Janssen Vaccines & Prevention B.V.*

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled, First-in-human Phase 1/2a Study to Evaluate Safety, Reactogenicity and Immunogenicity of a Universal Influenza (Uniflu) Vaccine with INFLUENZA G1 mHA in Healthy Adults

Protocol VAC21148FLZ1001; Phase 1/2a
Version: Amendment 2
VAC21148 Uniflu Vaccine

* Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study. The sponsor is identified on the Contact Information page that accompanies the protocol.

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	02-Mar-2023
Amendment 1	23-May-2022
Original Protocol	15-Jan-2020

Amendment 2 (02 March 2023)

Overall Rationale for the Amendment: To remove Ad26.FLU.003 from the VAC21148FLZ1001 study due to changes in the sponsor's vaccine development strategies.

The changes made to the clinical protocol VAC21148FLZ1001 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.8, Appendix 8: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Protocol Title; 1.1. Synopsis; 2. Introduction; 3. Objectives and Endpoints; 4. Study Design; 5.2. Exclusion Criteria; 6.1. Study Vaccine(s) Administered; 6.8. Study Pausing Rules; 7.1. Discontinuation of Study Vaccine; 8.3. Adverse Events, Serious Adverse Events and Other Safety Reporting; 9.2. Sample Size Determination; 10.3. Regulatory, Ethical, and Study Oversight Considerations; 10.4. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Recording; 10.6. Clinical Laboratory Tests; 10.7. Thrombotic Events to be Reported as AESIs	Removed Ad26.FLU.003, its related background information, and its related objectives/endpoints and exclusion criteria. Removed adverse event of special interest for thrombosis with thrombocytopenia syndrome.	Removed due to changes in sponsor's vaccine development strategies. Removed due to removal of Ad26.FLU.003.
1.1. Synopsis; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 6.3. Measures to Minimize Bias: Randomization and Blinding; 7.4. Staggered Vaccination; 9.2. Sample Size Determination; Figure 2. Participant Enrollment	Adjusted cohorts and groups, as well as the number of participants in each group. Adjusted Cohort 1: removed the Ad26.FLU.003 group, and increased the number of participants in the remaining 3 groups to a total of 60 participants (25 participants for low-dose active regimen [Groups 1 & 2] and 10 participants for placebo [Group 3]). Adjusted Cohort 2: removed the Ad26.FLU.003 group, and added	Ad26.FLU.003 groups were removed based on changes in the sponsor's vaccine development strategies. Single-dose groups were added to evaluate longevity of immune responses elicited by single-dose of INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant. The number of participants for high-dose groups

Section Number and Name	Description of Change	Brief Rationale
and First Dose Safety Strategy	2 single-dose groups (25 participants for high-dose active regimen [Groups 4-7] and 10 participants for placebo [Group 8]). Cohort 3 was removed. The total number of participants for the study remains as 170. Cohort 1 was no longer called a safety cohort, and Cohort 2 was no longer called a regimen selection cohort. Updated that 1 participant from each group in Cohort 2 including 1 placebo will be enrolled in the sentinel subset, and 2 participants from each group in Cohort 2 including 2 placebo will be enrolled in the safety ramp-up subset. Updated randomization ratios for Cohort 1 and 2.	remained 25 in Cohort 2 in the amendment #2, same as the number of participants in high-dose groups combined from Cohort 2 & 3 in the amendment #1. The number of participants for low-dose groups was increased from 15 to 25, to match the number for high-dose groups. The sample size calculation is detailed in Section 9.2, Sample Size Determination in the amendment #2. Updated because 2 single-dose groups are added in Cohort 2 at the same dose level of 2-dose groups. Updated to reflect the revisions to cohorts and participant numbers.
Protocol Title page	Replaced EudraCT number with IND number	Replaced due to the planned study conduct in the United States (not Europe).
1.1. Synopsis; 4.1. Overall Design	Removed that the maximum number participants to be vaccinated on the same day should not exceed 26.	Removed based on re-assessment of safety risk after removal of Ad26.FLU.003.
1.1. Synopsis Objectives and Endpoints; 1.2. Schema; 1.3.1. Schedule of Activities – Assessments for all Participants; 3. Objectives and Endpoints; 4.1. Overall Design; 8 Study Assessment and Procedures	Changed Visit 6 from Day 148 (3 months post second vaccination) to Day 238 (6 months poste second vaccination).	Changed to better assess durability of immune responses elicited by the study vaccine.
1.1. Synopsis Objectives and Endpoints; 1.1. Synopsis Immunogenicity Evaluations; 3. Objectives and Endpoints; 8.1. Immunogenicity Assessments	Removed the term “humoral and cellular” from exploratory objectives for immunogenicity. Removed the term “stem” from the exploratory endpoint below for immunogenicity: HA stem- or epitope-specificity as measured by ELISAs using HA stem protein, or competition ELISAs using broadly neutralizing antibodies (bnAbs) or HA ~~stem~~ protein. Added antibody-dependent cellular phagocytosis assay for functional	Removed to avoid confusion on humoral and cellular immune responses for assays included in the exploratory endpoints. Removed to allow additional type of hemagglutinin (HA) protein to be used in a competition enzyme-linked immunosorbent assay (ELISA). Added to allow additional assays for functional characterization.

Section Number and Name	Description of Change	Brief Rationale
	characterization of antibody response as an exploratory endpoint for immunogenicity. Clarified that sequencing for T cell receptor or B cell receptor repertoire analysis may be included in vaccine-induced changes in gene expression profiles by ribonucleic acid (RNA) sequencing or other transcriptional profiling methods as an exploratory endpoint for immunogenicity. Added an exploratory objective to evaluate the immune responses in participants with confirmed influenza infection, using assays included for secondary and exploratory immunogenicity endpoints.	Clarified the expectation for assessment on gene expression. Added to allow assessment of immune responses in participants with confirmed influenza infection.
1.1. Synopsis Immunogenicity Evaluations; 8.1. Immunogenicity Assessments	Added hemagglutination inhibition assays in the table for immunogenicity assays.	Added to reflect exploratory endpoints.
1.1. Synopsis ILI Procedures; 8.1.1. ILI Procedures	Added that the blood samples collected for influenza virus exposure confirmation may additionally be used to evaluate immune responses during the ILI.	Added for the newly added Virology exploratory endpoint in the amendment #2.
1.1. Synopsis Planned Analyses; 9.5. Planned Analyses	Added immunogenicity data on quantification of antibody binding to HA stem protein in the primary analysis. Updated that only sponsor and external partnerships personnel who are involved in the data analysis and decision making will be unblinded at the time of the primary analysis. Updated the additional analysis to occur after 6 months post-Dose-2 visit or discontinued earlier. Updated that the additional analyses will include additional safety data up to the 6 months post-Dose 2 visit and immunogenicity data required per the sponsor's assessment.	Added based on the sponsor's assessment on data required for decision making. Updated to clarify expectation. Updated because Visit 6 was changed from Day 148 (3 months post second vaccination) to Day 238 (6 months poste second vaccination). Updated to clarify expectation.
1.1. Synopsis; 1.3.1. Schedule of Activities – Assessments for all Participants; 2.1. Study Rationale; 3. Objectives and Endpoints; 4.1. Overall Design; 6.3. Measures to Minimize Vias: Randomization and Blinding; 8. Study	Sample collection, assays and exploratory endpoints for peripheral blood mononuclear cells (PBMCs) in the in-depth immunogenicity (IDI) subset were removed.	PBMCs were included in the previous protocol amendment #1 to evaluate cellular responses elicited by study vaccines as exploratory endpoints, in order to facilitate decision making on regimen selection. With removal of Ad26.FLU.003, the sponsor has decided not to include these exploratory endpoints in this

Section Number and Name	Description of Change	Brief Rationale
Assessment and Procedures; 9.3. Population for Analyses; 9.4.3. Secondary Endpoint (s)		first-in-human study and will consider to include in future studies.
1.1. Synopsis; 1.3.1. Schedule of Activities – Assessments for all Participants; 3. Objectives and Endpoints; 8.1. Immunogenicity Assessments	Added PAX gene sample collection. Added nasosorption sample collection and an exploratory endpoint on nasal antibody response.	Added for the exploratory endpoint on vaccine-induced changes in gene expression. Added to explore nasal antibody response induced by the study vaccine.
1.1. Synopsis Study Vaccine; 6.1. Study Vaccine(s) Administered	Updated that alternative location for study vaccination is only allowed for second dose in case both deltoids cannot be used due to a medical or other contraindication.	Updated to clarify expectation.
1.1. Synopsis Population for Analyses; 9.3. Population for Analyses	Updated per-protocol immunogenicity population to exclude samples taken on or after the date when a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes.	Updated to clarify expectation.
1.3.1. Schedule of Activities – Assessments for all Participants	Adjusted visit window for Day 8 and Day 64 visits from ± 2 days to + 2 days. Removed coagulation tests from all timepoints and hematology tests from Day 28 and Day 85 visits. Added participant wallet card distribution at screening visit. Added insulated cooler bag training and distribution along with nasal swab kit training and distribution Updated footnote b to include a phone call 3 to 5 days after Day 1 and Day 57 visits. Updated footnote c to clarify the visit window calculation should be based on the last vaccination visit. Updated footnote i to clarify that additional blood may be collected for participants with influenza-like illness. Updated footnote g for re-assessment of inclusion and exclusion criteria prior to study vaccination.	Adjusted to ensure participants' diaries are completed up to Day 8 after study vaccination at Day 8 and Day 64 visits for investigators to review. Removed based on re-assessment of safety risk after removal of Ad26.FLU.003. Added to ensure participant wallet card distribution. Added to clarify expectation. Updated to ensure that participants are completing diaries without issues. Updated to ensure that the safety follow-up and sample collection are completed on time in respective to the last vaccination. Updated to clarify expectation. Updated based on changes made in Section 5.1. Inclusion Criteria and 5.2. Exclusion Criteria.

Section Number and Name	Description of Change	Brief Rationale
	Added footnote o for diary review with participants. Added footnote p in case the screening visit and Day 1 visit may occur on the same day (Day 1).	Added to clarify expectation. Added to clarify expectation.
1.3.1. Schedule of Activities – Assessments for all Participants; 8. Study Assessment And Procedures	Updated blood volume.	Updated based on changes made on sample collection.
2.3.1 Risks Related to Study Vaccination	Added risks from Nasal Swab Sampling.	Added as nasal swab sampling is a required study procedure in Section 1.3.2 Schedule of Activities – Assessments for Participants With Influenza-like Illness (ILI).
2.3.3 Benefit-Risk Assessment Related to Study Vaccination	Clarified that any serious clinically significant abnormalities (including those serious events persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable endpoint is reached.	Clarified expectation for serious clinically significant abnormalities.
4.1. Overall Design	Added that additional temperature measurements may be taken if a participant does not feel well.	Added to clarify expectation.
4.2.1 Study-Specific Ethical Design Considerations	Removed reference to Belgian Red Cross guidelines for blood volume collected.	The study will be conducted in the United States (US) and will follow the US regulations and requirements.
5.1. Inclusion Criteria	Inclusion Criterion #1 and #5: changed he or she to the participant and changed women to female participants. Inclusion Criterion #2: changed prohibitions and restrictions to lifestyle restrictions.	Changed based on FDA feedback to remove gender terminology. Changed for consistency with Section 5.3. Lifestyle Considerations.
5.2. Exclusion Criteria	Exclusion Criterion #2: Added Fahrenheit unit for temperature. Exclusion Criterion #4: Clarified to exclude participants with history of severe allergic reaction (eg, anaphylaxis) or other serious adverse reactions to vaccines or vaccine excipients (specifically the excipients of the study vaccine[s]). Exclusion Criterion #5: Added treatments to clinical conditions that are expected to have an impact on the immune response elicited by the study vaccine. Exclusion Criterion #7: Added chronic for eczema and atopic dermatitis.	Added in consideration of the study conduct in the US. Clarified to include other serious adverse reactions to vaccines or vaccine excipients (specifically the excipients of the study vaccine[s]). Added to clarify expectation. Added to clarify expectation.

Section Number and Name	Description of Change	Brief Rationale
	Exclusion Criteria #8: Added immunoglobulins (including monoclonal antibodies) expected to impact the vaccine-induced immune response.	Added to clarify expectation.
	Exclusion Criteria #10: Added to exclude participants who received an investigational biological product within 3 months or 5 half-lives, whichever is longer, before the planned study intervention, and added a note to clarify a couple of exceptions.	Added to clarify expectation.
	Exclusion Criterion #14: Added examples for major surgeries and updated to exclude participants who has major surgery planned within 3 months after any dose of study vaccination	Updated to clarify expectation.
	Exclusion Criterion #24: removed exclusion criterion for participants who has taken any disallowed therapies as noted in Section 6.5 Concomitant Therapy.	Removed as the updated Section 6.5 Concomitant Therapy now references Section 5.2, Exclusion Criteria for disallowed therapies and all disallowed therapies have been covered in other exclusion criteria.
6.3. Measures to Minimize Vias: Randomization and Blinding	Added language for unblinding of selected sponsor personnel in rare circumstances.	Added to clarify expectation on unblinding for rare circumstances.
6.5. Concomitant Therapy	Added that any vaccination within 6 months before screening must be recorded at screening.	Added to clarify expectation.
	Added that any vaccination must be recorded until the end of the study.	Added to clarify expectation.
	Removed details on the disallowed therapies and referenced Section 5.2, Exclusion Criteria instead.	Updated for simplification of the protocol.
	Added that any use of disallowed medication is to be recorded in the CRF.	Added to clarify expectation.
7.1. Discontinuation of Study Vaccine	Added severe hypersensitivity reaction following study vaccination, not attributable to causes other than vaccination, as a criterion to discontinue study vaccine.	Added to clarify expectation.
	Added withdrawal of consent to receive further vaccination as a criterion to discontinue study vaccine.	Added to clarify expectation
7.1.1 Criteria for Temporarily Delaying Study Vaccine Administration	Added Fahrenheit unit for temperature	Added in consideration of the study conduct in the US.
	Added an illness which in the judgement of the investigator may interfere with reactogenicity/Day 1-8 safety assessments	Added to clarify expectation.

Section Number and Name	Description of Change	Brief Rationale
	after each vaccination, as a criterion for temporarily delay study vaccination. Added that vaccination may be delayed for reasons other than acute illness at investigator's discretion. Vaccination must be completed within the specified window and upon approval of the sponsor. A check of eligibility criteria may be repeated as necessary.	 Added to clarify expectation.
7.2. Participant Discontinuation/Withdrawal From the Study	Added the following reasons for possible participant withdrawal: • Decision by the sponsor or the investigator to stop or cancel the study • Decision by local regulatory authorities or IRB/IEC to stop or cancel the study	Added in consideration of regulatory requirements.
8. Study Assessment and Procedures; 8.1.1. ILI Procedures	Added insulated cooler bag as study-specific materials to be provided to sites for participants to transfer nasal swab samples collected at home to sites at defined temperature.	Added to clarify expectation.
8.1. Immunogenicity Assessments	Added that samples collected for immunogenicity analyses may additionally be used to evaluate serology (HAI assays).	Added to allow assessment of influenza infection by HAI assays if needed for participants who don't have symptoms of influenza-like illness reported during the study.
8.2.1. Physical Examinations	Added that weight will be measured lightly clothed and without footwear, and height will be measured without footwear. Added that any clinically relevant abnormalities or changes in severity observed during the review of body systems should be documented in the eCRF as an AE or SAE if it meets the criteria for an AE or SAE according to the protocol reporting requirements, and any abnormalities or changes in severity that occurred after signing of the ICF until immediately before vaccination would be recorded if due to participation in the study.	Added to clarify expectation. Added to clarify expectation.
8.2.2. Vital Signs	Added that vital signs will be examined as specified in Section 1.3, Schedule of Activities.	Added to clarity expectation.
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 8.3.5. Pregnancy; 10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording,	Updated that AEs of Grade 3 or above, SAEs, pregnancy events and product quality complaints must be reported to the sponsor by study-site personnel immediately, but no later than 24 hours of their knowledge of the event.	Updated to clarify expectation.

Section Number and Name	Description of Change	Brief Rationale
Evaluating, Follow-up, and Reporting		
8.3.2 Method of Detecting Adverse Events and Serious Adverse Events	Added that the study staff will verbatim transcribe the information provided by the participant into the relevant sections of the CRF. Review of diary entries with participants and grading of symptoms must be done by a qualified and delegated study staff member under the oversight of the investigator or a delegated physician.	Added to clarify expectation.
10.1. Appendix 1: Abbreviations	Updated abbreviations.	Updated based on changes in the amendment #2.
10.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information	Updated definition of permanently sterile for female participant not of childbearing potential.	Updated per the sponsor assessment.
10.3. Appendix 3: Regulatory, Ethical and Study Oversight Considerations Long-term Retention of Samples for Additional Future Research	Added that no additional research on study participants, study samples, or data derived from the study will be conducted by the institution(s) or by a third party, without the prior written consent of the sponsor. Added that sample will be used to understand influenza or other respiratory diseases, and the study intervention platform. Removed DNA testing.	Added to clarify expectation. Added to clarify expectation. Removed since samples are not collected for DNA testing.
10.6. Appendix 6: Clinical Laboratory Tests	Removed coagulation test and tests related to adverse event of special interest.	Removed based on change in the amendment #2.
10.8. Appendix 8: Protocol Amendment History	Updated to include summary of changes table for amendment #1.	Updated to reflect amendment history.
11. References	Removed some references.	Removed references that are no longer cited based on changes in the amendment #2.
Throughout the protocol	Reference to gender (woman, etc.) was replaced by sex (male and female).	Updated based on FDA feedback to remove gender terminology.
Throughout the protocol	Minor language updates were made for consistency and clarification.	Minor language updates made throughout the protocol to clarify and be consistent with the changes noted in the sections listed above.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Double-blind, Placebo-controlled, First-in-human Phase 1/2a Study to Evaluate Safety, Reactogenicity and Immunogenicity of a Universal Influenza (Uniflu) Vaccine with INFLUENZA G1 mHA in Healthy Adults

A candidate vaccine covering Influenza A Group 1 that is composed of INFLUENZA G1 mHA (with or without $Al(OH)_3$ adjuvant) has shown promise in nonclinical animal models of influenza and will be assessed in this study.

- INFLUENZA G1 mHA (JNJ-67920320) is an Influenza A Group 1 (G1) hemagglutinin (HA) stem-derived protein vaccine antigen (mini-HA) derived from H1N1 A/California/07/2009 virus strain.

This will be the first-in-human (FIH) study for the INFLUENZA G1 mHA protein; therefore, no clinical experience is available.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Safety	
• Primary objective: To evaluate safety/ reactogenicity of INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant in participants ≥18 to ≤45years of age.	• Primary endpoints: – Occurrence, severity, duration and relationship of solicited local and systemic adverse events (AEs) for 7 days after each vaccination. – Occurrence, severity, duration and relationship of unsolicited AEs for 28 days after each vaccination. – Occurrence and relationship of serious adverse events (SAEs) from first vaccination to the end of the study.
Immunogenicity	
• Secondary objective: To evaluate the humoral immune responses to INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant in participants ≥18 to ≤45 years of age.	• Secondary endpoint: The magnitude of antibodies binding to the stem or the full-length HA protein as measured by enzyme-linked immunosorbent assay (ELISA).
• Exploratory objectives: To further assess the immune responses elicited by INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant in participants ≥18 to ≤45 years of age.	• Exploratory endpoints may include, but are not limited to assessing: – Vaccine-induced changes to the breadth of the antibody response within Group 1 or beyond as measured by ELISA using full-length HA proteins indicative of clade or group coverage – HA stem- or epitope-specificity as measured by ELISAs using HA stem protein, or competition ELISAs using broadly neutralizing antibodies (bnAbs) or HA proteins – Functional characterization of the antibody response as measured by assays assessing Fc-mediated functions (eg, Fc gamma receptor [FcγR] binding

Objectives	Endpoints
	assays to the stem or full-length HA protein, or antibody-dependent cytotoxicity assay, or antibody-dependent cellular phagocytosis assay), HA conformational change assays, or other assays – Vaccine-induced changes to the functional breadth of the antibody response within Group 1 or beyond as measured by virus neutralization assays or serum transfer into animal challenge models – Molecular characterization of the antibody response as measured by assays assessing the epitope-specificity, glycosylation status, or other characteristics of the antibody (eg, by systems serology arrays) – Vaccine-induced changes in innate immune responses by transcript- or cytokine profiling – Vaccine-induced changes in gene expression profiles by ribonucleic acid (RNA) sequencing or other transcriptional profiling methods, including but not limited to sequencing for T cell receptor or B cell receptor repertoire analysis – Nasal antibody response as measured by immunoglobulin (Ig) G or IgA ELISA in nasal secretions
• Exploratory objective: To evaluate longevity of immune responses elicited by INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant in participants aged ≥18 to ≤45 years.	• Exploratory endpoint: The magnitude and functionality of antibodies binding to the stem or the full-length HA protein of various strains as measured by ELISA, virus neutralization assays, and FcγR binding assays on Days 238 and 365.
• Exploratory objective: To evaluate the immune responses in participants with confirmed influenza infection.	• Exploratory endpoint: During the influenza season: – Immune responses by assays included for secondary and exploratory immunogenicity endpoints
Virology	
• Exploratory objective: To monitor symptoms of influenza-like illness (ILI) via the Influenza Intensity and Impact Questionnaire (Flu-iiQ™) as well as rapid molecular diagnosis and characterization to evaluate infection rate in participants aged ≥18 to ≤45 years and in relation to immunological markers.	• Exploratory endpoints: During the influenza season: – Signs and symptoms of ILI – Confirmation of infection by reverse transcriptase polymerase chain reaction (RT-PCR) or response to influenza-like infection by serology

Hypothesis

No formal statistical hypothesis is to be tested. The study will evaluate whether INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant is safe, well tolerated and immunogenic in healthy adults aged ≥18 to ≤45 years.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, FIH Phase 1/2a study to evaluate safety, reactogenicity and immunogenicity of a universal influenza (Uniflu) vaccine INFLUENZA G1 mHA in healthy male and female adults aged ≥18 to ≤45 years.

The study is designed to determine a regimen for further clinical development in adults based on safety and immunogenicity data. The selected regimen should have a favorable safety profile and induce immune responses with desired magnitude and functionality, as supported by the secondary endpoints.

