taken when administering an IMP intramuscularly. As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccination.

8.3 Randomization Code Creation and Storage

Randomization as conducted using an IWRS. The system ensures proper distribution of subjects across group assignments; treatment assignments known only to the responsible unblinded trial personnel/vaccine administrators at the study center. Subjects and the main study team and clinical staff will remain blinded for the duration of the study unless emergency unblinding is necessary.

Randomization information is stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Medicinal Product Blind Maintenance

This trial is an observer-blind trial. Assignment to IMP is known only to the responsible unblinded trial personnel/vaccine administrators at the trial sites. The subjects, data collectors (e.g., investigator) and data evaluators are blinded to the material administered. Randomization and IMP administration must be done by designated unblinded site staff who must not be involved with data collection of any sort including safety evaluation of the subject after administration of IMP.

All care must be taken to ensure that the unblinded reports and documents are shared only with unblinded personnel and properly stored in a secured area, accessible only by authorized personnel.

8.5 Unblinding Procedure

The IMP blind shall not be broken by the investigator unless information concerning the IMP is necessary for the medical treatment of a subject, or if a subject requests it. In the event of a medical emergency, if possible, the medical monitor should be contacted before the IMP blind is broken to discuss the need for unblinding.

For unblinding a subject, the IMP blind can be obtained by the investigator, by accessing the IWRS.

The L pharmacovigilance department must be notified as soon as possible if the IMP blind is broken by the investigator and the completed SAE form, if applicable, must be sent within 24 hours. The date, time, and reason the blind is broken must be recorded in the source document.

If any subject is unblinded, the subject should continue to be monitored for safety follow-up.

All subjects will be unblinded at their Day 365 visit.

8.6 Accountability and Destruction of Sponsor-supplied Investigational Medicinal Products, and Other Clinical Trial Materials

The investigator or designee must ensure that the sponsor-supplied IMP are used in accordance with the approved protocol and is administered only to subjects enrolled in the trial. To document appropriate use of sponsor-supplied IMP, the investigator must maintain records of all sponsor-supplied IMP delivery to the site, site inventory, administration and use by each subject, and destruction or return to the sponsor or designee.

The investigator must maintain 100% accountability for all sponsor-supplied IMPs and other CTM (including ancillary materials, as applicable) received and administered during their entire participation in the trial. Inventory, tracking and accountability forms will be maintained in the pharmacy files.

Prior to site closure or at appropriate intervals throughout the trial, before any IMP, or CTM are destroyed or returned to the sponsor or designee for destruction, a representative from the sponsor will perform CTM accountability and reconciliation.

9.0 TRIAL PLAN

9.1 Trial Procedures

The following sections describe the trial procedures and data to be collected. The time and events schedules for the main trial and for the extension are located in Section 2.1 and Section 2.2, respectively. All procedures must be performed by qualified and trained staff.

9.1.1 Informed Consent and Eligibility

The requirements of the ICF are described in Section 15.2.

Informed consent must be obtained before any protocol-directed procedures are performed.

A unique subject number is assigned to each subject after informed consent is obtained. If all eligibility criteria are fulfilled and the subject is randomized, this subject number is used throughout the trial. Subject numbers assigned to subjects who are not randomized should not be reused.

IVX-A12a and placebo recipients must sign a second consent if they agree to participate in the trial extension period.

9.1.2 Demographics, Medical History and Medication History

Demographic information to be obtained will include age/date of birth (if applicable), sex, race (and ethnicity) as described by the subject.

Medical history is also collected, including but not limited to any medical history that may be relevant to subject eligibility for trial participation such as prior vaccinations, medication history, concomitant medications, and previous and ongoing illnesses and/or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation if it represents an exacerbation of an underlying disease/pre-existing problem. Information about the º ŇˇºL vć qć *.v makeup and interactions with people of different age groups is collected. History of the use of alcohol, tobacco, and marijuana will also be collected.

Medical history (including corresponding medication) to be obtained includes any significant conditions or diseases that have disappeared or resolved at or prior to signing of the ICF.

Adverse medical occurrences emerging during the time between signing of the ICF and the administration of IMP are recorded in the AE electronic case report form (eCRF). If such an adverse medical occurrence is assessed as related to a screening procedure this should be recorded as an AE related to trial procedure in the eCRF.

All medications, vaccines and blood products taken or received by the subjects are collected as prior and concomitant medications (Section 7.2):

a) Medications: 1 month prior to screening.

b) Vaccines: 1 year prior to screening for any investigational, for any non-registered vaccines and for any licensed vaccines.

c) Blood products: 3 months prior to screening.

The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment*) must be documented. Administration of the IMP should be delayed by 24 hours.

*Medications taken for prophylaxis are those intended to prevent the onset of AEs following vaccination. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Assess and record concomitant therapy (prescription medications ONLY) and vaccine history as described above in the source documents.

See Section 9.2.8 for recording of medications during the trial extension, i.e., 12-month observational follow-up.

9.1.3 Documentation of Trial Entry/Randomization

Only subjects who have a signed ICF and meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization/entry into the active phase. Xćqv ºL… U ˇ º ˇ Lv qNBNº ˇ Lv º vº q…Y vćqv L v ˚*v º ˇ ˚NLSv v designee.

If the subject is ineligible for randomization, the investigator should record the primary reason for failure on the subject screening and enrollment log using the following categories:

- Screen failure (did not meet one or more inclusion criteria or did meet one or more exclusion criteria);
- Withdrawal by subject;
- Enrollment target reached;
- Trial terminated by the sponsor.

Subject numbers assigned to subjects who fail screening cannot be reused.

In the event of major protocol violations/deviations (such as failure to collect Day 0 samples for serology or safety analyses) occurring during the active phase of entry/randomization leading to dosing of eligible subjects, replacement of an approximate equal number of subjects is allowed.

9.1.4 Physical Examination

Physical examinations must be performed by a qualified health professional in accordance with local regulations and as listed within the site responsibility delegation log. A complete physical exam is performed at screening according to ćqvǏL q ˇ´o v ºL…º ..v ºN ǏNqbvO.....ˇˇ Lº*v ć ǏNº*vq ºU ǏLº ˇL vUº vYqv q B U q..vǏBvǏL…ǏNº q..vY v q ˇq v Bvćqv YĞqN vU q…ǏNº*vćˇ bvXćqvBǏL…Ǐ´ v ć *..vYqv.. N U qL q..vǏLvćqv YĞqN v Nqv.. N U qL b

Symptom-directed physical examination may be performed at subsequent visits if deemed necessary.

9.1.5 Vital Signs

A subject will have their vital signs measured at the screening visit, prior to dosing, and at all regularly scheduled clinic visits, including body temperature, blood pressure, heart rate, respiratory rate, oxygen level (SpO_2), weight (at screening only) and height (at screening only). Follow standard of care for trial population and operational feasibility. SpO_2 will not be performed during the trial extension unless clinically indicated.

9.1.6 Immunogenicity Assessments

Blood sampling for immunogenicity is taken at Days 0, 28, 180, and 365, and for the trial extension population subset at Day 770. All subjects are followed for persistence of antibody responses through the entire duration of the clinical trial (approximately 12 months), and then antibody responses will be checked in the trial extension subset at Day 730. All samples must be collected in accordance with acceptable laboratory procedures.

In the event of local or national health related closures and limited ability for travel (e.g., as a consequence of SARS-CoV-2 circulation), the clinic may default to their institution guidelines to continue follow-up assessments with subjects as necessary.

The assays are described in Table 3. Refer to Table 5 for maximum volume of blood collected at any single visit.

Table 3 Phase 2a Core Clinical Bioanalytical Assays

Assay	Purpose	Comment
RSV neutralization (RSV/A, RSV/B)	1° and 2° immunogenicity endpoints	Neutralization titers define magnitude of functional immune response to RSV/A and RSV/B
hMPV neutralization (hMPV/A, hMPV/B)	1° and 2° immunogenicity endpoints	Neutralization titers define magnitude of functional immune response to hMPV/A and hMPV/B
RSV pre F protein binding ELISA	1° and 2° immunogenicity endpoints	Total IgG response for use in analysis of quality metric as defined by relative rise in [illegible]
hMPV pre F protein binding ELISA	1° and 2° immunogenicity endpoints	Total IgG response for use in analysis of quality metric as defined by relative rise in [illegible]
Anti-VLP core IgG ELISA (VLP Core)	Exploratory endpoint	Analysis of response to VLP core (without DS-Cav1 antigen) after vaccination to inform platform technology, interpretation of safety and immune responses to DS-Cav1 antigen.
BioFire Respiratory Panel 2.1 (RP.1)	2° safety endpoint and exploratory efficacy endpoint	Diagnostic assay to detect and identify nucleic acid targets in respiratory specimens from virological agents that cause the RSV and/or hMPV respiratory infection (and other agents).

