AMENDMENT 4 CLINICAL STUDY PROTOCOL

Study Title	A Double-Blind, Randomized, Placebo-Controlled Phase 2 Study to Evaluate the Efficacy and Safety of VIR-2482 for the Prevention of Illness Due to Influenza A
Brief Title	A Phase 2 Study to Evaluate the Efficacy and Safety of VIR-2482 for the Prevention of Illness Due to Influenza A
Study Number	VIR-2482-4002
Compound	VIR-2482
Indication	Prevention of Illness due to Influenza A
Study Phase	2
Study Sponsor	Vir Biotechnology, Inc. 499 Illinois Street, Suite 500 San Francisco, CA 94158, USA
Regulatory Agency Identifying Numbers	**IND**: 141155 **EudraCT**: TBD **NCT**:NCT05567783
Protocol Date	29 June 2023, Version 1.0
This study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents	

CONFIDENTIALITY STATEMENT

This document contains confidential information that is the property of Vir Biotechnology, Inc. This confidential information is being provided to you, your staff, the applicable Institutional Review Board/Independent Ethics Committee, and applicable regulatory authorities solely for the purpose of evaluating or conducting this clinical study. This confidential information will be protected by you and your staff against disclosure to or use by third parties, except as necessary for the evaluation or conduct of the study.

INVESTIGATOR SIGNATURE PAGE

VIR BIOTECHNOLOGY, INC

499 ILLINOIS STREET SUITE 500

SAN FRANCISCO, CA 94158

STUDY ACKNOWLEDGMENT

A Double-Blind, Randomized, Placebo-Controlled Phase 2 Study to Evaluate the Efficacy and Safety of VIR-2482 for the Prevention of Illness Due to Influenza A

This protocol has been approved by Vir Biotechnology, Inc. The following signature documents this approval.

[redacted]	[*See Appended Electronic Signature Page*]
Printed Name	**Signature and Date**

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Vir Biotechnology, Inc. I will discuss this material with them to ensure they are fully informed about the drugs and the study.

Principal Investigator Printed Name	**Signature**
	Date

PROTOCOL AMENDMENT 4 (29 JUNE 2023) SUMMARY OF CHANGES TABLE

Protocol Document History

Document	Date
Amendment 3	22 September 2022
Amendment 2	19 August 2022
Amendment 1	11 July 2022
Original Protocol	01 June 2022

Protocol Amendment 4 Summary of Changes

Major changes are defined as changes that affect the design of the study, the safety of participants, the scope of the investigation, or the scientific quality of the study. The major changes and rationale for the changes from protocol Amendment 3 (dated 22 September 2022) to protocol Amendment 4 (dated 29 June 2023), are as follows:

Section # and Name	Description of Change	Brief Rationale
1.2 Study Schema 1.3 Schedule of Activities 4.1 Overall Study Design	Clarification on follow up period for influenza season 2	Active influenza-like illness (ILI) symptom surveillance for influenza season 2 will be from Start of Influenza Season 2 (SOIS2) visit to End of Influenza Season 2 (EOIS2) visit, since no ILI expected after end of influenza season
1.3 Schedule of Activities 8.5.1 Influenza-Like Illness Monitoring and Influenza Confirmation Visit	Update of Influenza Illness Monitoring Schedule from Start of Influenza Season 2 [SOIS2] to End of Influenza Season 2 [EOIS2] from passive surveillance every 2 months to every 3 months	Maximize participant engagement and study retention during Influenza Season 2
	Removal of point-of-care respiratory viral panel RT-PCR testing from the season 2 ILI confirmation visit	Nasopharyngeal swabs will be tested centrally with an assay that detects circulating strains of influenza A in the second season

Section # and Name	Description of Change	Brief Rationale
	ILI confirmation visit influenza season 2 will be scheduled when participant experience both a systemic and respiratory symptom	Minimize unnecessary ILI visits that are not due to symptomatic influenza infection to maximize participant engagement and study retention during Influenza Season 2
9.3 Analysis Sets	Update of definitions of All Participant Set, Full Analysis Set, Safety Set, Pharmacokinetic Analysis Set, Immunogenicity Analysis Set and Virology Analysis Set	Align with the Statistical Analysis Plan (SAP)
9.4.2 Primary Endpoint(s)/Estimand(s) Analysis	Update of supplemental analysis and sensitivity analyses for primary endpoint	Align with SAP
1.1 Synopsis 10.1.5 Committee Structure	Clarification on role of Data Monitoring Committee (DMC)	Clarify that the DMC will not make recommendations on conclusion or further enrollment of the study as the study has been fully enrolled in the first hemispheric influenza season and that an independent statistician will monitor for antibody dependent enhancement through the incidence of protocol defined influenza A illness cases and inform the DMC of any statistically significant imbalance

Summary of Other Changes

Other changes not considered major include:

- Updated text throughout the protocol where relevant to specify for clarity regarding the start and end of influenza seasons in the study, including End of Influenza Season 1 (EOIS1), Start of Influenza Season 2 (SOIS2), and End of Influenza Season 2 (EOIS2)
- Updated text throughout the protocol where relevant to specify for clarity, influenza season 1 corresponding to 2022-2023 Northern hemisphere influenza season, and influenza season 2 corresponding to 2023-2024 Northern hemisphere influenza season
- Updated Section 9 to clarify that SAP will be finalized prior to treatment unblinding
- Addition of summary of major changes for previous protocol amendments in Section 10.5

Administrative changes are not listed and may have included formatting, syntax, and other minor edits.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Study Title

A Double-Blind, Randomized, Placebo-Controlled Phase 2 Study to Evaluate the Efficacy and Safety of VIR-2482 for the Prevention of Illness Due to Influenza A

Brief Title

A Phase 2 Study to Evaluate the Efficacy and Safety of VIR-2482 for the Prevention of Illness Due to Influenza A

Background and Rationale

VIR-2482 is a human monoclonal antibody (mAb) under development for the prevention of illness due to influenza A. VIR-2482 binds to a conserved epitope in the stem region of influenza A hemagglutinin (HA) protein that neutralizes influenza A virus and retains Fc effector functions in vitro. Additionally, VIR-2482 contains a 2-amino acid modification that is designed to increase half-life, potentially enabling therapeutic concentrations for an entire influenza season with a single dose.

VIR-2482 is being evaluated in this dose ranging, proof-of-concept Phase 2 study for the prevention of illness due to influenza A in healthy adults at low risk of developing serious influenza-related complications.

Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of VIR-2482 compared to placebo in the prevention of protocol-defined ILI with confirmed influenza A	• Proportion of participants with protocol-defined ILI with confirmed influenza A (by reverse transcription-polymerase chain reaction [RT-PCR])
To evaluate the safety and tolerability of VIR-2482 compared to placebo	• Occurrence of adverse events (AEs) • Occurrence of serious adverse events (SAEs) • Occurrence of adverse events of special interest (AESI) • Occurrence of solicited events • Vital signs and laboratory assessments

Objectives	Endpoints
Secondary	
To evaluate the efficacy of VIR-2482 compared to placebo in the prevention of CDC-defined or WHO-defined ILI with confirmed influenza A	• Proportion of participants with CDC-defined ILI with confirmed influenza A (by RT-PCR) • Proportion of participants with WHO-defined ILI with confirmed influenza A (by RT-PCR)

Overall Study Design

This is a double-blind, randomized, placebo-controlled, Phase 2 study of VIR-2482. A single dose of VIR-2482 or placebo will be administered intramuscularly (IM) to healthy adult volunteers, aged 18 to < 65, without pre-existing risk factors for serious complications from influenza infection, who have not received an influenza vaccination for influenza season 1 (2022-2023 Northern hemisphere influenza season). A single dose of 450 mg VIR-2482, 1200 mg VIR-2482, or placebo will be administered to study participants. Saline placebo was chosen as the control for this study to allow for an unconfounded assessment of the efficacy and safety of VIR-2482. The use of a placebo control in otherwise healthy participants who have chosen to forgo seasonal influenza vaccine is considered acceptable due to the low risk of serious influenza-related complications and the availability of effective treatment options in the event of infection.

Eligible participants will be randomized in a 1:1:1 ratio to receive 450 mg VIR-2482, 1200 mg VIR-2482, or volume-matched placebo. Randomization will be stratified by country, as applicable.

This is an event driven study. Based on a 2-sided type 1 error rate of 5%, a total of 36 events pooled across treatment arms will be needed to provide approximately 80% power to detect a true relative risk reduction of 70% in one of the VIR-2482 arms in the proportion of protocol-defined ILI with confirmed influenza A compared to placebo. The sample size will be approximately 3000 participants assuming the proportion of protocol-defined ILI with confirmed influenza A in the placebo arm is at least 2.25%. The minimum detectable relative risk reduction is approximately 54.5%.

An unblinded independent Data Monitoring Committee (DMC) will evaluate safety data.

Participants will continue to be monitored during influenza season 2 (2023-2024 Northern hemisphere influenza season).

Brief Summary

The purpose of this study is to evaluate the efficacy, safety, and tolerability of VIR-2482 compared to placebo in preventing influenza A illness in healthy adults 18 to <65 years of age without pre-existing risk factors for serious complications from influenza infection.

Number of Participants

Approximately 3000 participants will be randomized in a 1:1:1 ratio to receive 450 mg VIR-2482, 1200 mg VIR-2482, or volume-matched placebo. Participants are planned to be enrolled in multiple study sites. Enrollment will be stopped when at least 36 participants (blinded and pooled across treatment arms) have met the primary endpoint of protocol-defined ILI with confirmed influenza A.

Intervention Groups and Duration

Intervention groups include:

- 450 mg VIR-2482
- 1200 mg VIR-2482
- Volume-matched placebo

The total study duration for each participant is planned to be up to approximately 88 weeks. This includes a screening period of up to 28 days, a 1-day intervention period, and a follow-up period of approximately up to 84 weeks.

Study intervention will be administered only once as an IM injection of 450 mg VIR-2482, 1200 mg VIR-2482, or volume-matched placebo on Day 1.

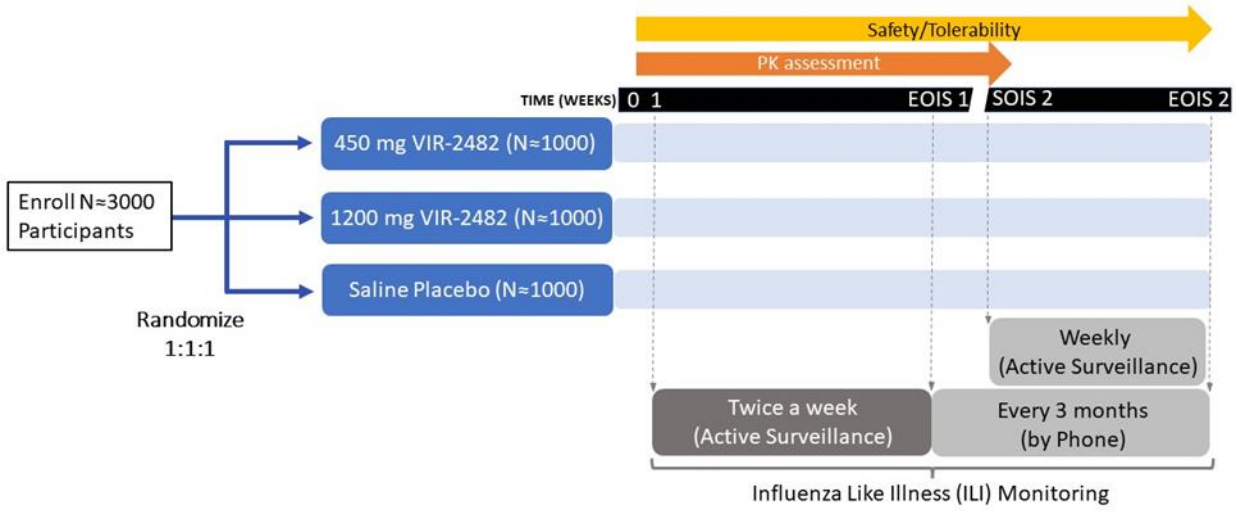
Key Eligibility Criteria

Eligible participants include healthy adult men and women aged 18 to < 65 years. Key inclusion criteria include body mass index (BMI) of 18.0 kg/m^2 to 35.0 kg/m^2, inclusive, as well as no clinically significant findings from physical examination, 12-lead electrocardiogram (ECG), vital signs, and laboratory values. Key exclusion criteria include prior or planned receipt of any influenza vaccine for influenza season 1, history or clinical evidence of conditions considered high risk for developing influenza-related complications, or any other clinically significant medical condition.

Independent Data Monitoring /Other Committee

An unblinded DMC will evaluate safety data throughout the study as appropriate.

