

**STATISTICAL ANALYSIS PLAN AMENDMENT V2.0**

Study Title	A Phase 1, Open-Label, Single-Dose, Parallel-Group Study of the Pharmacokinetics and Safety of VIR-2218 in Adult Participants with Renal Impairment
Brief Title	A Study to Investigate the Effect of Renal Impairment on the Pharmacokinetics and Safety of VIR-2218
Study Number	VIR-2218-V108
Compound	VIR-2218 (elebsiran)
Indication	Chronic Hepatitis B (HBV) Infection
Study Phase	1
Study Sponsor	Vir Biotechnology, Inc. 1800 Owens Street, Suite 900 San Francisco, CA 94158, USA
Effective Date	31 January 2025, Original Version 1.0 06 June 2025, Amendment Version 2.0

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

The statistical analysis plan (SAP) amendment v2.0 for study VIR-2218-V108 was developed based on the original SAP v1.0 dated 31 January, 2025.

SAP Version	Date	Section	Update
v1.0	31 Jan, 2025	--	Original version
v2.0	06 Jun, 2025	Section 6.2.1 Participant disposition	To update the percentage calculation is based on the All Enrolled Set.
		Section 6.2.2 Demographics and baseline characteristics	To add a listing for substance use.
		Section 6.2.5 Protocol deviation	To remove the content of the COVID-19 PD and the PD table.
		Section 6.2.6 COVID-19 impact	To remove the section on the COVID-19 impact.
		Section 6.4.1 PK variables	To add clarification for the summary of PK variables
		Section 6.4.3 Analysis of PK parameters	To add the analysis for the Metabolite-to-Parent ratio of individual participant PK parameters.
		Section 6.4.4 Comparison of PK between RI and healthy participants	To specify the ANOVA model, and replace CL _R by eGFR..
		Section 6.5.3.1 Summaries of laboratory results	To remove the Grade 0.
		Section 6.8.1 Modifications to the approved study protocol	To add the description of the sample size adjustment.
		Appendix 4: Severity (Toxicity) Grades for Laboratory Abnormalities	To add a footnote for Potassium (hypokalemia) and Glucose (hyperglycemia) to use a different grading criteria.
		Others: words/sentences, format, etc.	Other minor edits, updates, etc.

1. INTRODUCTION

This statistical analysis plan (SAP) for the final analysis is based on the approved clinical study protocol amendment 1 (version 1.0 dated on 18 April 2024), and most recent electronic case report form (eCRF) V4.0. This SAP documents the planned statistical analyses of pharmacokinetics (PK) and safety and tolerability for the final analysis of study VIR-2218-V108.

VIR Biometrics team and a designated contract research organization (CRO) will perform the statistical analysis. SAS version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). Any revisions and the reasons to the approved SAP will be documented in the CSR.

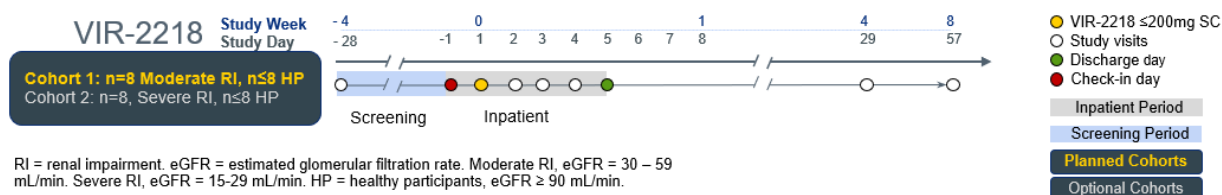
2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Assess the pharmacokinetics of VIR-2218 in adult participants with renal impairment (RI) and in matched healthy adult participants with normal renal function	AUC_{last}, AUC_{inf}, C_{max}, f_e%, Ae, CL_R for VIR-2218 and its metabolite AS (N-1)3'VIR-2218
Secondary	
Assess the safety and tolerability of single-dose VIR-2218 in adult participants with RI and in matched healthy adult participants with normal renal function	Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
Exploratory	
Determine the plasma protein binding of VIR-2218 in participants with RI and participants with normal renal function	VIR-2218 pre-dose and post-dose unbound fraction