Table: Study Design: VAC21148FLZ1001

Cohort	Group	N	Day 1	Day 57
1	1	25	INFLUENZA G1 mHA [redacted]	INFLUENZA G1 mHA [redacted]
	2	25	INFLUENZA G1 mHA [redacted] $Al(OH)_3$	INFLUENZA G1 mHA [redacted] $Al(OH)_3$
	3	10	Placebo	Placebo
2	4	25	INFLUENZA G1 mHA [redacted]	INFLUENZA G1 mHA [redacted]
	5	25	INFLUENZA G1 mHA [redacted] $Al(OH)_3$	INFLUENZA G1 mHA [redacted] $Al(OH)_3$
	6	25	INFLUENZA G1 mHA [redacted]	Placebo
	7	25	INFLUENZA G1 mHA [redacted] $Al(OH)_3$	Placebo
	8	10	Placebo	Placebo
TOTAL:		170		

$Al(OH)_3$ = aluminum hydroxide (aluminum content at 0.75 mg/dose); N = number of participants.

The study duration (excluding screening) will be approximately 365 days per participant. The study comprises a maximum 42-day screening period, study vaccination (active or placebo) with a 2-dose (on Day 1 and Day 57) regimen, a minimum 28-day follow-up period after each vaccination, and a long-term follow-up period until 1 year after the first vaccination. The end of the study is defined as the last participant's last visit 12 months after the first vaccination.

An internal DRC, consisting of members that are not directly involved in the study conduct, data management, or statistical analysis, will be commissioned for this study to evaluate (blinded) safety and reactogenicity data on a regular basis. The DRC will specifically review safety data (solicited and unsolicited AEs, SAEs, and available laboratory assessments) 7-day post-first and post-second dose in each cohort (participants in the sentinel and safety ramp-up subset).

If any of the pre-specified study vaccination pausing rules is met, further study vaccination may be paused after medical review and a DRC meeting will be convened.

The DRC may also review unblinded immunogenicity data during the course of the study if this is deemed necessary for future vaccine development-related decisions.

First-dose Cohort 1

In Cohort 1, 60 participants aged ≥18 to ≤45 years will be enrolled in a staggered approach with safety evaluations in place before extending enrollment in this cohort and progressing to Cohort 2. Initially, 5 sentinel participants will be enrolled and randomized; 2 participants in Groups 1 and 2 and 1 participant in Group 3 (placebo) will receive a single intramuscular (IM) injection of either CCI INFLUENZA G1 mHA, CCI INFLUENZA G1 mHA adjuvanted with $Al(OH)_3$ or placebo on Day 1. Sentinel participants will be contacted by telephone 48 hours post-vaccination to collect safety information. The blinded 48-hour post-vaccination safety data in these 5 sentinel participants will be reviewed by the principal investigator(s) (PIs) and sponsor's study responsible physician (SRP)/medical officer. Randomization of additional participants will be paused until this 48-hour sentinel safety evaluation is completed.

In the absence of any clinically significant findings, upon decision by PI(s) and SRP, an additional 12 participants will be enrolled (5 additional participants in Groups 1 and 2 and 2 additional participants in Group 3 [placebo] as safety ramp-up subset).

DRC will review blinded safety data of the initial 17 participants 7 days after the first vaccination. DRC review will be held to review available safety data of initial participants enrolled before these participants can receive the second vaccination. Further randomization in Cohort 1 will be paused until the DRC safety evaluation is completed. In the absence of findings from the DRC following the first vaccination, the remaining 43 participants in Cohort 1 will be enrolled in a 18:18:7 ratio and randomization in Cohort 2 may be initiated simultaneously.

First-dose Cohort 2

In Cohort 2, 110 participants aged ≥18 to ≤45 years will be enrolled in a staggered approach with safety evaluations in place before extending enrollment in this cohort. Initially, 5 sentinel participants will be enrolled and randomized; 1 participant in each of the 5 groups (Groups 4 to 8 [including 1 placebo]) will receive a single IM injection of either CCI INFLUENZA G1 mHA; CCI INFLUENZA G1 mHA adjuvanted with $Al(OH)_3$; or placebo on Day 1. Sentinel participants will be contacted by telephone 48 hours post-vaccination to collect safety information. The blinded 48-hour post-vaccination safety data in these 5 sentinel participants will be reviewed by the PIs and SRP. Randomization of additional participants will be paused until this 48-hour sentinel safety evaluation is completed.

In the absence of any clinically significant findings, upon decision by PI(s) and SRP, an additional 10 participants will be enrolled and randomized in parallel (2 additional participants in Groups 4 to 8 [including 2 placebo]) as safety ramp-up subset .

DRC will review blinded safety data of the 15 participants in Cohort 2, 7 days after the first vaccination. DRC review will be held to review available safety data of initial participants enrolled before these participants can receive the second vaccination. Further randomization in Cohort 2 will be paused until the DRC safety evaluation is completed. In the absence of findings from the DRC following the first vaccination, the remaining 95 participants in Cohort 2 will be enrolled in a 22:22:22:22:7 ratio.

Second-dose Safety

In alignment with the first-dose safety strategy, post-second dose 48-hour (sentinel participants) and 7-day safety assessments (participants in the sentinel subset and safety ramp-up subset) will be monitored by the

PI(s) and SRP, and the DRC, respectively [a]. The sequence in which participants in the sentinel subset and the safety ramp-up subset are vaccinated should be similar for Dose 1 and Dose 2. Administration of the second dose will also be staggered to allow safety assessments to be made 7 days after the second dose in participants in the safety ramp-up subset receiving low-dose protein (INFLUENZA G1 mHA CCI before administering the second dose to participants in the high-dose protein (INFLUENZA G1 mHA CCI groups. In the absence of clinically relevant findings and following the decision by the DRC, dosing the remaining participants will continue as described above.

For both cohorts, the DRC will review blinded 7-day post-first dose as well as post-second dose safety. Safety data for review will include solicited and unsolicited AEs, SAEs, and available laboratory assessments. If any pre-specified study vaccination pausing rule is met, vaccinations may be paused after medical review, and a DRC meeting will be convened. In addition, the DRC will also evaluate safety data over the course of the study and review any events that meet a specific study vaccine pausing rule or any other safety issue that may arise.

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the clinical trial agreement.

NUMBER OF PARTICIPANTS

A target of 170 participants will be enrolled in this study. The study design includes 2 sequential cohorts: Cohort 1 (60 participants) and Cohort 2 (110 participants).

Participants will be male or female, ≥18 to ≤45 years of age on the day of signing the informed consent form (ICF) and must be healthy as confirmed by medical history, physical examination, vital signs and laboratory assessments performed at screening.

STUDY VACCINE

Participants will be vaccinated at the study site according to the schedule detailed in the Table above.

Supplies will be provided by the sponsor in the following configuration:

- INFLUENZA G1 mHA (JNJ-67920320): supplied at a concentration of 900 µg/mL in a single use vial, dosed at CCI and CCI with or without $Al(OH)_3$ adjuvant. (Aluminum content at 0.75 mg/dose); 0.5 mL (extractable volume)
- Placebo: supplied as a sterile solution of Sodium Chloride 9 mg/mL in a single use vial; 10 mL (filling volume)
- Aluminum hydroxide adjuvant ($Al(OH)_3$): supplied at a concentration of 3.75 mg/mL in a single use vial for mixing according to the Investigational Product Preparation Instructions (IPPI); 1.0 mL (extractable volume)

[a] In case a participant in the sentinel subset or the safety ramp-up subset withdraws from the study prior to receiving Dose 2 or receives Dose 2 outside the prespecified visit window, the post-second dose 48-hour safety review by the PI(s) and SRP, as well as the 7-day safety review by the DRC will be performed as scheduled based on the available data.

- Formulation buffer for INFLUENZA G1 mHA (Diluent Uniflu 1): supplied in a single use vial for dilution of INFLUENZA G1 mHA according to IPPI; 0.8 mL (extractable volume)

For each participant, every injection will be 1.0 mL in volume. Instructions on study vaccine preparation (eg, dilution in formulation buffer) into the final dose that participants receive within each treatment group are outlined in detail in the IPPI.

Preferably the deltoid muscle of the non-dominant upper arm is used to administer the injection. If an injection cannot be given in either deltoid for the second dose of the vaccination due to a medical or other contraindication (for example, tattooed upper arms rendering it difficult to assess site reactogenicity), use alternative locations such as the hip, thigh, or buttocks (to be avoided in overweight participants). In this case, IM injections in other locations than the upper arm for the second dose of the vaccination are not considered protocol deviations.

An unblinded pharmacist, or other qualified staff member at the site with primary responsibility for study vaccine preparation, who will not participate in any other study evaluation, will prepare the appropriate vial and syringe, labeled with the participant's identification number, and provide the blinded syringe to the blinded vaccine administrator who will perform the injection.

IMMUNOGENICITY EVALUATIONS

Immunogenicity assessments may include, but are not limited to, the humoral immunogenicity assays (as available and applicable) summarized in the below Table.

Blood for humoral immune responses will be drawn from all participants. Influenza immunity in study participants will be determined on baseline (Day 1) and post-vaccination blood samples as described in Section 1.3, Schedule of Activities. Both assay variability and pre-existing immunity will be taken into consideration in the immunogenicity assessments. PaxGene samples will allow the performance of whole blood transcript profiling. Nasosorption samples (using SAM) will be used for the development of mucosal influenza-specific IgG and/or IgA ELISAs and the assessment of those responses in nasal secretion.

In addition to RT-PCR based diagnosis of influenza virus infection performed on nasal swab samples (collected when ILI symptoms develop during the influenza season), blood samples collected at baseline, between 2 and 4 days after symptom onset (ILI Days 3-5), and at 28 days after symptom onset (ILI Day 29) from participants with a suspected ILI will also be assayed by serology (including but not limited to hemagglutination inhibition (HAI) assay as available and applicable) for influenza virus exposure confirmation. Additionally, the nasal swab samples might be used to determine the presence of other respiratory pathogens upon the sponsor's request.

Table: Summary of Immunogenicity Assays

Endpoint	Assay
Secondary endpoints	
Quantification of antibody binding to HA stem or full-length HA	ELISA
Exploratory endpoints	
Neutralization	Virus neutralization assay
Fc-mediated functionality	Human FcγRIIIa reporter assay
Breadth of the antibody response within Group 1 or beyond	ELISA using full-length HAs indicative of clade or group coverage
HA stem- or epitope-specificity	ELISAs using HA stem protein or competition ELISAs using bnAbs or HA proteins

Functional breadth of the antibody response within Group 1 or beyond	Virus neutralization assays or serum transfer into animal challenge models
Functional characterization of the antibody response	Assays assessing Fc-mediated functions (eg, antibody-dependent cytotoxicity assay or antibody-dependent cellular phagocytosis assay), HA conformational change assays, or other assays
Molecular characterization of the antibody response	Assays assessing the epitope-specificity, glycosylation status, or other characteristics of the antibody (eg, systems serology arrays)
Innate immune responses	Transcript- or cytokine profiling
Gene expression profiles	RNA sequencing or other transcriptional profiling methods, including, but not limited to TCR or BCR repertoire analysis
Nasal antibody response	IgG and/or IgA ELISA in nasal secretions
Hemagglutination inhibition	HAI assays

BCR = B cell receptor; bnAbs = broadly neutralizing antibodies; ELISA = enzyme-linked immunosorbent assay; Fc = fragment crystallizable; HA = hemagglutinin; HAI = hemagglutination inhibition; Ig = immunoglobulin; RNA = ribonucleic acid; TCR = T cell receptor.

ILI Procedures

For the duration of the influenza season, participants will be followed-up to identify potential cases of influenza virus infection. During the influenza season, participants should record any signs and symptoms of ILI (such as cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue, or neck pain), including measurement of body temperature, on a daily basis until symptoms have resolved using a specific Flu-iiQ™ questionnaire and an ILI form.

If ILI symptoms develop during the influenza season, the following should take place:

- Participants should contact the site as soon as possible to notify the site of ILI.
- Participants should record signs and symptoms of the ILI daily using the Flu-iiQ™ questionnaire from onset of symptoms until the day of symptom resolution, and record body temperature daily using an ILI form provided by the sponsor until the day of symptom resolution.
- Participants should take a nasal sample at home on the day of symptom onset or the day thereafter (ILI Days 1-2). The sample should be stored refrigerated and brought to the site by the participant within 4 days (preferably) after collection.
- Participants should go to their study site, ideally between 2 and 4 days after symptom onset (ILI Days 3-5), where
  - the completed Flu-iiQ™ questionnaire and ILI form will be collected and reviewed by site staff;
  - the participant nasal self-swab sample (taken on ILI Days 1-2) will be collected;
  - an additional nasal swab will be taken by a qualified member of the site staff;
  - the presence of influenza virus infection will be assessed by qualified site staff by RT-PCR diagnostics and/or rapid-PCR detection (eg, by Cepheid GeneXpert®) on the nasal swab samples mentioned above;
  - a blood sample for seroconfirmation of influenza virus infection will be taken by a qualified member of the site staff;
  - and vital signs, including body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation, will be measured by a qualified member of the site staff. A clinical assessment, including a targeted physical examination, will be completed by qualified site staff, preferably by a physician, physician assistant, nurse practitioner, or equivalent.

- At ILI Day 29 (±7 days), participants will be asked to return to the site where
  - the completed Flu-iiQ™ questionnaire and ILI form will be collected and reviewed by site staff;
  - a blood sample for seroconfirmation of influenza virus infection will be taken by a qualified member of the site staff;
  - and vital signs, including body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation will be measured by a qualified member of the site staff. A clinical assessment (including a targeted physical examination) will be performed by qualified site staff, preferably by a physician, physician assistant, nurse practitioner, or equivalent.
- For all medically attended ILIs, including those resulting in hospitalization, additional information on any other diagnostics (eg, chest x-rays, spirometry, pulmonary function tests) or interventions during the clinical course of ILI will be collected.

During the influenza season, participants will be contacted by telephone or other means of communication approximately every 14±3 days (unless a planned visit has occurred or will occur within 14 days). These calls will remind participants to complete the Flu-iiQ™ questionnaire and ILI form in the event of any symptoms of ILI, and to contact the site and to take a nasal sample at the time of symptom onset. These calls will also check for any SAEs, and associated concomitant medications since the previous visit or telephone contact.

The presence of influenza virus will be assessed by site by RT-PCR diagnostics on the nasal swab samples, which may include viral load and influenza subtyping. In addition, blood samples from participants with a suspected ILI will also be assayed by serology by the sponsor (including but not limited to HAI assay as available and applicable) for influenza virus exposure confirmation. The blood samples may additionally be used to evaluate immune responses during the ILI.

Every effort should be made to collect data on the clinical course of ILIs including information on hospitalization, oxygenation status, supplemental oxygen requirements and specific drug treatments, as well as other concurrent respiratory illness present at the time of the diagnosis of the event and up to symptom resolution.

For participants who experience symptoms suggesting ILI, RT-PCR assay of the nasal swabs taken after symptom onset will be used to determine whether the infection was caused by influenza virus. For participants hospitalized with symptoms of ILI, confirmation of influenza virus infection using RT-PCR may be performed at the local (hospital) laboratory.

Any ILI and complications related to ILIs will be reported as an AE if it occurs between the time of any vaccination through the following 28 days. An ILI and complications related to ILIs that occur outside of this period does not require AE reporting unless ongoing at the time of subsequent vaccination. Any ILI and complications related to ILIs fulfilling the criteria of an SAE will be reported as such during the entire study period from the first vaccination.

SAFETY EVALUATIONS

On a daily basis, for 7 days after each vaccination, participants will be asked to record symptoms of the following AEs via the participant diary:

- Solicited injection site AEs: erythema (measured using the ruler supplied), swelling (measured using the ruler supplied), and pain/tenderness.

- Solicited systemic AEs: fatigue, headache, myalgia, nausea and fever (ie, body temperature ≥38 °C [100.4°F]).

Oral temperature should be measured at approximately the same time each day, preferably in the evening, using the thermometer supplied. Temperature 7 days after each vaccination may be collected earlier on the Day 8 or Day 64 to coincide with the clinic visit.

Adverse events and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal.

Solicited AEs, collected through a diary, will be recorded for each vaccination from the moment of vaccination until 7 days post-vaccination.

All other unsolicited AEs and special reporting situations, whether serious or non-serious, will be collected for each vaccination from the moment of vaccination until 28 days post-vaccination. Unsolicited AEs with the onset date outside the timeframe defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded on the electronic case report form (eCRF) AE page.

All SAEs and AEs leading to discontinuation from further study vaccination (regardless of the causal relationship) are to be reported from the moment of first vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

STATISTICAL METHODS

Sample Size Determination

With 25 participants per active regimen arm, the observation of no vaccine reactions after the first vaccination would be associated with a 95% confidence that the true rate is less than 11.3%. Across active regimens (N=150), the observation of 0 vaccine reactions after the first vaccination would be associated with a 95% confidence that the true rate is less than 2.0%.

Populations for Analyses

For purposes of analysis, the following populations are defined:

- Full Analysis Set (FAS): The FAS will include all participants with at least one vaccination documented.
- Per-protocol Immunogenicity (PPI): The PPI Set will include all randomized and vaccinated participants for whom immunogenicity data are available excluding samples taken on or after the date when a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes.

Primary Endpoints

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively per study group, with special attention for SAEs, Grade 3/4 AEs, and AEs leading to discontinuation of study vaccine. All safety analyses will be made on the FAS.

Secondary Endpoints

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% confidence interval, or median and quartile range [Q1-Q3], as appropriate) will be calculated for continuous immunological parameters at all time points and for changes from baseline. Graphical representations of immunological parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunological parameters as applicable. The immunogenicity analyses will be performed on the PPI set. An additional analysis might be done for the FAS.

Planned Analyses

The primary analysis will occur when all participants have completed the 28 days post-Dose 2 visit or have discontinued earlier. These analyses will include immunogenicity data on quantification of antibody binding to full-length HA and HA stem protein and safety data up to the 28 days post-Dose 2 visit. At the time of the primary analysis, the study will be unblinded for sponsor and external partnerships personnel who are involved in the data analysis and decision making. Participants and study-site personnel will remain blinded to the study vaccine allocation until the end of the study.

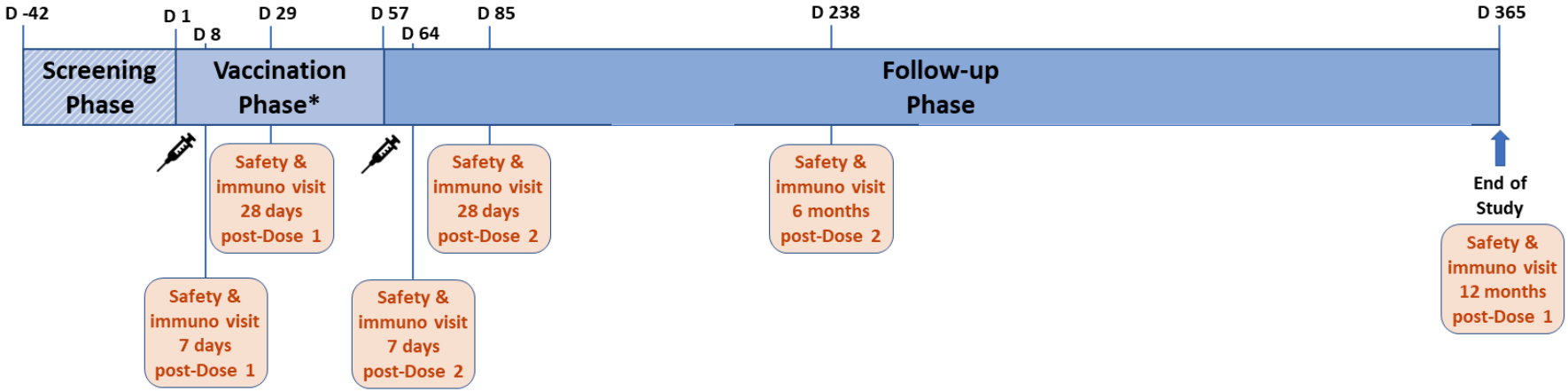
An additional analysis will occur when all participants have completed the 6-month post-Dose 2 visit or discontinued earlier. These analyses will include additional safety data up to the 6 months post-Dose 2 visit and immunogenicity data required per the sponsor's assessment. This analysis may allow to evaluate persistence of immune responses.

No study modifications are planned as a result of primary or additional analyses. The exact scope of each analysis will be defined based on the availability of immunogenicity data and findings from previous analyses. Additional interim analyses may be performed during the study for the purpose of informing future vaccine development-related decisions in a timely manner, or upon health authority request. If required, these unplanned interim analyses may replace or be combined with planned analyses, depending on the timing.

The final analysis will occur when the last participant has completed the final visit of the schedule of assessment (Day 365±30 days) or discontinued earlier. Final analyses will allow for determination of the durability of the immune response and analyze any additional safety and immunological data collected after the additional analysis.

1.2. Schema

Figure 1: Schematic Overview of the Study for all Cohorts



* Participants will be enrolled in a staggered approach with safety evaluations (Day 8) in place before extending enrollment in each cohort and progressing from one cohort to the next.

Further information on the overall design of the study can be found in Section 4.1, Overall Design.