1.2. Study Schema



EOIS = end of influenza season; SOIS = start of influenza season

1.3. Schedule of Activities

Table 1: Schedule of Activities

Study Stage	Screen	Intervention		Follow-Up Period						
				Active ILI Monitoring				Post EOIS1 ILI Monitoring		
Visit Week				W1	W4	W12	End of Influenza Season 1, ~2 weeks After (EOIS1)/ET1[a]	Post EOIS1 to Pre Start of Influenza Season 2 (SOIS2)	Start of Influenza Season 2 +56 days	Post SOIS2 to End of Influenza Season 2 (EOIS2)/ET2[b]
Visit Day±Visit Window	D-28 to -1	D1		D8±2 days	D29±7 days	D85±14 days				
		Predose	Postdose[c]							
Informed consent	X									
Demography	X									
Medical history	X									
Inclusion/ exclusion criteria	X	X								
Physical examination	X	X		X[d]	X[d]		X[d]			
Body weight, height, and BMI	X									
Vital signs[e]	X	X[e]	X[e]	X			X			
12-lead ECG	X	X								
Laboratory assessments[f]	X[f]	X		X	X	X	X			
Pregnancy test[g]	X	X					X			

Study Stage	Screen	Intervention		Follow-Up Period						
				Active ILI Monitoring				Post EOIS1 ILI Monitoring		
Visit Week				**W1**	**W4**	**W12**	**End of Influenza Season 1, ~2 weeks After (EOIS1)/ET1[a]**	**Post EOIS1 to Pre Start of Influenza Season 2 (SOIS2)**	**Start of Influenza Season 2 +56 days**	**Post SOIS2 to End of Influenza Season 2 (EOIS2)/ET2[b]**
Visit Day±Visit Window	**D-28 to -1**	**D1**		**D8±2 days**	**D29±7 days**	**D85±14 days**				
		Predose	**Postdose[c]**							
Anti-influenza A antibody titer		X					X			
Blood sample for PK analysis (serum)		X		X	X	X	X		X	
Nasopharyngeal swab for PK analysis							X			
Protein Biomarker profiling (serum)		X								
Immunogenicity (serum)[h]		X			X	X	X		X	
Optional PK Sub-study: Nasopharyngeal PK Sample[i]		X		X	X	X			X	
Optional Genotyping (Whole Blood)		X								

Study Stage	Screen	Intervention		Follow-Up Period						
				Active ILI Monitoring				Post EOIS1 ILI Monitoring		
Visit Week				**W1**	**W4**	**W12**	**End of Influenza Season 1, ~2 weeks After (EOIS1)/ET1[a]**	**Post EOIS1 to Pre Start of Influenza Season 2 (SOIS2)**	**Start of Influenza Season 2 +56 days**	**Post SOIS2 to End of Influenza Season 2 (EOIS2)/ET2[b]**
Visit Day±Visit Window	**D-28 to -1**	**D1**		**D8±2 days**	**D29±7 days**	**D85±14 days**				
		Predose	**Postdose[c]**							
Optional RNA expression Biomarkers (Whole Blood)		X								
Optional Future Biomedical Research (serum)		X	X	X			X			
Randomization		X								
Study intervention administration		X								
Local tolerability			X[j]							
Study Intervention Diary Card[k]			X[k]							
ILI symptom active surveillance[l]				X (twice weekly by PRO)					X (weekly by PRO)	

Study Stage	Screen	Intervention		Follow-Up Period						
				Active ILI Monitoring				Post EOIS1 ILI Monitoring		
Visit Week				**W1**	**W4**	**W12**	**End of Influenza Season 1, ~2 weeks After (EOIS1)/ET1[a]**	**Post EOIS1 to Pre Start of Influenza Season 2 (SOIS2)**	**Start of Influenza Season 2 +56 days**	**Post SOIS2 to End of Influenza Season 2 (EOIS2)/ET2[b]**
Visit Day±Visit Window	**D-28 to -1**	**D1**		**D8±2 days**	**D29±7 days**	**D85±14 days**				
		Predose	**Postdose[c]**							
ILI surveillance[m]								X (Every 3 Months by Phone)		
Review/record AEs[n]	X	X	X			X		X (Every 3 Months by Phone)	X	X (Every 3 Months by Phone)
Concomitant medications	X	X				X				

D = day; EOIS = end of influenza season; ET = early termination; ILI = influenza-like illness; INR = international normalized ratio; PK = pharmacokinetic; PRO = patient reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; SOIS = start of influenza season; W = week.

[a] For participants who early terminate prior to or during EOIS1.

[b] For participants who early terminate after EOIS1.

[c] Participants will remain at the clinical investigative site for a minimum of 2 hours post-dose.

[d] Physical examination on Weeks 1, 4 and EOIS1 will be symptom-directed.

[e] Measured within 1 hour pre-dose (+15 minutes) and 1 hour post-dose (+15 minutes).

[f] See Section 10.2 for laboratory tests; INR, PT and PTT to be performed only during screening.

[g] Applicable for women of childbearing potential. Blood pregnancy test will be performed at screening and urine pregnancy tests will be performed locally thereafter.

[h] This collection includes both an ADA and neutralizing antibody sample.

[i] Nasopharyngeal swabs will be collected at the indicated timepoints from a subset of approximately 300 participants, pooled across all treatment groups, who have consented to participate in this optional sub-study.

[j] To be assessed at 1 hour post-dose (+15 minutes), see Section 10.9.

[k] Study intervention diary card used on D1 to D7 (Section 8.3.6).

[l] Participants experiencing ILI will be followed per the Influenza-Like Illness Monitoring Schedule in Table 2 and Table 3.

[m] During phone visits, the clinical site must document any ILI confirmed influenza A, AEs, and visits to medical professionals.

[n] Refer to Section 10.3.6 for reporting instructions.

Table 2: Influenza-Like Illness Monitoring Schedule (D1 to End of Influenza Season 1 [EOIS1])

	In Person	Remote										In Person
Days After ILI Symptoms Onset	**ILI Confirmation Visit (D1 +3 days)**	**ILI-D1**	**ILI-D2**	**ILI-D3**	**ILI-D4**	**ILI-D5**	**ILI-D6**	**ILI-D7**	**ILI-D8**	**ILI-D9**	**ILI-D10**	**ILI-D28 ±3 days**
Symptom-directed PE	X											X
Vital signs	X											
Anti-influenza A Antibody titer	X											X
Nasopharyngeal swab for virology/PK[a]	X											
Nasopharyngeal swab for Point of Care Respiratory Viral Panel	X											
Blood sample for PK	X											
Immunogenicity (serum)[b]	X											
Laboratory assessment[c]	X											
Optional RNA expression biomarkers (Whole Blood)	X											
Protein Biomarker profiling (serum)	X											X
Optional Future Biomedical Research (serum)	X											X
Self-measured oral temperature[d]		X	X	X	X	X	X	X	X	X	X	
WPAI Questionnaire[e]		X							X			
Flu-iiQ™[f]		X	X	X	X	X	X	X	X	X	X	
ILI symptom monitoring	X											

	In Person	Remote										In Person
Days After ILI Symptoms Onset	**ILI Confirmation Visit (D1 +3 days)**	**ILI-D1**	**ILI-D2**	**ILI-D3**	**ILI-D4**	**ILI-D5**	**ILI-D6**	**ILI-D7**	**ILI-D8**	**ILI-D9**	**ILI-D10**	**ILI-D28 ±3 days**
Participant contact follow-up (phone call from site)[g]		X[h]	X	X	X	X	X	X	X	X	X	
Review/record AEs[i]	X											
Concomitant medications[j]	X											

AE = adverse event; D = day; ILI = influenza-like illness; PE = physical examination; PK = pharmacokinetic; PRO = patient reported outcome; RNA = ribonucleic acid; WPAI = Work Productivity and Activity Impairment.

[a] Obtain nasopharyngeal swab for virology/PK before nasopharyngeal respiratory viral panel as feasible.

[b] This collection includes both an ADA and neutralizing antibody sample.

[c] Only hematology, chemistry, and liver function panels from laboratory tests listed in Section 10.2.

[d] Temperature should be measured and recorded once daily at approximately the same time each day.

[e] WPAI Questionnaire will be completed on ILI-D1 and ILI-D8.

[f] Influenza intensity and impact questionnaire (Flu-iiQ™) will be completed twice daily up to and including ILI-D10.

[g] Participants will be asked if they have received medically attended healthcare for the ILI outside of the clinical study site and followed up regarding any reported symptoms via phone and during in-clinic visits on ILI Confirmation and ILI-D28.

[h] Study site will contact participant to schedule in-clinic ILI Confirmation Visit.

[i] Refer to Section 10.3.6 for reporting instructions. AEs will be assessed during in-person visits and phone calls from site.

[j] Includes any concomitant medications, including antibiotic courses, in the past 30 days prior to ILI-D1. Concomitant medications will be recorded during in person visits and phone calls from site.

Table 3: Influenza Illness Monitoring Schedule (Start of Influenza Season 2 [SOIS2] to End of Influenza Season 2 [EOIS2])

	In Person
Days After ILI Symptoms Onset	**ILI Confirmation Visit (D1 +3 days)**
Symptom-directed PE	X
Vital signs	X
Anti-influenza A Antibody titer	X
Nasopharyngeal swab for virology/PK	X
Blood sample for PK	X
Laboratory assessment[a]	X
Review/record AEs[b]	X
Concomitant medications[c]	X

AE = adverse event; D = day; ILI = influenza-like illness; PE = physical examination; PK = pharmacokinetic; RNA = ribonucleic acid; WPAI = Work Productivity and Activity Impairment.

[a] Only hematology, chemistry, and liver function panels from laboratory tests listed in Section 10.2.

[b] Refer to Section 10.3.6 for reporting instructions

[c] Includes any concomitant medications, including antibiotic courses, in the past 30 days prior to ILI-D1, any influenza vaccines received for influenza season 2, or anti-influenza antiviral therapeutics.

2. INTRODUCTION

2.1. Background

VIR-2482 is a human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) of the kappa class that targets a highly conserved epitope in the stem region of the influenza A hemagglutinin (HA) protein that is being developed for the prevention of illness due to influenza A. The parent molecule of VIR-2482, MEDI8852, was isolated from human memory B cells by the Vir Biotechnology, Inc. (VIR) subsidiary, Humabs, and was further optimized by in vitro affinity maturation by MedImmune (Kallewaard 2016). In vitro data demonstrates neutralization activity against a wide variety of seasonal and pandemic strains of influenza A virus and in vivo protection of otherwise lethal influenza A infection in animal models. In addition, the epitope recognized by VIR-2482 is highly conserved among circulating influenza A virus strains.

Influenza viruses are single-stranded, negative-sense, segmented, ribonucleic acid (RNA) viruses in the *Orthomyxoviridae* family which cause highly contagious respiratory illness. Annual influenza epidemics result in substantial morbidity and mortality with an estimated 3 to 5 million cases of severe disease requiring hospitalization worldwide and 290,000 to 650,000 deaths globally per the World Health Organization (WHO 2018). Of the circulating types of influenza virus, type A is the most common and most virulent and drives both seasonal hemispheric epidemics and periodic global pandemics characterized by marked increases in morbidity and mortality (Rambaut 2008).

Despite advances in vaccines and small molecule antivirals, there remains an unmet medical need for the prevention and treatment of influenza illness, especially in populations at high risk for morbidity and mortality from influenza A virus where severe complications can cause significant healthcare burden. The current cornerstone of influenza prevention and epidemic control is strain-specific seasonal vaccination, an approach that has varying degrees of efficacy ranging from 10 to 60% over the last 14 years (CDC 2022). Mismatches between strains used to prepare the vaccine and actual circulating strains result in reduced effectiveness. A mAb with activity against a broad range of influenza viruses that provides a season-long and a consistent year-to-year protection without the need to rely on baseline host immune status for efficacy and strain-specific matching would help to address the unmet needs associated with the current approach to influenza prevention and epidemic control.

2.2. Study Rationale

A mAb with activity against a broad range of influenza A viruses that provides a season-long and a consistent year-to-year protection without the need to rely on baseline host immune status for efficacy and strain-specific matching would help to address the unmet needs associated with the current approach to influenza prevention and epidemic control. Currently, there are no influenza mAbs that have been approved for the prevention or treatment of influenza. With activity against a broad range of influenza A strains and extended half-life, VIR-2482 has the potential to be an effective prevention agent against influenza A and fulfill an unmet need.

VIR-2482 has been evaluated in a Phase 1, randomized, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of VIR-2482 administered intramuscularly (IM) to healthy adult volunteers aged 18 to <65 years of age who have not received the seasonal influenza vaccine. The study was conducted in 2 Parts (Part A and Part B). Part A was a double-blind, single ascending dose of VIR-2482 study with 4 cohorts of 25 participants/cohort who received a single dose of VIR-2482 or placebo at 60, 300, 1200, or 1800 mg administered intramuscularly in a 4 (active): 1 (placebo) ratio to evaluate the safety and tolerability of VIR-2482. Part B was an open-label, safety and PK study portion following a second dose of VIR-2482. Enrollment is complete, with final results pending. Preliminary results indicate that VIR-2482 has a favorable safety and tolerability profile at doses up to 1800 mg. No treatment-emergent drug-related SAEs were observed and no AEs leading to study discontinuation were observed. Six of 100 participants reported mild injection site reactions that resolved within 48 hours. The majority of AEs were mild or moderate. No clinically significant laboratory abnormalities were observed. VIR-2482 exposures (C_{max} and AUC) were dose-proportional across the tested doses (60 to 1800 mg). T_{max} following intramuscular injection was 7 to 14 days. Apparent volume of distribution was typical for a monoclonal antibody (11.1 to 14.1 L). Terminal elimination half-life was 58 to 60 days, consistent with the half-life extending modification.

VIR-2482 is being evaluated in this study for the prevention of illness due to influenza A in healthy adults at low risk of developing serious influenza-related complications. This is a Phase 2 dose ranging, proof-of-concept study that will enroll healthy adults aged 18 to < 65 years of age without risk factors for serious complications from influenza infection who have chosen to forgo the seasonal influenza vaccination for influenza season 1 (2022-2023 Northern hemisphere influenza season). Placebo was chosen as the control for this study to allow for an unconfounded assessment of the efficacy and safety of VIR-2482. The use of a placebo control in otherwise healthy participants who have chosen to forgo seasonal influenza vaccine is considered acceptable due to the low risk of serious influenza-related complications and the availability of effective treatment options in the event of infection.

In this study, a single dose of either 450 mg or 1200 mg (divided equally between 2 intramuscular [IM] injections) VIR-2482 or volume-matched placebo will be administered at the beginning of the influenza season.

2.3. Benefit/Risk Assessment

Detailed information about the known, potential, and expected benefits and risks and reasonably expected adverse events (AEs) may be found in the VIR-2482 Investigator's Brochure (IB).