Abbreviations: ELISA, enzyme-linked immune absorbent assay; IgG, immunoglobulin G; hMPV, human metapneumovirus; RSV, respiratory syncytial virus; VLP, virus-like particle.

Serological samples will be assessed for primary or secondary immunogenicity endpoints using the following assays:

- RSV/A□specific and hMPV/A-specific NAb assay;
- RSV/B□specific and hMPV/B-specific NAb assay;
- Anti-RSV and anti-hMPV Pre F protein-specific IgG ELISAs.

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The anti-RSV Pre F protein IgG ELISA and anti-hMPV Pre F protein IgG ELISA have been qualified for the quantification of binding IgG antibodies to the Pre F protein in human serum samples.

Serological samples will be assessed for exploratory immunogenicity endpoints using the following assays:

- Anti-VLP core IgG ELISA.

An anti-VLP core ELISA was qualified for the quantification of binding IgG antibodies to VLP core in human serum samples.

CCI

9.1.8 Safety Assessments

Safety assessments: All solicited local (injection site) reactions and systemic ARs are collected for all subjects for 7 consecutive days, starting from the day of the single-dose administration (Day 0) through Day 6 (7 days total); unsolicited AEs through Day 28; and safety blood samples (clinical laboratory evaluation at screening, Day 0/baseline, Day 7, and Day 28).

AEs, SAEs, AESIs (Section 10.4.4.1 and Appendix D), MAAEs, AEs leading to trial withdrawal, and CESI are captured from the time of randomization to Day 365, approximately 12 months after vaccination. After the Day 365 visit, SAEs, AESIs, and MAAEs will be collected up to the Day 730 visit. Clinic staff (a trained healthcare provider) will contact the subject by phone call or using a digital application (e.g., SMS text) to facilitate the collection of relevant safety information such as concomitant medication use and occurrence of AEs/SAEs. Up to Visit Day 365, all subjects will complete a respiratory symptom surveillance tool approximately twice a week (i.e., approximately twice within 7-day intervals starting on Day 0 post-vaccination) to be monitored for the trial-defined CESI of mild, moderate, or severe LRTI caused by RSV or hMPV, using the established case definition and algorithm for evaluation of ARI and using NP swabs for the detection of RSV, hMPV, and other respiratory viruses. Subjects are instructed to return to the clinic for assessment within 3-7 days of onset of ARI (ideally within 3 days) to maximize detection of virus.

After subjects are unblinded to their trial group assignment at Day 365, consenting IVX-A12a and placebo recipients will be contacted by clinic staff by phone call or with a digital application (e.g., SMS text) to facilitate the collection of MAAEs, AESIs, and SAEs, at Day 545; MAAEs, AESIs and SAEs will also be collected at the clinic visit on Day 730.

Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.5.

The solicited ARs included in the safety assessments are listed in Table 8.

9.1.9 Clinical Safety Laboratory Variables

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood collected for clinical safety evaluation is approximately 10 mL and will be collected by the trial staff or designee and laboratory values will be determined at the central or local laboratory. Samples must be collected, prepared, and arranged for transport according to the instructions provided by the local laboratory.

Table 4 lists the clinical safety laboratory tests that will be performed.

Table 4 Clinical Safety Laboratory Tests

Hematology	Blood Chemistry	Urine	Other Safety Variables
Complete blood count: • Red blood cells (RBC) • Hemoglobin • Hematocrit • White blood cells (WBC) with differential • Platelet count	• Alanine aminotransferase (ALT) • Aspartate aminnotransferase (AST) • Creatinine • Blood urea nitrogen (BUN) • Total bilirubin	• pH • Glucose • Protein • Ketones • Urobilinogen • Specific gravity • RBC / Erythrocytes* • WBCs / Leukocytes*	• Human immunodeficiency virus (screening) • Hepatitis B virus (screening) • Hepatitis C virus serology (screening)

Urine dipstick test will be performed at screening. An abnormal result for glucose, ketones, pH, protein, specific gravity, and/or urobilinogen will trigger urine microscopy.
*Urine microscopy, if required.

9.1.10 Processing, Labeling and Storage of Biological Samples

All biological samples (e.g., blood, urine, etc.) will be processed, labeled, and stored according to the laboratory manual or other appropriate guideline provided to the site.

Subjects who complete all scheduled trial visits for the main portion of the trial will provide approximately 80 mL of blood in total for clinical safety and immunology (Table 5) by the end of the trial. Subjects in the extension subset population will provide an additional 10 mL of blood for immunology, for a total of approximately 90 mL of blood by the end of the trial. See Sections 9.1.6 and 9.1.9 for additional details.

Table 5 Blood Volumes

Day	Clinical Safety Laboratory	Immunogenicity Assessments	Total
Screening	10 mL	-	10 mL
Day 0	10 mL	10 mL	20 mL
Day 7	10 mL	-	10 mL
Day 28	10 mL	10 mL	20 mL
Day 180	-	10 mL	10 mL

Day 365	-	10 mL	10 mL
Day 730*		10 mL	10mL
Total for Trial	**40 mL**	**40- 50* mL**	**80- 90 *mL**

*Day 730, extra 10 mL of blood only for subjects in the trial extension period.

9.1.11 Contraception Procedures

Male subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process. Male subjects of childbearing potential will be required to use condoms from vaccination until 3 months afterwards, and to refrain from sperm donation during the same period. Male subjects not of child-bearing potential are permanently sterile by bilateral orchiectomy or vasectomy.

9.2 Time and Events Schedule

The time and events schedules for all trial-related procedures for all evaluations for the main study and for the extension are shown in Section 2.1 and Section 2.2, respectively. Assessments should be completed at the designated time points.

Specific information related to vaccination and post-vaccination procedures are outlined below.

9.2.1 Screening (Days -28 to -1)

- Informed consent (Section 9.1.1);
- Eligibility criteria (Section 7.1 and Section 7.2);
- Demographics (Section 9.1.2);
- Medical history (Section 9.1.2);
- Medication history (Section 9.1.2);
- Urine sample (Section 9.1.9);
- Physical examination (Section 9.1.4);
- Vital signs (Section 9.1.5);
- Safety blood sampling (Section 9.1.9);
- Concomitant medications (Section 9.1.2).

9.2.2 Prevaccination Procedures (Day 0)

- Physical examination (Section 9.1.4);
- Vital signs (Section 9.1.5);

- Safety blood sampling (Section 9.1.9);
- Serology blood draw for SNA (live virus neutralization assay), ELISA (Section 9.1.6);
- Confirm eligibility (Section 9.1.1);
- Randomization (Day 0 only; Section 9.1.3).

9.2.3 Vaccination Procedures (Day 0)

After confirming eligibility (Day 0) and randomizing the subject (Day 0), perform IMP administration according to the procedures described in Section 8.2.

9.2.4 Post-vaccination Procedures (Day 0)

The following post-vaccination procedures will be performed on Day 0:

After vaccination, the subject will be observed in the clinic for at least 60 minutes including observation for unsolicited AEs, solicited local (injection site) reactions, and body temperature measurement. Information should be recorded in the eCRF. The investigator or delegate will take the opportunity to remind the subject how to measure solicited local (injection site) reactions and body temperature as part of this observation period. All safety data will YqvN *qNq..vLvćqv YČqN v Nqv documents.

Diary distribution and training:

- Training of the subject on how to measure solicited local (injection site) reactions and body temperature, how to complete the diary and how often to complete the diary. Training should be directed at the individual(s) who will perform the measurements of solicited local (injection site) reactions and those who will enter the information into the diary. This individual may or may not be the subject, but if a person other than the subject enters information into the …ᵇ Svć˘v q L v˘..qL ˘ vU vYqv.. N U qL q..vLvćqv NqvºL..vć˘v q Lv must receive training on the diary. Training of the subject on how to measure an injection site reaction and how to take their temperature, as well as how to record the information in the diary, should be performed while the subject is under observation after vaccination.