1.3. Schedule of Activities (SoA)

1.3.1. Schedule of Activities – Assessments for all Participants

Clinic Visit #	1	2	3	4	5	6	7	8	9	
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 28 d	Vac 2	Vac 2 + 7 d	Vac 2 + 28 d	Vac 2 + 6 mo	Vac 1 + 12 mo	Early Exit [a]
Visit Day and Window	-42 to 1 [p]	1 [b,p]	8 [c]+2 d	29 [c]±3 d	57 [b]±3 d	64 [c]+2 d	85 [c]±3 d	238 [c]±14 d	365±30 d	
Visit Type	Screening	VAC 1	Safety and immuno.	Safety and Immuno.	VAC 2	Safety and immuno.	Safety and Immuno.	Safety and Immuno.	Safety and Immuno.	Early exit
Written informed consent form (ICF) [d]	●									
Inclusion/exclusion criteria	●									
Demographics	●									
Medical history/prestudy meds	●									
Physical examination [e]	●	❶			❶					
Vital signs [f] incl. body temperature	●	❷	●	●	❷	●	●		●	●
Serum pregnancy test (female participants of childbearing potential) [i]	● 2.5									
Urine pregnancy test (female participants of childbearing potential)		❶			❶					
Randomization		❶								
Verification of selected eligibility criteria [g]		❶			❶					
Pre-vaccination symptoms [h]		❶			❶					
Serology blood sample (HAI), mL [i]		❶ 4								
Hematology [i]	● 2	❶ 2	● 2		❶ 2	● 2				
Clinical Chemistry [i]	● 3	❶ 3	● 3		❶ 3	● 3				
Humoral immunogenicity sample (serum), mL [i]		❶ 30	● 10	● 30	❶ 10	● 10	● 30	● 30	● 30	❸ 30
Transcriptome (PAXgene®) sample, mL		❶ 2.5	● 2.5			● 2.5				❹ 2.5
Nasosorption sample (SAM)		❶		●			●	●		●
Vaccination		●			●					
30-minute post-vaccination observation [j]		●			●					
Solicited AE recording		*Continuous*			*Continuous*					❹
Unsolicited AE recording [k]	*Continuous*				*Continuous*					❺
SAE recording [k]		*Continuous*								●
Concomitant medications [l]	*Continuous*									●
Influenza infection [m]		*Continuous*								
Participant Wallet Card distribution	●									
Participant diary distribution and training		●			●					
Distribution and training of rulers and thermometers [n]		●			●					

Clinic Visit #	1	2	3	4	5	6	7	8	9	
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 28 d	Vac 2	Vac 2 + 7 d	Vac 2 + 28 d	Vac 2 + 6 mo	Vac 1 + 12 mo	Early Exit [a]
Visit Day and Window	-42 to 1 [p]	1 [b,p]	8 [c]±2 d	29 [c]±3 d	57 [b]±3 d	64 [c]±2 d	85 [c]±3 d	238 [c]±14 d	365±30 d	
Visit Type	Screening	VAC 1	Safety and immuno.	Safety and Immuno.	VAC 2	Safety and immuno.	Safety and Immuno.	Safety and Immuno.	Safety and Immuno.	Early exit
Flu-iiQ™ questionnaire and ILI form distribution [m]		*To be distributed before the start of the influenza season*								
Nasal swab kit and insulated cooler bag training and distribution		*To be distributed before the start of the influenza season*								
Participant diary review by qualified site staff [c, o]			●			●				
Blood Draw Volumes [i]***:*** ***Participants in the main study***										
Approximate daily blood draw, mL	7.5	41.5	17.5	30	15	17.5	30	30	30	32.5
Approximate cumulative study blood draw, mL	7.5	49	66.5	96.5	111.5	129	159	189	**219**	–

❶ pre-dose; ❷ pre- and post-dose; ❸ blood samples for immunogenicity will only be taken if the early exit is at least 14 days after the previous immunogenicity blood draw; ❹ if within 7 days of the last vaccination; ❺ if within 28 days of the last vaccination

a. For those participants who are unable to continue participation in the study up to Day 365±30 days, but for whom consent is not withdrawn, an exit visit will be conducted as soon as possible.
b. An additional telephone call will be made to sentinel participants 48 hours post-vaccination to collect safety information. A phone call or other means of communication should be made to all participants 3 to 5 days after Day 1 and Day 57 visits to ensure that participants are completing the diary without issues.
c. It is important to calculate visit window for Day 8, Day 29, Day 64, Day 85 and Day 238 visits with respective to the last vaccination visit. For example, Day 64 should be calculated with respect to vaccination 2 = VAC 2 + 7 days (+ 2 days window), and not as 64 days (+ 2 days window) after vaccination 1. If any of the participants for the 7-day post-dose safety review come in earlier than Day 8 for Visit 3 or Day 64 for Visit 6 (which will be a protocol deviation), a subsequent phone call will be made at the end of the diary period to collect diary card information recorded between the actual visit and the end of the 7-day post-dose diary period on Day 8 and Day 64, respectively.
d. Signing of the ICF should be done before any study-related activity.
e. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator. A symptom-directed physical examination may be repeated if deemed necessary by the investigator.
f. Supine systolic and diastolic blood pressure, heart rate and respiratory rate after at least 5 minutes rest. It is recommended that vital signs are measured before blood draws.
g. To include inclusion criteria 4, 6 and 8, and exclusion criteria 2, 8, 9, 10, 13, 14, and 21.
h. Investigator must check for acute illness or body temperature ≥38.0 °C (100.4°F) at the time of vaccination. In such cases, the participant may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn at the discretion of the investigator.
i. Blood sample volumes are approximate. Refer to the central laboratory manual or requirements of local laboratories for additional details. Additional blood samples may be collected for safety assessment and participants with influenza-like illness (Section 1.3.2, Schedule of Activities – Assessments for Participants With Influenza-like Illness [ILI]).
j. Participants will be closely observed for a minimum of 30 minutes post-vaccination. Any unsolicited, solicited injection site and systemic AEs, and vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) will be documented by study-site personnel following this observation period.
k. All AEs and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational (concomitant) sponsor products will be reported from the time a signed and dated ICF is obtained onwards. All SAEs and AEs leading to discontinuation from further study vaccination, will be reported from the day of first vaccination onwards until the end of the study.

l. Concomitant therapies will be collected from the signing of the ICF until 28 days after the first vaccination and from the second vaccination through the following 28 days, and additionally outside of these periods when associated with an SAE.
m. Signs and symptoms of influenza infection will be recorded during the influenza season using the Flu-iiQ™ questionnaire and ILI form. Participants will be notified of the influenza season. During the influenza season, they will be contacted by telephone or other means of communication every 14±3 days (unless a prescheduled clinic visit has occurred or will occur within 14 days). Calls will remind participants to complete the Flu-iiQ™ questionnaire and ILI form in the event of any symptoms of ILI, to contact the site and to take a nasal sample at home at the time of symptom onset. Calls will also check for any SAEs and associated concomitant medications since the previous visit or telephone contact. Details of these procedures are described in Section 8.1.1, ILI Procedures.
n. Ruler and thermometers will be distributed at Day 1 visit, and training will be conducted by the site staff at both Day 1 and Day 57 visits.
o. Review of diary entries with participants and grading of symptoms must be done by a qualified and delegated site staff member under the oversight of the investigator or a delegated physician. After review of the diary entries with the participant, the investigator or qualified delegate, will complete their own assessment and document in the relevant sections of the eCRF.
p. In case site staff are able to complete all required screening procedures and determine participant eligibility on the same day (including review of required clinical laboratory results), the screening visit and the Day 1 visit (first vaccination) may occur on the same day (Day 1), and repeat of Day 1 procedures (including physical examination, vital signs, urine pregnancy test, hematology and clinical chemistry) is not required.

AE = adverse event; d = day; Flu-iiQ™ = Influenza Intensity and Impact Questionnaire; HAI = hemagglutination inhibition; ICF = informed consent form; ILI = influenza-like illness; immuno. = immunogenicity; mo = month; SAE = serious adverse event; vac = vaccination; SAM = Synthetic Absorptive Matrix strips.

1.3.2. Schedule of Activities – Assessments for Participants With Influenza-like Illness (ILI)

Timing relative to ILI onset	ILI onset (ILI Day 1)	ILI Days 1-2	ILI Days 3-5	Daily after ILI onset until resolution [a]	ILI Day 29 (±7 days)
Location	**Home**	**Home**	**Site or Home**	**Home**	**Site**
Participant to contact study site as soon as symptoms of possible ILI occur	●				
Nasal swab (collected by the participant at home on Days 1-2 and brought to site staff on Days 3-5)		●[b]			
Nasal swab (collected by qualified site staff)			●[c]		
RT-PCR diagnostics and/or rapid-PCR detection for influenza virus infection on nasal swab samples collected on Days 1-2 and Days 3-5 (completed by qualified site staff)			●		
Serology blood sample for seroconfirmation of influenza virus infection (HAI), mL			● 4		● 4
Flu-iiQ™ questionnaire and ILI form (completed by the participant)	*Daily*				
Temperature [d] (measured by the participant)	*Daily*				
Collection and review of completed Flu-iiQ™ questionnaires and ILI forms (completed by site staff)			●		●
Clinical assessment [e] (collected by qualified site staff)			●		●
ILIs and complications of ILIs [f]	*Continuous*				
Concomitant medications associated with ILI [g]	*Continuous*				

a. Resolution is defined as 2 consecutive days with no symptoms listed on the Flu-iiQ™ questionnaire or, for participants who have Flu-iiQ™ questionnaire symptoms present at baseline (assessed pre-vaccination), 2 consecutive days where all symptoms on the Flu-iiQ™ questionnaire have returned to the severity level reported at baseline.
b. The nasal swab collected by the participant at home should preferably be taken between 12 to 24 hours after onset of symptoms.
c. The nasal swab collected by the site staff at the site or at the participant's home should ideally be taken at least 24 hours after the nasal swab collected by the participant at home on Days 1-2.
d. Oral temperature should be measured at approximately the same time each day, preferably in the evening, using the thermometer supplied, and documented in an ILI form.
e. Includes measurement of vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation [after at least 5 minutes rest] and body temperature) by a qualified member of the site staff, and a targeted physical examination by qualified site staff, preferably by a physician, physician assistant, nurse practitioner or equivalent. It is recommended that vital signs are measured before collection of nasal swabs and blood draws.
f. ILIs and complications related to ILIs will be reported as AEs in the eCRF from the time of vaccination through the following 28 days. An ILI and complications related to ILIs that occur outside of this period during influenza season does not require AE reporting unless ongoing at the time of subsequent vaccination. Any ILI and complications related to ILIs fulfilling the criteria of an SAE will be reported as such during the entire study period from the first vaccination. In addition, all ILIs and all complications related to ILIs will be captured on the ILI form and eCRF for all participants who experience ILI.
g. Concomitant medications associated with ILIs and with complications of ILI will be recorded for all participants during all ILI episodes for the duration of the influenza season. Concomitant medications associated with ILIs will also be captured on the ILI form for all participants who experience ILI.

eCRF = electronic case report form; Flu-iiQ™ = Influenza Intensity and Impact Questionnaire; HAI = hemagglutination inhibition; ILI = influenza-like illness; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event

2. INTRODUCTION

Study Vaccine

A candidate vaccine covering Influenza A Group 1 that is composed of INFLUENZA G1 mHA (with or without $Al(OH)_3$ adjuvant) has shown promise in nonclinical animal models of influenza and will be assessed in this study.

- INFLUENZA G1 mHA (JNJ-67920320) is an Influenza A Group 1 (G1) hemagglutinin (HA) stem-derived protein vaccine antigen (mini-HA) derived from H1N1 A/California/07/2009 virus strain.

For the most comprehensive nonclinical and clinical information regarding INFLUENZA G1 mHA, refer to the latest version of the Investigator's Brochure (IB) for INFLUENZA G1 mHA.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

Naming Conventions

Different naming conventions are being used for vaccine components. The following components will be used in the current study (VAC21148FLZ1001):

JNJ-number	Name	Description
JNJ-67920320	INFLUENZA G1 mHA	Group 1 mini-HA protein
N/A	$Al(OH)_3$	Aluminum hydroxide adjuvant

The component names will be used throughout the document to refer to the different vaccine components.

Safety Data Supporting Dose Selection for the INFLUENZA G1 mHA Protein

To date, INFLUENZA G1 mHA has not been tested in humans. Based on previous clinical experience in other vaccine programs by the sponsor, it is anticipated that the vaccine may be well tolerated. The dose levels of CCI and CCI of INFLUENZA G1 mHA were chosen based on the safety and immunogenicity profile of recombinant RSV preF proteins given at doses of 150 µg in approximately 8,499 participants aged 60 years and older in other studies up to 27 October 2021 by the sponsor (sponsor internal data).

2.1. Study Rationale

Influenza is a worldwide public health problem, responsible for significant morbidity and mortality, as well as a significant resource burden on countries. In a typical year, about 3 to 5 million cases of severe influenza illness and about 290,000 to 650,000 deaths are estimated to occur worldwide (WHO 2018). In the United States (US), more than 200,000 patients are hospitalized as a result of seasonal influenza-associated illnesses each year (CDC October 2021),

and about 90% of influenza-associated deaths occur among adults aged 65 years and older (CDC 2010).

Seasonal influenza vaccine effectiveness is generally variable and current seasonal vaccines do not cover all circulating strains in a matched, and even fewer in a mismatched season. Furthermore, seasonal vaccines must be adapted to current circulating strains (often yearly) based on World Health Organization (WHO) recommendations and by hemisphere. The vaccine with superior efficacy data in the elderly (Sanofi Fluzone® High-Dose) provides only 40-60% protection against clinical influenza (Diazgranados 2014). Overall, these data support the importance of developing an effective universal influenza vaccine for certain populations, such as the elderly.

One of the reasons for the limited efficacy provided by current influenza vaccines is the fact that they induce antibodies to the variable head domain of HA. Improving breadth by induction of antibodies against the more conserved stem domain of HA will lead to an improvement of overall vaccine efficacy. A desired profile of a universal influenza vaccine includes: (1) inducing high titers of broadly neutralizing antibodies (bnAbs) and antibodies with additional Fc-mediated functionality such as antibody-dependent cell-mediated cytotoxicity (ADCC) directed against epitopes in the more conserved HA stem; (2) inducing durable immune responses; (3) protecting against all human influenza strains; (4) to be safe and well tolerated.

There are different types of bnAbs. Some that bind and, to a certain extent, neutralize all influenza viruses are fairly rare in the human population. In addition, antibodies have been found which bind a subset of HA molecules within influenza A. Binding of these antibodies aligns with the 2 distinct groups of HA sequences seen in the phylogenic tree. Based on this finding and supported by nonclinical data generated by the sponsor with early stem-only vaccine antigens, it was determined that to provide broad protection against all circulating influenza viruses, the final universal influenza vaccine should include 3 HA-based antigens: one for responses against influenza A Group 1 viruses (eg, H1), one against influenza A Group 2 (eg, H3) and one against influenza B. The sponsor has chosen to first advance the antigen for Group 1 to obtain clinical proof-of-concept with this monovalent vaccine before introducing the other 2 molecules in subsequent clinical studies.

As part of the further development of the Uniflu vaccine, the sponsor plans to conduct this Phase 1/2a FIH safety and reactogenicity study in healthy participants (study VAC21148FLZ1001). The mini-HA antigen will be used as a soluble, purified, recombinant protein (INFLUENZA G1 mHA). To maximize the magnitude of the antibody titers, the protein antigen will be adjuvanted with aluminum hydroxide ($Al(OH)_3$).

The study is designed to determine a regimen for further clinical development in adults based on safety and immunogenicity data. The selected regimen should have a favorable safety profile and induce immune responses with desired magnitude and functionality, as supported by the secondary endpoints described in Section 3, Objectives and Endpoints.

2.2. Background

2.2.1. Nonclinical Studies

Nonclinical Pharmacology

Nonclinical studies were performed in different species to test the immunogenicity and protective efficacy of different vaccine candidates, leading to the selection of the current vaccines for the Phase 1/2a clinical study.

The $Al(OH)_3$ adjuvanted INFLUENZA G1 mHA vaccine was immunogenic in influenza-naïve mice, ferrets and nonhuman primates. The vaccine induced HA (stem)-specific humoral responses and neutralizing antibodies against a broad panel of Influenza A Group 1 strains in ferrets and nonhuman primates. A homologous 2-dose regimen with $Al(OH)_3$ adjuvanted INFLUENZA G1 mHA gave protection in murine efficacy models using H1N1 A/Brisbane/59/2007 or H5N1 A/Hong Kong/156/1997 challenge strains. A homologous 2-dose regimen with $Al(OH)_3$ adjuvanted INFLUENZA G1 mHA was protective (as defined by a significant reduction in lung infectious viral titers) in naïve ferrets after non-lethal challenge with a pandemic H1N1 A/Netherlands/602/2009 strain. In influenza virus (seasonal H1N1 A/Brisbane/59/2007) pre-exposed ferrets, a single vaccination with $Al(OH)_3$ adjuvanted INFLUENZA G1 mHA was immunogenic and gave protection against challenge with the H5N1 A/Indonesia/05/2005 strain.

Nonclinical Safety

Biodistribution

For recombinant protein vaccines (such as the INFLUENZA G1 mHA), pharmacokinetics studies (including biodistribution studies) are not normally needed (WHO 2005).

Toxicology

The nonclinical safety of the vaccine components (INFLUENZA G1 mHA and $Al(OH)_3$ adjuvant) has been tested in a Good Laboratory Practice (GLP) compliant, IM repeat-dose toxicity and local tolerance study in rabbits. Full human doses of the various vaccine components and combinations thereof were tested using a N+1 dosing regimen compared to the intended clinical study. The effects observed were the expected physiological/immunological responses to the injection of a vaccine and no adverse vaccine-related findings were noted in this study.

Per WHO Guidelines on Nonclinical Evaluation of Vaccines (WHO 2005), genotoxicity and carcinogenicity studies have not been performed. The components of the study vaccine are not expected to have genotoxic or carcinogenic potential.

2.2.2. Clinical Studies

This will be the FIH study for the INFLUENZA G1 mHA protein; therefore, no clinical experience is available.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of INFLUENZA G1 mHA may be found in the latest version of the IB.

2.3.1 Risks Related to Study Vaccination

This clinical study is a FIH study for the INFLUENZA G1 mHA protein vaccine. In this study, it will be the first time that this vaccine will be evaluated in humans.

The following risks for VAC21148 (INFLUENZA G1 mHA [with or without $Al(OH)_3$ adjuvant]) will be monitored during the study and are specified in the protocol:

Risks Related to INFLUENZA G1 mHA

This study will be the FIH study for INFLUENZA G1 mHA. No clinical data are available to date.

For the most comprehensive nonclinical information regarding INFLUENZA G1 mHA, refer to the latest version of the IB.

General Risks Related to Vaccination

In general, IM injection may cause local itching, warmth, pain, tenderness, erythema/redness, induration, swelling, arm discomfort, or bruising of the skin. Participants may exhibit general signs and symptoms associated with IM injection of a vaccine and/or placebo, including fever, chills, rash, myalgia, nausea/vomiting, headache, dizziness, arthralgia, general itching, and fatigue. These side effects will be monitored, but are generally short-term (typically lasting 2 to 3 days) and do not require treatment.

Syncope can occur in association with administration of injectable vaccines. Syncope can be accompanied by falls. Procedures should be in place to avoid falling injury. If syncope develops, participants should be observed until the symptoms resolve. Fear of injection might lead to fainting and fast breathing.

Participants may have an allergic reaction to vaccination. An allergic reaction may cause a rash, urticaria or even anaphylaxis. Severe reactions are rare. Participants with a history of severe allergic reaction, anaphylaxis or other serious adverse reactions to vaccines or vaccine excipients (specifically the excipients of the study vaccine) will be excluded from the study.

After each vaccination, participants will remain at the study site for at least 30 minutes and will be closely observed by site staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions.

Risks Related to Aluminum

Aluminum is one of the most common metals found in nature and is present in air, food, and water. Aluminum salts, such as aluminum hydroxide, aluminum phosphate, and aluminum potassium sulphate have been used safely in vaccines for more than 70 years. A few studies have reported an

association between vaccines containing aluminum adjuvants and persistent nodules at the injection site, at an estimated rate of 0.03% to 0.83% (Baylor 2002; Bergfors 2003; Bergfors 2014; Netterlid 2004). Two studies examining infant exposure to aluminum from both diet and vaccines concluded that aluminum adjuvants at the levels included in vaccines are well below the calculated safe body burden (Keith 2002; Mitkus 2011). A 2017 review found that current data do not support a causal relationship between aluminum-containing vaccines and a variety of autoimmune disorders (Ameratunga 2017).

Pregnancy and Birth Control

The effect of the study vaccine on a fetus or nursing baby is unknown.

Female participants of childbearing potential will be required to agree to practice an acceptable effective method of contraception and agree to remain on such a method of contraception from providing consent until 3 months after receiving study vaccine (see Section 5.1). Participants who are pregnant or breastfeeding will be excluded from the study. Participants who become pregnant during the study may not receive further study vaccine, but will remain in the study and will continue to undergo all procedures for surveillance and all safety follow-up as outlined in the protocol for all participants (see Section 7.1 Discontinuation of Study Vaccine). Follow-up information regarding the outcome of the pregnancy will be required.

Because the effect on sperm is unknown, male participants must inform the study-site personnel if their partner becomes pregnant during the study. Follow-up information regarding the outcome of the pregnancy will be requested upon the consent provided by the partner.

Participants with Immunosuppression/Reduced Immune Response

Participants with abnormal function of the immune system will be excluded from the study. Limited evidence indicates that inactivated vaccines (or non-replicating viral vaccines) generally have the same safety profile in immunocompromised patients as in immunocompetent individuals. However, the magnitude, breadth, and persistence of the immune response to vaccination may be reduced or absent in immunocompromised persons.

Risks from Blood Draws

Blood drawing may cause pain, tenderness, bruising, bleeding, dizziness, vaso-vagal response, syncope, and rarely, infection at the site where the blood is taken. Participants with contraindications to IM injections and blood draws (eg, bleeding disorders) will be excluded.

Risks from Genetic Testing

Genetic testing can be used to provide information about how susceptible participants are to certain diseases, as well as to provide other unique personal identifiable information. Used inappropriately, this information could be discriminatory (for example, by insurance companies). The results will be coded to protect participant identity. The results are for exploratory and future research purposes only and will not be provided to the participant.

Risks from Nasal Swab Sampling

The collection of specimens by nasal swabs can cause or exacerbate irritation of the nasal mucosa, which can result in bleeding/epistaxis.

Concomitant Vaccination

Concomitant vaccination might have an influence on both the safety profile and immunogenicity of the study vaccine. Likewise, the study vaccine might have an influence on both the safety profile and immunogenicity of any concomitant vaccination. As a result, licensed live attenuated vaccines should be given at least 28 days before or after vaccination. Other licensed (not live) vaccines (eg, influenza, tetanus, hepatitis A, hepatitis B, rabies, coronavirus disease 2019) should be given at least 14 days before or after vaccination to avoid potential confusion of adverse reactions and potential immune interference. Seasonal influenza vaccines should not be given within 4 months before planned administration of the first study vaccination until the end of the study. If a vaccine is indicated in a postexposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

Unknown Risks

There may be other risks that are not known. If any significant new risks are identified, the investigators and participants will be informed.

2.3.2 Benefits Related to Study Vaccination

Participants may benefit from clinical testing and physical examination, including the monitoring of influenza-like illness if it arises; others may benefit from the knowledge that they may aid in the development of a universal influenza vaccine.

The clinical benefits of the study vaccine have yet to be established. Currently, there are no effective universal vaccines for influenza and no efficacy can be concluded from current data. The overall benefit and risk balance for individual participants thus cannot be ascertained. Participants must be informed that this vaccine has not yet been proven to be effective, and it should be assumed that it is not the case until clinical studies are conducted that demonstrate its effectiveness.