The potential clinical risks of VIR-2482 are based on theoretical and known concerns associated with the mAbs class of therapeutics in general. The risk monitoring and mitigation strategy for the administration of VIR-2482 is outlined in the table below. The parent molecule of VIR-2482, MEDI8852, was found to be well tolerated at doses up to 3000 mg IV in studies of healthy volunteers (N = 32) and for treatment of patients with confirmed, uncomplicated influenza infection (N = 94). In patients with acute influenza, the most commonly reported AEs in all cohorts were those expected in a population with acute influenza illness, with no clear evidence of antibody-dependent enhancement (ADE) observed (Ali 2018). Although the theoretical risk of ADE with anti-influenza mAbs in the presence of infection remains, nonclinical in vitro and in vivo data, and ongoing clinical data with VIR-2482 suggest no evidence of ADE with influenza virus to date. One participant with acute influenza who received 3000 mg of MEDI8852 via intravenous infusion along with oseltamivir had a severe (Grade 3) investigational product related event of infusion-related reaction requiring termination of administration. The event resolved following treatment with IM dexamethasone, inhaled albuterol and oxygen.

VIR-2482 was well tolerated in the Phase 1 clinical study (VIR-2482-3001) at IM doses of up to 1800 mg. Most AEs were Grade 1 or 2 in severity and the majority were considered not related to VIR-2482. Injection site reactions (ISRs) were reported in 7.5% participants (6 of 80) that received VIR-2482, were mild (Grade 1) in severity, and resolved without sequelae. No subjects had a treatment-related SAE, or discontinued the study or study drug due to AEs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Anaphylaxis and other serious allergic reactions and injection-related reactions	Expected local discomfort following IM injection of VIR-2482 has been observed in prior studies, although no cases of systemic allergic reactions or anaphylaxis have been observed to date with IM VIR-2482.	• All participants will be monitored for at least 2 hours following the IM administration of VIR-2482 and specific guidance for the management of systemic reactions such as anaphylaxis is provided in Section 10.10. • Study personnel will be trained to recognize and treat anaphylaxis appropriately. • Trial participants will be educated to contact the clinical site at any point in time if there are any worsening, new, or unresolving symptoms at the injection site(s).
Development of Anti-Drug Antibodies (ADA)	The mAb class of therapeutics is recognized to have the potential to elicit ADA responses in recipients with repeated dosing that may impact the pharmacokinetics, pharmacodynamics, safety, and/or efficacy, of the drug.	• Participants in this study will be monitored for the development of ADA at regular intervals as outlined in the SoA in accordance with established guidance.
Antibody-Dependent Enhancement (ADE)	Although there is a theoretical risk of ADE with anti-influenza mAbs in the presence of infection, nonclinical in vitro and in vivo data, and ongoing clinical data with VIR-2482, suggest no evidence of ADE with influenza virus.	• Participants in this study will be monitored for important potential risks, including anaphylaxis, assessment of safety in the presence of influenza A infection and routine pharmacovigilance and risk minimization activities will be performed. • The DMC will be able to monitor cases of influenza A in an unblinded manner and recognize any imbalances in the treatment arms of the study and make recommendations accordingly • This study will enroll healthy adults aged 18 to <65 years of age. This approach is supported by the safety profile of the parent molecule (MEDI8852), the low risk of influenza-related complications in this otherwise healthy population, and low potential for antibodies to enhance viral disease (ie, ADE).

2.3.2. Benefit Assessment

This is a Phase 2 study being conducted in healthy participants. Clinical benefit of VIR-2482 has not been established. Participation in this study will contribute to the clinical development of VIR-2482 as a potential therapy for the prevention of illness due to influenza A.

2.3.3. Overall Benefit/Risk Conclusion

VIR-2482 is a mAb with activity against a broad range of influenza viruses that may provide safe, well tolerated, and highly effective season-long protection, and that does not rely on baseline host immune competency for efficacy. Therefore, VIR-2482 has the potential to address the unmet needs associated with the current approach to influenza prevention and epidemic control. Taking into account the measures taken to minimize risk described in the Risk Assessment Table to participants enrolling in this study, the potential risks identified in association with VIR-2482 are reasonable given the current unmet need for the prevention of serious illness due to influenza A. In addition, this study is being conducted in participants at low risk of complications to minimize the risk of severe influenza A disease in case of limited activity of VIR-2482. Safety of the participants will be monitored in this study through routine pharmacovigilance activities.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints
Primary	
To evaluate the efficacy of VIR-2482 compared to placebo in the prevention of protocol-defined ILI with confirmed influenza A	• Proportion of participants with protocol-defined ILI with confirmed influenza A (by reverse transcription-polymerase chain reaction [RT-PCR])
To evaluate the safety and tolerability of VIR-2482 compared to placebo	• Occurrence of adverse events (AEs) • Occurrence of serious adverse events (SAEs) • Occurrence of adverse events of special interest (AESI) • Occurrence of solicited events • Vital signs and laboratory assessments
Secondary	
To evaluate the efficacy of VIR-2482 compared to placebo in the prevention of CDC-defined or WHO-defined ILI with confirmed influenza A	• Proportion of participants with CDC-defined ILI with confirmed influenza A (by RT-PCR) • Proportion of participants with WHO-defined ILI with confirmed influenza A (by RT-PCR)
Exploratory/Other	
To evaluate the effect of VIR-2482 compared to placebo on the severity and duration of illness in participants with confirmed influenza A	• Severity and duration of participant-reported signs and symptoms of influenza-like illness (ILI) due to influenza A, as measured by Flu-iiQ™
To characterize the serum PK of VIR-2482 following a single dose	• Single-dose VIR-2482 serum PK parameters including but not limited to: C_{max}, C_{last}, T_{max}, T_{last}, AUC_{inf}, AUC_{last}, % AUC_{exp}, $t_{1/2}$, λ_z, V_z/F, CL/F.
To characterize the nasopharyngeal sample (NPS) PK of VIR-2482 following a single dose	• Single-dose VIR-2482 NPS PK parameters including but not limited to: C_{max}, C_{last}, T_{max}, T_{last}, AUC_{inf}, AUC_{last}, % AUC_{exp}, $t_{1/2}$, λ_z.
To evaluate the relationship between VIR-2482 exposure and the incidence of influenza A infection	• Exposure-response for VIR-2482
To evaluate the immunogenicity (induction of ADA) response to VIR-2482	• Incidence and titers (if applicable) of ADA to VIR-2482
Evaluate the effect of VIR-2482 versus placebo on potential biomarkers of host response in participants with confirmed influenza A	• Evaluation of host immune responses and exploratory biomarkers related to influenza A, and/or VIR-2482, including antibody, genetic, transcriptomic, virologic, and proteomic parameters

Objectives	Endpoints
To evaluate seroconversion to circulating strains of influenza A virus	• Proportion of subjects with symptomatic and asymptomatic seroconversion to circulating strains of influenza A as measured by serotype-specific HAI titers.
The occurrence of influenza infection by virus subtype	• Number and proportion of participants with laboratory-confirmed influenza subtype by treatment group
To evaluate the effect of VIR-2482 compared to placebo on the magnitude of viral load in nasopharyngeal samples at time of ILI	• Quantification of the influenza A viral load present in nasopharyngeal sample at the time of ILI visit by RT-qPCR
Monitor the emergence of influenza A resistance to VIR-2482	• Emergence of viral resistance to VIR-2482 in influenza A
Monitor the occurrence non-influenza A respiratory viral infections	• Occurrence of laboratory-confirmed (by RT-PCR) non-influenza A respiratory viral infections, including influenza B
Measure of Work Productivity and Activity Impairment (WPAI) due to influenza A illness	• Work time missed, work productivity loss, and activity impairment due to influenza A using the validated WPAI questionnaire

Primary Estimand/Coprimary Estimands

The primary clinical question of interest is:

What is the relative risk between VIR-2482 (450 mg or 1200 mg) versus placebo of protocol-defined ILI with confirmed influenza A after administration of study intervention, regardless of the receipt of any non-study influenza antiviral for treatment or prophylaxis or of an authorized influenza vaccine?

Refer to Section 9.4.2 for details regarding the primary estimand.

Secondary Estimand(s)

The clinical questions of interest for the secondary objectives are:

- What is the relative risk between VIR-2482 (450 mg or 1200 mg) versus placebo of CDC-defined ILI with Confirmed Influenza A after administration of study intervention, regardless of the receipt of any non-study influenza antiviral for treatment or prophylaxis or of an authorized influenza vaccine?
- What is the relative risk between VIR-2482 (450 mg or 1200 mg) versus placebo of WHO-Defined ILI with Confirmed Influenza A after administration of study intervention, regardless of the receipt of any non-study influenza antiviral for treatment or prophylaxis or of an authorized influenza vaccine?

Refer to Section 9.4.3 for details regarding the secondary estimand.

4. STUDY DESIGN

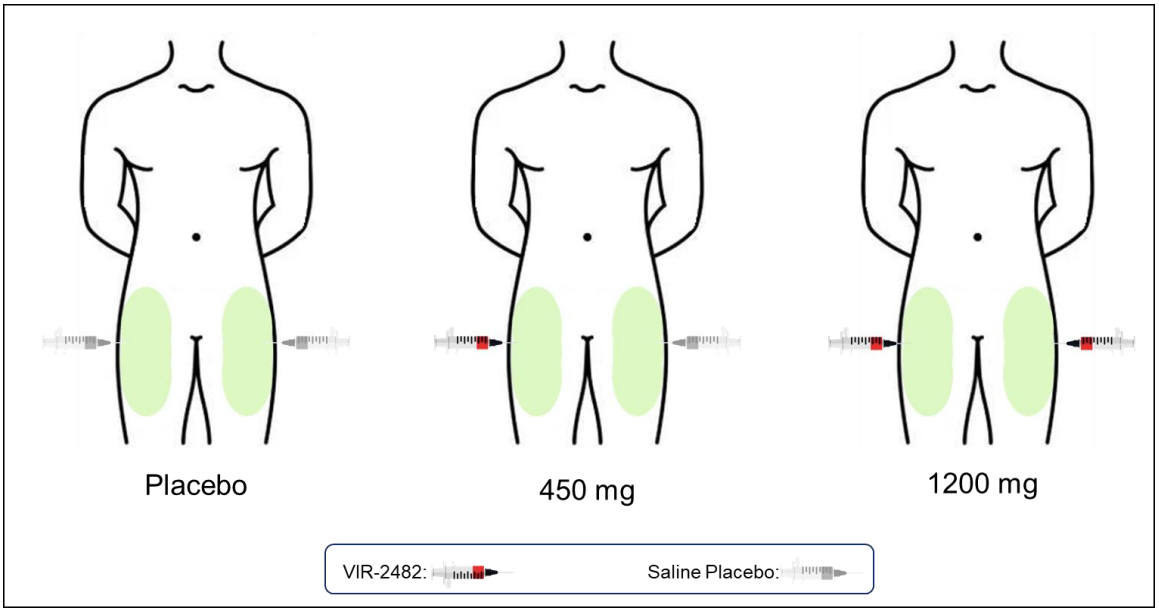
4.1. Overall Study Design

This is a double-blind, randomized, placebo-controlled, Phase 2 study of VIR-2482 administered intramuscularly (IM) to healthy adult volunteers aged 18 to < 65 years of age, who have not received an influenza vaccination for season 1 (2022-2023 Northern hemisphere influenza season). The study is designed to evaluate the safety, tolerability, and efficacy of VIR-2482 in preventing influenza A illness. An independent Data Monitoring Committee (DMC) will ensure thorough evaluation of safety data and early detection of potential safety signals.

Randomization will be stratified by country as applicable. Efforts will be made to enroll all study participants during the first 12 weeks of influenza season 1. Eligible participants will be randomized 1:1:1 to receive 450 mg VIR-2482, 1200 mg VIR-2482, or placebo on Day 1.

The preferred injection site is the vastus lateralis (thigh), with the dorsogluteal (buttock) site as an alternative. All participants will be administered 2 IM injections of blinded study intervention using identical administration procedures irrespective of study arm. Participants will be administered 2 doses of placebo (placebo arm), or 1 dose of VIR-2482 and 1 dose of placebo (450 mg arm), or 2 doses of VIR-2482 (1200 mg arm) under double blinded conditions as outlined in Figure 1. Each injection will be 4 mL in volume. Refer to Section 6.3 and the Pharmacy Manual for detailed study intervention preparation and administration instructions. Participants will remain at the clinical investigative site for a minimum of 2 hours post-dose to assess safety and local tolerability of VIR-2482 at injection site(s) and complete assessments per the Schedule of Activities.

Figure 1: Preferred IM Injection Schematic in Thigh by Study Arm.



Following study intervention, participants will also complete a daily Study Intervention Diary Card on Days 1 to 7 (Section 8.3.6). A thermometer and ruler will be provided to all participants to aid in recording the required information (Section 8.3.6) in the Study Intervention Diary Card.

Participants will be actively monitored for ILI throughout the study. Participants will complete ILI symptom surveillance questions twice a week from Day 1 through the EOIS1 visit via electronic instrument, see Section 10.8 for further details of EOIS1. Participants experiencing ILI will complete in-clinic evaluations, phone evaluations, self-reported symptoms, influenza symptom severity, and WPAI questionnaires, and be followed per the Influenza-Like Illness Monitoring Schedule (Section 8.5.1).

All participants will have a follow-up visit approximately 1, 4, and 12 weeks after receiving study intervention, an EOIS1 visit (approximately 2 weeks after the EOIS1), and a visit at approximately the Start of Influenza Season 2 (SOIS2) for the assessment of safety, PK, and ADA. In addition to the scheduled PK sampling for all trial participants as outlined in the SoA, PK sampling will also occur during any ILI confirmation visits as applicable.

Following the EOIS1 visit, participants will be contacted every 3 months by the study site to determine if the participant experienced an ILI during the previous months. During these phone visits, the clinical site must document any ILI with confirmed influenza A, AEs, and visits to medical professionals per the Schedule of Activities. From SOIS2 to the End of Influenza Season 2 (EOIS2), participants will also receive weekly reminders to complete ILI symptom surveillance questions via electronic instrument. Participants experiencing symptoms consistent with ILI will complete the in-clinic evaluation per Table 3 Influenza-Like Illness Monitoring Schedule (SOIS2 to EOIS2) (Section 8.5.1).

In the event participants experience influenza illness, participants should be offered standard of care therapy per local treatment guidelines, which may include antiviral therapy. Consistent with the different mechanisms of action of the current licensed influenza antivirals and stem-directed mAbs, available data suggests that VIR-2482 will not interfere with their mechanism of action.