3. STUDY DESIGN

3.1. Overall Design

Study VIR-2218-V108 is a Phase 1, open-label, single-dose, parallel-group study to evaluate the pharmacokinetics (PK) characteristics and safety of VIR-2218 monotherapy therapy in adult participants with renal impairment (RI) and matched health (MH) participant (1:1) by race, sex, age (± 10 years), and body mass index (BMI) ($\pm 20\%$) at screening, as shown in the study design schema below.



Participants are planned to be enrolled in multiple sites in the United States. Each participant will receive a single SC dose of VIR-2218 up to 200 mg on Day 1. The study includes cohort 1 and optional cohort 2:

- Cohort 1- Participants with moderate RI and matched healthy participants: 8 (moderate RI) participants with estimated glomerular filtration rate (eGFR) = 30-59 mL/min/1.73m² as calculated by the Modification of Diet in Renal Disease (MDRD) equation and up to 8 matched healthy participants with eGFR ≥ 90 mL/min/1.73m² will receive a single dose SC VIR-2218 (200 mg)
- (Optional) Cohort 2 - Participants with severe RI: 8 (severe RI) participants with eGFR = 15-29 mL/min/1.73m² as calculated by the MDRD equation and up to 8 matched healthy participants with eGFR ≥ 90 mL/min /1.73m² will receive a single dose SC VIR-2218 (≤ 200 mg)

Cohort 1 is planned to be enrolled first. Cohort 2 will be enrolled after sponsor's review of the safety, tolerability, and PK data from participants with moderate RI (Cohort 1) compared to matched healthy controls.

Each participant will be in the study for a total of approximately 12 weeks. Participation will include a screening evaluation within 28 days prior to dosing Day 1, and a 6-day (5-night) inpatient period (from Day -1 through Day 5). Participants will be discharged from the clinic after completing the Day 5 procedures (approximately 96 hours post-dose). Participants will return to the clinic for scheduled visits per the Schedule of Activities (SoA) until up to 8 weeks post-dose for safety and PK assessments (Protocol Section 1.3).

3.2. Sample Size

The sample size for this study is not based on statistical consideration. Up to approximately 32 participants will be enrolled for two cohorts, including participants with moderate RI, matched healthy adults, participants with severe RI, and matched healthy adults. A sample size of 8 participants per renal function group per cohort will be enrolled to ensure the precise estimation

of relevant PK parameters, AUClast and Cmax of VIR-2218 and metabolite AS(N-1)3'VIR-2218, so that the 95% confidence interval of the geometric mean estimate is within 60% and 140% of the estimate in each renal function group with at least 80% power. The assumption is based on the PK data obtained from a prior clinical study of VIR-2218 administered as a single SC dose in healthy participants (Study VIR-2218-1001).

3.3. Blinding and Unblinding

This is an open-label study that does not include blinding.

3.4. Planned Analysis

No formal interim analysis will be performed for this study.

A safety review meeting will be held between the sponsor and investigators to evaluate PK, safety, and tolerability results of VIR-2218 from participants in Cohort 1 (moderate RI) prior to enrolling Cohort 2 (severe RI). See Protocol Section 9.4.3 for details on the estimation of PK parameters.

The final analysis will be conducted when all participants have completed or prematurely discontinued the study and the data have been cleaned, finalized, and locked.

4. STATISTICAL HYPOTHESES

There are no formal statistical hypotheses planned for this study.

This study is exploratory in nature. No multiplicity adjustment will be made.