2.3.3 Benefit-Risk Assessment Related to Study Vaccination

Based on the available data and proposed safety measures, the overall benefit-risk assessment for this clinical study is considered acceptable for the following reasons:

- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5, Study Population) will be allowed to participate in this study. The eligibility criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study:
  - In general, safety evaluations will be performed at scheduled visits during the study, as described in Section 1.3, Schedule of Activities.

  - After each vaccination, participants will remain at the study site for at least 30 minutes and will be closely observed by site staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions. Participants will use a diary to document solicited signs and symptoms. Details are provided in Section 8.2, Safety Assessments and Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting.
  - The investigator or the designee will document unsolicited adverse events (AEs) as indicated in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting and Section 10.4, Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.
  - Any serious clinically significant abnormalities (including those serious events persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:
  - Sentinel participants will be evaluated for safety before extending enrollment in each cohort. The blinded 48-hour post-vaccination safety data in these sentinel participants will be reviewed by the principal investigator(s) (PIs) and sponsor's study responsible physician (SRP)/medical officer. Randomization of additional participants will be paused until this 48-hour sentinel safety evaluation is completed.
  - For both cohorts, an internal data review committee (DRC) will review blinded [a] 7-day post-first dose safety in participants in the sentinel subset and safety ramp-up subset. Additional participants will only be enrolled following a favorable decision by the DRC. For both cohorts, the DRC will also review blinded [b] 7-day post-second dose safety in participants in the sentinel subset and safety ramp-up subset. Participants in the high-dose protein (INFLUENZA G1 mHA CCI groups will only be given the second dose following a favorable decision by the DRC regarding the low dose (INFLUENZA G1 mHA CCI
  - There are pre-specified rules for all participants, that would result in pausing of further vaccinations if predefined conditions occur, preventing exposure of new participants to study vaccine until the DRC reviews all safety data (see Committee Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations).
  - Participants will be discontinued from study vaccine for the reasons included in Section 7.1, Discontinuation of Study Vaccine.
  - Contraindications to vaccination are included in Section 7.1.1, Criteria for Temporarily Delaying Study Vaccine Administration.

[a] The DRC will review blinded data first but may review unblinded data if deemed necessary.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Safety	
• Primary objective: To evaluate safety/ reactogenicity of INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant, in participants ≥18 to ≤45 years of age.	• Primary endpoints: – Occurrence, severity, duration and relationship of solicited local and systemic AEs for 7 days after each vaccination. – Occurrence, severity, duration and relationship of unsolicited AEs for 28 days after each vaccination. – Occurrence and relationship of SAEs from first vaccination to the end of the study.
Immunogenicity	
• Secondary objective: To evaluate the humoral immune responses to INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant in participants ≥18 to ≤45 years of age.	• Secondary endpoint: The magnitude of antibodies binding to the stem or the full-length HA protein as measured by enzyme-linked immunosorbent assay (ELISA).
• Exploratory objectives: To further assess the immune responses elicited by INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant in participants ≥18 to ≤45 years of age.	• Exploratory endpoints may include, but are not limited to assessing: – Vaccine-induced changes to the breadth of the antibody response within Group 1 or beyond as measured by ELISA using full-length HA proteins indicative of clade or group coverage – HA stem- or epitope-specificity as measured by ELISAs using HA stem protein or competition ELISAs using bnAbs or HA proteins – Functional characterization of the antibody response as measured by assays assessing Fc-mediated functions (eg, Fc gamma receptor [FcγR] binding assays to the stem or full-length HA protein, or antibody-dependent cytotoxicity assay, or antibody-dependent cellular phagocytosis assay), HA conformational change assays, or other assays – Vaccine-induced changes to the functional breadth of the antibody response within Group 1 or beyond as measured by virus neutralization assays or serum transfer into animal challenge models – Molecular characterization of the antibody response as measured by assays assessing the epitope-specificity, glycosylation status, or other characteristics of the antibody (eg, by systems serology arrays) – Vaccine-induced changes in innate immune responses by transcript- or cytokine profiling – Vaccine-induced changes in gene expression profiles by ribonucleic acid (RNA) sequencing or other transcriptional profiling methods, including but not limited to

Objectives	Endpoints
	sequencing for T cell receptor or B cell receptor repertoire analysis – Nasal antibody response as measured by immunoglobulin (Ig) G or IgA ELISA in nasal secretions
• Exploratory objective: To evaluate longevity of immune responses elicited by INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant in participants aged ≥18 to ≤45 years.	• Exploratory endpoint: The magnitude and functionality of antibodies binding to the stem or the full-length HA protein of various strains as measured by ELISA, virus neutralization assays, and FcγR binding assays on Days 238 and 365.
• Exploratory objective: To evaluate the immune responses in participants with confirmed influenza infection.	• Exploratory endpoint: During the influenza season: – Immune responses by assays included for secondary and exploratory immunogenicity endpoints
Virology	
• Exploratory objective: To monitor symptoms of influenza-like illness (ILI) via the Influenza Intensity and Impact Questionnaire (Flu-iiQ™) as well as rapid molecular diagnosis and characterization to evaluate infection rate in participants aged ≥18 to ≤45 years and in relation to immunological markers.	• Exploratory endpoints: During the influenza season: – Signs and symptoms of ILI – Confirmation of infection by reverse transcriptase polymerase chain reaction (RT-PCR) or response to influenza-like infection by serology

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

No formal statistical hypothesis is to be tested. The study will evaluate whether INFLUENZA G1 mHA, with or without Al(OH)3 adjuvant, is safe, well tolerated and immunogenic in healthy adults aged ≥18 to ≤45 years.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, FIH Phase 1/2a study to evaluate safety, reactogenicity and immunogenicity of a universal influenza (Uniflu) vaccine INFLUENZA G1 mHA in healthy male and female adults aged ≥18 to ≤45 years.

A target of 170 participants will be enrolled in this study. The study design includes 2 sequential cohorts comparing INFLUENZA G1 mHA (with or without Al(OH)3 adjuvant) at 2 dose levels (see Table 1).

Table 1: Study Design: VAC21148FLZ1001

Cohort	Group	N	Day 1	Day 57
1	1	25	INFLUENZA G1 mHA CCI	INFLUENZA G1 mHA CCI
	2	25	INFLUENZA G1 mHA CCI $Al(OH)_3$	INFLUENZA G1 mHA CCI $Al(OH)_3$
	3	10	Placebo	Placebo
2	4	25	INFLUENZA G1 mHA CCI	INFLUENZA G1 mHA CCI
	5	25	INFLUENZA G1 mHA CC [redacted] $Al(OH)_3$	INFLUENZA G1 mHA CC [redacted] $Al(OH)_3$
	6	25	INFLUENZA G1 mHA CCI	Placebo

	7	25	INFLUENZA G1 mHA [redacted] $Al(OH)_3$	Placebo
	8	10	Placebo	Placebo
TOTAL:		170		

$Al(OH)_3$ = aluminum hydroxide (aluminum content at 0.75 mg/dose); N = number of participants.

The study duration (excluding screening) will be approximately 365 days per participant. The study comprises a maximum 42-day screening period, study vaccination (active or placebo) with a 2-dose (on Day 1 and Day 57) regimen, a minimum 28-day follow-up period after each vaccination, and a long-term follow-up period until 1 year after the first vaccination. The end of the study is defined as the last participant's last visit 12 months after the first vaccination.

A diagram of the study design is provided in Section 1.2, Schema.

An internal DRC, consisting of members that are not directly involved in the study conduct, data management, or statistical analysis, will be commissioned for this study to evaluate (blinded) safety and reactogenicity data on a regular basis. Refer to Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations for details.

First-dose Cohort 1

In Cohort 1, 60 participants aged ≥18 to ≤45 years will be enrolled in a staggered approach with safety evaluations in place before extending enrollment in this cohort and progressing to Cohort 2. Initially, 5 sentinel participants will be enrolled and randomized; 2 participants in Groups 1 and 2 and 1 participant in Group 3 (placebo) will receive a single IM injection of either [redacted] INFLUENZA G1 mHA, [redacted] INFLUENZA G1 mHA adjuvanted with $Al(OH)_3$, or placebo on Day 1. Sentinel participants will be contacted by telephone 48 hours post-vaccination to collect safety information. The blinded 48-hour post-vaccination safety data in these 5 sentinel participants will be reviewed by the PI(s) and SRP. Randomization of additional participants will be paused until this 48-hour sentinel safety evaluation is completed (Figure 2).

In the absence of any clinically significant findings, upon decision by PI(s) and SRP, an additional 12 participants will be enrolled (5 additional participants in Groups 1 and 2 and 2 additional participants in Group 3 [placebo] as safety ramp-up subset; Figure 2).

DRC will review blinded safety data of the initial 17 participants 7 days after the first vaccination. DRC review will be held to review available safety data of initial participants enrolled before these participants can receive the second vaccination. Further randomization in Cohort 1 will be paused until the DRC safety evaluation is completed. In the absence of findings from the DRC following the first vaccination, the remaining 43 participants in Cohort 1 will be enrolled in a 18:18:7 ratio and randomization in Cohort 2 may be initiated simultaneously (Figure 2).

First-dose Cohort 2

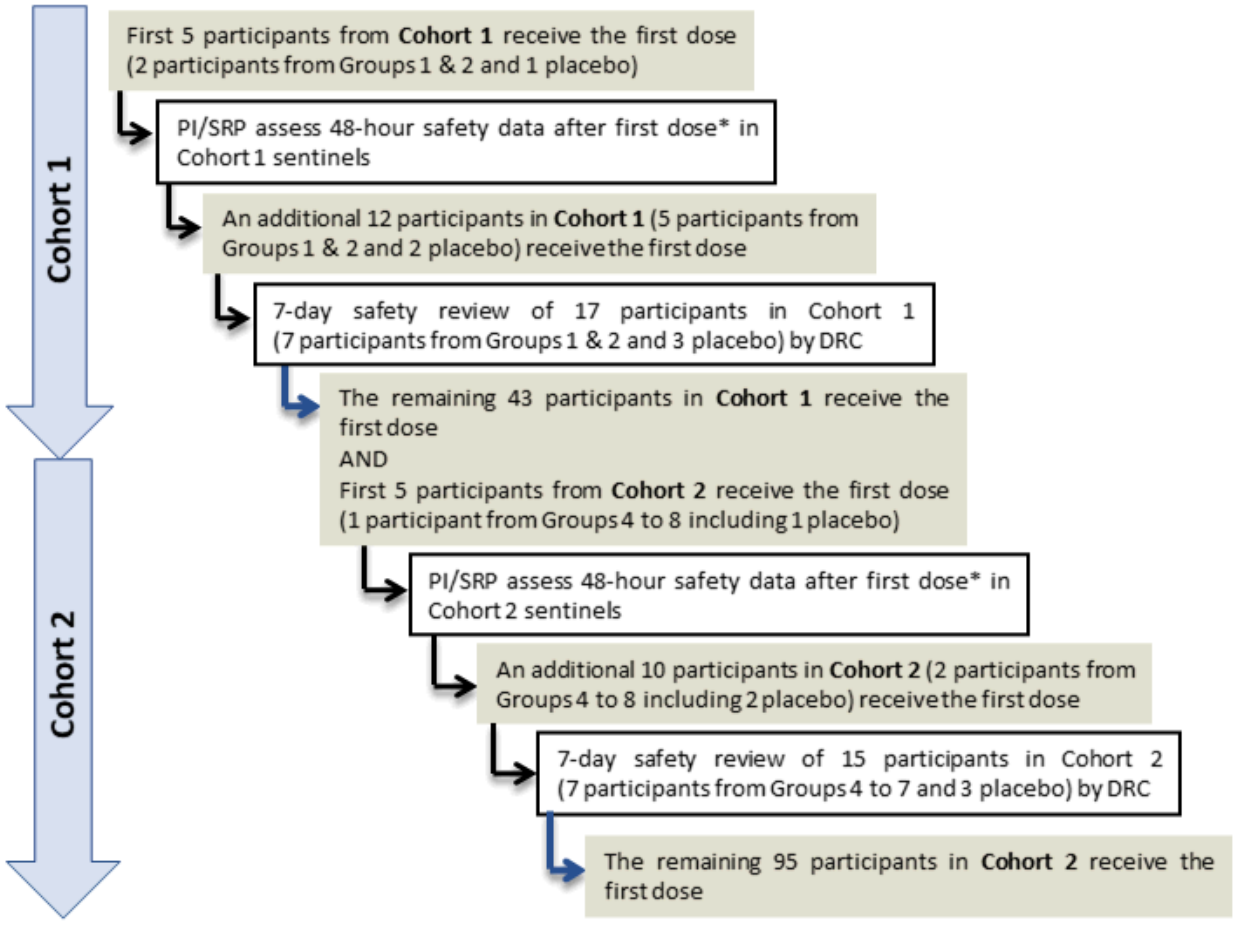
In Cohort 2, 110 participants aged ≥18 to ≤45 years will be enrolled in a staggered approach with safety evaluations in place before extending enrollment in this cohort. Initially, 5 sentinel participants will be enrolled and randomized; 1 participant in each of the 5 groups (Groups 4 to 8 [including 1 placebo]) will receive a single IM injection of either [redacted] INFLUENZA G1 mHA;

CCI INFLUENZA G1 mHA adjuvanted with $Al(OH)_3$; or placebo on Day 1. Sentinel participants will be contacted by telephone 48 hours post-vaccination to collect safety information. The blinded 48-hour post-vaccination safety data in these 5 sentinel participants will be reviewed by the PIs and SRP. Randomization of additional participants will be paused until this 48-hour sentinel safety evaluation is completed (Figure 2).

In the absence of any clinically significant findings, upon decision by PI(s) and SRP, an additional 10 participants will be enrolled and randomized in parallel (2 additional participants in Groups 4 to 8 [including 2 placebo]) as safety ramp-up subset (Figure 2).

DRC will review blinded safety data of the 15 participants in Cohort 2, 7 days after the first vaccination. DRC review will be held to review available safety data of initial participants enrolled before these participants can receive the second vaccination. Further randomization in Cohort 2 will be paused until the DRC safety evaluation is completed. In the absence of findings from the DRC following the first vaccination, the remaining 95 participants in Cohort 2 will be enrolled in a 22:22:22:22:7 ratio (Figure 2).

Figure 2: Participant Enrollment and First Dose Safety Strategy



DRC = data review committee; PI = principal investigator; SRP = study responsible physician.
* Sentinel participants will be contacted 48 hours post-vaccination by telephone to collect safety information.

Second-dose Safety

In alignment with the first-dose safety strategy, post-second dose 48-hour (sentinel participants) and 7-day safety assessments (participants in the sentinel subset and safety ramp-up subset) will be monitored by the PI(s) and SRP, and the DRC, respectively [a] (see Figure 2). The sequence in which participants in the sentinel subset and the safety ramp-up subset are vaccinated should be similar for Dose 1 and Dose 2. Administration of the second dose will also be staggered to allow safety assessments to be made 7 days after the second dose in participants in the safety ramp-up subset receiving low-dose protein (INFLUENZA G1 mHA CCI before administering the second dose to participants in the high-dose protein (INFLUENZA G1 mHA CCI groups. In the absence of clinically relevant findings and following the decision by the DRC, dosing the remaining participants will continue as described above.

For both cohorts, the DRC will review blinded [b] 7-day post-first dose as well as post-second dose safety. Safety data for review will include solicited and unsolicited AEs, SAEs, and available laboratory assessments. If any pre-specified study vaccination pausing rule is met, vaccinations will be paused, and a DRC meeting will be convened. For details on the pausing rules, see Section 6.8, Study Pausing Rules. In addition, the DRC will also evaluate safety data over the course of the study and review any events that meet a specific study vaccine pausing rule or any other safety issue that may arise.

Study Procedures

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. In addition, participants will record solicited signs and symptoms in a diary for 7 days post-vaccination, beginning each study vaccine dosing day. Participants will be given a thermometer, ruler and daily assessment (participant) diary with instructions for the proper recording of events. Oral temperatures should be taken at approximately the same time each day,[c] and additional temperature measurements may be taken if a participant does not feel well. Study-site personnel will collect and review participant diary information and confirm the entries at subsequent site visits.

AEs will be collected as outlined in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

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[a] In case a participant in the sentinel subset or the safety ramp-up subset withdraws from the study prior to receiving Dose 2 or receives Dose 2 outside the prespecified visit window, the post-second dose 48-hour safety review by the PI(s) and SRP, as well as the 7-day safety review by the DRC will be performed as scheduled based on the available data.

[b] The DRC will review blinded data first but may review unblinded data if deemed necessary.

[c] Temperature 7 days after each vaccination may be collected earlier on the Day 8 or Day 64 to coincide with the clinic visit.

All AEs, including any that are ongoing at 28 days after each dose, will be followed until clinical resolution or stabilization. Concomitant therapies will be collected from the signing of the ICF until 28 days after the first vaccination and from the second vaccination through the following 28 days, and additionally outside of these periods when associated with an SAE.

Blood and urine samples for clinical laboratory assessments will be collected as indicated in Section 1.3 Schedule of Activities and Section 10.6, Appendix 6: Clinical Laboratory Tests.

Blood will be collected from all participants to assess humoral immune responses pre-vaccination on each dosing day, at 7 days and at 28 days after each dose, at 6 months after the second dose, and at 12 months after the first dose (or at the early exit visit if the participant prematurely terminates the study without withdrawing consent [a]).

Participants should record signs and symptoms of influenza during the influenza season using a specific Influenza Intensity and Impact Questionnaire (Flu-iiQ™) and an ILI form. Participants will be informed of the timing of the start and end of the influenza season in accordance with the country/region-specific influenza local surveillance system. Procedures for Flu-iiQ™ questionnaire and ILI form completion are described in Section 8.1.1, ILI Procedures. The Flu-iiQ™ questionnaire and ILI form will be the primary source for influenza monitoring. Participants will be contacted by telephone or other means of communication every 14±3 days (unless a planned clinic visit has occurred or will occur within 14 days). Calls will remind the participants to complete the Flu-iiQ™ questionnaire and ILI form in the event of any symptoms of influenza infection, to contact the site at the time of symptom onset, and to take a nasal swab at home preferably on the day of symptom onset or the day thereafter (ILI Days 1-2). Calls will also check for any SAEs and associated concomitant medications since the previous visit or telephone contact.

Full details of ILI procedures, including the collection of nasal swabs are provided in Section 8.1.1, ILI Procedures.

The presence of influenza virus infection will be assessed by qualified site staff by RT-PCR diagnostics and/or rapid-PCR detection (eg, by Cepheid GeneXpert®) on the nasal swab samples.

Seasonal Influenza Vaccination

Seasonal influenza vaccination is not allowed during a time window starting 4 months prior to Dose 1 until the end of the study. Participants should be willing to forego any influenza vaccination during the entire study period and will have to consent to this. This will allow to assess longevity of the immune response without interference of a seasonal influenza vaccine. Although seasonal influenza vaccination is recommended in the US but not generally recommended in Europe for participants in this age group (Grohskopf 2019), several placebo-controlled clinical studies have been conducted in this age group (Treanor 2007; Treanor 2011). All participants will be closely

[a] Immunogenicity blood samples will only be taken if early exit is at least 14 days after the previous immunogenicity blood draw.

monitored for symptoms of influenza infection (using the Flu-iiQ™ questionnaire) to ensure that early diagnosis and treatment can be provided if necessary. In this age group, influenza infections are generally mild with non-serious consequences.

4.2. Scientific Rationale for Study Design

Dose Selection

The rationale behind the selection of the doses is described in Section 4.3, Justification for Dose.

Regimen Selection

In **Cohort 1**, initial safety and immunogenicity assessment of a 2-dose regimen of INFLUENZA G1 mHA (CCI with or without $Al(OH)_3$ adjuvant, will be performed.

In **Cohort 2**, safety and immunogenicity of high-dose (CCI INFLUENZA G1 mHA (with and without $Al(OH)_3$ adjuvant) administered in a 2-dose or single-dose regimen will be assessed.

The vaccination regimens are with administration of study vaccination (active or placebo) on Day 1 and Day 57 (8-week interval). The interval is based on data from other studies by the sponsor in which higher antibody responses were observed in studies with an 8-week interval regimen compared to studies with a 4-week interval regimen (Milligan 2016). A longer (eg, 12-week interval) regimen was not considered for the current study because this would be impractical for an influenza vaccine.

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Biomarker Collection and Limited Genetic Testing

It is recognized that genetic variation can be an important contributory factor to interindividual differences in response to vaccination. Limited genetic testing (eg, gene expression profiling) may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to vaccination. The goal of the gene expression profiling component is to collect RNA to allow the identification of genetic factors that may influence the safety, reactogenicity and immunogenicity of INFLUENZA G1 mHA.

Biomarker samples will be collected to evaluate the immunogenicity of INFLUENZA G1 mHA or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to vaccination. The goal of the biomarker analyses is to evaluate

the immunogenicity of INFLUENZA G1 mHA and aid in evaluating the intervention-clinical response relationship.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is that this study will be performed in healthy adult participants who will receive no benefit from participation in the study, except for compensation for the time and inconveniences that may arise from participation in the study. Refer to Section 2.3, Benefit-risk Assessment for details on potential and known benefits and risks, and for the safety measures taken to minimize risk to participants.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the US Department of Health and Human Services Office for Human Research Protections, and US Food and Drug Administration (FDA) guidelines of 550 mL in any 8-week period (OHRP 1998; FDA 1998).

4.3. Justification for Dose

The CCI dose was selected as the initial dose for INFLUENZA G1 mHA as this is in line with the Influenza A Group 1 HA dose in the licensed Flublok vaccine, which contains CCI of each HA and is well tolerated (Cox 2015). Furthermore, data from other programs by the sponsor showed this dose of protein to be safe (sponsor internal data). However, it is anticipated that doses higher than this will be required to achieve optimal immune responses, due to the inherent lower immunogenicity of the HA stem domain compared to the head domain of the molecule (Tan 2019). Therefore, the CCI dose was selected as it represents an approximately 0.5 log increase over the CCI dose, representing a meaningful difference given the biological response and typical assay variability. As it is anticipated that the final Uniflu vaccine may consist of a mixture of 3 different proteins (covering Influenza A hemagglutinin Group 1, Group 2 and Influenza B), a dose of CCI per protein in the regimen approaches a practical limit for this vaccine. The dose levels of CCI and CCI of INFLUENZA G1 mHA to be used were also chosen as the initial dose based on the safety and immunogenicity profile of recombinant RSV preF proteins given at doses of 150 µg in approximately 8,499 participants aged 60 years and older in other studies up to 27 October 2021 by the sponsor. These recombinant RSV proteins were given directly mixed with Ad26-vectored RSV vaccine.