Study enrollment will conclude following EOIS1 if there are at least 36 participants across all 3 treatment arms who meet the primary endpoint. Details will be described in the Statistical Analysis Plan (SAP).

4.1.1. Number of Participants

Assuming the attack rate of 2.25% for influenza A in the placebo arm, approximately 3000 participants will be randomized at a 1:1:1 ratio to receive 450 mg VIR-2482, 1200 mg VIR-2482, or volume-matched placebo:

- 1000 participants to receive 450 mg VIR-2482
- 1000 participants to receive 1200 mg VIR-2482
- 1000 participants to receive volume-matched placebo

A total of 36 events will be needed to provide approximately 80% power with alpha=0.05, to detect a true relative risk reduction of 70% in one VIR-2482 arm in the primary endpoint. No further enrollment will be required once 36 events (protocol-defined ILI with confirmed influenza A) are observed (blinded and pooled across treatment arms). The study has selected a conservative attack rate of 2.25% for influenza A in unvaccinated individuals based on observed historical attack rates from multiple placebo-controlled influenza vaccine studies (Jayasundara 2014; Osterholm 2012).

4.1.2. Intervention Groups and Duration

Table 4: Intervention Groups

Intervention	Dose	Route	Number of Doses	Schedule
VIR-2482	450 mg	IM	1 (2 injections)	Single dose on Day 1
VIR-2482	1200 mg	IM	1 (2 injections)	Single dose on Day 1
Placebo	NA	IM	1 (2 injections)	Single dose on Day 1

The total study duration for each participant is planned to be up to approximately 88 weeks. This includes an up to 28-day screening period, 1-day intervention period, and approximately up to 84-week follow-up period.

4.2. Scientific Rationale for Study Design

VIR-2482 is being evaluated for the prevention of illness due to influenza A in healthy adults at low risk of developing serious influenza-related complications. VIR-2482 has high in vitro potency against a wide variety of seasonal and pandemic strains of influenza A virus and is effective in the prevention of otherwise lethal influenza A infection in animal models. In addition, the epitope recognized by VIR-2482 is highly conserved among influenza A virus and has a high barrier to the development of resistance in vitro.

This randomized, placebo-controlled, Phase 2 study is designed to evaluate the safety, tolerability, and efficacy of VIR-2482 for the prevention of influenza A illness in healthy adults without risk factors for serious complications from influenza infection. To adequately assess the ability of VIR-2482 to prevent influenza A illness, the study will commence prior to influenza season 1.

The study is designed to assess the efficacy of VIR-2482 in the prevention of influenza A illness and to collect additional safety, tolerability, and PK data. VIR-2482 was previously studied in an ascending dose Phase 1 study in which doses of up to 1800 mg were generally well tolerated.

This study will enroll healthy adults aged 18 to <65 years of age, without risk factors for serious complications from influenza infection who have chosen to forgo the seasonal influenza vaccination for season 1. This approach is supported by the safety profile of VIR-2482 in the completed Phase 1 study and the safety profile of the parent molecule (MEDI8852), the low risk of influenza-related complications in this otherwise healthy population, and low potential for antibodies to enhance viral disease (ADE).

Placebo was chosen as the control for this study to allow for an unconfounded assessment of the efficacy and safety of VIR-2482. The use of a placebo control in otherwise healthy participants who have chosen to forgo seasonal influenza vaccine is considered acceptable due to the low risk of serious influenza-related complications and the availability of effective antiviral treatment options in the event of infection.

4.3. Justification for Dose

In this study, a single dose of either 450 mg or 1200 mg VIR-2482 will be administered at the beginning of influenza season 1. These doses were selected based on the acceptable safety and

tolerability of doses up to 1800 mg in the earlier Phase 1 study (VIR-2482-3001), in vitro neutralization data, a range of lung tissue distribution assumptions, and serum PK simulations based on data collected in VIR-2482-3001. The doses of 450 mg and 1200 mg were selected to generate data to characterize the PK/PD relationship and optimize the dose for Phase 3 clinical development.

The in vitro neutralization activity of VIR-2482 has been characterized through multiple microneutralization studies, which collectively have determined neutralizing activity against 26 H1N1 and 37 H3N2 wild-type live viruses (details in the VIR-2482 Investigator's Brochure Edition 3). [redacted] However, the potential contribution of mAb effector function to clinical efficacy has not been characterized. Additionally, the extent of mAb distribution to human lung tissue is also not precisely defined, with conflicting estimates ranging from 5% to 31% reported in the literature (Aweda 2022, Magyarics 2019; Shah 2013; Chigutsa 2022; Chigutsa 2021; Jones 2021; Eigenmann 2017; Baxter 1994; Covell 1986). Furthermore, it is not known whether mAb distribution to lung tissue is dose-proportional, or if mAb elimination half-life in the lung differs from mAb serum elimination half-life. Therefore, it is unclear if a simple plasma:tissue partitioning coefficient is an accurate metric for estimating VIR-2482 levels at the site of drug action.

VIR-2482-4002 is designed as a proof-of-concept dose ranging study, intended to generate PK and clinical data that will help address these uncertainties surrounding lung tissue distribution and whether mechanisms other than neutralizing activity may contribute to clinical effect. [redacted] (not considering the potential contribution of effector functions that are intact in VIR-2482), 1200 mg is anticipated to maintain efficacious exposures for 6 months, while 450 mg is anticipated to maintain efficacious exposures for 4 months. The dose of 450 mg was selected to generate data to inform on the lower threshold of VIR-2482 exposure required for efficacy, and to assess whether clinical effect may be superior to that predicted by neutralization data alone.

4.4. End of Study Definition

The end of study is defined as the last scheduled visit (or completed contact) of the last participant.

5. STUDY POPULATION

Healthy adult male and nonpregnant, nonlactating females aged 18 to < 65 years.

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 to < 65 years of age, at time of randomization.

Type of Participant and Disease Characteristics

2. Participants must be in good health, determined from medical history (eg, chronic conditions such as hypertension, hyperlipidemia, gastroesophageal reflux disease, anxiety and depression must be controlled with a stable dose of medication, defined as no change to dose or frequency within the previous 30 days), and no clinically significant findings from physical examination, 12-lead electrocardiogram (ECG), vital signs, and laboratory values.

Weight

3. Body mass index (BMI) 18.0 kg/m^2 to 35.0 kg/m^2, inclusive.

Sex and Contraceptive/Barrier Requirements

4. Female participants must have either negative pregnancy testing, documented permanent infertility, or confirmation of post-menopausal status.

   Female participants who are Women of childbearing potential (WOCBP) must have a negative blood pregnancy test at screening, a negative urine pregnancy test on Day 1, and cannot be breastfeeding. WOCBP will agree to use effective or highly effective methods of contraception 14 days before the first dose of study intervention through last scheduled follow-up visit, and will also agree to refrain from egg donation and in vitro fertilization from the time of study intervention administration through last scheduled follow-up visit .

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. History or clinical evidence of conditions considered high risk for developing influenza-related complications listed below:

   Established diagnosis of:

   - Asthma
   - Neurological and neurodevelopmental conditions (such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
   - Chronic lung disease (such as chronic obstructive pulmonary disease [COPD], emphysema, and cystic fibrosis)
   - Heart disease (such as congenital heart disease, congestive heart failure and coronary artery disease)
   - Blood disorders (such as sickle cell disease and Thalassemia)
   - Endocrine disorders (such as diabetes and adrenal insufficiency)
   - Chronic kidney disease
   - Chronic liver disease
   - Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
   - Weakened immune system due to disease or medication (such as individuals with HIV or AIDS, or cancer, or those on chronic steroids)
   - People younger than 19 years of age who are receiving long-term aspirin therapy
2. History of confirmed influenza infection within 3 months prior to randomization.
3. Febrile illness with or without respiratory symptoms (eg, cough, nasal congestion) within 5 days prior to randomization.
4. History of malignancy within 5 years (treated squamous or non-invasive basal cell skin cancers are permitted) or participant is under evaluation for malignancy.
5. Any condition or receipt of any medication contraindicating IM injection, as judged by the investigator.
6. History of a severe allergic reaction with generalized urticaria, angioedema or anaphylaxis within the 2 years prior to randomization.
7. Participant has a clinically significant medical condition, physical exam finding, or abnormal laboratory result at screening that in the clinical judgment of the investigator make the participant at undue risk to forgo seasonal influenza vaccination or safely participate in the study.

Prior/Concomitant Therapy

8. Prior or planned receipt of any influenza vaccine for the upcoming season (relative to Day 1 dosing). Influenza vaccination is permitted following completion of the EOIS visit.
9. Received any investigational agent within 90 days or within 5 half-lives of the investigational agent, whichever is longer, before study intervention administration.

5.3. Lifestyle Considerations

Lifestyle considerations are not applicable to this study.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study subsequently does not enter the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table 5: Study Intervention(s) Administered

Intervention Label	450 mg VIR-2482	1200 mg VIR-2482	Placebo
Intervention Name	VIR-2482	VIR-2482	Placebo
Type	Biologic	Biologic	Placebo to biologic
Dose Formulation	Solution of lyophilized solid, reconstituted with sterile water for injection, USP	Solution of lyophilized solid, reconstituted with sterile water for injection, USP	Sterile 0.9% (w/v) sodium chloride solution
Unit Dose Strength(s)	300 mg	300 mg	0 mg
Dosage Level(s)	450 mg once	1200 mg once	Once
Route of Administration	IM	IM	IM
Use	Experimental	Experimental	Experimental
IMP and NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided by the sponsor.	Provided by the sponsor.	Provided locally by the study site, subsidiary, or Sponsor.
Packaging and Labeling	Study intervention will be provided in vial. Each vial will be labeled as required per country requirement.	Study intervention will be provided in vial. Each vial will be labeled as required per country requirement.	Provided by site or may be provided by the sponsor in its commercially available packaging.

6.2. Preparation, Handling, Storage, and Accountability

Detailed instructions for study interventions will be provided in the Pharmacy Manual.

6.3. Dosage and Administration of VIR-2482

On the day of dosing, the pharmacist or designee will prepare the drug per Pharmacy Manual instructions. A qualified clinical investigative site staff member under the general supervision of the investigator or designee will administer study intervention to study participants via IM injections.

Study intervention administration should be performed in a setting where personnel and equipment are available for the management of severe systemic reactogenicity including anaphylaxis.

Management guidelines for these potential symptoms are provided in Section 10.10.

Refer to the Pharmacy Manual for detailed study intervention preparation and administration instructions.

6.4. Measures to Minimize Bias: Randomization and Blinding

6.4.1. Randomization

Randomization will be used to minimize participant selection bias. All participants will be centrally randomized to receive study intervention (VIR-2482 1200 mg or VIR-2482 450 mg or placebo) using an Interactive Response Technology (IRT) system. Before the study is initiated, training on the IRT system will be provided to each site.

6.4.2. Blinding

This study will be double-blind: the sponsor, investigators, study staff participating in participant care or clinical evaluations, and participants will remain blinded to each participant's assigned study intervention throughout the course of the study. To help maintain this blind, designated unblinded study staff will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization. In addition, only unblinded staff may receive, store, and handle study intervention. The study intervention should be prepared away from view of the blinded staff and the participant. Every IM injection must be labeled to maintain the blind.

6.4.3. Unblinding

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain treatment assignment for that participant. If the event requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

At the initiation of the study, study site personnel will be instructed on the method for breaking the blind. The unblinding method will be either manual or electronic. A participant should continue in the study if that participant's intervention assignment is unblinded.

Unblinding of Individual Participant Treatment Assignments by Investigator for Medical Emergencies or Urgent Clinical Situations

Unblinding of the individual participant's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the participant's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss unblinding. If investigators deem it unnecessary to unblind immediately, they will first attempt to contact the medical monitor to discuss unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding.

Contact information for the medical monitor (or appropriate backup) will be in a separate document.

If a participant's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the participant's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with sponsor, the contract research organization (CRO), or any site personnel (other than the physician treating the participant). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to sponsor or designee, per Section 10.3.2.

Unblinding of Individual Participant Treatment Assignments by Sponsor or Designee for SAEs or Safety Concerns

Sponsor or designee will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, the sponsor may, for matters relating to safety, unblind individual participants at any time.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. Refer to Pharmacy Manual for further details.

6.6. Dose Modification

This is a single-dose study and dose modifications are not applicable.

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

No access to study intervention will be available to participants after the end of the study.

6.8. Treatment of Overdose

No specific treatment is recommended for an overdose. The treating physician may provide supportive measures depending on the symptoms.

In the event of an overdose, the treating physician should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until the overdose is considered to be resolved.
- Refer to Section 10.3.5 for reporting of Overdose to sponsor.

6.9. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the electronic case report forms (eCRFs).

Participants will be counseled to make efforts to proactively inform the site about starting new over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements over the course of the study.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Concomitant Therapy Not Permitted During the Study

Any other experimental or authorized influenza vaccine or anti-influenza antiviral therapeutic is not permitted during influenza season 1 with the exception of participants who acquire laboratory diagnosed, symptomatic influenza illness.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.9.

7.1. Discontinuation of Study Intervention

A participant will be permanently discontinued from completion of the injection or injections if they experience life-threatening, injection related reactions (IRRs) including severe allergic or hypersensitivity reactions or severe cytokine release syndrome.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for follow-up assessments. See the SoA in Section 1.3 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, [3] telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to be lost to follow-up from the study.

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

7.4. Participant Replacement

Participants who withdraw or are withdrawn before the first study intervention administration may be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria, were performed within the timeframe defined in the SoA and the participant's consent for use in the study was obtained.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.1. Screening Period

Informed consent must be obtained before conducting any study-related procedures. Participant eligibility will be evaluated during the screening period and includes the assessments outlined in the SoA. The screening period duration is up to 28 days before a participant's first dose of study intervention.