5. ANALYSIS SETS

5.1. All Enrolled Set

The All Enrolled Set includes all participants who were assigned to study intervention. This analysis set will be used for individual participant data listings and disposition data summary tables, unless otherwise specified.

5.2. PK Analysis Set

The PK Analysis Set includes all enrolled participants who received one dose of study drug and at least one measurable post-dose concentration. The PK Analysis Set will be used for all PK analyses.

5.3. Safety Analysis Set

The Safety Analysis Set includes all participants (participants with moderate and severe renal function and matched controls) who received any amount of study drug. All safety, demographics, baseline characteristics, and concomitant medications will be summarized based on the Safety Analysis Set.

6. STATISTICAL ANALYSES

6.1. General Considerations

The study assessments and time points schedule are provided in the study protocol. All individual participant data from both scheduled and unscheduled visits will be presented in data listings based on the All Enrolled Set.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, Q1 (first quartile), Q3 (third quartile), minimum value (min), and maximum value (max), unless otherwise specified.

In general, 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. Unless otherwise specified, raw data will be presented with the same number of decimals as collected, and derived data will be presented with an appropriate number of decimals based on general practice, mathematical rationale, or scientific rationale. 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. Generally, percentages will be presented to 1 decimal place.

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

If a measurement collected on the day of study intervention cannot be determined to be pre-dose or post-dose, the scheduled measurement will be treated as pre-dose observation, and the unscheduled measurement will be treated as post-dose observation. If multiple measurements that are prior to dosing are recorded on the same date and with the same time or if time is not available, then the average of these measurements will be considered the baseline value.

Absolute change from baseline will be calculated as post-baseline value - baseline value.

Treatment-emergent (TE) period: defined as the time period from the dose of study intervention to the dose of study intervention +30 days.

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

1. In scheduled visit windows per specified analysis window rules, if applicable
2. In the derivation of baseline
3. In the derivation of maximum and minimum values, and maximum and minimum change from baseline values during a specified time period
4. In individual participant data listings as appropriate

Analysis window: The analysis window rules for protocol-defined visits are provided in [Appendix 2](#).

Incomplete/Missing data: In general, missing data will not be imputed, unless specified otherwise.

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.

6.2. Background Characteristics

6.2.1. Participant Disposition

A disposition table will be provided with the number of study participants by renal function group (RI participant and MH participant) and by cohort in:

- All Enrolled Set
- PK Analysis Set
- Safety Analysis Set

The number and percentage of study participants (based on the All Enrolled Set) in each of the following disposition categories will be summarized:

- Completed study
- Prematurely discontinued study and the primary reason for discontinuation

Individual participant listing for disposition data will be listed.

6.2.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by renal function group and by cohort based on the Safety Analysis Set.

Demographic data will include the following:

- Age at baseline (years)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, or unknown)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other)

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m²)
- Estimated glomerular filtration rate (eGFR, mL/min/1.73 m²), calculated by the Modification of Diet in Renal Disease (MDRD) as in protocol Appendix 6. The baseline eGFR will be the average of two measurements of samples that are collected during screening.

Listings of participant data for demographics and baseline characteristics will be presented. In addition, informed consent, inclusion/exclusion criterion for participant with any such violations and substance use will also be listed.

6.2.3. Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA, version 25.0). For the Safety Analysis Set, medical history will be summarized descriptively by System Organ Class (SOC) and Preferred Term (PT) and by renal function group and by cohort. The corresponding data listing will also be provided.

6.2.4. Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHODD, March 2022), and are categorized as follows:

Prior medication: any medication that was administrated prior to the first dose of study intervention, regardless of when it ended.

Concomitant medication: defined as medication started on or after the date of the first dose of study intervention, or medication started prior to the first dose of study intervention and continued after dosing of study intervention. Concomitant medication will be collected up to the last study visit.

A given medication may be classified as follows: prior, concomitant, both prior and concomitant treatment.