There might be a need for the use of an adjuvant in this vaccine program. As it is the most widely used adjuvant, $Al(OH)_3$ has been chosen for this study. The $Al(OH)_3$ adjuvant with an aluminum content of 0.75 mg/dose was chosen to be well within the FDA recommendation of maximal 0.85 mg per dose. Aluminum-containing vaccines have been in use for over 70 years and have

rarely been associated with SAEs. However, local reactions such as redness, swelling and/or tenderness at the injection site are common (Eickhoff 2002; Jefferson 2004).

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the clinical trial agreement.

Participant Study Completion Definition

A participant will be considered to have completed the study if the participant has completed assessments at Day 365±30 days of the follow-up phase.

Participants who prematurely discontinue study vaccine for any reason before completion of the vaccination phase can be considered to have completed the study if they have completed follow-up and the scheduled assessments.

5. STUDY POPULATION

Screening for eligible participants will be performed within 42 days before administration of the study vaccine. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Criterion modified per Amendment 2:
   - 1.1 must sign an ICF indicating that the participant understands the purpose, procedures and potential risks and benefits of the study, and is willing to participate in the study.
2. Criterion modified per Amendment 2:
   - 2.1 willing and able to adhere to the lifestyle restrictions specified in this protocol.
3. Criterion modified per Amendment 1:
   - 3.1 male or female, ≥18 to ≤45 years of age on the day of signing the ICF and expected to be available for the duration of the study.
4. Criterion modified per Amendment 1:

4.1 must be healthy as confirmed by medical history, physical examination, and vital signs performed at screening.

Note: A participant must be healthy per the investigator's judgement prior to study vaccine administration on Day 1 and Day 57.

5. Criterion modified per Amendment 1:

5.1 Criterion modified per Amendment 2:

5.2 contraceptive (birth control) use by female participants should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies. Before randomization, participants who were born female must be either (as defined in Section 10.2, Appendix 2, Contraceptive Guidance and Collection of Pregnancy Information):

a. not of childbearing potential

b. of childbearing potential and practicing a highly effective method of contraception and agreeing to remain on such a method of contraception from signing the informed consent until 3 months after the last dose of study vaccine. Use of hormonal contraception should start at least 28 days before the first administration of study vaccine. Highly effective methods for this study include:

1) hormonal contraception

2) intrauterine device

3) intrauterine hormone-releasing system

4) bilateral tubal occlusion/ligation procedures

5) vasectomized partner (the vasectomized partner should be the sole partner for that participant)

6) sexual abstinence [a]

6. Criterion modified per Amendment 1:

6.1 all female participants of childbearing potential must:

a. have a negative highly sensitive serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening

b. have a negative urine β-hCG pregnancy test immediately prior to each study vaccine administration

7. agrees to not donate blood until 3 months after receiving the last dose of study vaccine.

8. must be able to read, understand, and complete questionnaires in the Diary and Flu-iiQ™ questionnaire.

[a] Sexual abstinence is considered an effective method only if defined as refraining from heterosexual intercourse from signing the informed consent until 3 months after the last dose of study vaccine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. must be willing to provide verifiable identification, have means to be contacted and to contact the investigator during the study.
10. Criterion added per Amendment 1:

    10.1 must be healthy on the basis of clinical laboratory tests performed at screening. If the results of the laboratory screening tests are outside the laboratory normal reference ranges and additionally within the limits of toxicity Grade 2 according to the US FDA toxicity tables in Section 10.5, Appendix 5, Toxicity Grading Scale, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant and appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.

    Note: If laboratory screening tests are out of laboratory normal ranges and deemed clinically significant, repeat of screening tests is permitted once, using an unscheduled visit during the screening period to assess eligibility.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. contraindication to IM injections and blood draws eg, bleeding disorders.
2. Criterion modified per Amendment 2:

    2.1 clinically significant acute illness (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature ≥38.0ºC (100.4°F) within 24 hours prior to the planned first dose of study vaccine; randomization at a later date is permitted at the discretion of the investigator and after consultation with the sponsor.[a]
3. history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).
4. Criterion modified per Amendment 1:

    4.1 Criterion modified per Amendment 2:

    4.2 history of severe allergic reaction (eg, anaphylaxis) or other serious adverse reactions to vaccines or vaccine excipients (specifically the excipients of the study vaccine[s]) (refer to the IB).
5. Criterion modified per Amendment 1:

    5.1 Criterion modified per Amendment 2:

    5.2 abnormal function of the immune system resulting from:

    a. clinical conditions (eg, autoimmune disease or immunodeficiency) or their treatments expected to have an impact on the immune response elicited by the study vaccine.

[a] If within the screening window. Otherwise, rescreening is required.

b. chronic or recurrent use of systemic corticosteroids within 2 months before administration of study vaccine and during the study.
Note: Ocular, topical, intra-articular, or inhaled steroids are allowed.

c. administration of antineoplastic and immunomodulating agents or radiotherapy expected to have an impact on the immune response elicited by the study vaccine within 6 months before administration of study vaccine and during the study.
Note: Topical immunomodulating agents may be allowed upon sponsor approval.

6. Criterion modified per Amendment 1:

6.1 history of acute polyneuropathy (eg. Guillain-Barré syndrome) or chronic idiopathic demyelinating polyneuropathy.

7. Criterion modified per Amendment 2:

7.1 history of chronic urticaria (recurrent hives), chronic eczema or chronic atopic dermatitis.

8. Criterion modified per Amendment 2:

8.1 received treatment with immunoglobulins (including monoclonal antibodies) expected to impact the vaccine-induced immune response in the 2 months or blood products in the 3 months before the planned administration of the first dose of study vaccine or has any plans to receive such treatment during the study.

Note: Given that not all immunoglobulins/monoclonal antibodies are expected to impact the vaccine-induced immune response, the investigator should contact the sponsor to discuss eligibility of participants on immunoglobulin treatment.

9. Criterion modified per Amendment 1:

9.1 received or plans to receive:

a. Licensed live attenuated vaccines - within 28 days before or after planned administration of the first or subsequent study vaccination[s].

b. Other licensed (not live) vaccines (not including seasonal influenza vaccines) - within 14 days before or after planned administration of the first or subsequent study vaccination[s].

c. Seasonal influenza vaccines - within 4 months before planned administration of the first study vaccination until the end of the study. (ie, any individual who requires a seasonal influenza vaccination for occupational or other reasons will be excluded).

10. Criterion modified per Amendment 1:

10.1 Criterion modified per Amendment 2:

10.2 received an investigational drug or used an invasive investigational medical device within 30 days or received an investigational vaccine within 6 months before the planned administration of the first dose of study vaccine, or received an investigational biological product within 3 months or 5 half-lives, whichever is longer, before the planned study intervention, or is currently enrolled or plans to participate in another investigational study or observational clinical study during the course of this study.

Note: Participants can be included if the investigational product received was subsequently licensed or authorized for emergency use (eg, Emergency Use

Authorization, Emergency Use Listing, or similar program). Participants with proof of having received only placebo can also be included. Such participants can, however, only be included in the absence of follow-up that involves invasive procedures that would interfere with study requirements or safety follow up.

11. has received a pandemic influenza vaccine (other than H1N1) in a previous pandemic influenza vaccine study at any time prior to randomization.
12. Criterion modified per Amendment 1:

    12.1 pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study vaccine. Oocyte donation is prohibited while enrolled in this study.

13. history of an underlying clinically significant acute or uncontrolled chronic medical condition or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
14. Criterion modified per Amendment 1:

    14.1 Criterion modified per Amendment 2:

    14.2 had major surgery (eg, impacting immune response to the study intervention, or requiring a >2-night hospitalization) within 4 weeks before dosing, or will not have fully recovered from major surgery, or has major surgery planned within 3 months after any dose of study vaccine administration.

    Note: The investigator is encouraged to contact the sponsor to discuss eligibility of participants in case it's not clear whether a prior or planned surgery should be considered major.

15. employee of the investigator or study site with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor.
16. has chronic active hepatitis B or hepatitis C infection, per medical history.
17. is positive for HIV, per medical history.
18. has had major psychiatric illness or drug or alcohol abuse which in the investigator's opinion would compromise the participant's safety or compliance with the study procedures.
19. cannot communicate reliably with the investigator.
20. who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or is unlikely to complete the full course of vaccination and observation.
21. has significant scarring, tattoos, abrasions, cuts, or infections over the deltoid region of both arms that, in the investigator's opinion, could interfere with evaluation of injection site local reactions.
22. Criterion added per Amendment 1:

    22.1 Criterion deleted per Amendment 2

23. Criterion added per Amendment 1:

    23.1 Criterion deleted per Amendment 2

24. Criterion added per Amendment 1:

    24.1 Criterion deleted per Amendment 2

Note: Investigators must ensure that all study enrollment criteria have been met prior to the first vaccination. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study vaccine is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. The clinical laboratory results on Day 1 and Day 57 are not required for eligibility assessment. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 5.2, Exclusion Criteria for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant randomization number and age at initial informed consent. In cases where the participant is not randomized into the study, the participant screening number, date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at the discretion of the sponsor.

Retesting and Rescreening

Exceptional and limited retesting of abnormal screening values that lead to exclusion are allowed only once using an unscheduled visit during the screening period (to reassess eligibility).

If a participant does not meet all inclusion and exclusion criteria (is a screen failure) but at some point in the future is expected to meet the participant eligibility criteria, the participant may be rescreened on 1 occasion only. Participants who are rescreened will be assigned a new participant screening number, undergo the informed consent process, and then restart a new screening phase.

6. STUDY VACCINE

6.1. Study Vaccine(s) Administered

Participants will be vaccinated at the study site according to the schedule detailed in Section 4.1, Overall Design (Table 1). For description of the vaccinations, see below.

INFLUENZA G1 mHA, adjuvant and diluent will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

The placebo for this study will be supplied by the sponsor as a commercially available injectable solution of 9 mg/mL Sodium Chloride.

Supplies will be provided by the sponsor in the following configuration:

- INFLUENZA G1 mHA (JNJ-67920320): supplied at a concentration of 900 µg/mL in a single use vial, dosed at CCI and CCI with or without $Al(OH)_3$ adjuvant. (Aluminum content at 0.75 mg/dose); 0.5 mL (extractable volume)
- Placebo: supplied as a sterile solution of Sodium Chloride 9 mg/mL in a single use vial; 10 mL (filling volume)
- Aluminum hydroxide adjuvant ($Al(OH)_3$): supplied at a concentration of 3.75 mg/mL in a single use vial for mixing according to the Investigational Product Preparation Instructions (IPPI); 1.0 mL (extractable volume)
- Formulation buffer for INFLUENZA G1 mHA (Diluent Uniflu 1): supplied in a single use vial for dilution of INFLUENZA G1 mHA according to IPPI; 0.8 mL (extractable volume)

For each participant, every injection will be 1.0 mL in volume. Instructions on study vaccine preparation (eg, dilution in formulation buffer) into the final dose that participants receive within each treatment group are outlined in detail in the IPPI.

Preferably the deltoid muscle of the non-dominant upper arm is used to administer the injection. If an injection cannot be given in either deltoid for the second dose of the vaccination due to a medical or other contraindication (for example, tattooed upper arms rendering it difficult to assess site reactogenicity), use alternative locations such as the hip, thigh, or buttocks (to be avoided in overweight participants). In this case, IM injections in other locations than the upper arm for the second dose of the vaccination are not considered protocol deviations.

For information on vaccination windows, see Section 8, Study Assessments and Procedures. If a participant cannot be vaccinated within the allowed window or if the window is missed due to a study pause (see Section 6.8, Study Pausing Rules), the decision regarding vaccination will be assessed on a case-by-case basis, upon discussion between sponsor and investigator.

Study vaccine administration must be captured in the source documents and the electronic case report form (eCRF).

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study vaccine must be stored in a secured location with no access for unauthorized personnel and at controlled temperatures as indicated on the clinical labels. If study vaccine is exposed to temperatures outside the specified temperature range, all relevant data will be sent to the sponsor to determine if the affected supplies can be used or will be replaced. The affected study vaccine must be quarantined and not used until further instruction from the sponsor is received.

Refer to the Site Investigational Product and Procedures Manual (SIPPM) and/or the IPPI for additional guidance on study vaccine preparation, handling, and storage and stability.

An unblinded pharmacist, or other qualified staff member at the site with primary responsibility for study vaccine preparation, who will not participate in any other study evaluation, will prepare the appropriate vial and syringe, labeled with the participant's identification number, and provide the blinded syringe to the blinded vaccine administrator who will perform the injection.

All study vaccines were manufactured and packaged in accordance with Current Good Manufacturing Practice. All study vaccines will be packaged and labeled under the responsibility of the sponsor. Study vaccine labels will contain information to meet the applicable regulatory requirements.

No study vaccine can be repacked or relabeled without prior approval from the sponsor.

Accountability

The investigator is responsible for ensuring that all study vaccine received at the site is inventoried and accounted for throughout the study.

The study vaccine administered to the participant must be documented on the intervention accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study vaccine containers.

Study vaccine must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study vaccine must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study vaccine will be documented on the intervention return form. When the study site is an authorized destruction unit and study vaccine supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials containing hazardous liquids, such as used ampules, needles, syringes and vials, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study vaccine should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study vaccine will be supplied only to participants participating in the study. Returned study vaccine must not be dispensed again, even to the same participant. Study vaccine may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study vaccine from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study vaccines are provided in the SIPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

Vaccine Allocation

Procedures for Randomization

Participants will be randomly assigned to 1 of the study vaccine groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization within each cohort will be performed in different steps. Allocation to the sentinel subset, to the safety ramp-up subset, or to the main study subset will be monitored by the randomization system which will indicate the specific subset that a participant is included in. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study vaccine kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

If randomized participants are withdrawn from vaccination before the first dose of study vaccine is administered, additional participants may be recruited to replace these participants at the discretion of the sponsor. Any replacement participant will be assigned to the same group as the original (discontinued) participant. The replacement participant's randomization number will equal the randomization number of the discontinued participant +1000 (eg, participant 0001 would be replaced by participant 1001). These additional participants should also be randomized through IWRS.

In Cohort 1, a total of 60 participants will be enrolled in a staggered approach (Figure 2). Initially, 5 sentinel participants will be randomized; 2 participants to Groups 1 and 2 and 1 participant to Group 3 (placebo). Randomization of additional participants will be paused until a blinded 48-hour sentinel safety evaluation of these 5 sentinel participants is completed. In the absence of any clinically significant findings, upon decision by PI(s) and SRP, an additional 12 participants will be randomized (5 additional participants in Groups 1 and 2 and 2 additional participants in Group 3 [placebo]). DRC will review blinded safety data of the initial 17 participants 7 days after the first vaccination. DRC review will be held to review available safety data of initial participants enrolled before these participants can receive the second vaccination. Further randomization in Cohort 1

will be paused until the DRC safety evaluation is completed. In the absence of findings from the DRC following the first vaccination, the remaining 43 participants in Cohort 1 will be randomized and randomization in Cohort 2 may be initiated.

In Cohort 2, a total of 110 participants will be enrolled in a staggered approach (Figure 2). Initially, 5 sentinel participants will be randomized; 1 participant in each of the 5 groups (Groups 4 to 8 [including 1 placebo]). Randomization of additional participants will be paused until a blinded 48-hour sentinel safety evaluation of these 5 sentinel participants is completed. In the absence of any clinically significant findings, upon decision by PI(s) and SRP, an additional 10 participants will be randomized in parallel (2 additional participants in Groups 4 to 8 [including 2 placebo]). DRC will review blinded safety data of the 15 participants in Cohort 2, 7 days after the first vaccination. DRC review will be held to review available safety data of initial participants enrolled before these participants can receive the second vaccination. Further randomization in Cohort 2 will be paused until the DRC safety evaluation is completed. In the absence of findings from the DRC following the first vaccination, the remaining 95 participants in Cohort 2 will be randomized.

Refer to Section 4.1, Overall Design and Figure 2.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, immunogenicity data, study vaccine accountability data, study vaccine allocation, biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

The participants, study-site personnel (including vaccine administrator) and investigator will be blinded to study vaccine allocation throughout the study, except for the pharmacist or qualified staff member with primary responsibility for study vaccine preparation and dispensing.

At the time of the primary analysis, the study will be unblinded for sponsor and external partnerships personnel. Participants, clinical staff and study-site personnel will remain blinded to the study vaccine allocation until the end of the study.

The investigator may in an emergency determine the identity of the intervention. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding

must be documented by the IWRS, in the appropriate section of the eCRF, and in the source document.

Participants who have had their study vaccine assignment unblinded should continue to return for scheduled evaluations.

In general, the randomization list will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into study vaccine and placebo groups will be disclosed to those authorized and only for those participants included in the interim analysis.

In rare circumstances when a potential safety issue that may impact the overall benefit-risk assessment of the investigational product has been identified in this study, selected sponsor personnel may be unblinded to safety-related data in order to investigate the safety issue and determine if additional actions are required. The safety data should be kept blinded to any personnel not essential to the safety review.

If other rare, unforeseen circumstances arise that may necessitate unblinding of selected sponsor personnel, these will be assessed and documented on a case-by-case basis. The data should be kept blinded to any personnel not essential to the review or investigation.

6.4. Study Vaccine Compliance

Study vaccines will be administered intramuscularly by blinded qualified study-site personnel at the study site. Details of each administration will be recorded in the eCRF (including date and time of injection and location used for injection). For blinding procedures, see Section 6.3, Measures to Minimize Bias: Randomization and Blinding.

6.5. Concomitant Therapy

Prestudy specific therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, or antihistamines administered up to 30 days before first dose of study vaccine must be recorded at screening.

Any vaccination within 6 months before screening must be recorded at screening. Seasonal influenza vaccination administered during the previous season (and, if possible, during the past 5 seasons) will be recorded at screening, if available.

Concomitant therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, or antihistamines must be recorded until 28 days after administration of study vaccine and thereafter, pre-dose on the day of vaccination and for 28 days after each subsequent dose of study vaccine. Any vaccination must be recorded until the end of the study. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per-protocol requirements outlined in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

Refer to Section 5.2, Exclusion Criteria for details on which medication is disallowed before study drug administration and during the study. If any of these medications are indicated in a disease or a post-exposure setting, these must take priority over the study intervention.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. Any use of disallowed medication is to be recorded in the CRF.

6.6. Dose Modification

Dose modification is not applicable in this study.

6.7. Intervention After the End of the Study

There will be no study intervention following the end of the study.

6.8. Study Pausing Rules

If a study vaccination is considered to raise significant safety concerns (and a specific set of pausing criteria have been met), further vaccination of participants may be paused after medical review as described below. The concerned data will then be reviewed by the DRC, after which the DRC will recommend whether the pause can be lifted or not, or whether other steps are needed.

1. The occurrence of any of the following events may lead to a pause in further study vaccination. This list is only applicable for concerned AEs that occur up to 4 weeks after each vaccination and for concerned SAEs from the first vaccination throughout the study. Death of a participant, considered related to study vaccine or if the causal relationship to the study vaccine cannot be excluded; OR

   Note: All cases of death will be sent for DRC information. Upon their review, DRC may then decide whether a study pause is required.

2. One or more participants experience an SAE, a Grade 4 (solicited or unsolicited) AE, or a persistent (upon repeat testing) Grade 4 laboratory abnormality that is determined to be related to study vaccine; OR

3. One or more participants experience anaphylaxis or generalized urticaria within 24 hours of vaccination, clearly not attributable to other causes than vaccination with study vaccine; OR

4. Three or more participants experience a Grade 3 unsolicited AE of the same type (as per medical judgment of the sponsor), that is determined to be related to study vaccine, that persists for 72 hours or longer; OR one participant from sentinel cohort experiences a Grade 3 unsolicited AE that is determined to be related to study vaccine; OR

5. Three or more participants experience a persistent (upon repeat testing) Grade 3 laboratory abnormality related to the same laboratory parameter and considered related to study vaccine; OR One participant from sentinel cohort experiences a persistent (upon retesting) Grade 3 laboratory abnormality that is determined to be related to study vaccine; OR

6. Three or more participants experience a Grade 3 solicited AE of the same type, determined to be related to study vaccine, and persisting as Grade 3 for longer than 3 consecutive days (ie,

the day of occurrence of the AE is counted as Day 1); OR one participant from sentinel cohort experiences a Grade 3 solicited systemic AE that is determined to be related to study vaccine.

For number 2 and number 5: to assess abnormal laboratory values, the test must be repeated at least once, within 48 hours of the site becoming aware of the abnormal value.

For number 4, number 5 and number 6: after each DRC review of similar AEs, the Committee will indicate the conditions under which it requires further notification and review of the subsequent similar AEs.

To enable prompt response to a situation that could trigger pausing rules, the investigator should notify the sponsor's medical officer or designee (AND transmit SAE form [if applicable] in a secure manner electronically or by facsimile [fax] to the sponsor), immediately and no later than 24 hours after becoming aware of any related AE of Grade 3 or above AND update the eCRF with relevant information on the same day the AE information is collected. A thorough analysis of all Grade 3 (or above) cases will be carried out by the sponsor's medical officer or designee, irrespective of whether the criteria for pausing the study are met. Based on the pausing criteria, the sponsor's medical officer or designee then decides whether a study pause is warranted. All sites will be notified immediately in case of a study pause. The sponsor's medical officer or designee is responsible for the immediate notification of DRC members and coordination of a DRC meeting in case of a study pause.

Vaccinations for an individual participant may be suspended for safety concerns other than those described in the pausing criteria, at the discretion of the investigator if he/she feels the participant's safety may be threatened. The sponsor's medical officer or designee or the investigator(s) (upon consultation with the sponsor's medical officer or designee) may initiate DRC review for any single event or combination of multiple events which, in their professional opinion, could jeopardize the safety of the participants or the reliability of the data.

Vaccinations for the study may be suspended for safety concerns other than those described above, or before pausing rules are met, if, in the judgment of the DRC, participant safety may be threatened.

Resumption of vaccinations will start only upon receipt of written recommendations by the DRC. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. The communications from the DRC will be forwarded by the investigator to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and by the sponsor to the relevant health authorities, according to local standards and regulations.