Diary instructions must include the following:

- The individual(s) who will enter the information into the diary must understand that timely completion of the diary on a daily basis is a critical component of trial participation.

Please note:

There are two types of diaries utilized for the trial:

- Diary used for the collection of solicited local (injection site) reactions and systemic ARs (including body temperature measurements). The diary will be the only source document allowed for remote collection of solicited ARs.
- Any new unsolicited safety information would be recorded in the subject source document as a verbally reported event and therefore captured as an AE and recorded in the AE eCRF.
- Starting on the day of vaccination, the subject will check for specific types of events at the injection site, any specific generalized symptoms (solicited systemic ARs), body temperature (any method), any other symptoms or change ŀLvćqv YČqN vćqº*ćv º SvºL…vºL vUq…ŇºˇL vº:qLvq N* …Ŀ´vˇºUŀ v and minerals). These solicited ARs and body temperature will be recorded in the diary. Assessments should preferably take place in the evening.
- Temperature measurement is to be performed using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the diary.
- The measurements of solicited local (injection site) reactions are to be performed using the ruler provided by the site.
- The collection on the diary of body temperature, solicited local (injection site) reactions, and solicited systemic ARs will start from the day of the single-dose administration (Day 0) through Day 6 (7 days total).
- Subjects will be prompted by the diary to contact the site to report any unsolicited AEs and medications throughout the trial:
  - For 28 days following vaccine administration, any new unsolicited safety information would be recorded in the subject source document as a verbally reported event and therefore captured as an AE and recorded in the AE eCRF.
  - Throughout the main portion of the trial (through Day 365), any events reported in the diary will be evaluated to determine whether MAAE, SAE, AESIs, or CESI criteria are met. If these criteria are met, the information would be captured in the subject source document, recorded in the applicable q, R3SvºL…vq q…v vćqv L v v L v.q ˇˇLqq v pharmacovigilance department as applicable.

- Diary for Respiratory Surveillance Survey (RSS) for the collection symptoms that may meet the definition of an ARI. See Section 10.1.3.
    - Starting on the day of vaccination and through visit Day 365, the subject will be prompted twice a week to record the incidence of any symptoms meeting ARI criteria.

The site should schedule the next trial activity.

The subject will be reminded to complete the diary daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an ER visit. All contact details will be provided to the subject.

Refer to Section 10.4 for the reporting of AEs, SAEs, AESIs, MAAEs, LRTI cases of any severity not caused by RSV or hMPV, AEs leading to withdrawal, and CESIs (mild, moderate, or severe LRTI caused by RSV and/or hMPV).

9.2.5 Main Trial Site Visits after Vaccination (Days 7, 28, 90, 180, and 365)

Site visits that do NOT include a vaccination will be performed on Days 7, 28, 90, 180, and 365. At the site visit for Day 7, the diary will be reviewed. The healthcare professional reviewing these data will discuss the AEs/ARs (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present and/or if concomitant medications have been used.

The site should:

- Schedule the next site visit or other trial activity with the subject;
- Provide a reminder of the next planned trial activity;
- Remind the subject to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an ER visit.

Refer to Section 10.4 for the reporting of AEs, SAEs, AESIs, MAAEs, LRTI cases of any severity not caused by RSV or hMPV, AEs leading to withdrawal, and CESIs (mild, moderate, or severe LRTI caused by RSV and/or hMPV). See Section 10.4.4.1 and Appendix D for AESIs.

9.2.6 Main Trial Phone Contacts – Safety Calls (Days 3, 14, 56, 135, and 270)

A safety call will be performed on Days 3, 14, 56, 135, and 270. Safety calls are calls made to the subject by a trained healthcare provider. These calls will facilitate the collection of relevant safety information including concomitant medication, and

any AEs/SAEs the subject may have experienced since receiving the IMP. All safety information described by the subject must be written down and kept with the [illegible] data capture (EDC) system (Section 12.1). Sites should contact the subject if data has not been entered in the EDC system within 1 day of the prompt. Sites will follow-up with subjects if relevant safety information is captured. The site should schedule the next clinic visit with the subject. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an ER visit.

Refer to Section 10.4 for the reporting of AEs, SAEs, AESIs, MAAEs, LRTI cases of any severity not caused by RSV or hMPV, AEs leading to withdrawal, and CESI (mild, moderate, or severe LRTI caused by RSV or hMPV).

9.2.7 Visit Day 365

The last visit for the main part of the trial will be performed on Day 365. If a subject terminates earlier, the final (end of trial) visit procedures should be performed at their last trial visit, if possible. The investigator must complete the end of trial eCRF for all subjects who received IMP.

Refer to Section 10.4 for the reporting of AEs, SAEs, AESIs, MAAEs, LRTI cases of any severity not caused by RSV or hMPV, AEs leading to withdrawal, and CESIs (mild, moderate, or severe LRTI caused by RSV and/or hMPV). Only after all Visit Day 365, assessments are performed will the Subject be unblinded to their vaccine group.

9.2.8 Observational Extension: Phone Contact (Day 545) and Site Visit (Day 730)

A safety call will be performed on Day 545 by a trained healthcare provider to collect any MAAEs, AESI or SAEs since Visit Day 365. This call will collect relevant safety information. All concomitant medications used immediately prior to and for treating the respective AE will be recorded in the source documents. All designated safety data and medications (except for MAAEs) must also be entered into the EDC system (Section 12.1). Resolution of the MAAE or SAE should also be captured in the EDC. Sites will follow-up with subjects if relevant safety information is captured and should schedule a clinic visit with the subject if deemed medically relevant. The subject will be reminded to contact the site if with any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an ER visit.

Refer to Section 10.4 and Appendix D for the reporting of AESIs. A reminder should also be provided to subjects that they have committed to return to the clinic at

Day 730. A scheduled Site visit will occur at Visit Day 730 to perform a blood collection for immunogenicity; the subject should also be queried about any safety information, specifically MAAEs, AESI or SAEs since the Day 545 phone call. Record all ongoing concomitant medications and those used to treat the respective AE in the source documents. In addition, all designated safety data and medications (except for MAAEs) must be entered into the EDC system (Section 12.1). Resolution of the MAAE or SAE should also be captured in the EDC. All SAEs should be followed up until there is either a resolution or a permanent outcome to the event, or the outcome is otherwise explained.

9.2.9 Unscheduled Visits

For Study Day 0 through Day 365 Only

An unscheduled visit describes a non-routine trial visit triggered by a specific anticipated or unanticipated AE, missed intervention or any investigator-determined need outside of the scheduled trial visits. The following assessments may be performed as appropriate:

- Collect vital signs including: heart rate, respiratory rate, oxygen level (SpO_2) blood pressure, and/or temperature, height (if applicable) and weight (if applicable);
- A symptom-directed physical examination may be performed by a qualified health care practitioner;
- The subject may be evaluated to assess any SAEs, AESIs, MAAEs, and AEs leading to withdrawal, and concomitant medications or vaccinations associated with SAEs and AESIs will also be collected;
- Blood may be collected for clinical safety assessment for previously-missed visits or insufficient amount collected;
- Collection of specimens to test for RSV, hMPV, and other respiratory viruses or bacteria by reverse transcriptase polymerase chain reaction (RT-PCR) if the unscheduled visit is triggered by suspected ARI.

Unscheduled Visits For the Trial Observational Extension Only

- The subject may be evaluated at an unscheduled visit to assess any SAEs, AESIs, and MAAEs; concomitant medications or vaccinations associated with SAEs and AESIs will also be collected.

9.2.10 Post-trial Care

No post-trial care will be provided.

9.3 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected as described in Section 9.1.6. After blood draw and serum processing, the serum samples will be preserved and retained at a central repository for up to but not longer than 20 years or as required by applicable law. The sponsor has put into place a system v qNvćqv YĞqN v q LºǂvǏLB Uº ˇ Lv vqL qv ǓUº*ǂN LBˇ..qL ˇº*ˇ vºL…v defined standard processes for sample and data collection, storage, analysis, and destruction.

Serum samples will be used for analyses defined in this protocol. Subjects who sign the study consent forms also consent to future specimen use. Specimens may be used to assess, improve, or develop tests related to RSV, hMPV, or IVX-A12 that will allow for more reliable measurements of immune responses to the investigational vaccine.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered an IMP; it does not necessarily have to have a causal relationship with IMP administration.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the administration of an IMP whether or not it is considered related to the IMP.