If a medication start date is at or after date of study dose, then the medication will be summarized as concomitant medication regardless of whether the medication end date is missing or not. If a medication end date is before the date of dosing of study intervention, then the medication will be summarized as prior medication regardless of whether the medication start date is missing or not. A medication that started prior to dosing of study intervention and continued after dosing of study intervention will be summarized as prior medication and separately as concomitant medication.

For the Safety Analysis Set, both prior and concomitant medications will be summarized descriptively by renal function group and by cohort, and by 1) preferred name (PN); and 2) anatomic class (ATC) level 1, ATC level 2, and PN.

If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the dose date of study drug, it will be classified as both prior and concomitant. Details for imputing missing or partial start/stop dates of medication are described in [Appendix 3](#).

6.2.5. Protocol Deviation

Protocol deviation data will be finalized before the final database lock. An important protocol deviation (IPD) 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. An individual data listing of participants IPDs will be provided.

6.3. Efficacy Analysis

No efficacy analysis will be conducted in this study.

6.4. Pharmacokinetics Analysis

The primary endpoints for this study are PK concentrations and PK parameters, and primary analysis will be performed based on the PK analysis set.

PK concentrations and PK parameters will be analyzed and summarized by renal function group for each cohort. Blood and urine samples of VIR-2218 and its metabolite AS(N-1)3'VIR-2218 will be obtained from each participant prior to study drug administration and at selected times after study drug administration as outlined in the study protocol.

Standard non-compartmental analyses will be used to estimate PK parameters based on VIR-2218 and its metabolite AS(N-1)3'VIR-2218 concentration data using Phoenix WinNonlin® software (Version 8.4 or higher). The linear-up / log-down trapezoidal rule will be used in conjunction with dosing time, concentration, and corresponding real-time values. If the real sampling time is not recorded or is missing, the planned time will be used for this time point instead.

For concentration data, values reported below the quantitation limit (BQL) will not be imputed in summary statistics with only the number of participants who have non-missing quantifiable results included at each time point.

For PK parameters estimation, samples BQL prior to the first quantifiable concentration will be set to a concentration value of zero, and BQL values that occur after the first quantifiable point will be considered as missing data.

If a missing value is reported due to no valid or missing of sample result in summary of concentration data and PK parameters, it will be presented as not reported "NR" and excluded from PK analyses and not imputed at any time points.

The actual reported values will be provided in individual participant listings.

Natural logarithm transformation may be used for analysis of PK parameters. PK parameters that are BQL will be imputed before log transformation or statistical model fitting. If the untransformed value is BQL, the corresponding log transformed value will be zero.

The precision of data reporting in both PK concentrations and PK parameters will follow the below rules:

- 3 significant digits in the same units as the laboratory source data in ng/mL
- 3 significant digits for descriptive statistics except for
 - 4 significant digits for standard deviation
 - percentage to 1 decimal place for CV% and Geometric CV%

6.4.1. PK Variables

PK variables include individual concentration measurements for VIR-2218 and its metabolite AS(N-1)3'VIR-2218 following the collection times provided in the study protocol, and the estimated PK parameters in evaluation of PK objectives including but not be limited to:

Parameter	Definition
Plasma	
$C_{\max}$	Maximum observed concentration of drug following a dose
C_{last}	Last measurable observed concentration of drug following a dose
$T_{\max}$	Time at which maximum concentration of drug is observed
T_{last}	Time at which last measurable concentration of drug is observed
AUC_{last}	Area under the concentration-time curve from time “0” to the last measured timepoint
AUC_{inf}	Area under the concentration-time curve from time “0” to time infinity
$\%AUC_{\text{exp}}$	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 (VIR-2218 only)
CL/F	Total body clearance measured after extravascular administration (VIR-2218 only)
Urine	
A_e	Amount of drug excreted in urine in a time intervals indicated in the SoA
$fe\%$	Percentage of the given dose of drug excreted in urine, calculated as: $fe\% = (A_e \text{ total}/\text{Dose}) \times 100$
CL_R	Renal clearance of drug, calculated as: $A_e \text{ total}/AUC_{\text{last}}$

