STATISTICAL ANALYSIS PLAN

AMENDMENT 2 (VERSION 2.0)

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
Date	13 Jun 2023

This study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

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VERSION HISTORY

This statistical analysis plan (SAP) for Study VIR-2482-4002 is based on the protocol amendment 3, dated 22 Sep 2022, version 1.

SAP Version	Date	Change	Rationale
Original	21 Dec 2022	Not applicable	Original version
Amendment 1	24 Mar 2023	Refer to Section 4.9.2	Refer to Section 4.9.2
Amendment 2	12 Jun 2023	Refer to Section 4.9.2	Refer to Section 4.9.2

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses to be included in the clinical study report (CSR) for VIR-2482-4002. The following documents were reviewed in preparation of this SAP:

- Protocol Amendment 3, 22 Sep 2022, Version 1
- Electronic case report forms (eCRFs), 31 Mar 2023

This SAP will be finalized and approved prior to treatment unblinding. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP. Important changes to the SAP, along with justifications for the changes, will be described in the CSR. Changes to the protocol will require a SAP amendment ONLY if the changes are to a principal feature of the protocol. Any post hoc or unplanned analyses that are performed and not specifically specified in this SAP will be clearly identified as such if they are included in the CSR.

The non-compartmental pharmacokinetic (PK) analysis will be described in an appendix of this SAP. Population PK (PopPK) analyses, analyses of the exploratory endpoint of emergence of influenza A viral resistance to VIR-2482, and exploratory biomarker analysis, excluding analyses of anti-influenza antibody (which will be covered in this SAP), will be documented separately in separate analysis plans.

1.1. Objectives

1.1.1. Primary Objectives

- To evaluate the efficacy of VIR-2482 compared to placebo in the prevention of protocol-defined influenza-like illness (ILI) with confirmed influenza A
- To evaluate the safety and tolerability of VIR-2482 compared to placebo

1.1.2. Secondary Objectives

- To evaluate the efficacy of VIR-2482 compared to placebo in the prevention of CDC-defined or WHO-defined ILI with confirmed influenza A

1.1.3. Exploratory/Other Objectives

- To evaluate the effect of VIR-2482 compared to placebo on the severity and duration of illness in participants with confirmed influenza A
- To evaluate the immunogenicity (induction of anti-drug antibody (ADA)) response to VIR-2482
- Evaluate the effect of VIR-2482 versus placebo on potential biomarkers of host response in participants with confirmed influenza A
- To evaluate seroconversion to circulating strains of influenza A virus

- The occurrence of influenza infection by virus subtype
- To evaluate the effect of VIR-2482 compared to placebo on the magnitude of viral load in nasopharyngeal samples at time of ILI
- Monitor the occurrence of non-influenza A respiratory viral infections
- Measure of Work Productivity and Activity Impairment (WPAI) due to influenza A illness

1.2. Study Design

1.2.1. Overall Design

This is a double-blind, randomized, placebo-controlled, Phase 2 study of VIR-2482 administered intramuscularly (IM) in healthy adult volunteers, aged 18 to < 65, without pre-existing risk factors for serious complications from influenza infection and who have not received an influenza vaccination for the upcoming influenza season.

Assuming an attack rate of 2.25% for protocol-defined ILI with confirmed influenza A in the placebo arm, approximately 3000 eligible participants will be randomized in a 1:1:1 ratio to receive VIR-2482 450 mg, VIR-2482 1200 mg, or volume-matched placebo. Given the seasonal nature of influenza, efforts will be made to enroll all participants during the first 12 weeks of each hemispheric influenza season, as applicable. Participants who withdraw before study intervention administration may be replaced. Study enrollment will conclude when at least 36 participants (blinded and pooled across treatment groups) in the Full Analysis Set (FAS) have met the primary endpoint of protocol-defined ILI with RT-PCR confirmed influenza A. Enrollment may continue into a second hemispheric influenza season to meet the number of participants in the FAS with protocol-defined ILI with RT-PCR confirmed influenza required to stop enrollment.

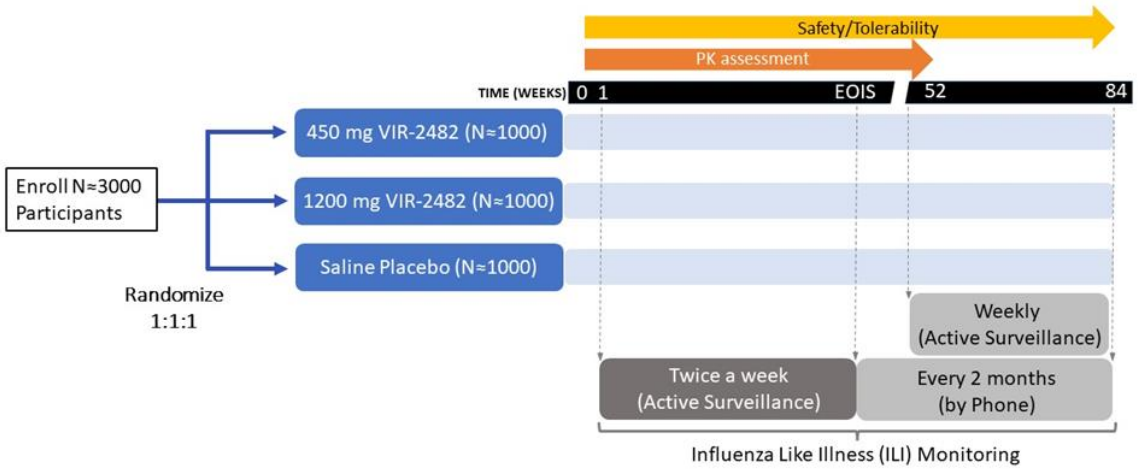
Study intervention will be administered only once on Day 1 as two 4 mL IM injections in the vastus lateralis (thigh) or the dorsogluteal (buttock) site as an alternative.

Participants will be actively monitored for ILI throughout the study and will complete ILI symptom surveillance questions twice per week from Day 1 through the End of Influenza Season (EOIS) visit. In the event a participant experiences ILI, standard of care therapy per local treatment guidelines, which may include antiviral therapy, should be offered to the participant. The EOIS visit will be defined based on the approximate end of an influenza season in a given hemisphere via a protocol clarification letter based on current hemispheric influenza epidemiology.

An unblinded independent Data Monitoring Committee (DMC) will review cumulative safety on an ongoing basis throughout the study. The first scheduled DMC data review meeting will occur after the first ten participants present with protocol-defined ILI with RT-PCR confirmed influenza A or approximately 2 weeks after the last study participant in a hemispheric influenza season is randomized, whichever is first. To evaluate the potential for ADE of influenza A illness in this study, an independent, unblinded statistician will monitor the number of RT-PCR

confirmed influenza A cases in placebo and VIR-2482 treatment groups and notify the DMC of any nominally statistically significant (at α=0.05) excess number of cases in the VIR-2482 treatment groups. A DMC safety data review meeting may be held to review safety data and make recommendations regarding further study conduct. Details are provided in the DMC charter.

1.2.2. Study Schema



1.2.3. Randomization

All participants will be centrally randomized to receive study intervention using an Interactive Response Technology (IRT) system. Eligible participants will be randomized 1:1:1 to receive VIR-2482 450 mg, VIR-2482 1200 mg, or volume-matched placebo on Day 1. The randomization will be stratified by country.

1.2.4. Blinding and Unblinding

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.

The primary analysis will occur following the first database freeze after all participants have completed the EOIS visit at the end of the influenza season. Per the study design, enrollment will conclude after a minimum of approximately 3000 participants have been randomized and when at least 36 participants (blinded and pooled across treatment groups) in the FAS have met the primary endpoint of protocol-defined ILI with RT-PCR confirmed influenza A. The final analysis will occur after database lock after all participants have completed the study. Measures will be taken to ensure study trial integrity between the time of the primary analysis to the final analysis. Details will be provided in a separate document.

2. 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. Confirmed influenza A is defined as sponsor-provided point-of-care (PoC) or central virology laboratory RT-PCR confirmed influenza A, referred to as 'RT-PCR confirmed' from this point on unless otherwise specified.

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 RT-PCR 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 RT-PCR 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 RT-PCR 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 RT-PCR 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 RT-PCR 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 RT-PCR confirmed Influenza A.

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 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 the upcoming influenza season (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 the study intervention received.
Pharmacokinetic Analysis Set	The Pharmacokinetic Analysis Set will include all participants in the Safety Set who 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.

4. STATISTICAL ANALYSES

4.1. General Considerations

All analyses will use SAS version 9.4 or higher.

Data will be provided in by-participant listings for the All Participants Set, unless otherwise specified.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures and derived listings. Minimum and maximum values will be reported with the same precision as the units of measure. The mean and median will be reported to 1 additional decimal place, and the SD will be reported to 2 additional decimal places. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

Categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places, and percentages will not be displayed for zero counts.