AEs will be graded for severity by the investigator in the following manner (based on the Food and Drug Administration (FDA) toxicity grading scale [38].

Mild	Grade 1	Awareness of symptoms that are easily tolerated, causing minimal discomfort, and not interfering with everyday activities. Relieved with or without symptomatic treatment.
Moderate	Grade 2	Sufficient discomfort is present to cause interference with normal activity. Only partially relieved with symptomatic treatment or requires repeated use of non-narcotic pain reliever >24 hours.
Severe	Grade 3	Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities. Not relieved with symptomatic treatment or requires use of narcotic pain reliever.
Potentially Life-threatening	Grade 4	Inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

10.1.2 Solicited Adverse Events

The occurrence of selected indicators of safety will be collected for 7 days starting from the day of IMP administration (Day 0 through Day 6) of the single IMP dose (including the day of administration) and will be recorded in the solicited AR eCRF (diary eCRF) as applicable and as listed in Table 6.

Any solicited local (injection site) reactions or systemic ARs observed as continuing on Day 7 following trial vaccination will be recorded as an AE on the AE eCRF for follow-up. For these persistent/prolonged solicited ARs the end date will be captured on the AE eCRF to permit a separate analysis from the unsolicited AEs (see Section 10.4.2).

Table 6 Solicited Local (Injection Site) Reactions and Systemic ARs

Solicited Local (injection site) reactions:	Pain Tenderness Erythema Swelling
Solicited Systemic ARs:	Headache Chills Fatigue Myalgia Arthralgia Vomiting Diarrhea Fever*

*Fever is defined as body temperature greater than or equal to 38°C (100.4°F) regardless of method used [39].

Body temperature will be collected and recorded.

The intensity of solicited safety parameters will be assessed as described in Table 7 and Table 8.

Table 7 Solicited Local (Injection Site) Reactions

Adverse Event	Intensity Grade	Intensity
Pain	0	None
	1	Mild (able to perform duties)
	2	Moderate (interferes with duties)
	3	Severe (prevents duties)
	4	ER visit or hospitalization
Tenderness	0	None
	1	Mild (discomfort to touch)
	2	Moderate (discomfort with movement)
	3	Severe (significant discomfort at rest)
	4	ER visit or hospitalization
Erythema [(a)]	0	<25 mm
	1	Mild: ≥25 Mc mm
	2	Moderate: >50 mcc mm
	3	Severe: >100 mm
	4	Necrosis or exfoliative dermatitis
Swelling [(a)]	0	<25 mm
	1	Mild: ≥25 Mc mm
	2	Moderate: >50 mcc mm
	3	Severe: >100 mm
	4	Necrosis

(a) Subjects are to record greatest surface diameter in mm on the diary.

Table 8 Solicited Systemic ARs

Adverse Reaction	Intensity Grade	Intensity
Headache	0	None
	1	Mild (no interference with activity)
	2	Moderate (some interference with activity)
	3	Severe (prevents daily activity)
	4	ER visit or hospitalization
Chills	0	None
	1	Mild (no interference with activity)
	2	Moderate (some interference with activity)
	3	Severe (prevents daily activity)
	4	ER visit or hospitalization
Fatigue	0	None
	1	Mild (no interference with activity)
	2	Moderate (some interference with activity)
	3	Severe (prevents daily activity)
	4	ER visit or hospitalization
Myalgia	0	None
	1	Mild (no interference with activity)
	2	Moderate (some interference with activity)
	3	Severe (prevents daily activity)
	4	ER visit or hospitalization
Arthralgia	0	None
	1	Mild (no interference with activity)
	2	Moderate (some interference with activity)
	3	Severe (prevents daily activity)
	4	ER visit or hospitalization
Vomiting	0	None
	1	Mild No interference with activity or 1-2 episodes/24 hours
	2	Moderate Some interference with activity or >2 episodes/24 hours
	3	Severe Prevents daily activity, requires outpatient intravenous (IV) hydration
	4	ER visit or hospitalization for hypotensive shock
Diarrhea	0	None
	1	Mild 2 3 loose stools or <400 g/24 hours
	2	Moderate 4 5 stools or 400 800 g/24 hours
	3	Severe 6 or more watery stools or >800 gms/24 hours or requires outpatient IV hydration
	4	ER visit or hospitalization for hypotensive shock

Table 8 Solicited Systemic ARs (continued)

Adverse Reaction	Intensity Grade	Intensity
Fever [(a)]	0	<38.0°C / <100.4°F
	1	38.0 38.4°C / 100.4 101.1°F
	2	38.5 38.9°C / 101.2 102.0°F
	3	39.0 40.0°C / 102.1 104.0°F

(a) Record body temperature in °C/°F. Fever is defined as body temperature greater than or equal to 38°C (100.4°F) regardless of method used [39].

10.1.3 Clinical Events of Special Interest

The single CESI for this trial that will be specifically highlighted to the investigator is mild (Grade 1), moderate (Grade 2), and severe (Grade 3) lower respiratory tract illness (mild, moderate, or severe LRTI) due to RSV or hMPV occurring in the subjects after vaccination.

An episode of LRTI caused by RSV or hMPV occurring from Day 0 (day of vaccination) to Day 365 (end of trial), is defined as the presence of *at least* two lower respiratory symptoms/signs for at least 24 hours in the category of mild or moderate and any single symptom/sign in the category of severe for at least 24 hours.

Lower Respiratory Symptoms/Signs:

Mild (Grade 1)

i. New or increased sputum production
ii. New or increased cough
iii. New or increased wheezing
iv. New or increased dyspnea (shortness of breath)

Moderate (Grade 2)

i. Decreased oxygenation (SpO_2 <94%, in those with baseline above 94%)
ii. Need for oxygen supplementation
iii. A respiratory rate pc breaths/min
iv. Found by an investigator/clinician to have new crackles/rhonchi based on chest auscultation
v. Found to have new or lung infiltrates on chest radiography

Severe (Grade 3)

i. Any participant meeting the criteria for moderate LRTI requiring hospitalization
ii. Any participant meeting the criteria for moderate LRTI requiring positive airway pressure therapy
iii. Any participant meeting the criteria for moderate LRTI requiring mechanical ventilation

Plus RT-PCR-confirmed RSV infection, hMPV infection or both RSV and hMPV infection, documented within 7 days of symptom onset.

Careful notation should be made of any medical interventions, including hospitalization, for this CESI.

The algorithm described below will be used to enhance detection for this CESI. The purpose of this algorithm is to identify subjects with ARI following vaccination, who are at risk for LRTI, and specifically for moderate to severe LRTI. In order to facilitate assessment of subjects potentially experiencing LRTI, surveillance for ARI will begin after vaccination and continue for the duration of the trial (through Day 365). Subjects will record, at a minimum, on a weekly basis, an RSS into an e-diary. Subjects will be instructed to notify the clinic should they develop ARI symptoms as described below. Any subject meeting the definition of ARI included below will be asked to return to the clinic for an unscheduled trial visit for evaluation (vital signs, medical history, directed physical exam, laboratories, as appropriate) and collection of a NP swab for virologic analysis. The NP swab will be sent to a clinical laboratory for multiplex RT-PCR including RSV, hMPV, and other respiratory pathogens. The visit evaluation and collection of NP swab should occur within 7 days of symptom onset.

LRTI is distinct from the AE of ARI. An ARI is characterized as a new onset or worsening of at least two symptoms (as defined below) that persist for a period of ph hours, either in a continuous or intermittent manner:

- **Two** respiratory symptoms:
    - Sore throat (pharyngitis);
    - Stuffy or runny nose [nasal congestion or discharge (rhinorrhea)];
    - Earache;
    - Cough;
    - Sputum production;
    - Wheezing;
    - Shortness of breath (dyspnea).

OR

- **One** respiratory symptom (from above) and **one** systemic symptom:
  - Feverishness* (defined as body temperature greater than or equal to 38°C [100.4°F] regardless of method used);
  - Tiredness (fatigue);
  - Decreased appetite;
  - Headache;
  - Muscle ache (myalgia).

    *The term Bq q ˇ ćLq is used as a symptom to inform subjects of their need to measure their temperature for presence of fever ’ qU q º qv v( )bc , v v vN U qv v ćqvN*L ˆNvB vOR4vq º* º ˇ Lbv Fever is defined as body temperature greater than or equal to 38°C (100.4°F) regardless of method used [36] (see Table 8, Section 10.1.2).