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 $T_{\max}$. For VIR-2218, λ_z is considered to be well-estimated if a minimum of three data points is used, these data points cover a time span of 2 or more elimination half-lives, and the adjusted 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 used or adjusted $r^2 < 0.80$), λ_z and the related parameters (AUC_{inf} , CL/F , V_z/F , and $t_{1/2}$) will be flagged in the report and may be excluded from the calculation of summary statistics at the discretion of the clinical pharmacologist. For metabolite AS(N-1)3’VIR-2218, only if adjusted $r^2 < 0.80$ (no requirement on span), λ_z and the related parameters (AUC_{inf} , CL/F , V_z/F , and $t_{1/2}$) will be flagged in the report

and may be excluded from the calculation of summary statistics at the discretion of the clinical pharmacologist

AUC will be computed using the linear up, log down trapezoidal rule. In cases where $\%AUC_{exp} > 20\%$ for VIR-2218 and $\%AUC_{exp} > 30\%$ for metabolite AS(N-1)3'VIR-2218, AUC_{inf} and the related parameters CL/F and V_z/F will be presented in listings but may be excluded from the calculation of summary statistics at the discretion of the clinical pharmacologist.

6.4.2. Analysis of PK Concentrations

Plasma concentrations and urine concentrations of VIR-2218 and its metabolite AS(N-1)3'VIR-2218 will be listed and summarized by the nominal sampling time using descriptive statistics (n, mean, SD, coefficient of variation [CV%], median, min, max, geometric mean, and Geometric CV% [GeoCV%]). Geometric CV% will be calculated using the following formula where SD is the standard deviation of the log-transformed data: $GeoCV\% = \sqrt{(\exp(SD^2) - 1)} \times 100$.

An additional listing of individual participant including actual sampling date and time and elapsed time relative to dosing time will be provided by cohort, renal function group, participant ID, and nominal sampling time, with time deviation (difference in minutes between nominal and actual sampling times) calculated, for participants with available concentration data.

Individual and aggregate mean ($\pm$ SD) of plasma concentrations of VIR-2218 and its metabolite AS(N-1)3'VIR-2218 will be displayed graphically in linear and semi-logarithmic plots of concentration versus time. Time will be displayed in units of hours of time elapsed relative to dosing, with dosing at time zero (clinical Day 1). The actual sample collection timepoints will be used for plots of individual concentrations and nominal sample collection timepoints will be used for plots of mean concentrations. The number of participants with quantifiable concentrations per timepoint will be displayed in each plot. Mean post dose concentration values that are BQL will not be displayed in the figures and remaining points connected.

6.4.3. Analysis of PK Parameters

PK parameter data summaries will include all participants for whom PK parameters can be derived. The sample size for each PK parameter will be based on the number of participants with non-missing data for that PK parameter.

Individual participant PK parameters for VIR-2218 and its metabolite AS(N-1)3'VIR-2218 will be listed and summarized using descriptive statistics (n, mean, SD, CV%, median, min, max, geometric mean, and GeoCV%) by renal function group for each cohort.

Metabolite-to-Parent ratio of individual participant PK parameters (AUC_{last} , AUC_{inf} , C_{max}) will be listed and summarized using descriptive statistics by renal function group for each cohort.

6.4.4. Comparison of PK between RI and Healthy Participants

To evaluate the PK of VIR-2218 and its metabolite AS(N-1)3'VIR-2218 between RI participants and the matched healthy participants, the natural log-transformed AUC_{last} , AUC_{inf} , C_{max} , $fe\%$, CL_R and A_e will be compared using analysis of variance (ANOVA) method. Each log-transformed PK parameter will serve as the dependent variable in an ANOVA model, and the renal function group (RI vs. matched healthy) is included as an independent variable. No covariates will be included in the model. The ratios of geometric least square mean (GLSM)

between RI and matched healthy participants and the corresponding 90% confidence intervals (CIs) will be estimated for each PK parameter of interest.