8.2. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1. Physical Examinations

- A complete physical examination will be conducted to determine study eligibility at screening. Height and weight will also be measured and recorded.
- A symptom-directed physical examination will be performed at subsequent visits as defined in the SoA. The symptom-directed physical examinations will be performed based on signs and symptom the participant has reported and/or in the opinion of the investigator.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Vital signs will be measured in a supine position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

8.3.3. Electrocardiograms

- Single 12-lead ECG(s) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and [QTc] intervals.

8.3.4. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE or SAE, if applicable (Section 10.3). The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal through the EOIS2 visit should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - If clinically significant values do not resolve within a period of time judged reasonable by the investigator, an evaluation to identify the etiology should be undertaken, and the sponsor notified.
  - All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA.
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.3.5. Local Tolerability

VIR-2482 has been well tolerated when administered by IM injection to date. In the prior VIR-2482-3001 study in which doses up to 1800 mg were administered as up to 3 separate IM injections, there were no cases of treatment-emergent immune reactions, no drug related Grade 3 or 4 AEs, and only Grade 1 (mild) injection site reactions were reported in 7.5% participants (6 of 80) that received VIR-2482. As IM VIR-2482 has generally been well tolerated to date, VIR-2482-4002 study participants will be monitored for at least 2 hours following the IM administration of study intervention and the local tolerability assessment to be conducted for each injection site will be performed approximately 1 hour post-dose per the SoA using the assessment tool in Section 10.9.

At the discretion of the investigator, unscheduled visits are permitted as needed for follow up of any unresolved local tolerability symptoms. Management guidelines for these symptoms are provided in Section 10.10.

8.3.6. Study Intervention Diary Card

After receipt of study intervention, study participants will record temperature at least daily (twice daily as able) from Days 1 to 7 in an electronic diary card. In addition, participants will record daily measurement and intensity grade of solicited injection site and systemic reactions in the electronic diary card from Days 1 to 7. Participants will be instructed on how to record temperature and solicited injection site and systemic reactions.

8.3.7. Pregnancy Testing

A pregnancy test or confirmation of post-menopausal status must be confirmed for all female participants. Post-menopausal status is defined as no menses for 12 months without an alternative medical cause. Confirmation of negative FSH is required to confirm post-menopausal status. Pregnancy tests will be performed for WOCBP only. Pregnancy testing will be performed per the SoA and any time pregnancy is suspected. A WOCBP who is known to be pregnant or who does not have a negative pregnancy test at screening is not eligible for study participation. A blood pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. During the study, the results of these pregnancy tests must be known prior to study intervention administration. A WOCBP determined to be pregnant while on study will be followed until the pregnancy outcome is known, as described in Section 8.4.9.1.

8.4. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs, SAEs, and other safety events are provided in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (Section 10.3.5).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

After signing of the ICF, but prior to initiation of study medication, AEs/SAEs related to protocol-mandated procedures should be reported. Following initiation of study intervention, all AEs/SAEs, regardless of cause or relationship, will be recorded for the entire duration of the study.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs, regardless of causal relationship, will be collected from signing of the ICF until the end of the study.

All SAEs must be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, from the investigator or designee awareness of the

event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and AEs of special interest, pregnancy, and special situation reports (as defined in Section 10.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.5.

8.4.3. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met. The investigator will record the SAE information on the appropriate form and submit it to sponsor or designee within 24 hours of awareness of the event.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review the information, document the review, file the safety report along with the relevant study documents and will notify the IRB/IEC, if appropriate according to local requirements.

Assessment of expectedness for SAEs will be determined by the sponsor using the reference safety information (RSI) as specified in the IB. Assessment of expectedness for marketed products will be determined by the sponsor using the product label.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.4. Adverse Events of Special Interest

Adverse events of special interest are defined as relevant known toxicities of other therapeutic mAbs or as a result of signals observed from previous studies in the nonclinical programs, or in the clinical program with VIR-2482 that the sponsor will monitor throughout the study. AESIs may be updated during the course of the study based on accumulating safety data.

Adverse events of special interest include:

- Hypersensitivity reactions
- Adverse events potentially related to ADA
- Adverse events potentially related to ADE

8.4.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or SAEs

Laboratory abnormalities without an associated AE (signs or symptoms) and/or which do not require medical intervention, are not themselves recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study intervention interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Section 10.3. If the laboratory abnormality is part of a clinical syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (presented in Section 10.3).

8.4.6. Unsolicited Adverse Events

An unsolicited AE is an AE that was not solicited during the Local Tolerability Assessment (Section 10.9) or the Study Intervention Diary Card (Section 8.3.6) and that is reported by a participant who has provided documented informed consent.

8.4.7. Solicited Events

Solicited events are predefined local and systemic reactions for which the participant is specifically questioned, and which are reported by the participant during the Local Tolerability Assessment (Section 10.9) and on the Study Intervention Diary Card (Section 8.3.6).

Solicited events that qualify as SAEs should be reported as SAEs, as applicable.

8.4.8. AE Reporting and Clinical Events

Cases of ILI with confirmed influenza A (Section 10.7), will be reported as Clinical Events, and should not be reported as adverse events unless the signs or symptoms of influenza A, are more severe than expected given the participant's clinical status and medical history or if the investigator considers that there is a causal relationship between the study treatment or protocol design/procedures and the disease progression.

Clinical Events that qualify as an SAE should be reported as SAEs as applicable.

8.4.9. Special Situation Reports

All special situation reports (SSR) will be collected from the start of intervention until the end of follow-up period and include all reports of medication error, abuse, misuse, overdose, pregnancy, drug interactions, exposure via breastfeeding, unexpected benefit, occupational exposure, transmission of infectious agents via the product, counterfeit or falsified medicine, and product complaints.

The investigator will record the special situation information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of the situation. These reports must consist of situations that involve study intervention and/or protocol-required concomitant medications but do not apply to non-required concomitant medications.

Special situations involving non-required concomitant medications do not need to be reported; however, for special situations that result in AEs due to a non-required concomitant medication, the AE should be reported.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse" but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs (from required and non-required medication) will be reported as AEs or SAEs. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8.4.9.1. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the end of study.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of the female participant or female partner of male participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner (after obtaining the necessary signed informed consent from the female partner) will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.3. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, if he/she learns of any SAE and considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Any female participant who becomes pregnant while participating in the study may continue study participation and continue safety follow-up visits as per SoA

Prior to continuation of study intervention following pregnancy, the following must occur:

- The sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

The study participant and/or pregnant female partner, as applicable, should receive any necessary counseling regarding the risk of continuing the pregnancy and the possible effects on the fetus.

8.5. Influenza-Like Illness (ILI) Surveillance

8.5.1. Influenza-Like Illness Monitoring and Influenza Confirmation Visit

For influenza season 1, participants will be actively monitored for ILI from Day 1 to the EOIS1 visit. See the SoA for details.

Participants experiencing symptoms consistent with ILI, such as those defined in Section 10.7, will report the symptoms of ILI by answering provided PRO questions in the affirmative. Electronic instrument will be used. Reporting should occur on the same day as symptom onset and an in-clinic evaluation per the Influenza-Like Illness Monitoring Schedule (Section 1.3) should be scheduled.

Efforts will be made to have first in-clinic evaluation within one day and preferably no longer than 3 days from symptom onset. An additional in-clinic evaluation should be scheduled approximately 28 days after symptom onset. Study participants will be educated on the symptoms of ILI and how to reach the study site. The participants will also be provided with contact information for the study site.

In-clinic evaluation to confirm ILI symptoms and influenza A will include, but not be limited to, physical examination (including vital signs), laboratory testing (including safety), nasopharyngeal swab for point of care respiratory viral panel for influenza A RT-PCR, blood collection for PK and ADA, and review of AEs and concomitant medications as appropriate. A nasopharyngeal swab for virology/PK testing will also be sent to a central laboratory for viral confirmation, quantitation, and/or sequencing; aliquots from this nasopharyngeal swab will also be used for PK analysis.

Each participant presenting with symptoms consistent with ILI will be followed via daily site outreach by telephone call through Day 10 following initial presentation. During the in-clinic visits and via phone calls, participants will be asked if they have received medically attended healthcare for ILI outside of the clinical study site and followed up with regarding any reported symptoms. During the in-clinic visits and via phone calls, AEs and concomitant medications should also be reported. At the discretion of the investigator, unscheduled in-clinic visits are permitted during the ILI monitoring period.

Participants will report ILI symptoms on the electronic device from ILI-D1 to ILI-D10. Oral body temperature will be measured daily from ILI-D1 to ILI-D10 (10 days inclusive) from symptom onset and recorded, by the participant. A thermometer will be proactively provided to participants prior to the ILI-D1 visit. Participants will complete self-reported influenza symptom severity assessments on the electronic device from ILI-D1 to ILI-D10 (10 days inclusive) after symptom onset as part of the Flu-iiQ™. Participants will also complete the WPAI questionnaire on ILI-D1 and ILI-D8 after symptom onset.

For participants who test negative for Influenza A at the ILI Confirmation Visit and have continued symptoms without an alternative diagnosis, investigators may bring them back for another ILI Confirmation Visit to retest for Influenza A infection if clinically indicated. For participants who are determined to not be positive for influenza A at the ILI confirmation visit, symptoms should be recorded and followed as AEs.

For influenza season 2, participants will also receive weekly reminders to complete ILI symptom surveillance questions via electronic instrument. Participants experiencing symptoms consistent with ILI will report the symptoms of ILI by answering provided PRO questions in the affirmative. An in-clinic evaluation per the Influenza-Like Illness Monitoring Schedule (SOIS2 to EOIS2) should be scheduled (Table 3); reported symptoms triggering in-clinic evaluations may be assessed by the investigators prior to scheduling the in-clinic visit to confirm they are consistent with ILI and that the visit is warranted. Efforts will be made to have the in-clinic evaluation within one day and preferably no longer than 3 days from symptom onset. In-clinic evaluation will be completed per Table 3.To minimize the attrition of trial participants in the second influenza season, the threshold to trigger an ILI visit has been optimized to enrich for scheduled ILI visits more likely to be associated with PCR confirmed Influenza A and will require both a systemic and a respiratory symptom as described in Section 10.7. To ensure that the confirmatory RT-PCR assay used in the second influenza season has acceptable sensitivity, confirmatory RT-PCR on NPS swabs collected at ILI visits will be run at the virology central lab using an assay that detects circulating influenza A strains.

8.5.2. Influenza Intensity and Impact Questionnaire

For influenza season 1, participants will complete the Flu-iiQ™, a self-assessment of systemic and respiratory symptoms associated with influenza (ie, cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue). They will score the severity of their symptoms using a 4-point rating scale (0, None; 1, Mild; 2, Moderate; 3, Severe). Additional items related to physical, social and emotional well-being will also be collected. This information will be captured per the Influenza-Like Illness Monitoring Schedule (Table 2). The 4-point rating scale will only be used in the exploratory endpoints to determine severity and duration of participant-reported signs and symptoms during an ILI due to influenza A through EOIS1.

8.5.3. Work Productivity and Activity Impairment (WPAI)

The WPAI is a validated, patient-reported, quantitative assessment of absenteeism (work time missed), presenteeism (reduced on-the-job effectiveness), work productivity loss and activity impairment due to a specific health problem. Participants who present with ILI through EOIS1 will complete the 6-item WPAI questionnaire on ILI-D1 and ILI-D8 (Reilly 1993).

8.5.4. Virology and Resistance Surveillance

Viral parameters including the virus type, subtype and viral load by qRT-PCR will be evaluated at the ILI visit for participants who present with laboratory-confirmed influenza A infection. Resistance surveillance for potential emergence of resistance to VIR-2482 will be conducted for all participants who received study intervention and present with laboratory-confirmed influenza A infection, as per the Influenza-Like Illness Monitoring Schedule (Table 2 and Table 3). Deep sequencing analysis of influenza A virus may be attempted on samples from nasopharyngeal swabs from participants with confirmed influenza A virus infection with viral load above the limit of the sequence assay. To evaluate the emergence of antiviral resistance, recombinant virus containing the HA gene from participants with confirmed influenza A virus infection will be generated using established reverse genetic procedures, and recombinant viruses will be subjected to in vitro phenotypic analysis to determine the neutralization activity of VIR-2482.

8.6. Pharmacokinetics

Blood samples will be collected and processed to serum for measurement of VIR-2482 concentrations using a validated assay. An aliquot of serum from PK samples will be used for blood urea nitrogen (BUN) analysis to normalize nasopharyngeal drug concentration values. Instructions for the collection and handling of blood samples will be provided by the sponsor in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample collection will be recorded.

Nasopharyngeal samples (NPS) will be collected to assess the concentration of VIR-2482 in nasal secretions using a qualified assay. NPS will be collected from all participants at the EOIS1 visit and the ILI confirmation visit. An optional NPS sub-study may be initiated at Sponsor discretion, and will include collection of additional NPS from a subset of approximately 300 participants pooled across all treatment groups, at timepoints specified in the SoA. The Sponsor will notify study sites of any decision to trigger initiation of the sub-study by Protocol Clarification Letter (PCL) and will also notify sites when sub-study enrollment is completed by a subsequent PCL. Instructions for the collection and handling of nasopharyngeal samples will be provided by the sponsor in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample collection will be recorded.

Sample collection timepoints for all trial participants are specified in the SoA (Section 1.3).

VIR-2482 concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.7. Genetics

See Section 8.9.2.

8.8. Immunogenicity Assessments

Blood samples will be collected for the measurement of immunogenicity (anti-drug antibody [ADA] and/ or neutralizing antibodies [Nab] as applicable) responses to VIR-2482. Specific blood collection timepoints are defined in the SoA. Analysis of ADA samples will be performed using a validated assay in a 3-tier format (screen, confirm, titer). Additional testing may be performed to detect the presence of NAb and/or characterize the immunogenicity response. Further details regarding the collection, processing, and analysis of immunogenicity samples are provided in the Laboratory Manual.