10.1.4 Medically-attended Adverse Events

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

10.1.5 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose meets any of the following criteria:

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

AEs which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that an SAE need not, by definition, be severe.

10.1.6 Suspected Unexpected Serious Adverse Reaction

Adverse drug reactions are all untoward and unintended responses to an investigational product related to any dose administered. Unexpected adverse reactions are suspected unexpected serious adverse reaction (SUSARs) if the following three conditions are met:

1) The event must be serious;
2) There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3) The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the IB for an IMP.

10.2 Causality of Adverse Events

Relationship (causality) to the IMP will also be assessed by the investigator. The relationship of each AE to the IMP, including solicited systemic ARs (solicited local (injection site) reactions are considered as related by default) will be assessed using the following categories:

Related:	There is suspicion that there is a relationship between the IMP and the AE (without determining the extent of probability); there is a reasonable possibility that the IMP contributed to the AE.
Not Related:	There is no suspicion that there is a relationship between the IMP and the AE; there are other more likely causes and administration of the IMP is not suspected to have contributed to the AE.

10.2.1 Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs.

The relationship should be assessed as Cq if the investigator considers that there is a reasonable possibility that an event is due to a trial procedure. Otherwise, the q*o ˇ L ć ˇ v ć *..vYqvo q q..vo v ” b

10.2.2 Outcome of Adverse Events

Resolved:	The subject has fully recovered from the event or the condition has returned to the level observed at Baseline.
Resolving:	The event is improving but the subject is still not fully recovered.
Not resolved:	The event is ongoing at the time of reporting and the subject has still not recovered.
Resolved with sequelae:	As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g., became blind, deaf or paralysed).
Fatal:	The subject died due to the event. If the subject died due to other circumstances than the event, the outcome of the event per se should be stated otherwise (e.g., not resolved or resolving).
Unknown:	If outcome is not known or not reported.

10.3 Additional Points to Consider for Adverse Events

An untoward occurrence generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. Intermittent events for pre-existing conditions or underlying disease should not be considered as AEs.
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require IMP discontinuation or a change in concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses *versus* signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately as AEs.

Worsening of a pre-existing condition:

- If the subject experiences a worsening or complication of a pre-existing condition after administration of the IMP, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., qL L´ B b

Changes in intensity of AEs:

- If the subject experiences a change in intensity of an AE, after administration of the IMP the event should be captured once with the maximum severity recorded.

New onset of chronic disease:

- An AE that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to trial enrollment.
- AEs leading to withdrawal:
- AEs leading to discontinuation from the trial or withdrawal of study treatment.

Preplanned or elective procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of the ICF are not considered as AEs. Elective procedures performed ćq qvćq qvˇvL vNćºL´qvˇLvćqv YĞqN vUq…ˇNº*N L…ˇˇ Lvć *…vL vYqv recorded as AEs. In either instance the procedure should be documented in the YĞqN source documents. Complications resulting from any planned or elective surgery, therapy or procedure should be reported as AEs.

Trial procedures:

- Adverse occurrences related to trial procedures after signing of the ICF are considered as AEs and should be reported as AEs.

10.4 Procedures

10.4.1 Collection and Reporting of Adverse Events

All AEs, whether considered related to the use of the IMP or not, must be monitored until symptoms subside and any abnormal laboratory values have returned to Baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full autopsy report should be supplied, if possible.

All findings must be reported on an AE eCRF and on the SAE form, if necessary (see Section 10.4.4). All findings in subjects experiencing AEs must also be documented ˇLvćqv YĞqN v Nqv… N UqL bvOL vunsolicited AE will be collected through Day 28. AEs leading to discontinuation from the trial are collected throughout the trial. All efforts should be made to continue the collection of safety data according to protocol.

The following information will be documented for each event:

i. Reported term for the AE;

ii. Start and end date, duration;

iii. Serious (Y/N);

iv. Intensity;

v. 4L q ˇ´o opinion of the causality (relationship) between the event and o..U ˙L ˇ o ˇ Lv B4x GV q*Þ q… v v L v q*Þ q… ≥

vi. 4L q ˇ´o opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure;

vii. Action taken;

viii. Outcome of event.

10.4.2 Collection and Reporting of Solicited Adverse Reactions

The occurrence of selected indicators of safety will be collected by the subjects for 7 days, starting from the day of IMP administration and will be recorded on the solicited AR eCRF (diary eCRF), as applicable. These will be summarized in the final report under the category *Ň q… OR to differentiate them from unsolicited AEs. Any solicited local (injection site) reaction or systemic AR observed as continuing on Day 7 following trial vaccination will be additionally recorded as an AR on the AE eCRF for follow-up. For these persistent/prolonged solicited ARs, the end date will be captured on the AE eCRF to permit a separate analysis from the unsolicited AEs.

Any solicited AR that meets any of the following criteria must be entered as an AE on the AE eCRF.

i. Solicited local (injection site) reactions or systemic ARs that lead the subject to withdraw from the trial;

ii. Solicited local (injection site) reactions or systemic ARs that lead to the subject being withdrawn from the trial by the investigator;

iii. Solicited local (injection site) reactions and systemic ARs that otherwise meet the definition of an SAE (see Section 10.1.2);

iv. Solicited local (injection site) reactions or systemic AR observed as continuing on Day 7 following each trial vaccination.

10.4.3 Collection and Reporting of Clinical Events of Special Interest and Medically-attended Adverse Events

The CESIs (mild, moderate, or severe LRTI caused by RSV and/or hMPV) and MAAEs will be collected from Day 0 up to Day 365. All CESIs and/or MAAEs must be recorded on the AE eCRF. The CESIs and/or MAAEs will be summarized separately through Day 365. MAAEs will be collected through Day 730.

10.4.4 Collection and Reporting of Serious Adverse Events

Collection of SAEs and AESIs will commence from the time that the subject is administered the dose of IMP (Day 0). Routine collection of SAEs and AESIs will continue until Day 365 for subjects in the main trial and Day 730 for subjects in the extension.

SAEs should be reported according to the following procedure:

A sponsor SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

i. A short description of the event and the reason why the event is categorized as serious.
ii. Causality assessment.
iii. Protocol number.
iv. Subject identification number.
v. 4L q ˇ′o name.

The SAE form should be transmitted within 24 hours to the safety mailbox or Fax:

e-mail: safetyreporting@syneoshealth.com

Fax: 1-877-464-7787

*10.4.4.1 **Adverse Events of Special Interest***

Any AESI occurring during the trial will be categorized and reported as an SAE. These AESIs include anaphylaxis, thrombocytopenia, and other pIMCs. Appendix D provides a list of pIMCs, which includes Guillain Barré syndrome.

10.5 Follow-up Procedures

10.5.1 Adverse Events

All AEs will be monitored until resolution, or a stable status is reached or until a formal diagnosis can be made or until the end of the trial, whichever occurs first. If the subject is unwilling to undergo the remaining trial procedures (e.g., blood draw[s] or visits), they should be asked whether they agree to continue participating for safety reasons.

10.5.2 Serious Adverse Events

If information not available at the time of the first report becomes available later, the investigator should complete a follow-up SAE form or provide other written

documentation immediately. Copies of any relevant data from the hospital notes (e.g., laboratory tests, discharge summary, postmortem results) should be sent to the sponsor/sponsor designee, after redaction for privacy. All SAEs should be followed up until resolution, permanent outcome of the event, or is otherwise explained. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.5.3 Safety Reporting to Investigators, Independent Ethics Committees or Investigational Review Boards, and Regulatory Authorities

The sponsor or designee will be responsible for the reporting of all SUSAR and any other SAEs to regulatory authorities, investigators, and IEC/IRB, as applicable, in accordance with national regulations in the countries where the trial is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. The sponsor or designee will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational vaccine or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the trial. The trial site will also forward a copy of all expedited reports to their IEC/IRB in accordance with national regulations.

10.5.4 Post-trial Events

Any SAE that occurs after the end of the trial but is considered to be caused by the IMP must be reported to the sponsor. These SAEs will be processed by the L v v L v..q ˇ´Lqq v ć º U ºN ˇ´ˇ»LNqv..q º U qL b4L N ˇ L vB v how to submit these SAEs are included on the SAE form.

11.0 TRIAL-SPECIFIC REQUIREMENTS

The following sections provide information on the trial-specific requirements.