No-interaction criteria will be met if the 90% confidence intervals (CIs) for the ratios of GLSM for the natural log-transformed PK parameters (AUC_{last} , AUC_{inf} , and C_{max}) of participants with moderate RI or severe RI, compared to healthy participants fall between 80.0% and 125.0%.

The relationships between estimated renal function (eGFR) and relevant PK parameters (C_{max} and AUCs) will be established using linear regression models with the PK parameters as the dependent variable and estimated renal function (eGFR) as the independent variable. Scatter plot with regression model parameters will be provided. Pearson correlation coefficient (r) will be displayed on each plot.

6.5. Safety Analyses

Safety analyses will be based on the Safety Analysis Set, unless otherwise specified. All safety data will be included in the individual participant listings. Descriptive analyses will be performed. Participants will be analyzed according to renal function for each cohort.

The overall safety profile of the study intervention will be assessed in terms of the following safety and tolerability assessments:

- Treatment-emergent Adverse Events (TEAEs)
- Clinical laboratory
- ECG
- Vital signs
- Physical examination

6.5.1. Extent of Exposure

Individual participant data listing for study intervention will be presented by cohort, renal functional group, and participant ID.

6.5.2. Adverse Events

The secondary endpoints of this study are incidences of treatment-emergent adverse events (TEAE) and serious adverse events (SAE).

TEAE: defined as any AE with an onset date on or after the administration of study intervention through the end of the TE period.

Pre-treatment AE: any AE that occurred before the first dose of study intervention.

Post-TE AE: any AE that occurred after the TE period. For AEs with completely missing or partial start dates, if there is no clear evidence that the AEs are pre-treatment or post-TE, the AEs will be classified as TEAEs. Details for imputing missing or partial start/end dates of adverse events are described in [Appendix 3](#).

An overview of all TEAEs by renal function group and by cohort will be summarized in the following categories:

- Number of TEAEs
- Participants with any TEAEs
- Participants with TEAEs by strongest relationship to study intervention
- Participants with TEAEs by maximum severity (toxicity grade)
- Participants with TEAEs leading to study discontinuation
- Participants with Grade 3/4/5 TEAEs
- Participants with study intervention related TEAEs
- Participants with serious TEAEs
- Participants with study intervention related serious TEAEs
- Participants with TEAE leading to death

The following summary tables of TEAEs will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts and percentages (i.e., number and percentage of participants), and by renal function group for each cohort. Participants with multiple occurrences of the same adverse event will be counted once.

- TEAEs
- TEAEs by maximum severity
- Study intervention related TEAEs
- Serious TEAEs

The following TEAEs tables will be summarized by MedDRA PT by renal function group for each cohort:

- TEAEs
- Study intervention related TEAEs
- Serious TEAEs

The following listings will be presented by renal function group and by cohort:

- SAEs
- AEs leading to death
- AEs leading to study discontinuation

All AEs will be presented in the individual participant listing based on the All Enrolled Set.

6.5.3. Clinical Laboratory

Clinical laboratory data collected (through central laboratories only, unless otherwise specified) will be analyzed and summarized. The analysis will be based on values reported in conventional units and presented by renal function group for each cohort.

6.5.3.1. Summaries of Laboratory Results

For the treatment-emergent laboratory measurements, the observed values and change from baseline values of serum chemistry, liver function, hematology, and coagulation data will be summarized at each visit during the TE period by renal function group and by cohort.

The Common Terminology Criteria for Adverse Events (CTCAE, v5.0) will be used as the reference on grading scale to assign severity (toxicity) grades (1 to 4) to abnormal results for the laboratory of interest as shown in [Appendix 4](#).