Baseline value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to study intervention administration. If time is not collected, Day 1 assessments scheduled to be performed prior to study intervention administration will be assumed to be taken prior to study intervention administration and used as baseline. Unless otherwise specified, if baseline cannot be determined due to missing data, no derivation will be performed, and baseline will be set to missing.

- For summaries of treatment-emergent laboratory abnormalities (Refer to Section 4.6.8), if baseline is missing, the baseline value will be assumed to be normal (i.e., no grade [Grade 0]).
- For summaries of treatment-induced ADA to VIR-2482 (Refer to Section 4.5.3), participants with missing baseline samples will be assumed to be negative for ADA at baseline.

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

Study Day is the number of days from study intervention administration, which is Study Day 1. If an assessment date is on or after the date of the study intervention administration, the study day is calculated as (date of assessment – date of study intervention administration, + 1). If the assessment date is prior to the date of study intervention administration, the study day is calculated as (date of assessment – date of study intervention administration).

Treatment-emergent (TE) period: for the primary analysis, the TE period will include the time period starting from the date of the first administration of study intervention to the participant's EOIS visit. If a participant does not have an EOIS visit, the time period will include data through

the last participant's EOIS visit. Completion of study participation through EOIS for each individual participant is defined as one of the following:

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

For the final analysis, the TE Period will include the time period starting from the date of the first administration of study intervention 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 week 84 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.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In the derivation of baseline, 'any' post-baseline, and last post-baseline measurements
- In the derivation of maximum, minimum, and worst values

Analysis Visit Windows: Unscheduled measurements will be recorded as such and not attributed to a scheduled measurement time point, unless otherwise specified.

Incomplete/Missing data*:*

- Details regarding handling of missing data for the primary and secondary estimands are provided in Section 4.3.2 and Section 4.4.1.
- For safety analyses, missing data other than missing dates will not be imputed. Details regarding handling of missing dates for AE and medications are provided in Section 4.2.4 and Section 4.6.3, respectively.

Data Handling Conventions: For analyses of clinical safety laboratory data that are continuous in nature, but are less than the lower limit of quantitation (LLOQ) or above the upper limit of quantitation, will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (e.g., if the result of a continuous laboratory test is < 30, a value of 29 will be assigned; if the result of a continuous laboratory test is < 30.0, a value of 29.9 will be assigned). If the results of continuous lab test is < 1, the imputed value should be 0.9; If the results of the lab test is < 0.1, the imputed value should be 0.09. The actual reported values will be provided in by-participant listings.

For analyses of viral load, values <LLOQ will be imputed as 2.78 since the LLOQ = 2.79 viral particles/ mL. Following the same logic for values reported <LLOQ, negative values (i.e. <LLOD) will be imputed as 2.59 since the LLOD of the assay is 2.60 vp/mL.

As is standard practice with hemagglutination inhibition (HAI) titers, any titer below LLOQ will be imputed as half the LLOQ. For analyses of HAI titers, values <LLOQ will be imputed as 5 since the LLOQ = 10.

For analyses of ADA titers, values < minimum required dilution (MRD) will be imputed as 20 since the MRD = 20. The ADA titer is obtained by serially diluting a confirmed positive sample until it reaches the cutpoint of the method and becomes negative. The titer is the reverse of this dilution. All samples are diluted at the MRD so, if the sample crosses the cutpoint at the MRD dilution, the minimum value for a titer is the MRD.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

Repeated Observations: Measurements recorded at different time points are defined as repeated observations. If an assessment has planned repeated measurements, then statistical summaries will present all planned time points, as appropriate.

If there are multiple records for a scheduled assessment timepoint, the records will be sorted in chronological order and the last record will be used for analysis.

Multicenter Considerations: Data from different sites will be pooled for analysis.

4.2. Background Characteristics

4.2.1. Participant Disposition

The number of participants screened (defined as providing informed consent) and who were screen failures, along with the reason for screen failure, will be summarized.

The number and percentage of participants in each treatment group in the All Participants Set, the FAS, PK Analysis Set, Immunogenicity Analysis Set, and Virology Analysis Set will be summarized by treatment group.

A by-participant listing of the as-implemented randomization schedule will be provided.

A summary table of total randomized participants and percentages in each study site will be provided.

The number and percentage of participants in the Safety Set who completed the study or prematurely discontinued the study and the primary reason for premature discontinuation from the study will be summarized overall and by treatment group. A similar summary will be provided for the FAS. The reasons for premature discontinuation from study will be provided in a by-participant listing.

4.2.2. Eligibility Criteria Violations and Protocol Deviations

Protocol deviations will be reviewed by Vir and categorized into general deviation categories and classified by importance (important or not important). An important protocol deviation is a protocol deviation that may significantly impact the completeness, accuracy, and/or reliability of study data or that may significantly affect a participant's rights, safety, or well-being, as defined in the study Protocol Deviations Management Plan. Final review of protocol deviations will be conducted prior to unblinding. Any protocol deviations identified after unblinding will be included in the analyses and identified as such in the CSR.

The number and percentage of participants in the All Participants Set with any important protocol deviation and with any important protocol deviation by deviation category will be summarized overall and by treatment group. A similar summary will be provided for the FAS. A by-participant listing of all important protocol deviations will be provided.

4.2.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics (country of enrollment, age (years), sex, ethnicity, race, height (cm), weight (kg), and BMI (kg/m^2) will be summarized overall and by treatment group for the FAS using descriptive statistics including n, mean, SD, median, Q1, Q3, min, and max for continuous variables and numbers and percentages of participants for categorical variables. This summary will also be provided for the Safety Set.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 or later and summarized by SOC, PT and treatment group for the FAS and Safety Set. Medical history will also be provided in by-participant listing(s).

4.2.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD), version WHODrugGlobalB3_SEP2022, and summarized separately for the Safety Set by treatment group, anatomic therapeutic chemical (ATC) classification level 3, and preferred term.

- **Prior medication**: medication received prior to administration of study intervention, regardless of when it was stopped, or with a missing start date
- **Concomitant medication**: medication received on or after administration of study intervention, prior to administration of study intervention and continued after administration of study intervention, or with a missing end date

Details for handling of missing or partial dates are provided in Section 6.2. Imputed dates will be used only for analyses of prior/ concomitant medications; the actual reported dates, not the imputed dates, will be displayed in by-participant listing(s).

All medications will be provided in a by-participant listing along with a column indicating whether the medication was prior, concomitant, or both.

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

All efficacy analyses described in this section will be based on the FAS, unless specified otherwise.

4.3.1. Primary Endpoint

The primary efficacy endpoint is the occurrence of protocol-defined ILI with confirmed influenza A (by reverse transcription-polymerase chain reaction [RT-PCR]) and is defined as follows:

Sponsor-provided PoC or central virology laboratory RT-PCR confirmed influenza A (referred to as RT-PCR confirmed from this point on) with:

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

AND

- At least one systemic symptom: investigator-confirmed chills, weakness, or myalgia or participant-reported temperature > 37.8°C

All investigator-confirmed respiratory and systemic symptoms from the earliest onset date of symptoms as reported by the participant or by the investigator and RT-PCR results within 10 days post the earliest symptom onset will be used to define the primary endpoint.

4.3.2. Primary Estimand

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 had influenza A infection within 3 months prior to dosing, have not received an influenza vaccination for the upcoming influenza season, and received study intervention.
- Variable: occurrence of protocol-defined ILI with RT-PCR confirmed influenza A through EOIS. Participants who die due to influenza A illness will be considered to have had protocol-defined ILI with RT-PCR confirmed influenza A. Protocol-defined ILI with RT-PCR confirmed influenza A and RT-PCR confirmed concomitant influenza B, RSV, or SARS-CoV-2 (referred to as coinfection from this point on) will be considered to not meet the endpoint since the causality of a participant's symptoms cannot be reliably attributed to 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, which will be handled by using the treatment policy strategy
  - Receipt of an authorized influenza vaccine, which will be handled by using the treatment policy strategy
  - Death for reason(s) other than influenza illness, which will be handled by using the while-alive approach, where data up until the time of death will be included

  - Participants who become unblinded to treatment assignment due to any reasons, which will be handled by using the treatment policy strategy
- Population-level summary: Relative risk

The number and percentage of participants in the FAS with each intercurrent event will be summarized by treatment group. The primary efficacy analysis will be the comparison of the proportion of participants in the FAS with protocol-defined ILI with RT-PCR-confirmed influenza A after administration of study intervention using a Poisson regression model with robust sandwich estimators (Zou 2004), where treatment group is the only factor in the model. Participants with multiple occurrences of protocol-defined ILI with RT-PCR confirmed influenza A will be counted once at the earliest occurrence. The number and percentage of participants with and without protocol-defined ILI with RT-PCR confirmed influenza A or with missing data for the primary endpoint will be summarized by treatment group. The relative risk reduction, calculated as 100% × (1 - 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 relative risk reductions and the corresponding 95% CIs will be calculated for the treatment comparisons of VIR-2482 450 mg vs placebo.