11.1 Stopping Rules

Monitoring of safety signals will be performed throughout the trial by an independent SMC. The clinical trial will be halted if there is clear evidence of potential harm or harmful effects. Vaccine administration may be paused for further review and assessment if any of the following events occur:

- In any trial subject:
    - Any death that could be related to vaccine as per the investigator, sponsor, or SMC chair occurring during the trial;
    - Any vaccine-related SAE during the trial;
    - Any life-threatening (Grade 4) vaccine-related AE/AR during the trial, which needs medical intervention including:
        - Ulceration, abscess or necrosis at the injection site;
        - Laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of vaccine.
    - An allergic or hypersensitivity reaction such as fever >40°C or generalized urticaria (defined as occurring at three or more body parts) within 72 hours after administration of vaccine.
- If 2 or more subjects in a single trial group experience the same severe (Grade 3) AE/AR (Preferred Term [PT] in a given Medical Dictionary for Regulatory Activities [MedDRA] system organ class [SOC]) within the first 7 days following vaccination that persists for at least 48 hours and cannot be clearly attributed to another cause:
    - Severe (Grade 3) vaccine-related solicited local (injection site) reactions (excluding measured grades of erythema and swelling alone) or systemic AR;
    - Severe (Grade 3) vaccine-related unsolicited AE during the trial;
    - Severe (Grade 3) vaccine-related vital sign(s) abnormality;
    - Severe (Grade 3) vaccine-related clinical laboratory abnormality.

In the case that a pre-defined safety signal is met in any trial group, subsequent dosing will be halted to permit a complete evaluation of the reported event(s), and to consult the SMC. Based on the review of the data, the SMC may recommend temporary or permanent stopping, or continuation of dosing. When dosing resumes after a halt, further measures for safety may be introduced.

11.2 Safety Review Committee and Safety Monitoring Committee

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

Details of the membership, roles, and functioning of the committee will be available in the SMC charter.

12.0 DATA HANDLING AND RECORD KEEPING

The full details of procedures for data handling will be documented in the data management plan. AEs, medical history, and concurrent medical conditions will be coded using MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 Electronic CRFs

Completed eCRFs are required for each subject.

The site will maintain adequate source documents for the recording and collection of subject data. Data will be entered into an EDC system. The sponsor will make arrangements to train appropriate site staff in the use of the EDC for completing the eCRFs. These forms are used to transmit the information collected in the performance of this trial to the sponsor and regulatory authorities. The eCRFs must be completed in English.

The principal investigator (or designee) must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The sponsor or designee will be permitted to q ˇq vćqv YĞqN vU q…ŇP*ºL…vć ˇº*v qN … v q ŀqL v vćqv ˇb*v vqL qv accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Appendix A and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records, temporary media (e.g., thermal sensitive paper, and should be copied and certified), source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), eCRFs, including the audit trail, and detailed records of vaccine disposition to enable evaluations or audits from regulatory authorities, the sponsor or designee. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified vaccine indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition,

ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical trial site agreement between the investigator and sponsor.

Refer to the clinical trial site agreement for the L requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized prior to unblinding of the trial groups. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A (blinded) data review will be conducted prior to unblinding of the trial groups. This review will assess the accuracy and completeness of the trial database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

Safety Set: The safety set will consist of all subjects who received a dose of IVX-A12 or placebo. Subjects will be analyzed as treated.

Full Analysis Set (FAS): The FAS will include all randomized subjects who received a dose of IVX-A12 or placebo. Subjects will be analyzed as randomized.

Per-Protocol Set (PPS): The PPS will include all subjects in the FAS who received a dose of IVX-A12 or placebo and have no major protocol deviations that have a significant impact on immunogenicity results. Subjects will be analyzed as randomized.

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

13.1.2 Analysis of Disposition, Demographics, Other Baseline Characteristics, Medical History and Medications

Subject disposition will be summarized for all enrolled subjects which will include the number of subjects enrolled, screen failed, and randomized. For subjects who are randomized, the number and percentage of subjects in each of the analysis sets will be summarized by treatment group.

Demographics (age, gender, race) and other baseline characteristics (including baseline RSV and hMPV NAb titers) will be summarized descriptively by treatment group for all randomized subjects.

Medical and surgical history will be summarized by primary SOC and PT and by vaccine group. All medical history data will be listed.

All prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical Level 4 and PT and by treatment group. All medications will be listed.

13.1.3 Immunogenicity Analyses

Immunogenicity data will be summarized for each group and strain (RSV/A, RSV/B, both RSV strains and either RSV strain; hMPV/A, hMPV/B, both hMPV strains and either hMPV strain). The GMT will be calculated for RSV/A, RSV/B, hMPV/A and hMPV/B titers separately along with their 95% CI. The adjusted GMT and corresponding 95% CI will be obtained from an analysis of covariance (ANCOVA) model, which will include log-transformed baseline titers, age group, and treatment group as terms. Durability will be assessed at Days 180,365, and at Day 730 by comparing to Day 28 data. The geometric mean of fold changes and corresponding 95% CI will be calculated.

Proportion of subjects with h-fold increase (SRR), 8-fold increase, and GMFR from prevaccination/baseline (Day 0) will be summarized for Days 28, 180, 365, and at Day730. RCD curves will be generated.

The VLP core-specific IgG titers will be summarized at Days 0, 28, 180, 365, and Day 730 with GMT and 95% CI.

Separate summaries will be provided for subjects that agreed to participate in the Y q º ˇ Lº*q qL ˇ Lv ˇ Lv Bvćqv ˇb*ºL…v ˇ*vˇLN* ..qvćq qv YČqN v..º ºv from the beginning of the trial through Day 730.

All immunogenicity data will be listed.

13.1.4 Efficacy Analysis

RSV and/or hMPV cases of mild, moderate, or severe LRTI and any severity LRTI due to RSV and/or hMPV (CESIs), meeting the protocol-specified definitions, will be summarized by vaccine group and placebo group starting on Day 14 through Day 365. Listings will be provided.

Vaccine efficacy will be calculated as 100 × (1 incidence rate ratio). The incidence rate is the number of subjects meeting the case definition divided by cumulative follow-up person time among all subjects at risk. The incidence rate ratio is the ratio between the incidence rates of vaccine group and placebo group.

13.1.5 Safety Analyses

Solicited local (injection site) reactions and solicited systemic ARs: Solicited ARs will be summarized for 7 days starting from the day of dosing (Day 0) through Day 6 (total of 7 days). The summary will be by day and overall, within 7 days. Solicited ARs by maximum severity will also be summarized.

Unsolicited AEs: Unsolicited AEs will be assessed from day of dosing (Day 0) through 28 days post-vaccination and coded according to MedDRA and summarized by SOC and PT. The summary tables will include the number and percentage of

subjects reporting unsolicited AE by SOC and PT, and by SOC, PT, and maximum severity. Subjects reporting 5 º..q 3 and vaccine-related unsolicited AEs will also be summarized.

SAEs, MAAEs, AESIs, AEs leading to withdrawal, and CESI (mild, moderate, or severe LRTI caused by RSV and/or hMPV) and mild, moderate, or severe LRTI cases not caused by RSV or hMPVwill be assessed throughout the trial (from randomization on Day 0) and coded using MedDRA and summarized by SOC and PT. For the trial extension, SAEs, MAAEs, and AESIs will be continue to be collected and coded. Separate summaries will be provided for subjects that agreed to participate in the extension portˇ Lv Bvćqv ˇº*ºL…v ˇ**ˇLN* ..qvćq qv YĞqN v..º ºv from the beginning of the trial through Day 730.

All solicited ARs and unsolicited AEs will be listed.

Clinical laboratory tests including hematology, chemistry, and urinalysis will be summarized by vaccine groups. For numeric laboratory parameters, the observed value and change from baseline will be summarized by visit. For categorical laboratory parameters, the number of subjects and percentages will be summarized by visit. Shift tables may be provided as well. All lab data will be listed.

All vital signs observed value and change from baseline will be summarized by vaccine groups. Listing will also be provided.

Physical examination results will be listed.

13.2 Interim Analysis/Data Reviews

Two IAs will be performed: The first IA will be performed after all subjects have completed the Day 28 safety assessments and when all Day 28 immunogenicity data are available; the second IA will be performed after all subjects have completed the Day 180 safety assessments, and when all Day 180 secondary immunogenicity data are available. A final analysis of main trial will be performed after Day 365 and an analysis of the observational extension will be performed after Day 730. These analyses will support further evaluation of safety and immunogenicity of IVX-A12 in older adults.