For treatment-emergent laboratory abnormalities, the number and percentage of participants who met at least 1 threshold criterion of severity grade will be summarized by renal function group for each cohort based on the most severe post-baseline abnormality grade during the TE period for a given laboratory test.

A listing containing individual participants with chemistry, hematology, coagulation and urinalysis values will be provided by cohort, renal functional group, participant ID and visit in chronological order including data collected from both scheduled and unscheduled visits. Values falling out of the relevant normal range (between the value of LLN and ULN) or having the severity grade of 1 or higher on laboratory abnormalities will be flagged as appropriate. Data from the local lab will be presented in the listing with a flag.

Listings of individual participant data of urine for drugs of abuse and pregnancy test will be listed.

6.5.4. 12-Lead Electrocardiogram

For the treatment-emergent 12-lead ECG measurements, a descriptive summary of observed values and change from baseline values by renal function group and by cohort will be provided at each visit during the TE period for the following ECG measurements (in msec): PR interval, QRS interval, QT interval, QT-c interval, and Heart Rate (beats per minute).

In addition, an individual listing containing ECG measurements including data from both scheduled and unscheduled visits will be provided. The abnormal assessment with clinical significance will be flagged as appropriate.

6.5.5. Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each visit during the TE period by renal function group and by cohort. The following vital signs parameters will be included: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute [bmp]), and respiratory rate (breaths per minute).

Additionally, an individual participant list will be provided using data collected from both scheduled and unscheduled visits.

6.5.6. Physical Examination

Physical examination data will be presented in an individual participant data listing. The abnormal assessment with clinical significance will be flagged as appropriate.

6.6. Exploratory Endpoint Analysis

For plasma protein binding analysis, the unbound fraction for VIR-2218 in plasma will be assessed in spiked-in pre-dose (0.2 and 4.0 µg/mL VIR-2218) and in 6 h post-dose samples. Individual VIR-2218 unbound fraction, and the percentage unbound fraction and percentage bound fraction in plasma will be listed and summarized using descriptive statistics (n, mean, SD, CV%, median, min, max, geometric mean, and GeoCV%) by renal function group and by cohort based on the PK Analysis Set.

6.7. Interim Analysis

No formal interim analysis is planned for this study.

6.8. Modifications

6.8.1. Modifications to the Approved Study Protocol

From the protocol amendment 1 Section 9.4.1, “Treatment-emergent Adverse Events (TEAE) will include any AE that is reported with an onset date on or after administration of study intervention until the last follow-up visit”.

From this SAP, TEAE is defined as any AE with an onset date on or after the administration of study intervention through the end of the TE period. The TE period is defined as the time period from the dose of study intervention to the dose of study intervention +30 days.

For participants with severe RI and matched healthy adults in the severe RI cohort, enrollment was closed after 6 participants were enrolled due to a sponsor decision. This change is not expected to impact the study objectives, endpoints, or interpretation of results, as sufficient data were collected to support the planned analyses.

6.8.2. Modifications to the Approved Statistical Analysis Plan

Section (SAP v1.0)	Update (SAP Amendment v2.0)
Section 6.2.1 Participant disposition	To update the percentage calculation is based on the All Enrolled Set.
Section 6.2.2 Demographics and baseline characteristics	To add a listing for substance use.
Section 6.2.5 Protocol deviation	To remove the content of the COVID-19 PD and the PD table.
Section 6.2.6 COVID-19 impact	To remove the section on the COVID-19 impact.
Section 6.4.1 PK variables	To add clarification for the summary of PK variables

Section 6.4.3 Analysis of PK parameters	To add the analysis for the Metabolite-to-Parent ratio of individual participant PK parameters.
Section 6.4.4 Comparison of PK between RI and healthy participants	To specify the ANOVA model, and replace CL_R by eGFR..
Section 6.5.3.1 Summaries of laboratory results	To remove the Grade 0.
Section 6.8.1 Modifications to the approved study protocol	To add the description of the sample size adjustment.
Appendix 4: Severity (Toxicity) Grades for Laboratory Abnormalities	To add a footnote for Potassium (hypokalemia) and Glucose (hyperglycemia) to use a different grading criteria.
Others: words/sentences, format, etc.	Other minor edits, updates, etc.