If the Poisson regression fails to converge, Fisher's exact test will be performed to compare the proportion of participants in the FAS with protocol-defined ILI with RT-PCR-confirmed influenza A after administration of study intervention between treatment groups. Exact unconditional 95% CI for the relative risk will be calculated.

Participants are considered to have missing data for the primary endpoint if the participant did not meet the primary endpoint prior to EOIS and met any of the following criteria:

- prematurely discontinued the study prior to EOIS
- had symptoms meeting protocol-defined ILI criteria but were missing RT-PCR results
- had RT-PCR results confirming influenza A but were missing symptom assessments

For participants who are missing data for the primary endpoint, the missing data pattern will be considered monotone and imputed using the observed rate within the placebo group. The imputation will be performed using SAS PROC MI: Monotone Logistic Regression, for monotone missing data with age group as a covariate. A sufficient number of imputations will be performed to ensure stability of the estimates. The results of the analyses using each imputed data set will be combined using Rubin's rule and SAS PROC MIANALYZE.

4.3.3. Sensitivity Analyses

Two sensitivity analyses will be performed to assess the sensitivity of results to the handling of missing data.

To assess the sensitivity of the results to varying follow-up time among participants at the time of the primary analysis, a sensitivity analysis will be performed in which the primary analysis will be repeated including the log of the follow-up time as an offset.
Follow-up time will be calculated as follows:

- For participants who meet the primary endpoint: (date of onset of protocol-defined ILI with RT-PCR-confirmed influenza A or date of death due to influenza A) – (date of study intervention) +1.
- For participants who do not meet the primary endpoint: (EOIS date) – (date of study intervention) +1.
- For participants who do not meet the primary endpoint and prematurely discontinue the study, withdraw consent, or are lost to follow-up prior to EOIS: (ET visit date/date of withdrawal of consent/date of last contact) – (date of study intervention) +1.

A tipping point analysis will be performed to assess the sensitivity of results to handling of missing data. For this analysis, the underlying proportion of protocol-defined ILI with RT-PCR confirmed influenza A among those participants missing primary endpoint data in each treatment group will be varied ranging between 0 and 1. This analysis will be two-dimensional, i.e. it will allow for assumptions about the assumed proportion of participants with protocol-defined ILI with RT-PCR confirmed influenza A in the two compared treatment groups to vary independently. For combinations of the assumed proportion of participants with protocol-defined ILI with RT-PCR confirmed influenza A in the treatment groups, the number of additional participants with protocol-defined ILI with RT-PCR confirmed influenza A among participants missing primary endpoint data will be imputed multiple times by drawing from a binomial distribution. The relative risk and associated standard error for each imputed dataset will be calculated using the primary analysis model and results combined using Rubin's rules to calculate the relative risk and two-sided p-value for the treatment comparison. Results will be presented in a heatmap.

4.3.4. Supplementary Analyses

The following supplemental estimands will be estimated for the FAS.

1. The first supplemental estimand will be similar to the primary estimand except that all intercurrent events will be handled using the while-on-treatment strategy with all other attributes being the same as for the primary estimand. To estimate this estimand, only data collected up to the earliest date of the intercurrent events will be used in the analysis. Missing data will be handled in the same manner as for the primary estimand.

2. The second supplemental estimand will be similar to the primary estimand except that only central virology laboratory RT-PCR results will be considered in the derivation of the endpoint. If central virology laboratory RT-PCR results are missing, the PoC RT-PCR results will be used. Missing data will be handled in the same manner as for the primary estimand.

3. The third supplemental estimand will be similar to the primary estimand except that only PoC RT-PCR results will be considered in the derivation of the endpoint. If PoC RT-PCR results are missing, the central virology laboratory RT-PCR results will be used. Missing data will be handled in the same manner as for the primary estimand.

4. The fourth supplemental estimand will be similar to the primary estimand except that the variable will be defined as the time to first occurrence of protocol-defined ILI with RT-PCR

confirmed influenza from study intervention administration through EOIS in the FAS. This supplemental analysis will be the comparison of the median time to the first occurrence of protocol-defined ILI with RT-PCR confirmed influenza A through EOIS. The number and percentage of participants with and without protocol-defined ILI with RT-PCR confirmed influenza A or who are censored will be summarized by treatment group. The time to first occurrence of protocol-defined ILI with RT-PCR confirmed influenza A through EOIS will be estimated using the Kaplan-Meier approach and the median and 25^{th} and 75^{th} percentiles, along with the 95% CI for each, will be summarized by treatment group. Kaplan-Meier estimates will also be displayed graphically. The analysis of the endpoint will be conducted using the hypothetical strategy for intercurrent events, where participants will be censored at the earliest date of the intercurrent event. The number and percentage of participants in the FAS with each intercurrent event will be summarized by treatment group. Participants with missing data for the endpoint will be censored at the last follow-up date. The last follow-up date is defined as the last visit or telephone contact date.

5. The fifth additional supplemental estimand will be similar to the primary estimand except that protocol-defined ILI with RT-PCR confirmed influenza A and RT-PCR confirmed concomitant influenza B, RSV, or SARS-CoV-2 will be considered to meet the endpoint.

6. The sixth additional supplemental estimand will be similar to the primary estimand except that protocol-defined ILI with RT-PCR confirmed influenza A with onset within 96 hours (inclusive) following study intervention will be considered to not meet the endpoint. The influenza A incubation period is 1-4 days and these could be incubating influenza A infections with onset prior to randomization.

4.3.5. Subgroup Analyses

Subgroup analyses by country will be performed using the same methodology as for the primary efficacy analysis, as applicable. A forest plot of the relative risk ratios and the corresponding 95% confidence intervals (CIs) will be generated.

Subgroups include the following:

- Sex at birth (female, male)
- Age (<25 years, 25-45 years, ≥45 years)
- Race (white, other)
- Ethnicity (hispanic, other)
- BMI (<25 kg/m^2, 25-30 kg/m^2, ≥30 kg/m^2)
- Study intervention injection site (thigh only, buttocks only, thigh and buttock, other)
- Region (northeast, midwest, south, west). Refer to Appendix 11 for further details regarding the definition of region.

Additional subgroup analyses may also be performed.

4.3.6. Multiplicity Adjustment

A hierarchical fixed sequence testing procedure will be used to control the overall type I error at $\alpha = 0.05$ for comparing VIR-2482 1200 mg versus placebo and VIR-2482 450 mg versus placebo for the primary and secondary efficacy estimands.

For the primary estimand, the comparison of VIR-2482 1200 mg versus placebo will be tested at $\alpha=0.05$ (two-sided). If the test is statistically significant and VIR-2482 1200 mg is superior to placebo, then the comparison of VIR-2482 450 mg versus placebo for the same estimand will be tested at $\alpha=0.05$ (two-sided).

Testing of VIR-2482 1200 mg versus placebo and VIR-2482 450 mg versus placebo for the secondary efficacy estimands/ endpoints will proceed as follows:

1. The proportion of CDC-defined ILI with RT-PCR confirmed influenza A for VIR-2482 1200 mg vs placebo
2. The proportion of WHO-defined ILI with RT-PCR confirmed influenza A for VIR-2482 1200 mg vs placebo
3. The proportion of CDC-defined ILI with RT-PCR confirmed influenza A for VIR-2482 450 mg vs placebo
4. The proportion of WHO-defined ILI with RT-PCR confirmed influenza A for VIR-2482 450 mg vs placebo

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 (two-sided).

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

4.4.1. Key Secondary Estimands/ Endpoints

Secondary efficacy endpoints are:

1. Occurrence of CDC-defined ILI with confirmed influenza A, defined as RT-PCR confirmed influenza A with patient-reported temperature > 37.8°C and investigator-confirmed sore throat or cough. All investigator-confirmed respiratory and systemic symptoms from the earliest onset date of symptoms as reported by the participant or by the investigator and RT-PCR results for 10 days post earliest symptom onset will be used to define the endpoint.

2. Occurrence of WHO-defined ILI with confirmed influenza A, defined as RT-PCR confirmed influenza A with participant-reported temperature > 38°C with cough. All investigator-confirmed cough from the earliest onset date of symptoms as reported by the participant and RT-PCR results for 10 days post earliest cough onset will be used to define the endpoint.

The secondary estimands are defined similarly to the primary estimand with all attributes being the same other than the variable. The primary analysis of the first and second secondary efficacy

endpoints will be the same as those specified for the primary 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.

4.4.1.1. Sensitivity Analyses

Sensitivity analyses for the secondary estimands may be performed.

4.4.1.2. Supplementary Analyses

Supplemental analysis of the first and second secondary efficacy endpoints may be performed.

4.4.2. Secondary Endpoint(s) Analysis

There are no other secondary endpoints.

4.4.3. Subgroup Analyses

Subgroup analyses may be performed using the same methodology as for the primary efficacy analysis, as applicable.

4.5. Exploratory Endpoint(s) Analysis

4.5.1. Severity and Duration of Participant-reported Signs and Symptoms of ILI due to Influenza A

Severity and duration of participant-reported signs and symptoms of ILI due to influenza A will be measured using Flu-iiQ™.