8.9. Biomarkers

Through EOIS1 biomarker samples will be collected from participants at baseline and after study intervention to evaluate host immune responses and exploratory biomarkers related to influenza A, non-influenza A respiratory viruses, and/or VIR-2482, including serology (anti-influenza antibody), transcriptomic, virologic, and proteomic parameters. To evaluate seroconversion, the proportion of subjects with seroconversion to circulating strains of influenza A as measured by serotype-specific HAI titers will be evaluated. To evaluate the effect of endogenous anti-influenza A antibodies, additional serum testing of anti-influenza A antibodies may be performed.

Serum samples will be collected to evaluate changes in serum biomarkers and proteins (including but not limited to inflammatory cytokines and chemokines, such as IL-6, IFN-alpha, IL-1, IL-3, TNF-alpha). Samples will be collected in accordance with the Laboratory Manual and SoA.

Sponsor may store samples for up to 15 years after the end of the study to achieve study objectives.

8.9.1. Optional Future Biomedical Research

An optional serum sample may be collected for future biomedical research studies from participants who have consented to participate in the Optional Future Biomedical Research component of the study. The specimens collected will be used to increase our knowledge of influenza A infection and identify biomarkers that inform the scientific understanding of influenza A infection and/or its treatments. Participation is optional. Participants who do not wish to provide samples for future biomedical research may still participate in the study.

8.9.2. Optional Genetics Research

Optional blood samples for DNA and RNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. The specimens collected will be used to evaluate associations between FcγR allelic expression, IgG1 allotype, and clinical outcomes. Sequencing of genomic polymorphisms, including but not limited to FCGR2A, FCGR2B, FCGR3A, and IGHG1 loci, will be performed on whole blood samples collected pre-dosing in participants who opt-in for the genetic research component of this study. Whole blood samples for RNA expression will be collected to evaluate cellular populations and transcriptomes. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

If a DNA sample is not obtained at the Day 1 visit, it may be drawn at any time in the study. In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Samples will be collected in accordance with the Laboratory Manual and SoA.

8.10. Medical Resource Utilization and Health Economics

For all participants throughout the study, the investigator and study-site personnel will collect data about health care resource utilization associated with medical encounters.

The data collected will:

- Include the reasons and duration of hospitalizations and emergency room visits and
- Exclude procedures, tests, and encounters mandated by the protocol.

The sponsor may use the collected data to conduct economic analyses.

9. STATISTICAL CONSIDERATIONS

This section provides a high-level summary of the planned statistical analyses. Details of the statistical analyses will be provided in the SAP, which will be finalized prior to treatment unblinding. Further details regarding timing of analyses will be provided in the SAP.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the SAP and/or the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.1. Statistical Hypotheses

The primary objective is to evaluate the efficacy of VIR-2482 1200 mg and VIR-2482 450 mg as compared to placebo in preventing protocol-defined ILI with confirmed influenza A. The null hypotheses to be tested corresponding to the primary estimand are as follows:

- Null hypothesis: VIR-2482 1200 mg is not different from placebo with respect to the proportion of participants with protocol-defined ILI with confirmed influenza A.
- Null hypothesis: VIR-2482 450 mg is not different from placebo with respect to the proportion of participants with protocol-defined ILI with confirmed influenza A.

The null hypotheses corresponding to the key secondary estimands are as follows:

- Null hypothesis: VIR-2482 1200 mg is not different from placebo with respect to the proportion of participants with CDC-Defined ILI with Confirmed Influenza A.
- Null hypothesis: VIR-2482 1200 mg is not different from placebo with respect to the proportion of participants with WHO-Defined ILI with Confirmed Influenza A.

- Null hypothesis: Null hypothesis: VIR-2482 450 mg is not different from placebo with respect to the proportion of participants with CDC-Defined ILI with Confirmed Influenza A .
- Null hypothesis: VIR-2482 450 mg is not different from placebo with respect to the proportion of participants with WHO-Defined ILI with Confirmed Influenza A.

9.1.1. Multiplicity Adjustment

A hierarchical fixed sequence testing procedure will be used to control the type I error at $\alpha = 0.05$ for testing VIR-2482 1200 mg versus placebo and VIR-2482 450 mg versus placebo for the multiple endpoints. For the primary endpoint, first we will test VIR-2482 1200 mg versus placebo at $\alpha=0.05$. If the test is statistically significant with VIR-2482 1200 mg superior to placebo, then we will proceed to test VIR-2482 450 mg versus placebo for the same endpoint $\alpha=0.05$. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level. The complete testing hierarchy will be further defined in the SAP.

Note that the formal comparisons precluded by the hierarchical testing strategy will be performed and the resulting p values considered as descriptive.

9.2. Sample Size Determination

This is an event driven study. Based on a 2-sided type 1 error rate of 5%, a total of 36 events will be needed to provide approximately 80% power, to detect a true relative risk reduction of 70% in one VIR-2482 arm in the proportion of protocol-defined ILI with confirmed influenza A over the entire influenza season 1 after the administration of study interventions. The sample size will be approximately 3000 participants (1000 per arm), if the proportion of protocol-defined ILI with confirmed influenza A in the placebo arm is 2.25%. The minimum detectable relative risk reduction is approximately 54.5%. The study has selected a conservative attack rate of 2.25% for influenza A in unvaccinated individuals based on observed historical attack rates from multiple placebo-controlled influenza vaccine studies.

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
All Participants Set	The All Participants Set will include all participants who are randomized or receive any amount of study intervention. This analysis set will be used for all individual participant data listings and disposition summary tables, unless otherwise specified.
Full Analysis Set (FAS)	The FAS will include all randomized participants who 1) have not had confirmed influenza infection within 3 months prior to randomization [protocol exclusion criterion 2], 2) have not received an influenza vaccination for influenza season 1 [protocol exclusion criterion 8], and 3) receive any amount of study intervention. The FAS will be used for summaries of demographics and baseline characteristics and all efficacy analyses, in which participants will be analyzed according to the randomized study intervention.
Safety Set	The Safety Set will include all participants who receive any amount of study intervention. This Safety Set will be used for all safety analyses in which participants will be analyzed according to study intervention received.
Pharmacokinetic Analysis Set	The Pharmacokinetic Analysis Set will include all participants in the Safety Set who have receive 1 full dose of study intervention and have at least 1 measurable post-dose VIR-2482 concentration.
Immunogenicity Analysis Set	All participants in the Safety set who have at least 1 sample that has undergone testing for immunogenicity including screening, titers, or neutralizing characterization, as applicable. The Immunogenicity Analysis Set will be used for analyses of ADA. Participants will be analyzed according to the study intervention received.
Virology Analysis Set	All participants in the FAS with a nasopharyngeal swab obtained at the ILI confirmation visit. The Virology Analysis Set will be used for analyses of all virology parameters. Participants will be analyzed according to the randomized study intervention.

Additional analysis sets related to the primary efficacy endpoint may be defined in the SAP, as appropriate.

9.4. Statistical Analysis

9.4.1. General Considerations

All individual participant data for the All Participants Set will be presented in data listings.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, SD, median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be specified in the SAP.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Baseline value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the initial administration of study intervention.

Change (absolute change) from baseline will be calculated as post-baseline value - baseline value.

Treatment-Emergent Adverse Events (TEAEs) are defined as any AEs reported with an onset date on or after the start of study drug through the end of the Treatment-Emergent (TE) period.

The TE Period will include the time period starting from the date of the first dose of study drug to the completion of study participation.

Completion of study participation for each individual participant is defined as one of the following:

- For participants who complete the Follow-up Period: the EOIS2 visit
- For participants who prematurely discontinue the study and do not withdraw consent: the Early Termination (ET) visit
- For participants who withdraw consent: the date of withdrawal of consent
- For participants are lost to follow-up: the date of the last contact.

9.4.2. Primary Endpoint(s)/Estimand(s) Analysis

The primary clinical question of interest is: What is the relative risk between VIR-2482 (450 mg or 1200 mg) versus placebo of protocol-defined ILI with confirmed influenza A after administration of study intervention, regardless of the receipt of any non-study influenza antiviral for treatment or prophylaxis or of an authorized influenza vaccine?

The primary estimand is defined as follows:

- Population: healthy adults 18 to <65 years of age, who have not received an influenza vaccination for the upcoming season.
- Primary Endpoint: proportion of participants in the FAS with protocol-defined ILI with confirmed influenza A
- Treatment comparison: VIR-2482 (1200 mg or 450 mg) vs placebo
- Potential intercurrent events:
  - Receipt of any non-study influenza antiviral for treatment or prophylaxis
  - Receipt of an authorized influenza vaccine
  - Death for reason(s) other than influenza illness
  - Participants who become unblinded to treatment assignment due to any reasons
- Population-level summary: Relative risk

The primary efficacy analysis will be the comparison of the proportion of participants in the FAS with protocol-defined ILI with confirmed influenza A after administration of study intervention using a Poisson regression model with robust sandwich estimators adjusted for treatment group. Multiple occurrences of protocol-defined ILI with confirmed influenza A within one study participant will be counted once at the earliest occurrence. The adjusted relative risk reduction, calculated as 100% × (1 - adjusted relative risk) of protocol-defined ILI with confirmed influenza A for VIR-2482 1200 mg vs placebo will be estimated, along with the corresponding 95% CI. Similarly, the adjusted relative risk reductions and the corresponding 95% CIs will be calculated for the treatment comparisons of VIR-2482 450 mg vs placebo.

The primary analyses for the primary endpoint will be conducted using treatment policy strategy for intercurrent events other than death. All observed data collected after the intercurrent events other than death will be used in the analyses.

A supplemental analysis of the primary endpoint will be based on responses prior to the intercurrent events by handling intercurrent events using 'while on treatment' strategy. Sensitivity analyses will be conducted as appropriate. Details will be specified in the SAP.

Different approaches to handling missing data may be conducted. Details will be specified in SAP.

9.4.3. Secondary Endpoint(s)/Estimand(s) Analysis

The first key secondary endpoint is the proportion of participants with CDC-defined ILI with Confirmed Influenza A. The second key secondary endpoint is the proportion of participants with WHO-defined ILI with Confirmed Influenza A. The key secondary estimands are defined similarly to the primary estimand. The analyses of the first and second key secondary endpoints will be similar to the analysis of the primary endpoint. The adjusted relative risk reductions and the corresponding 95% CIs will be calculated for the treatment comparisons of VIR-2482 1200 mg vs placebo and VIR-2482 450 mg vs placebo.

The primary analyses for the key secondary endpoints will also be conducted using treatment policy strategy for intercurrent events other than death. All observed data collected after the intercurrent events other than death will be used in the analyses. Supplemental analyses for the key secondary endpoints will also be based on responses prior to the intercurrent events by handling intercurrent events using 'while on treatment' strategy.

9.4.4. Exploratory Endpoint(s) Analysis

Serum and NPS PK parameters of VIR-2482 will be computed using standard noncompartmental methods. Parameters include, but are not limited to: C_{max}, C_{last}, T_{max}, T_{last}, AUC_{inf}, AUC_{last}, $\%AUC_{exp}$, $t_{1/2}$, λ_z, V_z/F, and CL/F. PK parameters will be listed by participant and summarized using descriptive statistics.

VIR-2482 serum and NPS concentration data may be pooled with data from other studies and used for estimation of population PK parameters.

PK/PD analyses will be conducted to explore the relationship between VIR-2482 exposure and response variables including incidence of Influenza A. These analyses may include graphical plots, tabular summaries, and linear and/or nonlinear analyses. These analyses will be exploratory in nature and will be described further in the PK/PD SAP.

The analysis set for immunogenicity will be the Immunogenicity Analysis Set. Immunogenicity testing results will be listed for each study participant. Immunogenicity data summaries will include the incidence of samples screened positive for ADA, incidence of samples confirmed positive for ADA, and summaries of ADA titers and NAb, if applicable.

Exploratory analyses may be conducted to establish correlations between immunogenicity results and safety, efficacy, or PK. These analyses may include graphical plots, tabular summaries, and linear or nonlinear analyses. Details of immunogenicity analyses will be provided in the SAP

9.4.5. Other Analyses

Other analyses, if any, will be provided in the SAP as appropriate.

9.5. Interim Analysis

No Interim Analysis (IA) will be conducted. Participants will be enrolled until a prespecified number is reached.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant [or their legally authorized representative] and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants [or their legally authorized representatives] will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

  When applicable, participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant [or their legally authorized representative].

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within the current 28 days screening period.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will be anonymized except for the identifier; participant names or any information which would make the participant identifiable will not be transferred.
- All participants must provide informed consent to the use and disclosure of their information obtained during the study. This includes informing the participant how his/her personal study-related data will be used by the sponsor, and the level of disclosure.
- The participant must also be informed and consent to the possible examination of his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities

10.1.5. Committees Structure

Independent Data Monitoring Committee

An unblinded DMC will review safety data including cumulative safety data from on an ongoing basis throughout the study as appropriate. The roles and responsibilities of the DMC, including membership, scope, frequency of meetings and communication plan are defined in the DMC charter.

The first formal DMC meeting to review safety data will occur after the first 10 participants present with protocol-defined ILI with confirmed influenza A or approximately 2 weeks after the last seasonal study participant is enrolled, whichever occurs first.

An independent statistician will monitor the incidence of protocol defined influenza A illness cases and inform the DMC of any statistically significant imbalance. Enrollment will be concluded after EOIS1 if there are at least 36 participants across all 3 treatment arms who meet the primary endpoint definition for protocol-defined ILI with confirmed influenza A. Details will be described in the DMC charter.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the data entry guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Electronic Case Report Forms (eCRFs)

- Data collected during the study will be recorded in each participant's eCRF provided by the sponsor or designee.
- The study site(s) will use an electronic data capture (EDC) system that is compliant with Food and Drug Administration (FDA) regulatory requirements per 21 CFR Part 11.
- Data queries and data correction on the eCRF will be handled through EDC.
- All transactions within the EDC system are fully documented within an electronic audit trail.
- Data reported on the CRF must be transcribed from a source document with consistency and accuracy.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm the accuracy of data entered into the eCRF. Each set of completed eCRFs must be reviewed after being source verified by the monitor and electronically signed and dated by the investigator.