7. DISCONTINUATION OF STUDY VACCINE AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccine

Study vaccine administration will be withheld for the reasons listed below. These participants should not receive any further doses of study vaccine but should remain on study for follow-up with assessments of safety and immunogenicity, unless the participant withdraws consent for study

participation. Additional unscheduled visits or telephone calls may be performed for safety/reactogenicity reasons, if needed. In case of questions, the investigator is encouraged to contact the sponsor.

- Any related AE, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, requires discontinuation from study vaccine
- The participant becomes pregnant
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data
- Anaphylactic reaction and/or severe hypersensitivity reaction following study vaccination, not attributable to causes other than vaccination
- SAE or potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Chronic or recurrent use of immunomodulators/suppressors, eg, cancer chemotherapeutic agents or systemic corticosteroids (see Section 5.2, Exclusion Criteria)
- The investigator believes that for safety reasons or reactogenicity reasons (eg, AE) it is in the best interest of the participant to discontinue study vaccination
- The participant withdraws consent to receive further vaccination

7.1.1. Criteria for Temporarily Delaying Study Vaccine Administration

The following events constitute a temporary contraindication to study vaccination:

- Clinically significant acute illness at the time of vaccination. This does not include minor illnesses, such as diarrhea or mild upper respiratory tract infection.
- Fever (body temperature ≥38.0°C [100.4°F]) within 24 hours prior to the planned time of vaccination.
- Medically indicated vaccinations, including SARS-CoV-2 vaccine boosters.
- An illness which in the judgement of the investigator may interfere with reactogenicity/Day 1-8 safety assessments after each vaccination.

If any of these events occur at the scheduled time for the first vaccination, randomization at a later date within the screening window is permitted at the discretion of the investigator and after consultation with the sponsor. If randomization cannot occur within the screening window, rescreening is required. If any of these events occur at the scheduled time for one of the subsequent vaccinations, the vaccination can be rescheduled, as long as this is in agreement with the allowed windows (see Visit Windows in Section 8, Study Assessments and Procedures).

Vaccination may be delayed for reasons other than acute illness at investigator's discretion. Vaccination must be completed within the specified window and upon approval of the sponsor. A check of eligibility criteria may be repeated as necessary.

If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent for study participation
- Death
- Any AE that requires discontinuation from the study
- Repeated failure to comply with protocol requirements
- Decision by the sponsor or the investigator to stop or cancel the study
- Decision by local regulatory authorities or IRB/IEC to stop or cancel the study

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. Participants who wish to withdraw consent from participation in the study will be offered a single exit visit for safety follow-up (prior to formal withdrawal of consent). They have the right to refuse.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site as permitted by local regulations.

7.4. Staggered Vaccination

The investigator is not permitted to start vaccinating additional study participants in Cohort 1 or progress to Cohort 2 until receipt of favorable written documentation of DRC safety evaluations (see Section 4.1, Overall Design and Figure 2).

Screening procedures may continue to facilitate enrollment of remaining participants.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

Section 1.3, Schedule of Activities summarizes the frequency and timing of safety and immunogenicity measurements applicable to this study. Additionally, a summary of assessments for participants with ILI is provided showing procedures applicable for the participant and the study site. See Section 1.3.2, Schedule of Activities – Assessments for Participants With Influenza-like Illness (ILI).

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: physical examination and vital signs before blood draws and nasal swab sample collection. If needed, assessments may be performed at another day within the applicable visit window. Actual dates and times of assessments will be recorded in the source document and in the eCRF.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

Participants will be provided with a thermometer (to measure body temperature), ruler (to measure injection site reactions), and participant diary to record body temperature and solicited injection site and systemic signs and symptoms.

The diary includes instructions on how to capture the data and grading scales to assess severity of the signs and symptoms. The site staff is responsible for providing appropriate training to the participant to avoid missing or incorrect data. The diary will be reviewed by the study personnel

at visits indicated in Section 1.3, Schedule of Activities. If the diary review is missed, the diary will be reviewed during the following visit. If a participant misses a vaccination, the diary covering the period after the missed vaccination does not have to be filled in.

Participants will be provided with a Flu-iiQ™ questionnaire and ILI form to record signs and symptoms of influenza during the influenza season. See Section 8.1.1, ILI Procedures.

The total blood volume to be collected from each participant will be approximately 219 mL. The maximum volume of blood to be drawn at any given visit will be approximately 41.5 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Visit Windows

Visit windows will be allowed as indicated in Table 2.

The timings of the post-vaccination visits will be determined relative to the actual day of the corresponding vaccination. If a participant misses a vaccination, the post-vaccination visits will be calculated from the imputative vaccination date according to protocol.

Table 2: Visit Windows

VISIT	Visit Day	Window	Primary Purpose
Visit 1	Day -42 to 1	–	Screening visit
Visit 2	Day 1	–	FIRST STUDY VACCINATION
Visit 3	Day 8 (Vac 1+7 days)	+2 days	7-day post-first study vaccination safety and immunogenicity visit [a]
Visit 4	Day 29 (Vac 1+28 days)	±3 days	28-day post-first study vaccination safety and immunogenicity visit
Visit 5	Day 57	±3 days	SECOND STUDY VACCINATION
Visit 6	Day 64 (Vac 2+7 days)	+2 days	7-day post-second study vaccination safety and immunogenicity visit [a]
Visit 7	Day 85 (Vac 2+28 days)	±3 days	28-day post-second study vaccination safety and immunogenicity visit
Visit 8	Day 238 (Vac 2+6 months)	±14 days	6-month post-second study vaccination safety and immunogenicity visit
Visit 9	Day 365 (Vac 1+12 months)	±30 days	FINAL VISIT: 12-month post-first study vaccination safety and immunogenicity visit

[a] Sentinel participants will additionally be contacted by telephone 48 hours post-vaccination to collect safety information.

Screening

Screening may be conducted in part via a sponsor- and IRB/IEC-pre-approved non-study specific screening consent process, but only if the relevant pre-screening tests are identical to the per-protocol screening tests and are within 6 weeks prior to first vaccination. However, no study-specific procedures, other than these pre-approved pre-screening assessments, will be performed until the participant has signed the study-specific ICF. The study specific ICF date will be entered into the eCRF. The non-study specific ICF will be considered source data.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to Section 1.3, Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided, or per the requirements of local laboratories. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual, or per the requirements of local laboratories.

Study-Specific Materials

The investigator will be provided with the following materials:

- IB for Uniflu Vaccine
- Thermometer
- Ruler (to measure diameter of any erythema and swelling)
- Pharmacy manual/study SIPPM
- Laboratory manual
- IWRS Manual
- Electronic Data Capture (eDC) Manual/ eCRF completion guidelines
- Sample ICF
- Participant diaries
- Flu-iiQ^{TM} questionnaire
- ILI form to document body temperature, concomitant medication used, etc.
- Nasal swab kits and instructions
- Insulated cooler bag (for participants to transfer nasal swab samples collected at home to sites at defined temperature for ILI events)
- Contact information page(s)

8.1. Immunogenicity Assessments

Immunogenicity assessments may include, but are not limited to, the immunogenicity assays (as available and applicable) summarized in Table 3. Timings of blood draws are specified in Section 1.3, Schedule of Activities.

Immunogenicity assessments supporting the secondary endpoint were chosen to quantify the magnitude of the pre-existing influenza-specific immunity and vaccine-induced antibody responses that are thought to contribute to the protective capacity of HA stem-based vaccination approaches. Antibodies targeting the stem domain of the influenza HA molecule will be quantified by ELISA using full-length HA or stem-only antigens that are expected to sensitively and specifically detect responses targeting the conserved stem domain of the molecule.

Immunogenicity assessments supporting the exploratory endpoint were chosen to further quantify the magnitude and characterize pre-existing influenza-specific immunity and vaccine-induced immune responses. This characterization entails a deeper investigation of the breadth and functionality of the antibody response, the set-up of assays and characterization of mucosal targeting of the immune response, and characterization of cellular and molecular effects of vaccination.

Although this study is not designed to support the identification or validation of surrogates of protection against clinically manifest influenza infection, immunological assessments supporting the secondary and exploratory endpoints will be evaluated for their utility as potential surrogates of protection, to be applied to and further characterized in follow-up studies, such as challenge studies or Phase 2b proof-of-concept studies.

Blood for humoral immune responses will be drawn from all participants. Influenza immunity in study participants will be determined on baseline (Day 1) and post-vaccination blood samples as described in Section 1.3, Schedule of Activities. Both assay variability and pre-existing immunity will be taken into consideration in the immunogenicity assessments.

PaxGene tubes and proteome stabilization samples will be collected according to Section 1.3, Schedule of Activities. PaxGene samples will allow the performance of whole blood transcript profiling.

Nasosorption samples (using SAM), collected at the timepoints indicated in Section 1.3, Schedule of Activities, will be used for the development of mucosal influenza-specific IgG and/or IgA ELISAs and the assessment of those responses in nasal secretions.

In addition to RT-PCR based diagnosis of influenza virus infection performed on nasal swab samples (collected when ILI symptoms develop during the influenza season), blood samples collected at baseline, between 2 and 4 days after symptom onset (ILI Days 3-5), and at 28 days after symptom onset (ILI Day 29) from participants with a suspected ILI will also be assayed by serology (including but not limited to HAI assay as available and applicable) for influenza virus

exposure confirmation. Additionally, the nasal swab samples might be used to determine the presence of other respiratory pathogens.

Sample collection and processing will be performed by the staff at the clinical site according to current versions of approved standard operating procedures.

Samples collected for immunogenicity analyses may additionally be used to evaluate safety and serology (HAI) that address concerns arising during or after the study period. Participant confidentiality will be maintained.

Table 3: Summary of Immunogenicity Assays

Endpoint	Assay
Secondary endpoints	
Quantification of antibody binding to HA stem or full-length HA	ELISA
Exploratory endpoints	
Neutralization	Virus neutralization assay
Fc-mediated functionality	Human FcγRIIIa reporter assay
Breadth of the antibody response within Group 1 or beyond	ELISA using full-length HAs indicative of clade or group coverage
HA stem- or epitope-specificity	ELISAs using HA stem protein or competition ELISAs using bnAbs or HA proteins
Functional breadth of the antibody response within Group 1 or beyond	Virus neutralization assays or serum transfer into animal challenge models
Functional characterization of the antibody response	Assays assessing Fc-mediated functions (eg, antibody-dependent cytotoxicity assay, or antibody-dependent cellular phagocytosis assay), HA conformational change assays, or other assays
Molecular characterization of the antibody response	Assays assessing the epitope-specificity, glycosylation status, or other characteristics of the antibody (eg, systems serology arrays)
Innate immune responses	Transcript- or cytokine profiling
Gene expression profiles	RNA sequencing or other transcriptional profiling methods, including, but not limited to TCR or BCR repertoire analysis
Nasal antibody response	IgG and/or IgA ELISA in nasal secretions
Hemagglutination inhibition	HAI assays

BCR = B cell receptor; bnAbs = broadly neutralizing antibodies; ELISA = enzyme-linked immunosorbent assay; Fc = fragment crystallizable; HA = hemagglutinin; HAI = hemagglutination inhibition; Ig = immunoglobulin; RNA = ribonucleic acid; TCR = T cell receptor.

8.1.1. ILI Procedures

Participants will be informed of the timing of the start and end of the influenza season in accordance with the country/region-specific influenza local surveillance system.

For the duration of the influenza season, participants will be followed-up to identify potential cases of influenza virus infection. During the influenza season, participants should record any signs and symptoms of ILI (such as cough, sore throat, headache, nasal congestion, feeling feverish, body

aches and pains, fatigue, or neck pain), including measurement of body temperature [a], on a daily basis until symptoms have resolved using a specific Flu-iiQ™ questionnaire and an ILI form. Signs and symptoms of ILI recorded on the Flu-iiQ™ questionnaire and ILI form will be transferred onto the ILI symptoms page in the eCRF. The Flu-iiQ™ questionnaire and ILI form will be the primary source for ILI monitoring. Participants should complete a new questionnaire on each day they experience symptoms, including the day on which the symptoms resolve. Completed ILI questionnaires can either be mailed to the site or brought to the site at the next visit.

If ILI symptoms develop during the influenza season, the following should take place:

- Participants should contact the site as soon as possible to notify the site of ILI.
- Participants should record signs and symptoms of the ILI daily using the Flu-iiQ™ questionnaire from onset of symptoms until the day of symptom resolution, and record body temperature daily using an ILI form provided by the sponsor until the day of symptom resolution.
- Participants should take a nasal sample at home on the day of symptom onset or the day thereafter (ILI Days 1-2). The sample should be stored refrigerated and brought to the site by the participant within 4 days (preferably) after collection.
- Participants should go to their study site, ideally between 2 and 4 days after symptom onset (ILI Days 3-5), where
  - the completed Flu-iiQ™ questionnaire and ILI form will be collected and reviewed by site staff;
  - the participant nasal self-swab sample (taken on ILI Days 1-2) will be collected;
  - an additional nasal swab will be taken by a qualified member of the site staff;
  - the presence of influenza virus infection will be assessed by qualified site staff by RT-PCR diagnostics and/or rapid-PCR detection (eg, by Cepheid GeneXpert®) on the nasal swab samples mentioned above;
  - a blood sample for seroconfirmation of influenza virus infection will be taken by a qualified member of the site staff;
  - and vital signs, including body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation, will be measured by a qualified member of the site staff. A clinical assessment, including a targeted physical examination, will be completed by qualified site staff, preferably by a physician, physician assistant, nurse practitioner, or equivalent.[b]
- At ILI Day 29 (±7 days), participants will be asked to return to the site where

[a] Oral temperature should be measured at approximately the same time each day, preferably in the evening, using the thermometer supplied.

[b] It is recommended that vital signs are measured before collection of nasal swabs and blood draws.

  - the completed Flu-iiQ™ questionnaire and ILI form will be collected and reviewed by site staff;
  - a blood sample for seroconfirmation of influenza virus infection will be taken by a qualified member of the site staff;
  - and vital signs, including body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation will be measured by a qualified member of the site staff. A clinical assessment (including a targeted physical examination) will be performed by qualified site staff, preferably by a physician, physician assistant, nurse practitioner, or equivalent.[a]

- For all medically attended ILIs, including those resulting in hospitalization, additional information on any other diagnostics (eg, chest x-rays, spirometry, pulmonary function tests) or interventions during the clinical course of ILI will be collected.

The Flu-iiQ™ questionnaire, ILI form and nasal swab kits for use at home will be distributed before the start of the influenza season, along with an insulated cooler bag for participants to transfer nasal swab samples collected at home to sites at defined temperature.

During the influenza season, participants will be contacted by telephone or other means of communication approximately every 14±3 days (unless a planned visit has occurred or will occur within 14 days). These calls will remind participants to complete the Flu-iiQ™ questionnaire and ILI form in the event of any symptoms of ILI, and to contact the site and to take a nasal sample at the time of symptom onset. These calls will also check for any SAEs, and associated concomitant medications since the previous visit or telephone contact.

The presence of influenza virus will be assessed by qualified site staff by RT-PCR diagnostics on the nasal swab samples, which may include viral load and influenza subtyping. In addition, blood samples from participants with a suspected ILI will also be assayed by serology by the sponsor (including but not limited to HAI assay as available and applicable) for influenza virus exposure confirmation. The blood samples may additionally be used to evaluate immune responses during the ILI.

Every effort should be made to collect data on the clinical course of ILIs including information on hospitalization, oxygenation status, supplemental oxygen requirements and specific drug treatments, as well as other concurrent respiratory illness present at the time of the diagnosis of the event and up to symptom resolution.

For participants who experience symptoms suggesting ILI, RT-PCR assay of the nasal swabs taken after symptom onset will be used to determine whether the infection was caused by influenza virus. For participants hospitalized with symptoms of ILI, confirmation of influenza virus infection using RT-PCR may be performed at the local (hospital) laboratory.

[a] It is recommended that vital signs are measured before collection of nasal swabs and blood draws.

Any ILI and complications related to ILIs will be reported as an AE if it occurs between the time of any vaccination through the following 28 days. An ILI and complications related to ILIs that occur outside of this period during influenza season does not require AE reporting unless ongoing at the time of subsequent vaccination. Any ILI and complications related to ILIs fulfilling the criteria of an SAE will be reported as such during the entire study period from the first vaccination.

8.2. Safety Assessments

On a daily basis, for 7 days after each vaccination, participants will be asked to record symptoms of the following AEs via the participant diary:

- Solicited injection site AEs: erythema (measured using the ruler supplied), swelling (measured using the ruler supplied), and pain/tenderness.
- Solicited systemic AEs: fatigue, headache, myalgia, nausea and fever (ie, body temperature ≥38 °C [100.4°F]).

Oral temperature should be measured at approximately the same time each day, preferably in the evening, using the thermometer supplied. Temperature 7 days after each vaccination may be collected earlier on the Day 8 or Day 64 to coincide with the clinic visit.

Participants will record signs and symptoms of ILI during the influenza season using the Flu-iiQ™ questionnaire and ILI form: signs and symptoms of ILI will be collected on the Influenza Symptoms page in the eCRF; influenza infections, preferably as a diagnosis, will also be reported on the AE page of the eCRF if they occur within 28 days following vaccination.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting and Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and reactogenicity according to the time points provided in Section 1.3, Schedule of Activities.

8.2.1. Physical Examinations

A full physical examination, including height and body weight, will be carried out at screening, as specified in Section 1.3, Schedule of Activities. Weight will be measured lightly clothed and without footwear, and height will be measured without footwear. At all other study visits, an abbreviated, symptom-directed examination will be performed based on clinically relevant issues, clinically relevant symptoms, and medical history if determined necessary by the investigator. A symptom-directed physical examination may be repeated if deemed necessary by the investigator.

Physical examinations will be performed by the investigator or by a designated medically trained clinician. Any clinically relevant abnormalities or changes in severity observed during the review of body systems should be documented in the eCRF as an AE or SAE if it meets the criteria for an AE or SAE according to the protocol reporting requirements (see Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). Any abnormalities or changes in severity that occurred after signing of the ICF until immediately before vaccination would be recorded if due to participation in the study.

8.2.2. Vital Signs

Vital Signs will be examined as specified in Section 1.3, Schedule of Activities. Temperature (oral route preferred, or in accordance with the local standard of care), pulse/heart rate, respiratory rate, and blood pressure will be assessed.

Participants will utilize a diary to document the body temperature reading.

Blood pressure and pulse/heart rate measurements will be assessed (supine) with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Clinical Safety Laboratory Assessments

Blood samples for clinical laboratory assessments will be collected as indicated in Section 1.3 Schedule of Activities and Section 10.6, Appendix 6: Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

8.2.4. Pregnancy Testing

A negative serum pregnancy test for female participants of childbearing potential must be obtained at screening visit. A negative urine pregnancy test for female participants of childbearing potential must be obtained before the first dose of study vaccine on Day 1 and the second dose of study vaccine on Day 57.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety

information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

For further details on AEs, SAEs, and product quality complaints (PQC), refer to Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

Adverse events and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal.

Clinically relevant medical events not meeting the above criteria and occurring between signing of ICF and date of first vaccination will be collected on the Medical History eCRF page as pre-existing conditions.

Solicited AEs, collected through a diary, will be recorded for each vaccination from the moment of vaccination until 7 days post-vaccination.

All other unsolicited AEs and special reporting situations, whether serious or non-serious, will be collected for each vaccination from the moment of vaccination until 28 days post-vaccination. Unsolicited AEs with the onset date outside the timeframe defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded on the eCRF AE page.

All SAEs and AEs leading to discontinuation from further study vaccination (regardless of the causal relationship) are to be reported from the moment of first vaccination until completion of the participant’s last study-related procedure, which may include contact for safety follow-up. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

AEs of Grade 3 or Above that are Related to Study Vaccine

All AEs of Grade 3 or above that are related to study vaccine must be reported to the appropriate sponsor contact person by study-site personnel immediately, but no later than 24 hours of their knowledge of the events. Relevant AE information should be updated in the eCRF on the same day when the AE information is collected (see Section 6.8 Study Pausing Rules).

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately, but no later than 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor immediately, but no later than 24 hours of their knowledge of the event. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are used to assess the reactogenicity of the study vaccine and are predefined local (at the injection site) and systemic events for which the participant is specifically questioned and which are noted by participants in their diary.

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. In addition, participants will record solicited signs and symptoms in a diary for 7 days post-vaccination. All participants will be provided with a diary and instructions on how to complete the diary (see Overview in Section 8, Study Assessments and Procedures). The site staff will verbatim transcribe the information provided by the participant into the relevant sections of the eCRF. Review of diary entries with participants and grading of symptoms must be done by a qualified and delegated site staff member under the oversight of the investigator or a delegated physician. After review of the diary entries with the participant, the investigator or qualified delegate, will complete their own assessment and document it in the relevant sections of the eCRF. Once a solicited sign or symptom from a diary is considered to be of severity Grade 1 or above, it will be recorded as a solicited AE.

Solicited Injection Site Adverse Events

Participants will be asked to note in the diary occurrences of injection site pain/tenderness, erythema, and swelling at the study vaccine injection site daily for 7 days post-vaccination (day of vaccination and the subsequent 7 days). The extent (largest diameter) of any erythema and swelling should be measured (using the ruler supplied) and recorded daily. The case definitions for solicited injection site events can be found in Section 11, References (Gidudu 2012; Kohl 2007).

Solicited Systemic Adverse Events

Participants will be instructed on how to record daily temperature using a thermometer provided for home use. Participants should record the temperature in the diary in the evening of the day of vaccination, and then daily for the next 7 days approximately at the same time each day. If more

than one measurement is made on any given day, the highest temperature of that day will be used in the eCRF.

Fever is defined as endogenous elevation of body temperature ≥38° C (100.4°F), as recorded in at least one measurement (Marcy 2004).

Participants will also be instructed on how to note signs and symptoms in the diary on a daily basis for 7 days post-vaccination (day of vaccination and the subsequent 7 days), for the following events: fatigue, headache, nausea, and myalgia.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events and the special reporting situation of pregnancy will be followed by the investigator as specified in Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel immediately, but no later than 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study vaccine, but remain on study for follow-up with assessments of safety and immunogenicity (see Section 7.1 Discontinuation of Study Vaccine).

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

If the partner of a male participant becomes pregnant during the study, follow-up information regarding the outcome of the pregnancy will be requested upon the consent provided by the partner.

8.4. Treatment of Overdose

For this study, any dose of INFLUENZA G1 mHA greater than the assigned dose will be considered an overdose. The sponsor does not recommend specific interventions for an overdose.