Participants will complete the Flu-iiQ™, which is a self-assessment of systemic and respiratory symptoms associated with influenza (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pain, and fatigue (tiredness)). Participants will score the severity of their symptoms using a 4-point rating scale (0, None; 1, Mild; 2, Moderate; 3, Severe). Severity of symptoms and additional items related to physical, social, and emotional well-being will also be collected per the ILI Monitoring Schedule (Protocol Table 2).

Time to resolution of protocol-defined ILI with RT-PCR confirmed influenza A without coinfection will be summarized by treatment group for participants in the FAS with resolution of protocol-defined ILI with RT-PCR confirmed influenza A. If a participant has multiple protocol-defined ILI with RT-PCR confirmed influenza A, all will be included in this summary. Time to resolution is defined as the period of time (hours) from the onset of respiratory symptoms per Flu-iiQ to the resolution of all respiratory symptoms per Flu-iiQ (i.e., all symptoms are absent or mild for at least 24 hours). If a subject has protocol-defined ILI with symptoms of only mild severity, it will be considered to have resolved on the day of onset (i.e. duration will be 24 hours).

The number and percentage of participants with protocol-defined ILI with RT-PCR confirmed influenza A without coinfection (the primary estimand variable) with individual symptoms per Flu-iiQ will be summarized by treatment group, overall and by maximum severity, and will also be displayed graphically. If a participant has multiple protocol-defined ILI with RT-PCR confirmed influenza A, all will be included in this summary. Descriptive statistics for the time to

resolution of individual respiratory symptoms will be provided by treatment group for participants with resolution of protocol-defined ILI with RT-PCR confirmed influenza A. Time to resolution is defined as the period of time (hours) from the onset of a respiratory symptom per Flu-iiQ to the resolution of that symptom (i.e., symptom is absent or mild for at least 24 hours) per Flu-iiQ. Only those symptoms with onset prior to the date of resolution of protocol-defined ILI with RT-PCR confirmed influenza A will be included in this summary.

Similar summaries may be provided for CDC- and WHO-defined ILI with RT-PCR confirmed influenza A.

By-participant listings of all symptoms of illness from Flu-iiQ for participants with RT-PCR confirmed influenza A without coinfection will be provided.

4.5.2. Exposure-response (ER) for VIR-2482

The number and percentage of participants in the FAS with protocol-defined ILI with RT-PCR confirmed influenza A without coinfection (the primary estimand variable) from the beginning of the study through EOS, and from EOIS through EOS, will be summarized by treatment group. Detailed exposure-response analyses will be described separately in the PopPK/ ER analysis plan.

4.5.3. ADA to VIR-2482

The number and percentage of participants in the Immunogenicity Set with samples screened/confirmed negative (ADA negative) or confirmed positive for ADA to VIR-2482 (ADA positive) at baseline and each scheduled post-baseline study visit will be summarized by treatment group. Titers for participants confirmed positive for ADA to VIR-2482 will be summarized by treatment group using descriptive statistics (n, median, min, max).

The number and percentage of participants in the Immunogenicity Set with treatment-emergent ADA to VIR-2482, overall and by type (treatment-induced ADA and treatment-boosted ADA), or with treatment-unaffected ADA will be summarized by treatment group. Titers for participants with ADA to VIR-2482 will also be summarized by treatment group and type (treatment-induced ADA, treatment-boosted ADA, treatment-unaffected ADA). A participant can contribute >1 post-baseline titer to summaries of ADA titers. Treatment-induced ADA is defined as a baseline sample negative for ADA (or missing) and a post-baseline sample confirmed positive for ADA. Treatment-boosted ADA is defined as a baseline sample confirmed positive for ADA and a post-baseline ADA titer >4x the baseline ADA titer. Treatment-unaffected ADA is defined as a baseline sample confirmed positive for ADA and a post-baseline ADA titer ≤4x the baseline ADA titer or all post-baseline samples are negative for ADA.

The number and percentage of participants in the Immunogenicity Set with treatment-emergent transient or persistent ADA to VIR-2482 will be summarized by treatment group. Titers for participants with treatment-emergent transient or persistent ADA to VIR-2482 will also be summarized by treatment group. A participant can contribute >1 post-baseline titer to summaries of transient and persistent ADA titers. ADA is defined as transient if the last ADA result for a participant is negative but there is treatment-induced ADA at only one time point (excluding the last non-missing result) or there are ≥2 samples with treatment-induced ADA with fewer than 16

weeks between the first and last samples that are positive for ADA (irrespective of negative samples in between). ADA is defined as persistent if there are ≥2 samples at different timepoints with treatment-induced ADA with 16 or more weeks between the first and last samples that are positive for ADA or there is treatment-induced ADA at the final timepoint.

By-participant listings of the ADA titer for each positive sample, assigned and actual treatment group, nominal visit and timepoint for sample collection, serum and NPS VIR-2482 concentration, all solicited and unsolicited AEs reported, and any other safety markers will be provided for all participants confirmed positive for ADA.

4.5.4. Symptomatic and Asymptomatic Seroconversion

The number and percentage of participants who achieve symptomatic or asymptomatic seroconversion to circulating strains of influenza A as measured by serotype-specific HAI titers will be summarized by treatment group for the Safety Set. Participants who received an authorized seasonal influenza vaccine after receiving study intervention and prior to EOIS will be excluded from this analysis.

Seroconversion is defined as a HAI titer of ≥1:40 at EOIS if the baseline titer is <1:10, or a 4-fold increase in HAI titer at EOIS if baseline titer is ≥1:10. Symptomatic seroconversion is defined as seroconversion among participants who experience at least one ILI symptom (including patient-reported temperature >37.8°C) with RT-PCR confirmed influenza A without coinfection (the primary estimand variable); asymptomatic seroconversion is defined as seroconversion among participants who do not experience any ILI symptoms, or experience at least one ILI symptom but do not test positive for influenza A by RT-PCR.

All HAI titers will be provided in a by-participant listing.

4.5.5. Influenza A Subtype

The number and percentage of participants with protocol-defined ILI with RT-PCR confirmed influenza A without coinfection (the primary estimand variable) will be summarized by influenza A subtype and treatment group for the Virology Analysis Set.

The number and percentage of participants with RT-PCR confirmed influenza A will be summarized by influenza A subtype and treatment group for the Safety Set.

All influenza A subtype data will be provided in a by-participant listing.

4.5.6. Influenza A Viral Load

Influenza A viral load in nasopharyngeal secretions at the time of confirmation of protocol-defined ILI with RT-PCR confirmed influenza A without coinfection as determined by quantitative RT-PCR (log_{10} influenza A viral particles (vp)/mL) will be summarized (n, mean, SD median, Q1, Q3, min, and max) by treatment group for the Virology Analysis Set.

A similar summary will be provided for all nasopharyngeal secretions with RT-PCR confirmed influenza A for the Safety Set.

All viral load data will be provided in a by-participant listing.

4.5.7. Non-influenza A Respiratory Viral Infections

The number and percentage of participants in the Safety and Virology Analysis Sets with non-influenza A respiratory viral infections as determined from RT-PCR will be summarized by treatment group both overall and by virus type (Influenza B, RSV, SARS-CoV-2).

All respiratory virus panel results will be provided in a by-participant listing.

4.5.8. Neutralizing Antibodies

Blood samples for the measurement of neutralizing antibodies were collected for future analysis. Details of any future analysis will be provided in a separate document.

4.6. Safety Analyses

Safety is a co-primary objective of the study. The safety endpoints are as follows: occurrence of adverse events (AEs), occurrence of serious adverse events (SAEs), occurrence of adverse events of special interest (AESI), occurrence of solicited adverse events, and changes/ abnormalities in vital signs and clinical safety laboratory assessments.

All safety analyses will be based on data from the treatment-emergent period for all participants in the Safety Set. Participants will be analyzed according to the treatment they received. Only descriptive analysis of safety will be performed, and no statistical testing will be performed.

4.6.1. Extent of Exposure

The number and percentage of participants in the FAS who received 1 full dose of study intervention (2 full volume injections (4 mL/ injection)), a partial dose (2 injections, but one or both were not the full volume, or only 1 injection), or more than 1 full dose, and who received study intervention by injection site (e.g. thigh only, buttocks only, thigh and buttock) will be summarized by treatment group. A similar summary will be provided for the Safety Set.

4.6.2. Study Drug Compliance

Not applicable.

4.6.3. Adverse Events (AE)

Adverse events will be coded using MedDRA version 25.1 or later and graded using the Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (FDA 2007).

Pre-treatment AEs will be defined as AEs that started after informed consent up to the administration of study intervention.

Treatment-emergent AEs (TEAEs) will be defined as any AEs reported with an onset date on or after the administration of study intervention through the end of the TE period.

Details for handling of missing or partial dates are provided in Section 6.3. Imputed dates will be used only for analyses of AEs; the actual reported dates, not the imputed dates, will be displayed in by-participant listing(s).