10.1.9. Study and Site Start and Closure

10.1.9.1. First Act of Recruitment

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

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

10.1.9.2. Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

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

10.1.10. Dissemination of Clinical Study Data

- Where required by applicable law, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to appropriate study information and results.
- Sponsor or designee will provide all investigators who enrolled participants into the study with a summary of the study results
- Sponsor or its designee will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis
- The procedures and timing for public disclosure of study results summary will be in accordance with applicable laws.

10.1.11. Publication Policy

- Site-specific results of this study may be published or presented at scientific meetings subject to the terms and requirements of the clinical study agreement

10.2. Appendix Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6: Protocol-Required Safety Laboratory Tests

Chemistry	**Hematology**
Albumin Blood urea nitrogen (BUN) Calcium Bicarbonate Chloride Creatinine Gammaglutamyltransferase Glucose (non-fasting) Lactate dehydrogenase (LDH) Potassium Protein (total) Sodium Liver Function Tests: Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct)	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit White blood cell (WBC) count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils RBC indices: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), %reticulocytes
Coagulation Parameters	**Pregnancy Testing**
D-dimer International normalized ratio (INR) time Partial thromboplastin time (PTT)/activated PTT (aPTT) Prothrombin time (PT)	Highly sensitive (serum/plasma or urine) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
Urinalysis	**Other Tests**
Specific gravity Glucose, pH, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick Microscopic examination (if blood or protein is abnormal)	All scheduled laboratory tests should be performed by a central laboratory, with the exception of those outlined in the protocol: Respiratory Viral Panel RT-PCR Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test may be performed locally

Investigators must document their review of each laboratory safety report.

10.3. Appendix 2: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting AEs, SAEs, SSRs, AESIs

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • AEs may also include pre- or post-treatment complications that occur as a result of protocol-specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results or other safety assessments (eg, ECG, radiological scans, vital signs measurements) that require medical or surgical intervention or lead to study intervention interruption, modification, discontinuation, or are considered clinically significant in the medical and scientific judgment of the investigator • Laboratory or other abnormal assessments (eg, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE. If the laboratory abnormality is part of a clinical syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin). • Exacerbation of a chronic or intermittent pre-existing condition (recorded as medical history) including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected study intervention interaction, including drug/drug, drug/food, drug/device and drug/alcohol interactions • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy, transfusion, tooth extraction): the condition that leads to the procedure is the AE • Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, hospitalization for elective surgery) • Overdose of study intervention without clinical sequelae • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the screening visit that do not worsen

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:
Results in death
Is life threatening The term "life threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:
Is a congenital anomaly/birth defect
Other medically important events • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. – Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse, suspected transmission of any infectious agent via an authorized medicinal product

10.3.3. Definitions of Special Situations (SSR)

Special Situation Report (SSR) Definitions
Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, participant, or consumer. Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a participant. Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information. An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the pharmacist cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the additional dose(s) were administered to the participant. Occupational exposure is defined as exposure to a study intervention as a result of one's professional or nonprofessional occupation. Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction. Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial. Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Vir study intervention. Counterfeit or falsified medicine: Any study intervention with a false representation of (a) its identity, (b) its source, or (c) its history. Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product. The signs, symptoms, and/or clinical sequelae resulting from a special situation will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

10.3.4. Definition of Adverse Event of Special Interest (AESI)

AESI Definition
• An AESI is a noteworthy event for the particular product or class of products that the sponsor may wish to monitor carefully. It could be serious or non-serious (eg, hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.

10.3.5. Definition of Unsolicited AE and Solicited events

Unsolicited AE and Solicited events
• An unsolicited AE is an AE that was not solicited during the Local Tolerability Assessment or the Study Intervention Diary Card and that is communicated by a participant who has provided documented informed consent. • Solicited events are predefined events for which the participant is specifically questioned, and which are reported by the participant only during the Local Tolerability Assessment or the Study Intervention Diary Card.

10.3.6. Recording and Follow-Up of AEs, SAEs, SSRs (including Pregnancies), and/or AESIs

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information into the section of the participant's AE eCRF and the event description section of the SAE form. • All AEs/SAEs should be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor in lieu of completion of the required forms. • There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant's unique study ID number, will be redacted on the copies of the medical records before submission to the Sponsor. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. • For fatal or life-threatening events, copies of hospital case reports, discharge summaries, autopsy reports, and other documents should be submitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers. • Additional information may be requested to ensure the timely completion of accurate safety reports. • Any medications necessary for treatment of the AE/SAE must be recorded onto the concomitant medication section of the participant's eCRF and the event description section of the SAE form.

AE and SAE Recording

- Clinical endpoints that are specifically defined in the protocol, will be reported as Clinical Events and will not be collected as AEs in the CRF. The exception to this reporting requirement is when there is evidence suggesting a causal relationship between a drug and an event (eg, death from anaphylaxis). In this case, the investigator must immediately report the event to the sponsor.

SSR (including Pregnancy) and AESI

- When an SSR (including pregnancy)/AESI occurs, it is the responsibility of the investigator to review all documentation and record the relevant information on the corresponding case report form.
- If the SSR/AESI is associated with an AE/SAE, the information will also be recorded as per AE/SAE recording procedures.

Assessment of Severity

The investigator will assess severity for each AE and SAE reported during the study according to the standard toxicity grading in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials

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 applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Source: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials

- For each event, the highest grade attained should be reported.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. • An answer of Yes should be entered when, in the investigator's opinion, there is a reasonable possibility that the AE is associated with study intervention. Otherwise, relationship to study intervention should be categorized as No. • The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs, SAEs, SSRs (including Pregnancies), AESIs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to sponsor within 24 hours of receipt of the information.

10.3.7. Reporting of SAEs and SSRs (Including Pregnancies)

Safety (SAE, SSR, Pregnancy) Reporting via Paper Data Collection Tool
• Email or Facsimile transmission of the SAE/SSR paper data collection tool is the preferred method to transmit this information to the sponsor pharmacovigilance vendor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE/SSR data collection tool sent by overnight mail or courier services. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE/SSR data collection tool within the designated reporting time frames. • The investigator is responsible for assessing SAE/SSR for causality and severity, and for final review and confirmation of accuracy of event information and assessments on the reporting forms. • Contacts for SAE/SSR reporting will be included in the Study Specific Reporting Guidelines.

10.4. Appendix 3: List of Abbreviations and Definitions of Terms

ADA	anti-drug antibodies
ADE	antibody-dependent enhancement
ADL	activities of daily living
AE	adverse events
AESI	adverse event of special interest
ANOVA	analysis of variance
BMI	body mass index
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
DRE	disease-related events
DSUR	Development Safety Update Report
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
EOIS	End of Influenza Season
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HA	hemagglutinin
IA	interim analyses
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
DMC	data monitoring committee
IEC	independent ethics committees

ILI	influenza-like illness
IM	intramuscular
INR	international normalized ratio
IRB	institutional review boards
IRR	injection-related reactions
IRT	Interactive Response Technology
HRT	hormonal replacement therapy
LSM	least-square means
MCV	mean corpuscular volume
NAb	neutralizing antibody
NPS	nasopharyngeal sample
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
QTL	quality tolerance limits
RBC	red blood cell
RNA	ribonucleic acid
RSI	Reference Safety Information
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse events
SAP	Statistical Analysis Plan
SOIS	Start of Influenza Season
SSR	Special Situation Report
SUSAR	Suspected Unexpected Serious Adverse Reactions
TE	treatment-emergent
TEAE	treatment-emergent adverse event
WBC	white blood cell
WOCBP	women of childbearing potential
WONCBP	Women of non-childbearing potential
WPAI	Work Productivity and Activity Impairment

10.5. Appendix 4: Summary of Changes for Previous Protocol Amendments

Protocol Amendment 3 (22 September 2022) Summary of Changes

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 4.1 Overall Study Design 8.5 Influenza-Like Illness Surveillance	Addition of active ILI symptom surveillance from Week 52 to 84	To enhance detection of ILI cases due to influenza, enable viral testing and PK sampling, and assess illness severity during the following influenza season
1.3 Table 1. Schedule of Activities 4.1 Overall Study Design 8.3.6 Study Intervention Diary Card 8.4.6 Unsolicited and Solicited Adverse Events 10.3.5 Definition of Unsolicited and Solicited AEs	Addition of Study Intervention Diary Card	To incorporate collection of patient-reported local and systemic reactions from D1-D7 for added safety monitoring
1.3 Table 2. Schedule of Activities	ILI symptom surveillance in the ILI Monitoring Schedule	To clarify that participants will report ILI symptoms on the electronic device from ILI-D1 to ILI-D10
2.3 Benefit/Risk Assessment	Addition of safety data summary from Phase 1 VIR-2482-3001 study	Additional safety data available for VIR-2482

Section # and Name	Description of Change	Brief Rationale
3 Objectives, Endpoints, and Estimands	Revised primary safety endpoint to include the occurrence of solicited events	To clarify that solicited events will also be summarized in the summary of safety data
	Revised exploratory endpoint to include both symptomatic and asymptomatic seroconversion as part of the exploratory endpoint	To clarify that asymptomatic seroconversion will be accounted for in exploratory analyses
	Revised exploratory endpoint to include influenza B in monitoring the occurrence of non-influenza A respiratory viral infections	To clarify influenza B virus will be accounted for in exploratory analyses
4.3 Justification of Dose	Additional dose justification	To provide additional detailed rationale for the dose selection
8.4.4 Adverse Events of Special Interest	Removal of Injection Site Reactions from AESI	Injection site reactions will not need to be reported as AESIs based on tolerability data from VIR-2482-3001 study.
8.4.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or SAEs 10.3.6 Recording and Follow-Up of AEs, SAEs, SSRs (including Pregnancies), and/or AESIs	Replaced Common Terminology Criteria for Adverse Events (CTCAE) grading scale with the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Trials.	To use a grading scale that is appropriate for the trial population, as recommended by the FDA
8.4.6 Unsolicited Adverse Events 8.4.7 Solicited Events	Definition of unsolicited and solicited events	To provide additional clarity on the definition of unsolicited adverse events and solicited events
8.5 Influenza-Like Illness Surveillance	Participants will be educated on the ILI symptoms, how to reach the study site, and provided with contact information for the study site	To clarify study participant education

Protocol Amendment 2 (19 August 2022) Summary of Changes

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities, Table 1 2.3.1. Risk Assessment 4.1. Overall Study Design 8.3.5. Local Tolerability	Post-dose monitoring time	Post-injection monitoring time has been extended to a minimum of 2 hours for thorough safety and tolerability monitoring.
1.3. Schedule of Activities Table 2 8.5.1. ILI monitoring and Influenza Confirmation Visit 10.2. Appendix 2: Clinical Laboratory Tests, Table 5	Influenza Confirmation Visit and Influenza A RT-PCR Confirmatory Testing	Clarification of ILI evaluations, including using point-of-care as well as confirmatory central laboratory respiratory virus testing will be performed at the Influenza Confirmation Visit to facilitate rapid diagnosis and for endpoint determination.
1.3. Schedule of Activities, Table 1 8.6. Pharmacokinetics	Addition of nasopharyngeal PK sampling	Nasopharyngeal sampling at the EOIS visit, the ILI confirmation visit, and an optional sub-study for additional nasopharyngeal sampling are added to assess the concentration of VIR-2482 in nasal secretions.
1.3. Schedule of Activities, Table 1	Decrease frequency of ILI symptom monitoring, AE review, concomitant medication, physical examination, and vital signs	To streamline SoA and minimize participant burden.
3. Objectives, Endpoints, and Estimands 8.5.3. Virology and Resistance Surveillance 8.9. Biomarkers	Addition of exploratory objectives	Additional exploratory objectives added to further characterize asymptomatic infection, viral subtypes and dynamics, as well as nasopharyngeal PK to inform pharmacodynamics and pharmacokinetics.
5.2. Exclusion Criteria	Exclusion criteria # 9 update	To specify that participants who received any investigational agent within 90 days or within 5 half-lives of the investigational agent, whichever is longer, before study intervention administration will not be eligible.

Section # and Name	Description of Change	Brief Rationale
7.4. Participant Replacement	Removal of participant replacement	Subjects will not be replaced if they withdraw during the study for non-safety reasons.
9.4.2. Primary Endpoint(s)/Estimand(s) Analysis	Primary efficacy analyses	Treatment effect will be based on the treatment policy estimand, which considers the actual measurements of subjects regardless of adherence and rescue status. The “while on treatment” strategy will be considered for sensitivity analyses.
9.5. Interim Analyses	Interim analysis	No formal interim analysis will be conducted. Participants will be enrolled until a prespecified number is reached.
10.6. Appendix 6**:** Influenza A Illness Definitions	Protocol-defined ILI with confirmed influenza A	Updated criteria based on review of influenza case definitions and performance characteristics.

Protocol Amendment 1 (11 July 2022) Summary of Changes

Section # and Name	Description of Change	Brief Rationale
Section 1.3 (Schedule of Activities, Table 1)	Added monthly influenza-like illness (ILI) monitoring from post-end of influenza season (EOIS) to Week 48	To align the schedule for ILI monitoring following the EIOS visit with Section 4.1 (Overall Study Design).
	Specified that Week 52 physical examinations will be symptom-directed	To clarify the type of physical examination that will be performed at Week 52
Section 1.3 (Schedule of Activities, Table 2) Section 8.5.1 (ILI Monitoring and Influenza Confirmation Visit) Section 10.2 (Appendix 2: Clinical Laboratory Tests, Table 5)	Modified influenza A confirmation test to respiratory viral panel for influenza A reverse transcription-polymerase chain reaction (RT-PCR) confirmation	To clarify the type of test that will be used for influenza confirmation
Section 1.3 (Schedule of Activities, Table 2) Section 3 (Objectives, Endpoints, and Estimands) Section 8.5.1 (ILI Monitoring and Influenza Confirmation Visit) Section 8.5.2 (Influenza Intensity and Impact Questionnaire) - *section retitled*	Modified influenza intensity and impact questionnaire to Flu-iiQ™ (previously Flu-PRO)	Changed Flu-PRO to Flu-iiQ™ which captures more frequent assessments, and is more compliant, shorter, and less burdensome for participants.
Section 8.4.4 (Adverse Events of Special Interest)	Modified injection-related reactions to injection site reactions and hypersensitivity reactions into separate bullets under the list of adverse events of special interest (AESI)	To provide correct terminology and clarify injection site reactions and hypersensitivity reactions can be separate types of AESI

Section # and Name	Description of Change	Brief Rationale
Section 1.3 (Schedule of Activities, Table 1) Section 5.2 (Exclusion Criteria) Section 10.2 (Appendix 2: Clinical Laboratory Tests, Table 5)	Deleted the drug screen for cocaine, amphetamines, or opioids	Sponsor decided not necessary for the target participant population
Section 4.1.1 (Number of Participants)	Corrected the study drug name to state VIR-2482 in the bullet points (previously stated as 2218)	To clarify the name of the study drug

10.6. Appendix 5: Contraceptive and Barrier Guidance

10.6.1. Definitions

10.6.1.1. Woman of Non-Childbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):

   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L or mIU/mL) is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.6.1.2. Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless with permanent infertility, as defined in Section 10.6.1.1

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.6.2. Contraception Guidance

Contraceptives[a] Allowed During the Study Include:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[b]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview)
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. 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.*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[e]
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[c] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
[d] Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
[e] Male condom and female condom should not be used together (due to risk of failure from friction).