In the event of an overdose, the investigator should:

- Contact the sponsor's medical officer immediately.
- Closely monitor the participant for AE/SAE (ie, the participant will remain at the study site for at least 1 hour and will be closely monitored for allergic or other reaction by site staff. A follow-up telephone call 12 hours and 24 hours post-dose will be made).
- Document the quantity of the excess dose of the overdosing in the eCRF.

8.5. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the immunogenicity and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

9.1. Statistical Hypotheses

No formal statistical hypothesis for safety or immunogenicity will be tested.

9.2. Sample Size Determination

The study will evaluate whether INFLUENZA G1 mHA, with or without $Al(OH)_3$ adjuvant, is safe, well tolerated and immunogenic in healthy adults aged ≥18 to ≤45 years.

There are 170 participants planned to be randomized in this study.

With 25 participants in one vaccine regimen, the observation of no vaccine reactions after the first vaccination would be associated with a 95% confidence that the true rate is less than 11.3%. Across active regimens (N=150), the observation of 0 vaccine reactions after the first vaccination would be associated with a 95% confidence that the true rate is less than 2.0%.

Table 4 below shows the probabilities of observing at least one AE in samples of different sizes at given true AE rates. Placebo recipients will be shown pooled.

Table 4: Probability of Observing at Least One Adverse Event at a Given True Adverse Event Rate

True Adverse Event Rate	Probability of Observing at Least One Adverse Event in N Participants		
	N=25	N=50	N=150
0.5%	12%	22%	53%
1%	22%	39%	78%
2%	40%	64%	95%
5%	72%	92%	100%
10%	93%	99%	100%
25%	100%	100%	100%

N = number of participants

This is the first study in humans and standard deviation of selected immunological assays is not yet known in this population. Immunogenicity will be based on the estimation of geometric mean titer (GMT) ratios at each timepoint versus baseline and their corresponding 95% confidence intervals (CIs).

Assuming that approximately 12% of participants might be excluded from Per-protocol Immunogenicity (PPI) due to dropout or major protocol deviation impacting immunogenicity, we will have 22 participants per regimen. Table 5 below presents the power of the study to detect a significant difference for several true ratios, assuming a range of standard deviations for ELISA on the log10 scale (two-sided alpha = 0.05).

Table 5: Power to Detect a Significant Difference at a Given True Ratio

Fold Change (Difference on Log10 Scale)	Assumed Standard Deviation on Log10 Scale					
	0.181	0.301	0.421	0.542	0.643	0.783
1 (diff. on log10=0) - no difference	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%
1.5 (diff. on log10=0.176)	88.5%	47.4%	27.3%	18.4%	14.4%	11.3%
2 (diff. on log10=0.301)	100.0%	90.0%	63.9%	43.7%	32.9%	23.8%
3 (diff. on log10=0.477)	100.0%	100.0%	95.6%	81.4%	67.2%	50.6%

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Full Analysis Set (FAS)	The full analysis set will include all participants with at least one vaccination documented. All safety and participant information analyses will be based on the FAS.
Per-protocol Immunogenicity (PPI)	The PPI population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding samples taken on or after the date when a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes. In addition, samples obtained after missed doses or samples obtained after natural infection (if applicable) will be excluded from the analysis. • For participants who experience a natural influenza infection (based on RT-PCR, or other sources), samples collected at and after the natural infection will not be considered in the assessment of the immunogenicity of the selected regimen.

Population	Description
	• If a participant misses one or more active dose(s) of the selected regimen but continues the planned visit schedule, samples after the missed active dose(s) will not be considered. The analysis of all secondary and exploratory immunogenicity endpoints will be based on the PPI set. Depending on the number of samples excluded, a post-hoc exploratory analysis might be performed, including the excluded samples. To visualize excluded samples, participant profiles from several assays might be repeated, indicating the excluded samples.

Vaccine assignment will follow the as-treated principle.

9.4. Statistical Analyses

The SAP will be finalized prior to database lock for primary analyses (at the latest) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. A separate analysis plan will be created to support DRC meetings and this document will be finalized prior to the data extraction for the first DRC meeting to review 7-day safety data post-first study vaccination from Cohort 1 participants.

The safety and immunogenicity analysis will include the timepoints described in Section 1.3, Schedule of Activities.

9.4.1. General Considerations

Analysis populations are defined in Section 9.3, Populations for Analyses.

Planned analyses are defined in Section 9.5, Planned Analyses.

9.4.2. Primary Endpoint(s)

Safety Endpoints

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively per study group, with special attention for SAEs, Grade 3/4 AEs, and AEs leading to discontinuation of study vaccine. Safety will also be assessed throughout the study through routine vital signs and physical examination as well as through clinical safety laboratory assessments. All safety analyses will be made on the FAS.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe AE or an SAE.

Solicited injection site and systemic AEs will be summarized descriptively. The number and percentages of participants with at least one solicited injection site or systemic AE will be presented. The overall frequencies per vaccine group as well as frequencies according to severity and duration will be calculated for solicited AEs. Frequencies of unsolicited AEs, separately for all and vaccination-related only, will be presented by System Organ Class and preferred term, while those of solicited AEs will be presented only by preferred term.

9.4.3. Secondary Endpoint(s)

Immunogenicity Endpoints

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% CI, or median and quartile range [Q1-Q3], as appropriate) will be calculated for continuous immunological parameters at all time points and for changes from baseline. Graphical representations of immunological parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunological parameters as applicable. The immunogenicity analyses will be performed on the PPI set. An additional analysis might be done for the FAS.

9.4.4. Tertiary/Exploratory Endpoint(s)

Detailed statistical methodology will be described in the SAP.

9.5. Planned Analyses

The primary analysis will occur when all participants have completed the 28 days post-Dose 2 visit or have discontinued earlier. These analyses will include immunogenicity data on quantification of antibody binding to full-length HA and HA stem protein and safety data up to the 28 days post-dose 2 visit. At the time of the primary analysis, the study will be unblinded for sponsor and external partnerships personnel who are involved in the data analysis and decision making. Participants and study-site personnel will remain blinded to the study vaccine allocation until the end of the study.

An additional analysis will occur when all participants have completed the 6-month post-Dose 2 visit or discontinued earlier. These analyses will include additional safety data up to the 6 months post-Dose 2 visit and immunogenicity data required per the sponsor's assessment. This analysis may allow to evaluate persistence of immune responses.

No study modifications are planned as a result of primary or additional analyses. The exact scope of each analysis will be defined based on the availability of immunogenicity data and findings from previous analyses. Additional interim analyses may be performed during the study for the purpose of informing future vaccine development-related decisions in a timely manner, or upon health authority request. If required, these unplanned interim analyses may replace or be combined with planned analyses, depending on the timing.

The final analysis will occur when the last participant has completed the final visit of the schedule of assessment (Day 365±30 days) or discontinued earlier. Final analyses will allow for determination of the durability of the immune response and analyze any additional safety and immunological data collected after the additional analysis.

The SAP will describe the planned analyses in greater detail.

Based on safety and immunogenicity results, the sponsor's Vaccine Development Committee will decide which regimen will be taken forward. Additional factors such as data from other assays, literature, epidemiology data, manufacturability, and ease of administration will be taken into account to select the regimen for the next clinical study.

9.6. Data Monitoring Committee or Other Review Board

A DRC will be established as noted in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bnAbs	broadly neutralizing antibodies
BUN	blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CTM	Clinical Trial Manager
CRO	Contract Research Organization
DIC	disseminated intravascular coagulation
DRC	Data Review Committee
eCRF	electronic case report form
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FAS	full analysis set
FcγR	Fc gamma receptor
FDA	US Food and Drug Administration
FIH	first-in-human
Flu-iiQ™	Influenza Intensity and Impact Questionnaire
G1	Group 1
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
hpf	high power field
HPV	human papilloma virus
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
Ig	immunoglobulin
ILI	influenza-like illness
IM	intramuscular
IPPI	investigational product preparation instructions
IRB	Institutional Review Board
IV	Intravenous
IWRS	interactive web response system
LLN	lower limit of normal
LTM	Local Trial Manager
MedDRA	medical dictionary for regulatory activities
mini-HA	hemagglutinin stem-derived protein vaccine antigen
ML	medical leader
NSAID	non-steroidal anti-inflammatory drug
PCC	protocol clarification communication
PI	principal investigator
PPI	per-protocol immunogenicity

PQC	Product quality compliant
PRBC	packed red blood cell
RBC	red blood cell
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAM	Synthetic Absorptive Matrix strips
SAP	statistical analysis plan
SIPPM	Site Investigational Product and Procedures Manual
SoA	Schedule of Activities
SRP	study responsible physician
SSG	statistical support group
SUSAR	suspected unexpected serious adverse reaction
TOC	table of contents
ULN	upper limit or normal
Uniflu	universal influenza (vaccine)
US	United States
WBC	white blood cell

10.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.4, Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Female Participant of Childbearing Potential

A female participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Female Participant Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- **permanently sterile** (for the purpose of this study)
  - Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.

  - Has congenital abnormalities resulting in sterility.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal female participant experiences menarche) or the risk of pregnancy changes (eg, a female participant who is not heterosexually active becomes active), a female participant must begin a highly effective method of contraception, as described throughout the inclusion criteria.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with IECs/IRBs per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any

departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study vaccine to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study vaccine
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants

- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1, Study-Specific Ethical Design Considerations.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Informed consent may be obtained remotely per local regulations.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps

will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

No additional research on study participants, study samples, or data derived from the study will be conducted by the institution(s) or by a third party, without the prior written consent of the sponsor.

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand vaccines, to understand differential vaccine responders, to understand the study intervention platform, to develop tests/assays related to vaccines, to understand influenza or other respiratory diseases, and may include RNA testing. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

COMMITTEE STRUCTURE

Data Review Committee

An internal DRC, consisting of members that are not directly involved in the study conduct, data management, or statistical analysis, will be established for this study, and will monitor data to ensure the safety and well-being of the participants enrolled. The DRC will review data as indicated in Section 4.1, Overall Design. When appropriate, the conclusions of the DRC will be communicated to the investigators, the IRB/IEC, and the national regulatory authorities.

The DRC will specifically review safety data (solicited and unsolicited AEs, SAEs, and available laboratory assessments) 7-day post-first and post-second dose in each cohort (participants in the sentinel and safety ramp-up subset).

In addition, ad hoc review may be performed further to the occurrence of any AE/SAE leading to a study pausing situation as outlined in Section 6.8, Study Pausing Rules, or at request of the

sponsor's medical officer or designee. The PI(s) and SRP will inform the DRC of any AE of concern.

The DRC will review blinded data first, but is entitled to and has the right to require submission of unblinded data if deemed necessary.

It will also be possible for the DRC to review unblinded immunogenicity data during the course of the study if this is deemed necessary for future vaccine development-related decisions. If this is the case, a biomarker representative (not involved in the conduct of the study) will be part of the DRC.

The DRC will include medical experts in vaccines and at least one statistician. The DRC can include members from both inside and outside of the sponsor, but will not include any study team personnel or people otherwise directly involved in the study conduct, data management, or statistical analysis for the study. The DRC responsibilities, authorities, and procedures will be documented in its charter.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding INFLUENZA G1 mHA or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of INFLUENZA G1 mHA, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site and/or remote monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the

investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study vaccine administration information; and date of study completion and reason for early discontinuation of study vaccine or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Participant- and investigator-completed scales and assessments designated by the sponsor (ie, diary, Flu-iiQ^{TM} questionnaire, ILI form) will be recorded and will be considered source data. The participant’s diary used to collect information regarding solicited signs and symptoms after vaccination will be considered source data.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

MONITORING

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be

respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study vaccine development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: For time period of sponsor's AE collection, see All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

Any ILI and complications related to ILIs will be reported as an AE if it occurs between the time of any vaccination through the following 28 days. An ILI and complications related to ILIs that occur outside of this period does not require AE reporting unless ongoing at the time of subsequent vaccination.

Serious Adverse Event

An SAE based on ICH and European Union (EU) Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at 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.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may

require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study vaccine and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Any ILI and complications related to ILIs fulfilling the criteria of an SAE will be reported as such during the entire study period from the first vaccination.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For INFLUENZA G1 mHA, the expectedness of an AE will be determined by whether or not it is listed in the IB.

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study vaccine is determined by the investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

By definition, all solicited AEs at the injection site will be considered related to the study vaccine administration.

SEVERITY CRITERIA

All AEs and laboratory data will be coded for severity using a modified version of the FDA grading table, based on version of September 2007 (FDA 2007), included in Section 10.5 Appendix 5, Toxicity Grading Scale.

For AEs not identified in the grading table, the following guidelines will be applied:

Grade 1	Mild	Symptoms causing no or minimal interference with usual social and functional activities
Grade 2	Moderate	Symptoms causing greater than minimal interference with usual social and functional activities
Grade 3	Severe	Symptoms causing inability to perform usual social and functional activities and requires medical intervention
Grade 4	Potentially life-threatening	Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability OR emergency room visit or hospitalization

The severity of solicited signs and symptoms will be graded in the diary by the participant based on the severity assessment provided in the diary and then verified by the investigator using scoring system shown in Table 6 and Table 7 as follows (*Note*: severity of the measured events will be derived from the diameter [for erythema and swelling] and the temperature measurements [for fever]):

Adults/adolescents (≥12 years of age)

Table 6: Severity Assessment: Solicited Injection Site Events - Adults/Adolescents (≥12 years of age)

Grade	Definition
0	No pain/tenderness; Diameter of erythema, swelling<25 mm.
1	Aware of symptoms but easily tolerated; Does not interfere with activity; Discomfort only to touch; Diameter of erythema, swelling ≥25 mm and <50 mm.
2	Notable symptoms; Requires modification in activity or use of medications; Discomfort with movement; Diameter of erythema, swelling ≥50 mm and <100 mm.
3	Incapacitating symptoms; Inability to do work, school, or usual activities; Use of narcotic pain reliever; Diameter of erythema, swelling ≥100 mm.
4	Hospitalization; Pain/tenderness causing inability to perform basic self-care function; For erythema, swelling: necrosis or exfoliative dermatitis.

Table 7: Severity Assessment: Solicited Systemic Events - Adults/Adolescents (≥12 years of age)

Grade	Definition
0	Absent; Fever/Pyrexia: Below 38.0°C or 100.4°F.
1	Minimal symptoms; Causes minimal or no interference with work, school, or self-care activities; Fever/Pyrexia: 38.0 - 38.4°C or 100.4 - 101.1°F.
2	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities; Fever/Pyrexia: 38.5 - 38.9°C or 101.2 - 102.0°F.
3	Incapacitating symptoms; Requires bed rest or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever; Fever/Pyrexia: 39.0 - 40.0°C or 102.1 - 104.0°F.
4	Hospitalization; Inability to perform basic self-care functions; Fever/Pyrexia: Greater than 40°C or 104.0°F.

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study vaccine in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study vaccine
- Suspected abuse/misuse of a sponsor study vaccine
- Accidental or occupational exposure to a sponsor study vaccine
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study vaccine from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

Participant-specific special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study vaccine, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study vaccine or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). *Note*: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study, whether or not the event is expected or associated with the study vaccine, is considered an SAE.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and the eCRF form for AEs, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor immediately, but no later than 24 hours of their knowledge of the event. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel immediately, but no later than 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Toxicity Grading Scale

Adapted from the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007)

A: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain/Tenderness[#]	Aware of symptoms but easily tolerated; Does not interfere with activity; Discomfort only to touch	Notable symptoms; Requires modification in activity or use of medications; Discomfort with movement	Incapacitating symptoms; Inability to do work, school, or usual activities; Use of narcotic pain reliever	Hospitalization; Pain/tenderness causing inability to perform basic self-care function
Erythema[#]	25 – 50 mm	51 – 100 mm	> 100 mm	Hospitalization; Necrosis or exfoliative dermatitis
Swelling[#]	25 – 50 mm	51 – 100 mm	> 100 mm	Hospitalization; Necrosis

[#] Revised by the sponsor.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F)**	38.0 - 38.4 100.4 - 101.1	38.5 - 38.9 101.2 - 102.0	39.0 - 40.0 102.1 - 104.0	> 40 > 104.0
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	Hospitalization for arrhythmia[#]
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	Hospitalization for arrhythmia[#]
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	Hospitalization for malignant hypertension[#]
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension[#]
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Hospitalization for hypotensive shock[#]
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** For oral temperature: no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.
[#] Revised by the sponsor.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting[#]	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous (IV) hydration	Hospitalization; Hypotensive shock
Nausea[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities	Hospitalization; Inability to perform basic self-care functions
Diarrhea[#]	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800 gms/24 hours or oral rehydration necessary	Hospitalization; Hypotensive shock OR IV fluid replacement indicated
Headache[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions
Fatigue[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions
Myalgia[#]	Minimal symptoms; causes minimal or no interference with work, school, or self-care activities	Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities	Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever	Hospitalization; Inability to perform basic self-care functions

[#] Revised by the sponsor.

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization[#]

[#] Revised by the sponsor.

B. Tables for Laboratory Abnormalities

Laboratory tests may be performed during routine medical care and assessment of AEs or other medical events based on the investigator's judgment.

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium - Hyponatremia mEq/L	132 - 134	130 - 131	125 - 129	< 125
Sodium - Hypernatremia mEq/L	144 - 145	146 - 147	148 - 150	> 150
Potassium - Hyperkalemia mEq/L	5.1 - 5.2	5.3 - 5.4	5.5 - 5.6	> 5.6
Potassium - Hypokalemia mEq/L	3.5 - 3.6	3.3 - 3.4	3.1 - 3.2	< 3.1
Glucose - Hypoglycemia mg/dL	65 - 69	55 - 64	45 - 54	< 45
Glucose - Hyperglycemia Fasting mg/dL Random - mg/dL	 100 - 110 110 - 125	 111 - 125 126 - 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen (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
Calcium - hypocalcemia mg/dL	8.0 - 8.4	7.5 - 7.9	7.0 - 7.4	< 7.0
Calcium - hypercalcemia mg/dL	10.5 - 11.0	11.1 - 11.5	11.6 - 12.0	> 12.0
Magnesium - hypomagnesemia mg/dL	1.3 - 1.5	1.1 - 1.2	0.9 - 1.0	< 0.9
Phosphorous - hypophosphatemia mg/dL	2.3 - 2.5	2.0 - 2.2	1.6 - 1.9	< 1.6
Creatine phosphokinase (CPK) - mg/dL	1.25 - 1.5 x ULN***	1.6 - 3.0 x ULN	3.1 -10 x ULN	> 10 x ULN
Albumin - Hypoalbuminemia g/dL	2.8 - 3.1	2.5 - 2.7	< 2.5	--
Total Protein - Hypoproteinemia g/dL	5.5 - 6.0	5.0 - 5.4	< 5.0	--
Alkaline phosphate - increase by factor	1.1 - 2.0 x ULN	2.1 - 3.0 x ULN	3.1 - 10 x ULN	> 10 x ULN
Liver Function Tests -ALT, AST increase by factor	1.1 - 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 10 x ULN	> 10 x ULN
Bilirubin - when accompanied by any increase in Liver Function Test increase by factor	1.1 - 1.25 x ULN	1.26 - 1.5 x ULN	1.51 - 1.75 x ULN	> 1.75 x ULN

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Bilirubin - when Liver Function Test is normal; increase by factor	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.0 - 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 - 210	211 - 225	> 226	---
Pancreatic enzymes - amylase, lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.0 x ULN

* 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 mEq/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

*** ULN is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 - 12.0	9.5 - 10.9	8.0 - 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease - 1.5	1.6 - 2.0	2.1 - 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 - 13.5	10.5 - 12.4	8.5 - 10.4	< 8.5
Hemoglobin (Male) change from baseline value - gm/dL	Any decrease - 1.5	1.6 - 2.0	2.1 - 5.0	> 5.0
WBC Increase - cell/mm3	10,800 - 15,000	15,001 - 20,000	20,001 - 25, 000	> 25,000
WBC Decrease - cell/mm3	2,500 - 3,500	1,500 - 2,499	1,000 - 1,499	< 1,000
Lymphocytes Decrease - cell/mm3	750 - 1,000	500 - 749	250 - 499	< 250
Neutrophils Decrease - cell/mm3	1,500 - 2,000	1,000 - 1,499	500 - 999	< 500
Eosinophils - cell/mm3	650 - 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm3	125,000 - 140,000	100,000 - 124,000	25,000 - 99,000	< 25,000
PT - increase by factor (prothrombin time)	1.0 - 1.10 x ULN**	1.11 - 1.20 x ULN	1.21 - 1.25 x ULN	> 1.25 ULN
PTT - increase by factor (partial thromboplastin time)	1.0 - 1.2 x ULN	1.21 - 1.4 x ULN	1.41 - 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 - 500	501 - 600	> 600	--
Fibrinogen decrease - mg/dL	150 - 200	125 - 149	100 - 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* 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.

** ULN is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) - red blood cells per high power field (rbc/hpf)	1 - 10	11 - 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* 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.

10.6. Appendix 6: Clinical Laboratory Tests

The following tests will be performed according to Section 1.3, Schedule of Activities:

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	Timepoints
Testing done locally	Hematology • Platelet count • Hemoglobin • White Blood Cell (WBC) count with Differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils Clinical Chemistry • Sodium • Potassium • Blood urea nitrogen (BUN) • Creatinine • Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) Serum pregnancy β-hCG test (qualitative; female participants of childbearing potential)	According to Section 1.3, Schedule of Activities Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.
Testing done locally	Urine pregnancy test (female participants of childbearing potential)	According to Section 1.3, Schedule of Activities
Testing done locally	Nasal swab for influenza virus testing	According to Section 1.3, Schedule of Activities Note: Virology test may be repeated at a central laboratory upon sponsor request including but not limited to influenza virus.
Testing done centrally	Serology blood sample for seroconfirmation of influenza virus infection (HAI)	According to Section 1.3, Schedule of Activities Note: Seroconfimation test may be performed including but not limited to HAI assay as available and applicable.

10.7. Appendix 7: Study Conduct During a Pandemic

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

The sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the COVID-19 pandemic, scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key immunogenicity endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study intervention, performing study assessments, and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

Screening and Randomization

- Enrollment of new participants may continue based on the investigator's assessment of risks versus benefits, depending on the situation at a particular site, and the ability to monitor participant safety.

Site Visits

- When site visits are not possible due to local/national guidelines, sites should collect the assessments via telephone visits or home-based visits, if the participant allows. The actual visit date and the type of visit (ie, telephone or home-based visit) should be captured in the eCRF according to the eCRF completion guidelines. Procedures that cannot be performed during a home-based visit (eg, blood samples, and physical examination), should be excluded.