An overview of all TEAEs will be provided and will include the number and percentage of participants in each treatment group and overall with:

- any TEAE
- any non-serious TEAE
- any TEAE by strongest relationship to study intervention
- any TEAE by maximum toxicity grade
- any Grade 3/4 TEAE
- any study intervention-related non-serious TEAE
- any TEAE leading to study intervention discontinuation or interruption
- any TEAE leading to study discontinuation
- any serious TEAE
- any study intervention-related serious TEAE
- any serious TEAE leading to study discontinuation
- any TEAE leading to death

For the above summary, a participant with multiple occurrences of the same adverse event will be counted only once, at the maximum toxicity grade or strongest relationship to study intervention.

The following summaries of TEAEs will be provided by SOC, PT, and treatment group (unless otherwise specified below). For these summaries, a participant with multiple occurrences of the same adverse event will be counted only once, at the maximum toxicity grade or strongest relationship to study intervention.

- TEAEs
- TEAEs by PT, sorted by descending frequency of PT in the pooled VIR-2482 treatment group
- non-serious TEAEs
- non-serious TEAEs with ≥1% threshold frequency
- TEAEs by study intervention relatedness
- TEAEs by maximum severity
- Grade 3/4 TEAEs
- TEAEs leading to study discontinuation
- Serious TEAEs
- Serious TEAEs by study intervention relatedness
- Serious TEAEs leading to study discontinuation
- TEAEs leading to death

By-participant listings will be provided for pre-treatment AEs, non-serious TEAEs related to study intervention, Grade 3/4 TEAEs, and TEAEs leading to study discontinuation.

4.6.4. Solicited Adverse Events

Solicited adverse events are predefined local and systemic reactions for which the participant is specifically questioned during the local tolerability assessment and that are reported by the participant on the study intervention diary card.

The following local injection site reactions will be assessed and graded (using the grading table in Section 6.4) by the investigator: pain, swelling, erythema (redness), bruising, and pruritis. The number and percentage of participants in each treatment group with a local injection site reaction as assessed by the investigator will be summarized overall and by maximum grade; by symptom, both overall and by maximum grade; and by injection site (thigh vs buttock) and symptom, both overall and by maximum grade.

The following local injection site reactions will be assessed by the participant in diaries: pain, erythema (redness), induration (hardened patch), swelling, and bruising. Pain will be self-graded by the participant using the functional scale provided in the diary instructions; erythema, induration, swelling, and bruising will be measured by the participant, but not graded by the participant. These will be programmatically graded using the grading table in Section 6.4 and the grading table for induration and swelling from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (Section 6.6), and the longest diameter. The number and percentage of participants in each treatment group with a local injection site reaction as assessed by the participant will be summarized overall and by maximum grade; by symptom, both overall and by maximum grade; and by injection site (thigh vs buttock) and symptom, both overall and by maximum grade.

The following systemic reactions will be assessed by the participant in diaries: headache, myalgia (muscle pain), malaise (general sense of discomfort/ feeling unwell), shivering, and oral temperature. All symptoms other than temperature will be self-graded by the participant using the functional scale provided in the diary instructions (Section 6.5). Temperature will be recorded but not graded by the participant. Fever will be programmatically graded using the grading table for vital sign abnormalities from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (Section 6.8). The number and percentage of participants in each treatment group with a systemic reaction as assessed by the participant will be summarized overall and by maximum grade, and by symptom, both overall and by maximum grade. Temperature will also be summarized by treatment group for each diary day using descriptive statistics.

In addition, the time to onset (from study intervention administration) and duration of local injection site and systemic reactions reported in participant diaries will be summarized by treatment group. Duration will be calculated as the total number of days the reaction was reported with at least mild severity.

All solicited adverse events will be presented in by-participant listing(s).

4.6.5. Deaths and Serious adverse events (SAEs)

Serious TEAEs will be summarized by SOC, PT, and treatment group. All deaths, including the cause(s) of death, and SAEs will be provided in by-participants listings.

4.6.6. Adverse Events of Special Interest (AESI)

AESIs for this study include:

- Hypersensitivity reactions: Hypersensitivity reactions will be identified using the hypersensitivity standardized MedDRA query (SMQ), both broad and narrow PT lists.
- Anaphylaxis: Anaphylaxis will be identified using the anaphylaxis MedDRA SMQ, algorithmic approach.
- Adverse events potentially related to ADA: Any events will be identified post-database lock and unblinding through review of AEs in participants who have confirmed ADA.
- Adverse events potentially related to antibody dependent enhancement (ADE) of influenza A illness: Potential ADE of influenza A illness will be assessed by the study team and DMC through review of safety data, including severity and duration of protocol-defined influenza A illness, for participants with protocol-defined influenza A illness.

The number and percentage of participants with any treatment-emergent hypersensitivity reaction, overall and within each of the broad and narrow PT lists for the hypersensitivity SMQ, will be summarized by treatment group, as well as by treatment group and PT. The number and percentage of participants with any treatment-emergent hypersensitivity reaction within 72 hours of study intervention administration, overall and within each of the broad and narrow PT lists for the hypersensitivity SMQ, will also be summarized by treatment group, as well as by treatment group and PT. For these summaries, a participant with multiple occurrences of the same adverse event will be counted only once. A by-participant listing will be provided for all participants with a hypersensitivity reaction and will include the time to onset from administration of study intervention for each hypersensitivity reaction.

The number and percentage of participants with any treatment-emergent anaphylaxis, overall and by PT, will be summarized by treatment group. The number and percentage of participants with any treatment-emergent anaphylaxis within 72 hours of study intervention administration, overall and by PT, will also be summarized by treatment group. For these summaries, a participant with multiple occurrences of the same adverse event will be counted only once. A by-participant listing will be provided for all participants with any anaphylaxis and will include the time to onset from administration of study intervention for each anaphylaxis event.

Refer to Section 4.5.3 for details regarding a programmed listing to support assessment of AEs potentially related to ADA.

4.6.7. Vital signs

Values for systolic and diastolic blood pressure (mmHg), pulse (beats per minute (bpm)), respiratory rate (breaths/min), and oral temperature (°C) at baseline and each scheduled study visit and the change from baseline at each scheduled study visit will be summarized by treatment group.

Values will be programmatically graded using the grading table for vital sign abnormalities from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (Section 6.8). The number and percentage of participants

with vital sign abnormalities, overall and by maximum toxicity grade, including unscheduled assessments within the TE period, and by scheduled study visit will be summarized for each vital sign parameter by treatment group.

All vital sign values for participants with any graded vital sign value will be provided in by-participant listings.

4.6.8. Clinical Laboratory

Values at baseline and each scheduled study visit for the chemistry, liver function, hematology, and coagulation (D-dimer only) parameters listed in Protocol Appendix 2, and the change from baseline at each scheduled post-baseline visit for each parameter, will be summarized (n, mean, SD, median, Q1, Q3, min, and max) in SI units by treatment group.

Abnormal values be graded using a grading scale based on the grading table for laboratory abnormalities from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (Section 6.7).

The number and percentage of participants in each treatment group with any graded abnormality overall and for each laboratory parameter will be summarized overall and by maximum toxicity grade.

The number and percentage of participants in each treatment group with a treatment-emergent laboratory abnormality will be summarized by maximum toxicity grade for each graded laboratory parameter and direction of the abnormality (e.g. high, low), both overall (including any unscheduled assessments within the TE period) and by scheduled study visit. For this analysis, a treatment-emergent abnormality is defined as a value that increases at least 1 toxicity grade from baseline. If baseline is missing, any post-baseline abnormality of at least Grade 1 will be considered a treatment-emergent abnormality.

A shift table will be provided to summarize the number and percentage of participants with shifts from baseline in toxicity grade for each laboratory parameter and direction of the abnormality (e.g. high, low), both overall (including any unscheduled assessments within the TE period) and by scheduled post-baseline visit.

All laboratory results for participants with any laboratory result outside of the reference range, all laboratory results for participants with treatment-emergent laboratory abnormalities, and all laboratory results for participants with any graded abnormality will be provided in by-participant listings.

4.6.9. Physical Examinations and 12-Lead Electrocardiograms

Abnormal, clinically significant physical examination and 12-lead electrocardiogram findings will not be summarized or listed since these were recorded as medical history or adverse events, as appropriate.

4.7. Other Analyses

4.7.1. Work Productivity and Activity Impairment (WPAI)

The WPAI is a quantitative assessment of absenteeism (work time missed), presenteeism (reduced on-the-job effectiveness), work productivity loss, and activity impairment due to ILI. Participants with ILI will complete the 6-item WPAI questionnaire. The questionnaire and scoring instructions for the subscales for absenteeism, presenteeism, work productivity loss, and activity impairment are provided in Section 6.9.

WPAI will be summarized using descriptive statistics for each subscale (n, mean, SD, median, Q1, Q3, min, and max) by treatment group and scheduled study visit (ILI-Day 1 and ILI-Day 8) for all participants in the FAS with protocol-defined ILI with RT-PCR confirmed influenza A without coinfection (the primary estimand variable) along with the change from ILI-Day 1 at ILI-Day 8. If a participant has multiple cases of protocol-defined ILI with RT-PCR confirmed influenza A without coinfection, the responses to the WPAI for all cases will be included in the summary (Reilly 1993).