13.3 Primary and Secondary Analyses for the CSR

A CSR will be prepared when Day 365 analyses have been completed for the primary and secondary objectives of the trial. Additional analyses including safety and immunogenicity through Day 730 may be provided in a Clinical Study Addendum.

13.4 Sample Size Justification

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

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Trial Site Monitoring Visits

Monitoring visits to the trial site will be made periodically during the trial to ensure that all aspects of the protocol are being followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or designee (clinical research organization) and by the IEC or IRB.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult the sponsor (or designee) and/or the medical monitor, if an immediate safety issue is identified (and IEC or IRB, as required) to determine the appropriate course of action.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site may be subject to quality assurance audits by the sponsor or designee. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the vaccine is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of foreign governments (e.g., the FDA, the Medicines and Healthcare Products Regulatory Agency of United Kingdom [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all trial documents as described in Section 14.1.

14.4 Risk Management

The ICH E6 addendum (R2) guidance encourages a risk-based approach to the management of clinical studies and includes requirements for risk control and risk reporting [2].

When the primary and secondary analyses are complete, the quality management approach implemented will be described in the CSR. If applicable, the CSR will summarize important deviations and the remedial actions taken.

15.0 ETHICAL ASPECTS

This trial will be conducted with the highest respect for the subjects according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki [1], and the ICH Harmonised Tripartite Guideline for GCP E6 (R2) [2]. Each investigator will conduct the trial according to applicable local or regional regulatory q ˇqU qL vºL…vº*´Lvć ˇ v vćq vN L… NvŽLvºNN …ºLNqv ˇćvćqv Rq L Ž Y*´ˇq v Bvćqv4L q ˇ´º vćº vº qv*´ q…vˇn Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 Independent Ethics Committee and/or Institutional Review Board Approval

IECs and IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IEC or IRB. If any member of the IEC or IRB has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IEC or IRB for the N * review and approval. This protocol, the IB, a copy of the ICF and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IEC or IRB for approval. The 41, v v4RH v ˇ qLvº º*v Bvćqv N *vºL…v YĞqNv4, 3vU vŸqv Y ºŽLq… and submitted to the sponsor or designee before commencement of the trial (i.e., before trial-specific screening activity). The IEC or IRB approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives approval no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IEC or IRB. This may include notification to the IEC or IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the trial at intervals specified by the respective IEC or IRB, and submission of the Ž L q ˇ´º vBŽLº*v tatus report to IEC or IRB. All IEC and IRB approvals and relevant documentation for these items must be provided to the sponsor or designee.

Incentives should not be used to exert undue influence on subjects for participation. Payments to subjects must be approved by the IEC or IRB and sponsor.

15.2 Subject Information, Informed Consent and Subject Authorization

For both the main trial and the trial extension, the following applies:

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki [1] and the ICH Guidelines for GCP [2] and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet describe the *ºLLq…vºL…v q U ˇ q…v q Sv ºL Bq SvºL…v…ˇN* q v Bvćqv YĞqN v q Lº* and personal health information for the purpose of conducting the trial. The ICF and the subject information sheet further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the subject and the fact that the subject is free to withdraw at any time without giving a reason and without prejudice to the YĞqN vB ćq vU q…ǸºvNº qb

The investigator is responsible for the preparation, content, and IEC or IRB approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet must be approved by both the IEC or IRB and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The subject must be given ample opportunity to: (1) inquire about details of the trial and (2) decide whether or not to participate in the trial. If the subject determines he or she will participate in the trial, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject at the time of consent and prior to the subject entering into the trial. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to the subject entering into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent, subject authorization form (if applicable), and subject information sheet will be stored in the ǸL q ˇ˝º site file. The investigator must document the date the subject signs the ICF in the YĞqN vU q…ǸºvqN …vºL…vq, R3bv, ˇq v Bvćqv ˇ˝Lq…vǸLB U q…vN Lsent, the

signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by the subject in the same manner as the original ICF. The date the revised consent was obtained should be recorded in the YĞqN medical record and eCRF, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

Xćqv L vºL…v..q ˇ´LqqvºBB˘ U vºL…v ć *..vćqv ˙LN˘ *qv Bvćqv YĞqN v ˇ´ć v v qN ˇ Lvº´o˙L vL o ˇ Lv Bv ˇ ºN bvXć ´ć vć ˇ v ˇb*SºvYĞqN v Nqv..º ov ˇ**v L* vYqv*L:q..v vćqv L vN*L˙Nº*v ˇb*v..o oYo qv v.. N U qL o ˇ Lv ˇbºv unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the YĞqN unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee, representatives from any regulatory authority (e.g., FDA, MHRA, PMDA), the L v..q ˇ´Lº q…vº …˘ SºL…vćqvº ˇb qv41, j4RH v vq ˇq vćqv YĞqN v ˇ´˙Lº*U q…˙Nº*v qN … v Nqv..º ov v.. N U qL SvLN* …˙L´SY vL v limited to, laboratory test result reports, electrocardiogram reports, admission and …˘ Nćº ´qv U U º ˇq vB vć ˇº*º..U ˘ ˇ L v NN ˙L´v.. ˙L´ºv YĞqN v ˇb*v º ˙N˘ º ˇ LSºL…vº vq bvONNq v vºv YĞqN v ˇ´˙Lº*U q…˙Nº*v qN … v requires the specific authorization of the subject as part of the ICF process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, º….. q SºL…v ćq v..qL ˇBq vBq*.. vL vN *qN q…v Lvćqv YĞqN vq, R3 b

15.4 Clinical Trial Registration, Publication and Disclosure Policy

15.4.1 Clinical Trial Registration

In order to ensure that information on clinical studies reaches the public in a timely manner and to comply with applicable law, regulation and guidance, the sponsor will, as a minimum register all clinical studies conducted in subjects that it sponsors anywhere in the world, on publicly accessible websites such as ClinicalTrials.gov and EudraCT, according to local requirements, before trial initiation. The sponsor N L ºNvǏLB U º ˇ LSº* L´v ˇćvćqvǏL q ˇ´º vNˇ SvN L SvºL…vqN ˇǏL´v status will be registered and available for public viewing.

15.4.2 Clinical Trial Results Disclosure

The sponsor will post the results of this clinical trial within 12 months after end of the trial regardless of outcome, on publicly accessible websites such as ClinicalTrials.gov and/or EudraCT, as required by applicable laws and/or regulations.

Completion of the trial corresponds to the date on which the final subject was examined or received an intervention for the purpose of final collection of data (usually corresponds to last subject last visit).

15.4.3 Publication of Trial Results

Publication of trial results will follow Icosavax, Inc publication policies, applicable international standards and guidelines for good publication practice, applicable laws, and/or regulations.

15.4.4 Insurance and Compensation for Injury

Each subject in the trial must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or L designee will obtain clinical trial insurance against the risk of injury to clinical trial subjects. Refer to the clinical trial site agreement regarding the sponso policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should N L ºNvćqv L v v L v..q ˇ´Lqqb

16.0 REFERENCES

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APPENDIX A RESPONSIBILITIES OF THE INVESTIGATOR

The investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with the protocol.
2. Supervise the staff that will assist in the trial.
3. Ensure that trial-related procedures are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Obtain approval for the trial and any changes by an appropriate IEC/IRB that conforms to ICH, and local regulatory requirements.
5. Report all changes in research activity and all anticipated risks to subjects to the IEC/IRB.
6. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
7. Obtain valid informed consent from each subject who participates in the trial, ºL…v… N U qL vćqv…º qv BvN L qL vĽvćqv YČqN vU q…Ňº*vŃćº b
8. Maintain adequate documentation of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc., for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
9. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
10. Maintain current records of the receipt, administration, and disposition of sponsor-supplied vaccines, and return all unused sponsor-supplied vaccines to the sponsor.
11. Report AEs leading to withdrawal, SAEs, and pregnancies to the sponsor promptly.
12. Review and provide a signature as approval of the content of the CSR, if needed.

APPENDIX B TOXICITY TABLES

Standard Toxicity Grading Scales: adapted from Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Food and Drug Administration [38].