10.7. Appendix 6: Influenza A Illness Definitions

Protocol definitions of influenza A illness for the primary and secondary study efficacy endpoints are as defined below.

10.7.1. Protocol-Defined ILI with Confirmed Influenza A

RT-PCR confirmed influenza A with:

- At least one respiratory symptom: sore throat, cough, sputum production, wheezing, or difficulty breathing

  AND

- At least one systemic symptom: temperature> 37.8°C, chills, weakness, or myalgias

10.7.2. CDC-Defined ILI with Confirmed Influenza A

- Temperature > 37.8°C with sore throat or cough with RT-PCR confirmed influenza A

10.7.3. WHO-Defined ILI with Confirmed Influenza A

- Temperature > 38°C with cough with RT-PCR confirmed influenza A

10.8. Appendix 7: Hemispheric Influenza Season Definitions

End of Influenza Season 1, Start of Influenza Season 2, and End of Influenza Season 2 will be defined based on the approximate start and end of flu seasons in a given hemisphere. Given recent deviations in influenza seasons from established historical patterns, the hemispheric Start and End of Influenza Season dates will be defined by protocol clarification letter based on current hemispheric influenza epidemiology. EOIS1 was defined by protocol clarification letter as April 17, 2023.

10.9. Appendix 8: Local Tolerability Assessment

Injection Time: _____

Time Assessment Performed: _____

Injection Site: _____Injection Location (check ONE): ☐LEFT ☐RIGHT ☐N/A

Local Reaction to Injectable Product	**Absent (Grade 0)**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)***
Pain	Absent	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hr or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ED visit or hospitalization
Swelling	Absent	Mild discomfort to touch	Discomfort with movement but minimal interference with daily activity	Significant discomfort at rest OR prevents daily activity	ED visit or hospitalization
Erythema (Length) cm	Absent	2.5 to 5.0 cm _____cm	5.1 to 10.0 cm _____cm	☐ > 10.0 cm _____cm	Necrosis or exfoliative dermatitis
Bruising	Absent	2.5 to 5.0 cm _____cm	5.1 to 10.0 cm _____cm	> 10.0 cm _____cm	ED visit or hospitalization
Pruritis	Absent	Itching localized to injection site	Itching beyond the injection site that is not generalized OR local itching >48hrs despite treatment	Generalized itching that prevents daily activity	ED visit or hospitalization

_____
First Initial & Surname (print)

_____/_____/_____
Signature Date

* Grade 4 assessments must be documented as an AE or SAE.

10.10. Appendix 9: Management of Injection-Related Reactions Including Systemic Symptoms (Anaphylaxis)

All participants should be monitored closely, as there is a risk of injection reaction and hypersensitivity with any biological agent. Pre-medications will be permitted at the investigator's discretion and will be appropriately documented.

Local Injection Site Reactions

Signs and Symptoms	Management
Redness, soreness or swelling at the injection site	Apply a cold compress to the injections site Consider giving an analgesic (eg, ibuprofen, acetaminophen paracetamol)
Itching and redness	Consider giving an antipruritic (eg, diphenhydramine) Observe patient closely for the development of generalized symptoms
Slight bleeding	Apply pressure and an adhesive compress
Continuous bleeding	Place gauze pads over the site and maintain direct and firm pressure

Source: adapted from IAC 2019

If a participant has evidence of necrosis/ulceration, the participant should be referred to a higher level of acute care (eg, hospital emergency room) for appropriate management.

Systemic Reactions/Anaphylaxis

As with any antibody, allergic reactions to study intervention are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis (IAC 2019; ACIP 2022; Sampson 2006).

Diagnosis of Anaphylaxis

The most common signs and symptoms of anaphylaxis are cutaneous (eg, sudden onset of generalized urticaria, angioedema, flushing, pruritis). However, 10-20% of patients have no skin findings.

Danger Signs Include:

- Rapid progression of symptoms
- Evidence of respiratory distress (stridor, wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis)
- Vomiting
- Abdominal pain
- Hypotension
- Dysrhythmia
- Chest pain
- Collapse

Management of Anaphylaxis

The following procedures should be followed in the event of a suspected anaphylactic reaction:

1. Do not give additional doses of investigational product
2. Call for additional medical assistance; activate emergency medical services
3. Ensure appropriate monitoring is in place, such as continuous ECG and pulse oximetry
4. First-line treatment:
    a. Administer epinephrine (1.0 mg/ml) aqueous solution (1:1000 dilution) – 0.5 mg (0.5ml) IM in the anterolateral thigh
    b. If using an epinephrine auto-injector – use 0.3 mg IM into the anterolateral thigh
    c. May be repeated every 5-15 minutes up to 3 times
5. Optional treatment (antihistamine):
    a. Diphenhydramine 50 mg oral/IV/IM OR
    b. Hydroxyzine 25 mg oral/IM
6. Give oxygen (8-10 L/minute) via facemask, as needed
7. Normal saline rapid bolus – treat hypotension with rapid infusion of 1-2 liters IV
8. Monitor patient until emergency medical services arrive.

11. REFERENCES

ACIP (Advisory Committee on Immunization Practices). Preventing and Managing Adverse Reactions. Jan 21, 2022. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/adverse-reactions.html

Ali SO, Takas T, Nyborg A, Shoemaker K, Kallewaard NL, Chiong R, Dubovsky F, Mallory RM. Evaluation of MEDI8852, an Anti-Influenza A Monoclonal Antibody, in Treating Acute Uncomplicated Influenza. Antimicrob Agents Chemother. 2018 Oct 24;62(11):e00694-18. doi: 10.1128/AAC.00694-18. PMID: 30150460; PMCID: PMC6201130.

Tolulope A Aweda, Shih-Hsun Cheng, Stephen Lenhard et al. Biodistribution of Sotrovimab, a SARS-CoV-2 monoclonal antibody, using PET imaging in cynomolgus monkey, 13 July 2022, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-1832581/v1]

Baxter LT, Zhu H, Mackensen DG, Jain RK. Physiologically based pharmacokinetic model for specific and nonspecific monoclonal antibodies and fragments in normal tissues and human tumor xenografts in nude mice. Cancer Res. 1994 Mar 15;54(6):1517-28. PMID: 8137258.

CDC (Centers for Disease Control). CDC Seasonal Flu Vaccine Effectiveness Studies. https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm. Last reviewed March 11, 2022. Accessed May 28, 2022.

Covell DG, Barbet J, Holton OD, Black CD, Parker RJ, Weinstein JN. Pharmacokinetics of monoclonal immunoglobulin G1, F(ab')2, and Fab' in mice. Cancer Res. 1986 Aug;46(8):3969-78. PMID: 3731067.

Chigutsa E, Jordie E, Riggs M, Nirula A, Elmokadem A, Knab T, Chien JY. A Quantitative Modeling and Simulation Framework to Support Candidate and Dose Selection of Anti-SARS-CoV-2 Monoclonal Antibodies to Advance Bamlanivimab Into a First-in-Human Clinical Trial. Clin Pharmacol Ther. 2022 Mar;111(3):595-604. doi: 10.1002/cpt.2459. Epub 2021 Nov 17. PMID: 34687040; PMCID: PMC8653169.

Chigutsa E, O'Brien L, Ferguson-Sells L, Long A, Chien J. Population Pharmacokinetics and Pharmacodynamics of the Neutralizing Antibodies Bamlanivimab and Etesevimab in Patients With Mild to Moderate COVID-19 Infection. Clin Pharmacol Ther. 2021 Nov;110(5):1302-1310. doi: 10.1002/cpt.2420. Epub 2021 Sep 24. PMID: 34514598; PMCID: PMC8652670.

Eigenmann MJ, Karlsen TV, Krippendorff BF, Tenstad O, Fronton L, Otteneder MB, Wiig H. Interstitial IgG antibody pharmacokinetics assessed by combined in vivo- and physiologically-based pharmacokinetic modelling approaches. J Physiol. 2017 Dec 15;595(24):7311-7330. doi: 10.1113/JP274819. Epub 2017 Oct 29. PMID: 28960303; PMCID: PMC5730850.

IAC (Immunization Action Coalition). Medical Management of Vaccine Reactions in Adults in a Community Setting. Version July 2019. https://www.immunize.org/catg.d/p3082.pdf.

Jayasundara K, Soobiah C, Thommes E, Tricco AC, Chit A. Natural attack rate of influenza in unvaccinated children and adults: a meta-regression analysis. BMC Infect Dis. 2014 Dec 11;14:670. doi: 10.1186/s12879-014-0670-5. PMID: 25495228; PMCID: PMC4272519.

Jones BE, Brown-Augsburger PL, Corbett KS, Westendorf K, Davies J, Cujec TP, Wiethoff CM, Blackbourne JL, Heinz BA, Foster D, Higgs RE, Balasubramaniam D, Wang L, Zhang Y, Yang ES, Bidshahri R, Kraft L, Hwang Y, Žentelis S, Jepson KR, Goya R, Smith MA, Collins DW, Hinshaw SJ, Tycho SA, Pellacani D, Xiang P, Muthuraman K, Sobhanifar S, Piper MH, Triana FJ, Hendle J, Pustilnik A, Adams AC, Berens SJ, Baric RS, Martinez DR, Cross RW, Geisbert TW, Borisevich V, Abiona O, Belli HM, de Vries M, Mohamed A, Dittmann M, Samanovic MI, Mulligan MJ, Goldsmith JA, Hsieh CL, Johnson NV, Wrapp D, McLellan JS, Barnhart BC, Graham BS, Mascola JR, Hansen CL, Falconer E. The neutralizing antibody, LY-CoV555, protects against SARS-CoV-2 infection in nonhuman primates. Sci Transl Med. 2021 May 12;13(593):eabf1906. doi: 10.1126/scitranslmed.abf1906. Epub 2021 Apr 5. PMID: 33820835; PMCID: PMC8284311.

Kallewaard NL, Corti D, Collins PJ, Neu U, McAuliffe JM, Benjamin E, Wachter-Rosati L, Palmer-Hill FJ, Yuan AQ, Walker PA, Vorlaender MK, Bianchi S, Guarino B, De Marco A, Vanzetta F, Agatic G, Foglierini M, Pinna D, Fernandez-Rodriguez B, Fruehwirth A, Silacci C, Ogrodowicz RW, Martin SR, Sallusto F, Suzich JA, Lanzavecchia A, Zhu Q, Gamblin SJ, Skehel JJ. Structure and Function Analysis of an Antibody Recognizing All Influenza A Subtypes. Cell. 2016 Jul 28;166(3):596-608. doi: 10.1016/j.cell.2016.05.073. Epub 2016 Jul 21. PubMed PMID: 27453466; PubMed Central PMCID: PMC4967455.

Magyarics Z, Leslie F, Bartko J, Rouha H, Luperchio S, Schörgenhofer C, Schwameis M, Derhaschnig U, Lagler H, Stiebellehner L, Firbas C, Weber S, Campanaro E, Jilma B, Nagy E, Stevens C. Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose Study of the Penetration of a Monoclonal Antibody Combination (ASN100) Targeting Staphylococcus aureus Cytotoxins in the Lung Epithelial Lining Fluid of Healthy Volunteers. Antimicrob Agents Chemother. 2019 Jul 25;63(8):e00350-19. doi: 10.1128/AAC.00350-19. PMID: 31138568; PMCID: PMC6658777.

Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis. 2012 Jan;12(1):36-44. doi: 10.1016/S1473-3099(11)70295-X. Epub 2011 Oct 25. Erratum in: Lancet Infect Dis. 2012 Sep;12(9):655. PMID: 22032844.

Rambaut A, Pybus OG, Nelson MI, Viboud C, Taubenberger JK, Holmes EC. The genomic and epidemiological dynamics of human influenza A virus. Nature. 2008 May 29;453(7195):615-9. doi: 10.1038/nature06945. Epub 2008 Apr 16. PMID: 18418375; PMCID: PMC2441973.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993 Nov;4(5):353-65. doi: 10.2165/00019053-199304050-00006. PMID: 10146874.

Sampson HA Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al, Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-7

Shah DK, Betts AM. Antibody biodistribution coefficients: inferring tissue concentrations of monoclonal antibodies based on the plasma concentrations in several preclinical species and human. MAbs. 2013 Mar-Apr;5(2):297-305. doi: 10.4161/mabs.23684. Epub 2013 Feb 13. PMID: 23406896; PMCID: PMC3893240.

Food and Drug Administration (FDA) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials. https://www.fda.gov/media/73679/download. Published September 2007. Accessed September 16, 2022.

WHO (World Health Organization). Influenza (Seasonal). http://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal). Published January 2018. Accessed October 01, 2018.

Signature Page for VV-CLIN-001039 v8.0

Approval Task	[redacted] 2023 05:11:11 GMT+0000

Signature Page for VV-CLIN-001039 v8.0