The responses to all questions in the WPAI questionnaire and derived subscale scores will be provided in a by-participant listing.

4.7.2. Healthcare Encounters

The number and percentage of participants with a healthcare encounter overall and by type of encounter (in-patient: accident and emergency (observation), general ward, intensive care unit; out-patient: emergency room visit, home healthcare visit, internal medicine/ general practitioner, urgent care, telehealth, and other) and the reason for the healthcare encounter (ILI, other) will be summarized by treatment group for all participants in the FAS with protocol-defined ILI with RT-PCR confirmed influenza A without coinfection (the primary estimand variable). In addition, the duration (days) of the healthcare encounter will be summarized by treatment group using descriptive statistics.

All healthcare encounter data will be provided in a by-participant listing.

4.8. Interim Analysis

No interim analyses are planned for this study.

4.9. Modifications

4.9.1. Modifications to the Approved Study protocol

The following modifications were made in the original final statistical analysis plan to definitions provided in the protocol to provide additional clarity:

- The primary and secondary efficacy endpoints were re-worded from “proportion of participants with…” to “occurrence of…” since occurrence is a participant-level endpoint and proportion is a population-level summary measure.

- The primary clinical question of interest was updated to clarify the clinical question in the context of handling of intercurrent events.
- The definition of the primary endpoint was updated to clarify that protocol-defined ILI with central virology laboratory RT-PCR confirmed influenza A after EOIS will be excluded from the primary endpoint.
- The primary estimand was updated to include the intercurrent event of death due to influenza A. This intercurrent event will be handled using the composite strategy where death due to influenza A will be considered as having met the primary endpoint of protocol-defined ILI with central virology RT-PCR confirmed influenza A. The primary estimand was also updated to clarify that the target population should not have prior exposure to influenza A.
- The All Participants Set definition was revised to include all participants who are randomized or receive any amount of study intervention. This analysis set is a superset of all randomized participants and all participants who receive any amount of study intervention, regardless if randomized or not.
- The Full Analysis Set definition was revised to 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 the upcoming influenza season (protocol exclusion criterion 8), 3) have not had protocol-defined ILI symptom onset within 1 day following study intervention administration, and 4) have received any amount of study intervention. The changes were made to 1) clarify that participants who receive study intervention, but not 1 full dose of study intervention, will be included in the Full Analysis Set and 2) to clarify that participants who have had influenza within 3 months prior to randomization or who have protocol-defined ILI symptom onset within 1 day of study intervention administration (indicating prior exposure to influenza A prior to randomization due to the influenza A incubation period of 1-4 days) will be excluded from the Full Analysis Set.
- The Safety Set definition was revised to include all participants who receive any amount of study intervention as opposed to 1 dose of study intervention to provide clarity that participants who receive study intervention, but not 1 full dose of study intervention, will be included in the Safety Set.
- Details were added regarding the identification of anaphylaxis as an AESI. Anaphylaxis is a form of hypersensitivity reaction with a specific approach for identification using MedDRA.

4.9.2. Modifications to the Approved Statistical Analysis Plan

The following modifications were made to the original final statistical analysis plan:

- The Full Analysis Set definition was revised to exclude participants with protocol-defined ILI symptom onset within 4 days (inclusive) following study intervention administration. The change was made to clarify that participants who have protocol-defined ILI symptom onset within 4 days (inclusive) following study intervention administration are considered to have exposure to influenza A prior to randomization due

to the influenza A incubation period of approximately 1-4 days and thus should be excluded from the Full Analysis Set, consistent with protocol exclusion criterion 2.

- To best ensure the detection of all circulating influenza A variants in the VIR-2482-4002 study, results from both available, validated RT-PCR assays will be used to detect in-study episodes of influenza A infection: the Cepheid Xpert® Xpress CoV-2/Flu/RSV point of care assay in use at each clinical site, and the Seegene Allplex Respiratory Panel 1 assay performed at Viroclinics-DDL, the study central virology lab. The primary endpoint was updated to be based on the sponsor-provided point-of-care RT-PCR or the central virology laboratory RT-PCR confirmation of influenza A. This definition was updated throughout the SAP.
- The PK analysis set definition was updated to be based on the Safety Set and to include participants who receive 1 full dose of study intervention.
- The primary estimand was updated to exclude death due to influenza A as an intercurrent event however the handling of death due to influenza A has not changed from the original SAP: participants who die due to influenza A will be considered to have protocol-defined ILI with RT-PCR confirmed influenza A.
- The primary estimand was updated such that participants with protocol-defined ILI with RT-PCR confirmed influenza A and RT-PCR confirmed concomitant influenza B, RSV, or SARS-CoV-2 will be considered to not have protocol-defined ILI with RT-PCR confirmed influenza A, as the causality of a participant's symptoms cannot be reliably attributed to influenza A.
- The primary analysis was updated to remove country, since this study ended up only enrolling participants in one country. Fisher's exact test was added as an alternative test if the Poisson regression fails to converge.
- Definitions of follow-up time were added to Section 4.3.3, Sensitivity Analysis/Analyses.
- The second supplemental estimand was updated to be consistent with the primary estimand in regard to the definition of the primary endpoint and intercurrent event of coinfection with influenza B, RSV, or SARS-CoV-2 confirmed by RT-PCR.
- A third supplemental estimand was added and is defined similarly to the primary estimand except that participants with protocol-defined ILI with RT-PCR confirmed influenza A and RT-PCR confirmed concomitant influenza B, RSV, or SARS-CoV-2; such participants will be considered to have protocol-defined ILI with RT-PCR confirmed influenza A.
- The subgroup analysis by coinfection status was removed since this had been mis specified as a subgroup analysis in the original SAP.
- Additional summaries of disposition, medical history, protocol deviations, study intervention exposure, TEAEs, influenza A subtype, influenza A viral load, non-influenza A respiratory vital infections, and clinical laboratory parameters were added.
- The analysis set for the summaries of prior and concomitant medications and seroconversion was changed from the FAS to the Safety Set.

- Editorial changes were made to section 1.2.4 and 4.3.2, to the specifications of listings in Section 4.2 and Appendix 10, to the summaries of seroconversion, ADA, solicited AEs, secondary endpoints, and to Appendix 7.

The following modifications were made to the amended final statistical analysis plan (amendment 1):

- Added details regarding the TE period for the primary analysis after EOIS and the final analysis after the end of the study.
- Removed country from summaries since no longer applicable. This study ended up only enrolling participants in one country.
- The LLOQ for viral load was updated to reflect the LLOQ of the new assay. Additional detail regarding the imputation of viral load, HAI titers, and ADA titers reported <LLOQ was added.
- The Full Analysis Set definition was revised to include participants with protocol-defined ILI symptom with RT-PCR confirmed influenza A onset within 4 days (inclusive) following study intervention administration.
- Definitions of missing data for efficacy endpoints were added.
- The primary analyses of the primary and secondary endpoints were updated such that multiple imputation will be used to impute missing data based on the observed placebo rate.
- Additional supplemental estimands were added for which the primary efficacy endpoint will be based on a) only central virology laboratory RT-PCR results and b) only PoC RT-PCR results.
- A definition of the last follow-up date was added to the 'time-to first occurrence' supplemental estimand.
- An additional supplemental estimand was added for which protocol-defined ILI with RT-PCR confirmed influenza A with onset within 96 hours (inclusive) following study intervention administration will be considered to not meet the endpoint. The influenza A incubation period is 1-4 days and these could be influenza A infections which were incubating prior to randomization.
- Subgroup analyses were added.
- Text was added to descriptions of exploratory analyses based on the subset of participants with protocol-defined ILI with RT-PCR confirmed influenza to clarify that only participants with protocol-defined ILI with RT-PCR confirmed influenza without coinfection (the primary estimand variable) should be included.
- Text was added to clarify the derivation of time to resolution of ILI for participants with only absent/ mild symptoms and time to resolution of a symptom of only mild severity.
- The safety laboratory toxicity grading table was updated to include criteria in the International System of Units (SI), in addition to conventional units (CV).

- Minor editorial changes were made throughout.

5. 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 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 at least 2.25%. The sample size calculations are based on Fisher's Exact test. The total number of events (36) is calculated under the assumption that both treatment groups have the same event rate of 0.675%. 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 (Jayasundara 2014; Osterholm 2012).