Table 9 FDA Toxicity Grading Scales for Clinical Laboratory Abnormalities[a]

Serum Chemistry and Hematology*	**Mild**	**Moderate**	**Severe**	**Potentially Life-threatening**
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4****
Urea (i.e., BUN) (mg/dL)	23 26	27 31	>31	Requires dialysis
Creatinine (mg/dL)	1.5 1.7	1.8 2.0	2.1 2.5	>2.5 or requires dialysis
Total protein hypoproteinemia (g/dL)	5.5 6.0	5.0 5.4	<5.0	
Liver function tests ALT, AST; increase by factor	1.1 2.5 × ULN***	2.6-5.0 × ULN	5.1 10 × ULN	>10 × ULN
Total bilirubin when accompanied by any increase in liver function test; increase by factor	1.1 1.25 × ULN	1.26 1.5 × ULN	1.51 1.75 × ULN	>1.75 × ULN
Total bilirubin when liver function test is normal; increase by factor	1.1 1.5 × ULN	1.6 2.0 × ULN	2.0 3.0 × ULN	>3.0 × ULN
Hemoglobin (Female) (g/dL)	11.0 12.0	9.5 10.9	8.0 9.4	<8.0
Hemoglobin (Female) change from baseline value (g/dL)	Any decrease 1.5	1.6 2.0	2.1 5.0	>5.0
Hemoglobin (Male) (g/dL)	12.5 13.5	10.5 12.4	8.5 10.4	<8.5
Hemoglobin (Male) change from baseline value (g/dL)	Any decrease 1.5	1.6 2.0	2.1 5.0	>5.0
WBC increase (cell/mm^3)	10,800 15,000	15,001 20,000	20,001 25,000	>25,000
WBC decrease (cell/mm^3)	2,500 3,500	1,500 2,499	1,000 1,499	<1,000
Lymphocytes Decrease - cell/mm^3	750 1,000	500 749	250 499	<250
Neutrophils Decrease - cell/mm^3	1,500 2,000	1,000 1,499	500 999	<500
Eosinophils - cell/mm^3	650 1500	1501 5000	>5000	Hypereosinophilic syndrome
Platelets decreased (cell/mm^3)	125,000 140,000	100,000 124,000	25,000 99,000	<25,000

Abbreviations: ALT, alanine transaminase, AST; aspartate transaminase; BUN, blood urea nitrogen; WBC, white blood cell.
* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
––– A"" is the upper limit of the normal range.
Values provided in this table will be included in vaccination pause rules for the trial.

Table 10 FDA Toxicity Grading Scale for Vital Sign Abnormalities

Vital Sign Abnormalities*	Mild	Moderate	Severe	Potentially Life-threatening
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Tachycardia (bpm)	101 115	116 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia (bpm)**	50 54	45 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) (mm Hg)	141 150	151 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) (mm Hg)	91 95	96 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) (mm Hg)	85 89	80 84	<80	ER visit or hospitalization for hypotensive shock
Respiratory Rate (breaths per minute)	17 20	21 25	>25	Intubation

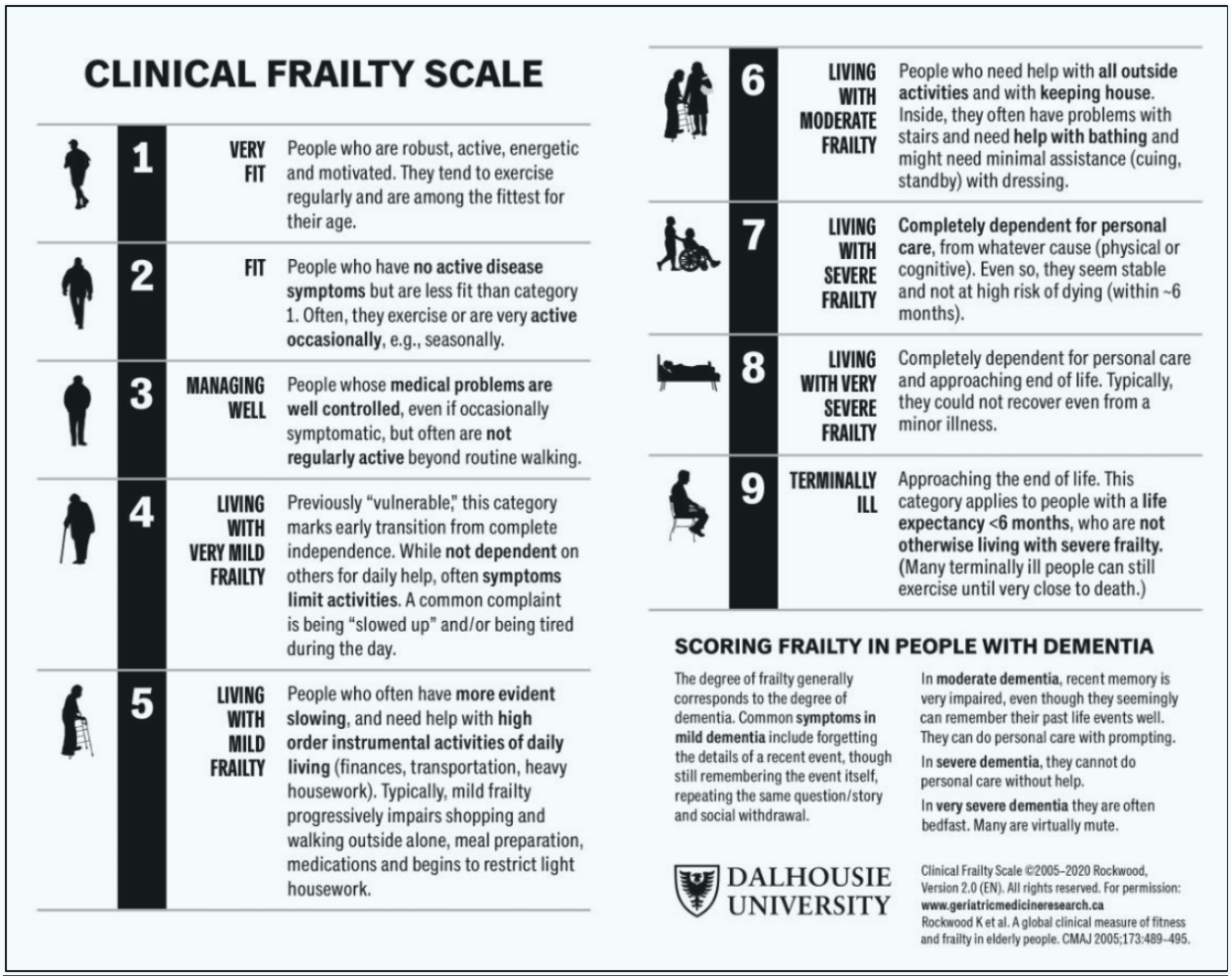
Abbreviations: bpm, beats per minute; ER, emergency room.
* Subject should be at rest for all vital sign measurements.
** When resting heart rate is between 60 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Table 11 FDA Toxicity Grading Scale for Urinalysis Abnormalities

Urinalysis Abnormalities*	Mild	Moderate	Severe	Potentially Life-threatening
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) (rbc/hpf)	1 - 10	11 - 50	>50 and/ or gross hematuria	Hospitalization or PRBC transfusion

Abbreviations: hpf, high power field; PRBC, packed red blood cells; RBC, red blood cells.
* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

APPENDIX C DALHOUSIE UNIVERSITY CLINICAL FRAILY SCALE



CLINICAL FRAILTY SCALE

1 VERY FIT — People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.

2 FIT — People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g., seasonally.

3 MANAGING WELL — People whose **medical problems are well controlled**, even if occasionally symptomatic, but often are **not regularly active** beyond routine walking.

4 LIVING WITH VERY MILD FRAILTY — Previously "vulnerable," this category marks early transition from complete independence. While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up" and/or being tired during the day.

5 LIVING WITH MILD FRAILTY — People who often have **more evident slowing**, and need help with **high order instrumental activities of daily living** (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.

6 LIVING WITH MODERATE FRAILTY — People who need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 LIVING WITH SEVERE FRAILTY — **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).

8 LIVING WITH VERY SEVERE FRAILTY — Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.

9 TERMINALLY ILL — Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise living with severe frailty.** (Many terminally ill people can still exercise until very close to death.)

SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

In **very severe dementia** they are often bedfast. Many are virtually mute.

DALHOUSIE UNIVERSITY

Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

Appendix D Adverse Events of Special Interest (AESIs): Potential Immune-mediated Conditions (pIMCs)

(*Defined according to the MEDRA preferred terms*)

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

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

Adapted from Tavares Da Silva (2013) [42]