Vaccine Administration

- When planning for vaccination visits, local/national or institutional guidelines will be followed. The study vaccine must be administered by a blinded qualified individual at the study site. If this is not possible, a solution may be considered in consultation with the sponsor and taking into consideration participant safety.

Informed Consent Form

- Consenting and re-consenting of participants for the measures taken (including also remote consenting by phone or video consultation) will be performed as applicable and according to local guidance for informed consent applicable during the COVID-19 pandemic. The process is to be documented in the source documents.

Source Data Verification/Monitoring

- In case on-site monitoring visits are not possible, the site monitor may contact the investigator to arrange monitoring visits and activities remotely (in accordance with site and local requirements). Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

Site Audits

- During the COVID-19 pandemic and at the impacted sites, study site GCP audits with direct impact/engagement from the investigator and study site personnel would not be conducted in order to comply with national, local, and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study-related documents may take place with limited impact/engagement if possible.

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (23 May 2022)

Overall Rationale for the Amendment: To include additional potential risks and adverse events of special interest, and adjust study objectives, endpoints and enrollment criteria for study population.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis Objectives and Endpoints; 1.1. Synopsis Overall Design; 3. Objectives and Endpoints; 4.1. Overall Design; 5.1. Inclusion Criteria; 9.2. Sample Size Determination	Age range for study participants was changed from ≥18 to ≤39 years of age to ≥18 to ≤45 years of age.	This change of age range will facilitate study enrollment and does not impact assessment of study objectives and endpoints and does not impact participant safety.
1.1. Synopsis Objectives and Endpoints; 3. Objectives and Endpoints	Changes on primary endpoints: Specified that occurrence, severity, duration and relationship of solicited and unsolicited adverse events (AEs), and occurrence and relationship of serious adverse events (SAEs), will be assessed. Added an additional endpoint to assess occurrence and relationship of adverse events of special interest (AESIs) from first vaccination dose to 6 months after the second vaccination dose.	Parameters on the AE and SAE assessment were added for clarification on safety analyses. Assessment for AESI was added based on inclusion of AESI in newly added Section 8.3.6 Adverse Events of Special Interest.
1.1. Synopsis Objectives and Endpoints; 1.1. Synopsis Table Summary of Immunogenicity Assays; 3. Objectives and Endpoints; 8.1. Immunogenicity Assessments	Changes on secondary and exploratory endpoints: The functionality tests of antibodies binding to the stem or the full-length HA protein was moved from secondary endpoint to exploratory endpoint. The timepoints for secondary endpoint assessment were removed. Memory B cell response was added as an exploratory endpoint. The exploratory endpoint for nasal targeting of the antibody response was removed.	Removed based on change of study vaccine development strategy per the sponsor. Removed as the magnitude tests will be completed for all timepoints listed in Section 1.3 Schedule of Activities. Added based on the sponsor's assessment on assay requirement for decision-making. Removed based on the sponsor's assessment on assay requirement for decision-making.
1.1. Synopsis Overall Design; 2.3.3. Benefit-Risk Assessment Related to Study Vaccination; 4.1. Overall Design; 6.3.3 Measures to Minimize Bias:	The following sentences were removed: These sentinel participants will be enrolled at the same site. These sentinel participants will be dosed at least 1 hours apart. The maximum number of sentinel participants to be vaccinated on the same day should not exceed 4.	Removed based on the sponsor's assessment on the updated safety data of adenovirus 26 (Ad26)-vectored vaccines.

Section Number and Name	Description of Change	Brief Rationale
Randomization and Blinding		
1.1. Synopsis Overall Design; 4.1. Overall Design; 6.3.3 Measures to Minimize Bias: Randomization and Blinding	The following language was added for all 3 Cohorts: DRC review will be held to review available safety data of initial participants enrolled before these participants can receive the second vaccination.	Added to clarify that DRC review will be held before the initial participants can receive the second vaccination.
1.1. Synopsis Table: Study Design: VAC21148FLZ1001; 1.1. Synopsis First-dose Safety Cohort 1; 1.1. Synopsis First-dose Safety Cohort 2; 1.1. Synopsis First-dose Safety Cohort 3; 1.1. Synopsis Number of Participants; 1.1. Synopsis Immunogenicity Evaluations; 1.3.1 Schedule of Activities – Assessments for All Participants; 4.1. Overall Design; 6.3. Measures to Minimize Bias: Randomization and Blinding; 8.1. Immunogenicity Assessments	Changes to the number of participants in certain Cohorts/Groups: Two participants from Group 4 (placebo) in Cohort 1 and Group 8 (placebo) in Cohort 2 were moved to Group 13 (placebo) in Cohort 3. In-depth immunogenicity subset was changed from up to 5 participants per regimen in Cohort 1 and 3 to up to 9 participants per regimen in Cohort 3 (9 subjects in Group 9-12 and 6 subjects in Group 13). The number of total participants for Cohort 1, 2 and 3 was changed from 52, 28, and 90 to 50, 26 and 94, respectively.	Modified based on the sponsor's assessment on data requirement to support regimen selection.
1.1. Synopsis Study Vaccine; 6.1. Study Vaccine(s) Administered; 6.4. Study Vaccine Compliance	Language was added that instructions on study vaccine preparation (eg, dilution in formulation buffer) into the final dose that participants receive within each treatment group are outlined in detail in the Investigational Product Preparation Instructions. Language added to allow alternative location for study vaccine injection if an injection cannot be given in the deltoids due to a medical or other contraindication.	Added for clarification. Added to allow alternative location for study vaccine injection.
1.1. Synopsis Immunogenicity Evaluations; 1.3.1. Schedule of Activities – Assessments for All Participants; 4.1 Overall Design; 8.1. Immunogenicity Assessments;	Nasosorption, PAXGene, and proteome stabilization sample collection and analysis were removed.	Removed based on the sponsor's assessment on data requirement to support decision-making.
1.1. Synopsis ILI Procedures; 1.3.2. Schedule of Activities – Assessments for Participants With Influenza-Like Illness (ILI); 8.1.1. ILI Procedures;	One additional activity for Days 3-5 was added for reverse transcriptase polymerase chain reaction (RT-PCR) diagnostics and/or rapid-PCR detection for influenza virus infection on collected nasal swab samples on Days 1-2 and Days 3-5, which should be completed by qualified site staff.	Added to clarify that RT-PCR diagnostics and/or rapid-PCR detection for influenza virus infection on collected nasal swab samples will be completed by sites.

Section Number and Name	Description of Change	Brief Rationale
	ILI form was added for participants to complete daily from onset of ILI to resolution. One additional activity for Days 3-5 and Day 29 was added for site staff to collect and review completed Flu-iiQ™ questionnaire and ILI form.	Added to clarify the documentation for temperature measured daily. Added to clarification.
1.1. Synopsis ILI Procedures; 1.3.2. Schedule of Activities – Assessments for Participants With Influenza-like Illness (ILI) 8.1.1. ILI Procedures; 8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 10.4. Appendix 4: Adverse Events: Definitions and Procedures for Reporting, Evaluating, Follow-up, and Reporting	Requirements on AE reporting for ILI with/out influenza virus infection were revised: Any ILI and complications related to ILIs will be reported as an AE if it occurs between the time of any vaccination through the following 28 days. An ILI and complications related to ILIs that occur outside of this period does not require AE reporting unless ongoing at the time of subsequent vaccination.	Modified for consistent AE reporting.
1.1. Synopsis ILI Procedures; 8.1.1. ILI Procedures; 10.4. Appendix 4: Adverse Events: Definitions and Procedures for Reporting, Evaluating, Follow-up, and Reporting	SAE downgrading for ILI with a positive RT-PCR test for influenza virus is no longer allowed. Any ILI and complications related to ILIs fulfilling the criteria of an SAE will be reported as such.	Modified for consistent SAE reporting criteria and process.
1.1. Synopsis Safety Evaluations; 1.3.1. Schedule of Activities – Assessments for All Participants; 4.1. Overall Design; 8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	The monitoring duration for AESIs was added from the day of first vaccination until 6 months after second vaccination.	Added based on inclusion of primary endpoint for AESI in Section 3 Objectives and Endpoints.
1.1. Synopsis Populations for Analyses; 9.3. Populations for Analyses	Enrolled population for analyses was removed.	Removed based on the sponsor's assessment on the analyses required.
1.1. Synopsis Planned Analyses; 9.5. Planned Analyses	Blinded interim analysis was removed. Language was added to allow additional interim analysis if needed. Language added that only immunogenicity data on quantification of antibody binding to full-length hemagglutinin (HA) up to the 28 days post-dose 2 visit are required for the primary analysis, in addition to safety data.	Blinded interim analysis is no longer required. The study data will be analyzed in the planned primary analysis instead. Additional interim analysis may be performed if needed. Added for clarification.

Section Number and Name	Description of Change	Brief Rationale
1.2. Schema; 1.3.1 Schedule of Activities – Assessments for All Participants; 4.1. Overall Design; 5.1. Inclusion Criteria; 8. Study Assessments and Procedures Table 2	Language to allow Screening visit and Day 1 visit to occur on the same day was removed, and Figure 1 was updated accordingly.	The investigator will need to review clinical safety laboratory results from the Screening visit to determine participant eligibility, which was added as a new inclusion criterion #10 in Section 5.1 Inclusion Criteria. Considering the time required to receive and review laboratory results by the sites, it is not possible to have the Screening visit and Day 1 visit on the same day.
1.3.1. Schedule of Activities – Assessments for All Participants	Physical examination was added for Day 1 and Day 57 visits. AESI recording and clinical safety laboratory tests were added. Blood volume was adjusted to include clinical safety laboratory tests. Footnote i was added for blood sample collection. Urine pregnancy test at screening visit was changed to serum pregnancy test. Updated footnote g to include additional inclusion criteria 6 and exclusion criteria 21, 22, 23 and 24. Footnote n was added that ruler and thermometers will be distributed at Day 1 visit, and training will be conducted by the site staff at both Day 1 and Day 57 visits.	Additional safety measurements are added to be aligned with other Ad26-based vaccine studies and the updates in the Investigator Brochure. Modified to include a more sensitive pregnancy test for screening visit. Updated based on updated inclusion and exclusion criteria in Section 5 Study Population of the amendment. Added for clarification.
1.3.2. Schedule of Activities – Assessments for Participants With Influenza-Like Illness (ILI)	Language was added that nasal swab samples collected by the participant at home on Days 1-2 should be delivered to site staff on Days 3-5.	Added for clarification.
2. Introduction; 2.3.1. Risks Related to Study Vaccination	Safety data supporting dose selection for study vaccines were updated, and new risks related to Ad26-vectored vaccines were added.	Included new safety data and risks from clinical studies for other Ad26-based vaccines that have become available after the original protocol finalization in January 2020.
2.2.1. Nonclinical Studies	Language on nonclinical experience with Ad26-based vaccines using various transgene inserts are removed. Language was added that genotoxicity and carcinogenicity studies have not been performed and the components of the study	Removed as the clinical experience with Ad26-based vaccines using various transgene inserts have been included in Section 2 Introduction and Section 2.3.1. Risks Related to Study Vaccination, and therefore supersede the nonclinical data. Added based on the Investigator Brochure v2.0.

Section Number and Name	Description of Change	Brief Rationale
	vaccine are not expected to have genotoxic or carcinogenic potential.	
2.3.1. Risks Related to Study Vaccination; 8.3.5. Pregnancy	Language added to follow up the outcome of pregnancy for the partner of a male participant who becomes pregnant during the study and consents for the follow-up.	Added to ensure safety follow-up for the partner of a male participant in case of pregnancy.
2.3.1. Risks Related to Study Vaccination	Risks related to concomitant vaccination were added.	Included to clarify potential risks with concomitant vaccination.
2.3.3. Benefit-Risk Assessment Related to Study Vaccination	AESI was added as part of safety monitoring for the study.	Added based on inclusion of AESI in newly added Section 8.3.6 Adverse Events of Special Interest.
4.1. Overall Design; 6.3. Measures to Minimize Bias: Randomization and Blinding	The following language was removed: These in-depth immunogenicity participants will be enrolled at the same site.	Removed based on process change on sample collection and processing for peripheral blood mononuclear cells by the sponsor.
4.1. Overall Design; 8.2.3. Clinical Safety Laboratory Assessment; 10.6. Appendix 6: Clinical Laboratory Tests	Clinical safety laboratory assessments were added.	Added to provide investigators additional safety parameters for eligibility and safety assessment.
4.1. Overall Design; 8.1.1. ILI Procedures; 10.6. Appendix 6: Clinical Laboratory Tests	The presence of influenza virus infection will be assessed by qualified site staff on the nasal swab samples, instead of by the sponsor. The test may be repeated at a central lab upon sponsor request.	Updated based on change of study operation plan.
4.2.1. Study-Specific Ethical Design Considerations	The Belgian Red Cross guidelines on the volume for blood collection was updated from 450-470 mL up to 4 times a year to 430-470ml up to 4 times a year.	Updated based on updated information in Belgian Red Cross websites.
5.1. Inclusion Criteria	Inclusion criterion#4. A note was added to ensure that a participant must be healthy per the investigator's judgement prior to study vaccine administration on Day 1 and Day 57. Inclusion criterion #5. Male or female condom with or without spermicide was removed from the list of highly effective contraception methods. Inclusion criterion #6. The criterion was modified to have a negative highly sensitive serum pregnancy test at screening. Inclusion criterion #10. New inclusion criterion was added that participant must be healthy on the basis of clinical laboratory tests performed at screening.	Added for clarification. Male or female condom with or without spermicide is no longer considered as a highly effective contraception method. Modified based on the change in Section 1.3.1 Schedule of Activities – Assessment for all Participants. Added based on inclusion of clinical safety laboratory tests in Section 1.3 Schedule of Activities and Section 8.2.3 Clinical Safety Laboratory Assessments of the amendment.
5.2. Exclusion Criteria	Exclusion criterion #4. Criterion was updated to exclude participants with history of severe	Updated based on changes in Investigator Brochure.

Section Number and Name	Description of Change	Brief Rationale
	allergic reaction (eg, anaphylaxis) to any component of the study vaccines or severe allergic reaction after a dose of any other adenovirus-based vaccine.	
	Exclusion criterion #5. Further details were added for expectation on abnormal function of immune system.	Further details were added to clarify the expectation.
	Exclusion criterion #6. History of chronic idiopathic demyelinating polyneuropathy was added as an exclusion criterion.	Added based on new risks included in Investigator Brochure and the amendment.
	Exclusion criterion #9. Day 365 was removed as an indication for the end of the study.	Minor edit made to avoid confusion.
	Exclusion criterion #10. Participation in an observational clinical study is no longer allowed during the course of the study.	Modified in consideration of participant safety.
	Exclusion criterion #12. The following criterion was added: Oocyte donation is prohibited while enrolled in this study.	Added to clarify requirement for oocyte donation.
	Exclusion criterion #14. Participate has major surgery planned during the study duration are excluded. The requirement 'within 6 months after the last dose of study vaccine administration' was removed.	Modified to clarify that the requirement applies for the entire study duration.
	Exclusion criterion #22. New exclusion criterion was added to exclude participants with history of thrombocytopenia, thrombosis with thrombocytopenia syndrome (TTS), immune thrombocytopenic purpura, or heparin-induced thrombocytopenia with thrombosis.	Added based on new risks included in Investigator Brochure and the amendment.
	Exclusion criterion #23. New exclusion criterion was added to exclude participants who receive or plan to receive an Ad26-vectored vaccine.	Added due to possible induction of anti-Ad26 antibody in participants with previous exposure to Ad26-vectored vaccines, which may impact study endpoint analysis.
	Exclusion criterion #24. New exclusion criterion was added to exclude participants who have taken any disallowed therapies noted in Section 6.5 Concomitant Therapy.	Added to ensure that the requirements of prohibited medications are met.

Section Number and Name	Description of Change	Brief Rationale
	Language was added that the clinical laboratory results on Day 1 and Day 57 are not required for eligibility assessment.	Added for clarification.
6.3. Measures to Minimize Bias: Randomization and Blinding	Cohort and site were removed as stratification factors. Language added that the randomization codes will be disclosed if required for an interim analysis.	Adjusted based on the change of randomization and enrollment plan per the sponsor. Added to allow randomization code disclosure for interim analysis if required.
6.5. Concomitant Therapy	Language added that Ad26-vectored vaccines are not allowed at any time prior to randomization until 28 days after the last study vaccination. Prohibited chronic or recurrent use of systemic corticosteroids was changed from 6 months to 2 months before administration of study vaccine until the end of the study. Radiotherapy was added as an example for immunomodulators/suppressors and prohibited from 6 months before the first study vaccination until the end of the study.	Added due to possible induction of anti-Ad26 antibody in participants with previous exposure to Ad26-vectored vaccines, which may impact study endpoint analysis. Modified in consideration of short half-life of systemic corticosteroids. Added for clarification.
6.8. Study Pausing Rules	Language was modified that further vaccination of participants may (instead of will) be paused after medical review as described. AESIs and laboratory abnormality were added in study pausing rules.	Modified for clarification. Added based on inclusion of Clinical safety laboratory assessments in newly added Section 8.2.3. Clinical Safety Laboratory Assessment and inclusion of AESI in newly added Section 8.3.6 Adverse Events of Special Interest.
6.8. Study Pausing Rules; 8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 10.4. Appendix 4: Adverse Events: Definitions and Procedures for Reporting, Evaluating, Follow-up, and Reporting	Transmission method for SAE form was updated from fax or email to a secure manner electronically or by fax to the sponsor. Transmission method for AESI form was added via a secure manner electronically or by fax to the sponsor.	Modified based on change of safety reporting process per the sponsor. Added based on inclusion of AESI in newly added Section 8.3.6 Adverse Events of Special Interest.
7.1. Discontinuation of Study Vaccine	Study vaccine related confirmed TTS, and safety reasons and reactogenicity reasons	Added based on inclusion of AESI in newly added Section

Section Number and Name	Description of Change	Brief Rationale
	were added to the list of criteria for discontinuation of study vaccine in participants.	8.3.6 Adverse Events of Special Interest and consideration for participant safety.
7.1.1. Criteria for Temporarily Delaying Study Vaccine Administration	Medically indicated vaccinations was added as one of the criteria for temporarily delaying study vaccine administration.	Added in consideration of new risks included for concomitant vaccination in Section 2.3.1 of the amendment.
7.2. Participant Discontinuation/Withdrawal From the Study	AE that requires discontinuation from the study was added as one of the reasons to withdraw participants from the study.	Added in consideration of participant safety.
8. Study Assessments and Procedures	Blood volume was updated to include clinical safety laboratory assessments.	Updated based on changes in Section 1.3 Schedule of Activities of the amendment
8.1. Immunogenicity Assessments	Language added to allow immunogenicity samples to be used for safety assessment.	Added in consideration of participant safety.
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Language below was added: All AEs of Grade 3 or above must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event. Relevant AE information should be updated in the eCRF on the same day when the AE information is collected (see Section 6.8 Study Pausing Rules).	Added to be consistent on the AE reporting requirement based on Section 6.8 Study Pausing Rules.
8.3.2. Method of Detecting Adverse Events and Serious Adverse Events	Text regarding transcription of participant diary entries into the eCRF was updated.	Modified to clarify the expectation and process.
8.2.4. Pregnancy Testing	New section added	Added to provide further expectation and details for pregnancy testing.
8.3. Adverse Events, Serious Adverse Events, Adverse Events of Special Interest, and Other Safety Reporting	Section title was updated to include AESI and other safety reporting.	Updated based on changes made in this section of the amendment.
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 8.3.6. Adverse Events of Special Interest; 8.4. Treatment of Overdose; 10.4. Appendix 4: Adverse Events: Definitions and Procedures for Reporting, Evaluating, Follow-up, and Reporting; 10.7. Appendix 7: Thrombotic Events to be Recorded as AESIs	Details for AESI were added.	Added based on new risks and AESI included in Investigator Brochure and the amendment.
8.3.3. Follow-up of Adverse Events and Serious Adverse Events	Language added for the investigators to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated.	Added to clarify the investigators' responsibilities.

Section Number and Name	Description of Change	Brief Rationale
9.4. Statistical Analyses	Language added to create a separate analysis plan to support DRC meeting.	Added for clarification.
9.4.2. Primary Endpoint(s)	AESI was added for primary endpoints. Summary language added to include vital signs, physical examination and clinical safety laboratory assessments for safety assessment, and more detailed description for vital signs and Physical Examinations are removed.	Added based on change of primary endpoints in Section 3 Objectives and Endpoints of the amendment. Modified to clarify the additional safety analyses in addition to the primary endpoints listed for safety assessment.
10.1. Appendix 1: Abbreviations	Abbreviations were updated.	Updated based on changes in the amendment.
10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	Language for use of Protocol Clarification Communications was added. Language added to allow remote consenting per local regulations. Language added on how the sponsor handles an event of a data security breach. AESI was added for data review by Data Review Committee.	Added based on process change per the sponsor. Added to allow flexibility on consenting method for participants and site staff. Added to clarify expectation in case of a data security breach. Added based on inclusion of AESI in Section 8.3.6 Adverse Event of Special Interest of the amendment.
10.4. Appendix 4: Adverse Events: Definitions and Procedures for Reporting, Evaluating, Follow-up, and Reporting	Reporting of participant pregnancy or participant partner(s) pregnancy was added as one of special reporting situations.	Added based on reporting requirement per the sponsor.
10.5. Appendix 5: Toxicity Grading Scale	Table B was added for laboratory abnormalities.	Added to provide guidance on assessment of clinical laboratory tests included in Appendix 6 Clinical Laboratory Tests and Section 8.3.6 Adverse Events of Special Interest added as part of this amendment, as well as other laboratory tests performed based on the investigator's judgment.
10.8. Appendix 8: Study Conduct During a Pandemic	New section added.	Added to clarify expectation on study conduct during Coronavirus Disease 2019 pandemic.
10.9. Appendix 9: Protocol Amendment History	Language updated to reference protocol amendment summary of changes table before the Table of Contents.	Updated to reflect amendment history.
11. References	New references added and reference format updated throughout the protocol amendment.	Updated based on review of references by the sponsor
Investigator Agreement	Sponsor's responsible medical officer was changed from Jerald Sadoff to Bridgette Franey.	Changed based on the sponsor team change

Section Number and Name	Description of Change	Brief Rationale
Throughout the protocol	Minor language updates were made for consistency and clarification.	Minor language updates made throughout the protocol to clarify and be consistent with the changes noted in the sections listed above.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	02-Mar-2023 20:09:50 (GMT)	Document Approval