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: of Abbreviations and Definitions of Terms

Abbreviation	Term
ADA	anti-drug antibody
ADE	antibody-dependent enhancement
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransaminase
AST	aspartate aminotransaminase
ATC	anatomic therapeutic chemical
BMI	body mass index (kg/m^2)
bpm	beats per minute
°C	degrees Celsius
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CRO	contract research organization
CSR	clinical study report
CV	conventional unit
DMC	Data Monitoring Committee
eCRF	electronic case report form
EOIS	end of influenza season
EOS	end of study
FAS	full analysis set
Flu-iiQ™	influenza intensity and impact questionnaire[trademark]
HAI	hemagglutination inhibition
ILI	influenza-like illness
IRT	interactive response technology

LLOQ	lower limit of quantification
Log_{10}	logarithm base 10
MAR	missing at random
MAX	maximum value
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
N	number
MIN	minimum value
mL	milliliter
mmHg	millimeters of mercury
PK	pharmacokinetic/pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus
SD	standard deviation
SI	International System of Units
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

WHODD	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment

6.2. Appendix 2: Prior and Concomitant Medication Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for medication	D only	M and Y same as M and Y of study drug administration	Date of study drug administration
		M and/or Y not same as date study drug administration	First day of month
	M and D	Y same as Y of study drug administration	Date of study drug administration
		Y not same as Y of study drug administration	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date study drug administration
Stop date for medication	D only	M and Y same as M and Y of study drug administration	Date of study drug administration
		M and/or Y not same as date of study drug administration	Last day of month
	M and D	Y same as Y of study drug administration	Date of study drug administration
		Y not same as Y of study drug administration	Use Dec 31
	M, D, and Y	None - date completely missing and NOT ongoing	Date of study drug administration

6.3. Appendix 3: Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of study drug administration	Date of study drug administration
		M and/or Y not same as date study drug administration	First day of month
	D and M	Y same as Y of study drug administration	Date of study drug administration
		Y prior to Y of study drug administration but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of study drug administration
Stop date for AEs	D	M and Y same as M and Y of study drug administration	Date of study drug administration
		M and/or Y not same as date of study drug administration	Use last day of month
	D and M	Y same as Y of study drug administration	Date of study drug administration
		Y not same as Y of study drug administration	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

6.4. Appendix 4: Grading Table* for Investigator's Assessment of Local Tolerability

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	Absent	2.5 to 5.0 cm	5.1 to 10.0 cm	> 10.0 cm	Necrosis or exfoliative dermatitis
Bruising	Absent	2.5 to 5.0 cm	5.1 to 10.0 cm	> 10.0 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

*Refer to Protocol Appendix 8.

6.5. Appendix 5: Functional Grading Scales for Participant Diary

None	Mild	Moderate	Severe
No symptom experience	Symptom that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Symptom that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Symptom interrupts usual activities of daily living, of significantly affects clinical status, or may require intensive therapeutic intervention.

6.6. Appendix 6: Grading table* for Induration and Swelling from Participant Diary

Local Reaction to Injectable Product	Absent (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Induration/ Swelling	Absent	2.5 to 5.0 cm	5.1 to 10.0 cm	> 10.0 cm	--

*Based on the Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (FDA 2007).

6.7. Appendix 7: Grading Table for Laboratory Abnormalities*

	Unit Convention	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Chemistry					
Albumin g/dL – Low	CV	>2.7 – 3.1	2.5 – 2.7	< 2.5	--
Albumin g/L – Low	SI	>27 – 31	25 - 27	< 25	--
Blood Urea Nitrogen (BUN) mg/dL - High	CV	23 – <27	27 – 31	> 31	--
Blood Urea Nitrogen (BUN) mmol/L - High	SI	8.21 - <9.64	9.64 – 11.07	>11.07	--
Calcium mg/dL – High	CV	10.5 – <11.1	11.1 – <11.6	11.6 – 12.0	> 12.0
Calcium mmol/L – High	SI	2.63 - <2.77	2.77 - <2.90	2.90 – 3.00	>3.00
Calcium mg/dL – Low	CV	>7.9 – 8.4	>7.4 – 7.9	7.0 – 7.4	< 7.0
Calcium mmol/L – Low	SI	>1.98 – 2.10	>1.85 – 1.98	1.75 – 1.85	<1.75

Creatinine – mg/dL - High	CV	1.5 – <1.8	1.8 – <2.1	2.1 – 2.5	> 2.5
Creatinine – µmol/L - High	SI	133 – <159	159 - <186	186 – 221	>221
Glucose mg/dL - High	CV	110 – <126	126 – 200	>200	--
Glucose mmol/L - High	SI	6.1 – <7.0	7.0 – 11.1	>11.1	--
Glucose mg/dL – Low	CV	>64 – 69	>54 – 64	45 – 54	< 45
Glucose mmol/L - Low	SI	>3.6 – 3.8	>3.0 – 3.6	2.5 – 3.0	<2.5
Potassium mEq/L (mmol/L) – High	CV/ SI	5.1 – <5.3	5.3 – <5.5	5.5 – 5.6	> 5.6
Potassium mEq/L (mmol/L) – Low	CV/ SI	>3.4 – 3.6	>3.2 – 3.4	3.1 – 3.2	< 3.1
Sodium mEq/L (mmol/L) – High	CV/ SI	144 – <146	146 – <148	148 – 150	> 150
Sodium mEq/L (mmol/L) - Low	CV/ SI	>131 – 134	>129 – 131	125 – 129	< 125
Total Protein g/dL – Low	CV	>5.4 – 6.0	5.0 – 5.4	< 5.0	--
Total Protein g/L – Low	SI	>54 – 60	50 – 54	<50	--
Liver Function					
Alkaline phosphatase (ALP) - High	CV/ SI	1.1 – <2.1 x ULN	2.1 – <3.1 x ULN	3.1 – 10 x ULN	> 10 x ULN
Alanine aminotransferase (ALT) - High	CV/ SI	1.1 – <2.6 x ULN	2.6 – <5.1 x ULN	5.1 – 10 x ULN	> 10 x ULN
Aspartate aminotransferase (AST) - High	CV/ SI	1.1 – <2.6 x ULN	2.6 – <5.1 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin (total and direct) – High- when accompanied by any increase in Liver Function test values (ALP>=1.1xULN or AST>=1.1xULN or ALT>=1.1xULN)	CV/ SI	1.1 – <1.26 x ULN	1.26 – <1.51 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin (total and direct) – High when Liver Function test values are normal (ALP<1.1xULN and AST<1.1xULN and ALT<1.1xULN)	CV/ SI	1.1 – <1.6 x ULN	1.6 – <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Hematology					
Hemoglobin (Female) - gm/dL - Low	CV	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) - gm/L - Low	SI	110 – 120	95 – 109	80 – 94	< 80
Hemoglobin (Female)	CV	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0

change from baseline value - gm/dL					
Hemoglobin (Female) change from baseline value - gm/dL	SI	Any decrease – 15	16 - 20	21 - 50	> 50
Hemoglobin (Male) - gm/dL - Low	CV	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) - gm/L - Low	SI	125 – 135	105 – 124	85 – 104	< 85
Hemoglobin (Male) change from baseline value – gm/dL	CV	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) change from baseline value – gm/L	SI	Any decrease – 15	16 - 20	21 - 50	> 50
WBC cell/mm^3 – High	CV	10,800 – 15,000	>15,000 – 20,000	>20,000 – 25, 000	> 25,000
WBC x10^9/L– High	SI	10.8 – 15.0	>15.0 – 20.0	>20.0 – 25.0	>25.0
WBC cell/mm^3 – Low	CV	2,500 – 3,500	1,500 – <2,500	1,000 – <1,500	< 1,000
WBC x10^9/L– Low	SI	2.5 – 3.5	1.5 - <2.5	1.0 - <1.5	<1.0
Lymphocytes cell/mm^3 – Low	CV	750 – 1,000	500 – <750	250 – <500	< 250
Lymphocytes x10^9/L – Low	SI	0.75 – 1.0	0.50 - <0.75	0.25 - <0.50	<0.25
Neutrophils cell/mm^3 – Low	CV	1,500 – 2,000	1,000 – <1,500	500 – <1,000	< 500
Neutrophils x10^9/L – Low	SI	1.5 – 2.0	1.0 - <1.5	0.50 - <1.0	<0.50
Eosinophils - cell/mm^3 – High	CV	650 – 1,500	>1,500 – 5,000	> 5,000	
Eosinophils - x10^9/L – Low	SI	0.65 – 1.5	>1.5 – 5.0	>5.0	
Platelets cell/mm^3 – Low	CV	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
Platelets - x10^9/L – Low	SI	125 – 140	100 – 124	25 – 99	<25
Urinalysis					
Protein		Trace	1+	>= 2+	--
Glucose		Trace	1+	>= 2+	--
Blood (microscopic) – red blood cells per high power field (rbc/hpf)		1-5 or 6-8	9-14 or 15-30 or 31-50	>50	--

ULN = upper limit of the reference range.
*Based on the Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (FDA 2007).

6.8. Appendix 8: Grading Table for Vital Sign Abnormalities*

Vital sign	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)

Fever (°C) **	38.0 – 38.4	38.5 – 38.9	39.0 – 40	> 40
Fever (°F) **	100.4 – 101.1	101.2 – 102.0	102.1 – 104	> 104
Pulse (bpm) - High	101 – 115	116 – 130	> 130	--
Pulse (bpm) - Low	50 – 54	45 – 49	< 45	--
Systolic blood pressure (mmHg) - High	141 – 150	151 – 155	> 155	--
Systolic blood pressure (mmHg) - Low	85 – 89	80 – 84	< 80	--
Diastolic blood pressure (mmHg) - High	91 – 95	96 – 100	> 100	--
Respiratory rate (breaths/min)	17 – 20	21 – 25	> 25	--

*Based on the Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (FDA 2007).

6.9. Appendix 9: Work Productivity and Activity Impairment (WPAI) Questionnaire and Scoring Instructions

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1) Are you currently employed (working for pay)? _____NO ____ YES
If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2) During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*
_____ HOURS

3) During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
_____HOURS

4) During the past seven days, how many hours did you actually work?
_____HOURS *(If "0", skip to question 6.)*

5) During the past seven days, how much did health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

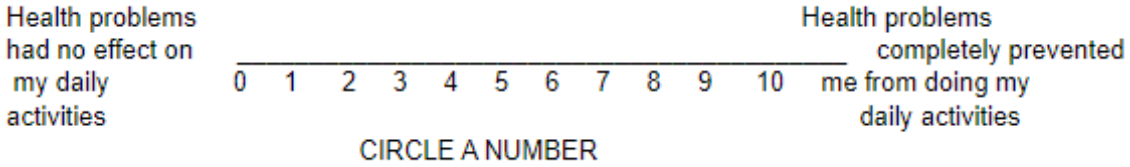
Health problems had no effect on my work 0 1 2 3 4 5 6 7 8 9 10 Health problems completely prevented me from working

CIRCLE A NUMBER

6) During the past seven days, how much did health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.



The WPAI yields four types of scores:
1. Absenteeism (work time missed)
2. Presenteeism (impairment at work / reduced on-the-job effectiveness)
3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)
4. Activity impairment

Scores are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:
1 = currently employed
2 = hours missed due to health problems
3 = hours missed other reasons
4 = hours actually worked
5 = degree health affected productivity while working
6 = degree health affected regular activities

Scores:
Multiply scores by 100 to express in percentages.

Absenteeism (Percent work time missed): Q2/(Q2+Q4)
Presenteesism (Percent impairment while working): Q5/10
Work productivity loss (Percent overall work impairment): Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)]
Activity impairment (Percent activity impairment): Q6/10

6.10. Appendix 10: VIR-2482-4002 Statistical Analysis Plan for Pharmacokinetic Data

SCOPE

Standard non-compartmental methods for analyses of pharmacokinetic (PK) data will be performed by Vir; listings, summary tables, and figures of VIR-2482 concentration data and PK parameters will be described in this Statistical Analysis Plan (SAP).

Additional exploratory analyses not necessarily defined in this SAP may be performed as deemed appropriate. Any post hoc or unplanned analyses that are performed and not specifically identified in this SAP will be clearly identified as such if they are included in the CSR.

STUDY OBJECTIVES

- To characterize the serum PK of VIR-2482 following a single dose.
- To characterize the nasopharyngeal sample (NPS) PK of VIR-2482 following a single dose.

STUDY ENDPOINTS

Objective	Endpoints
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_{180}, C_{last}, T_{max}, T_{last}, AUC_{last}, AUC_{0-180}, $\%AUC_{exp}$, AUC_{INF}, $t_{1/2}$, λ_z, V_z/F, and 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_{180}, C_{last}, t_{max}, t_{last}, AUC_{last}, AUC_{0-180}, $\%AUC_{exp}$, AUC_{inf}, $t_{1/2}$.

PHARMACOKINETIC ANALYSIS SET DEFINITION

The Pharmacokinetic Analysis Set will include all participants in the Safety Set who receive1 full dose of study intervention and have at least 1 measurable post-dose VIR-2482 concentration.

STATISTICAL METHODS

For analyses of PK concentrations, values below the limit of quantitation (BLQ) prior to the first quantifiable concentration will be set to zero. BLQ values that occur after the first quantifiable point will be considered missing in the calculation of PK parameters and summary statistics.

Serum and NPS concentrations of VIR-2482, as well as serum and NPS PK parameters, will be summarized with descriptive statistics using the following parameters: number of non-missing values (n), arithmetic mean, median, geometric mean, standard deviation (std), CV%, Geometric CV% (GeoCV%), minimum, and maximum values.

Serum and NPS PK concentration data will be reported to 3 decimal places in the same units as the laboratory source data. Descriptive statistics for serum and NPS PK concentrations will be reported to 3 significant figures except for standard deviation which will be reported to 4 significant figures and except for CV% and Geometric CV% which will be reported as a percentage to 1 decimal place.

Descriptive statistics for serum and NPS PK parameters will be reported to 3 significant figures, except for standard deviation which will be reported to 4 significant figures and except for CV and Geometric CV which will be reported as a percentage to 1 decimal place.

PK ANALYSES

The PK Analysis Set will be used for summaries of serum and NPS VIR-2482 concentrations and PK parameters.

PK CONCENTRATIONS

Tables
Individual serum and NPS VIR-2482 concentrations will be summarized using descriptive statistics by treatment group, visit, and nominal timepoint. Anomalous concentrations identified as sampling errors by the clinical pharmacologist will be excluded from summaries.

Plots

Aggregate (mean +/- standard deviation) serum and NPS VIR-2482 concentrations will be displayed graphically in linear and semi-logarithmic plots of concentration versus time. On semi-logarithmic plots, minor tick marks will be displayed on the vertical (logarithmic) axis. Time will be displayed in units of days as time elapsed relative to dosing, with dosing on day zeroBelow the plots of mean concentrations, a table containing the number of participants with quantifiable concentrations per timepoint will be displayed.

PK PARAMETERS

Serum and NPS PK parameters will be calculated using Phoenix WinNonlin Version 8.3.5 or higher (Certara, Princeton NJ, USA). The serum and NPS PK parameters that will be estimated using noncompartmental analysis (NCA) include but are not limited to C_{max}, C_{180}, C_{last}, t_{max}, t_{last}, AUC_{last}, AUC_{0-180}, $\%AUC_{exp}$, AUC_{INF}, $t_{1/2}$, λ_z, V_z/F, and CL/F. PK parameters will be summarized using descriptive statistics by treatment group.

The apparent terminal-phase elimination rate constant (λ_z) will be estimated by log-linear regression of the concentration-time data associated with this phase. The decision as to which data points describe the terminal elimination phase will be reached by inspecting the semilogarithmic plot of the data, only considering concentrations at time points beyond t_{max}. λ_z is considered to be well-estimated if a minimum of three data points are used, these data points cover a time span of 2 or more elimination half-lives, and the r^2 value of λ_z is > 0.80. In cases where λ_z is poorly estimated (i.e. a span of < 2 half-lives is not used or $r^2 \leq 0.80$), λ_z and the related parameters AUC_{INF}, CL/F, V_z/F, and $t_{½}$ may be excluded from the calculation of summary statistics at the discretion of the clinical pharmacologist.

Area under the curve (AUC) will be computed using the "linear up, log down" trapezoidal rule. AUC_{INF} is considered to be well-estimated if $\%AUC_{exp} < 20\%$. In cases where $\%AUC_{exp} > 20\%$, AUC_{INF} and the related parameters CL/F and Vz/F may be excluded from the calculation of summary statistics at the discretion of the clinical pharmacologist.

DOSE PROPORTIONALITY ASSESSMENT

Dose proportionality of VIR-2482 will be assessed using analysis of variance (ANOVA) based on natural log-transformed, dose-normalized AUC_{INF}, C_{max}, and AUC_{last}. The model will include the dose level as a continuous independent variable. Point estimates and 90% confidence intervals will be back transformed. Dose proportionality is concluded if the 90% confidence interval of the dose-normalized geometric mean ratios (GMR) of AUC_{INF}, C_{max}, or AUC_{last} between the two dose levels falls between 80-125%.

GLOSSARY OF PHARMACOKINETIC TERMS

Symbol	Definition
C_{max}	Maximum observed concentration of drug following a dose
C_{180}	Predicted concentration at day 180 post-dose
C_{last}	Last observed concentration of drug following a dose
t_{max}	Time at which maximum concentration of drug is observed
t_{last}	Time at which last concentration of drug is observed
AUC_{last}	Area under the concentration-time curve from time "0" to the last measured timepoint
AUC_{0-180}	Partial area under the concentration-time curve from time "0" to day 180
AUC_{INF}	Area under the concentration-time curve from time "0" extrapolated to time infinity
$\%AUC_{exp}$	Percent of the area under the concentration-time curve extrapolated from the last measured timepoint to time infinity
$t_{1/2}$	Terminal elimination half-life
λ_z	Terminal elimination rate constant
V_z/F	Apparent volume of distribution during the terminal elimination phase, measured after extravascular dosing
CL/F	Total body clearance measured after extravascular administration

6.11. Appendix 11: CDC Geographic Regions

Northeast: Includes Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont

Midwest: Includes Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin

South: Includes Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia

West: Includes Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming

7. REFERENCES

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