7. SUPPORTING DOCUMENTATION

Appendix 1: List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
BMI	body mass index (kg/m ²)
CI	confidence interval
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
GLSM	geometric least square mean
LLN	lower limit of normal
Max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
Min	minimum value
MH	matched healthy (participants)
PK	pharmacokinetic/pharmacokinetics
PR	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex
PT	preferred term
QRS	Q, R, and S-wave define the QRS-complex in an ECG
QT	QT interval represents the duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RI	renal impairment
LS	least square
SAE	serious adverse event

SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary

Appendix 2: Analysis Window for Safety Assessment

Assessment	Analysis Visit ¹	Target Study Day	Analysis Window (in study days) ^{2, 3, 4}
- Serum Chemistry - Hematology - ECG - Vital signs - Liver function tests	Day 1 (Baseline)	1	≤ 1 Pre-dose
	Day 2	2	(1, 2]
	Day 3	3	(2, 3]
	Day 4	4	(3, 4]
	Day 5	5	(4, 17]
	Week 4	29	(17, 43]
Coagulation	Week 8	57	(43, 71]
	Day 1 (Baseline)	1	≤ 1 Pre-dose
	Week 4	29	(1, 43]

Note:

- Visit name is used in tables and figures.
- The analysis windows will be applied using the following rules for both scheduled and unscheduled visits:
 - If no numerical measurement is available within an analysis window, the measurement will be considered missing for the visit.
 - If there is more than 1 numerical measurement available within an analysis window, use the following rules:
 - The scheduled visit measurement will be used if it is available.
 - If not, the unscheduled visit measurement closest to the target day will be used; or
 - If there are multiple unscheduled visit measurements with the same distance from the target day, the latest measurement will be used.
- For an assessment, e.g., laboratory, ECG and vital sign measurement collected on the date of dose of study drug, if it cannot be determined whether the measurement is before or after the dose:
 - Scheduled measurement will be treated as pre-dose observation.
 - Unscheduled measurement will be treated as post-dose observation.
- PK analysis window will follow the protocol-defined assessment visit window.

Appendix 3: Imputation Rules for Missing/Partial AE/Medication Dates

Imputation rules for missing/partial AE/medication start date are defined below.

- If only Day of AE/medication start date is missing:
 - ✓ If the full (or partial) AE/medication end date is NOT before the study drug administration date or AE/medication end date is missing, then
 - if AE/medication start year and month are equal to the year and month of study drug administration date, then impute the AE/medication start day as the day of study drug administration;
 - else impute the AE/medication start day as 1.
 - ✓ else impute the AE/medication start day as 1.
- If Day and Month of AE/medication start date are missing:
 - ✓ If the full (or partial) AE/medication end date is NOT before the study drug administration date or AE/medication end date is missing, then
 - if AE/medication start year is equal to the year of study drug administration date, then impute the AE/medication start month and day as the month and day of study drug administration;
 - else impute the AE/medication start month as January and day as 1.
 - ✓ else impute the AE/medication start month as January and day as 1.
- If Year of AE/medication start date is missing:

If the year of AE/medication start is missing or AE/medication start date is completely missing:

 - ✓ If the full (or partial) AE/medication end date is NOT before the study drug administration date or AE/medication end date is missing, then impute the AE/medication start date as the study drug administration date;
 - ✓ else impute the AE/medication start date as the informed consent date.

Imputation rules for partial/missing AE/medication end date are defined below:

- Impute the AE/medication end date as min (the last day of the month, end of study participation) if day is missing, or min (Dec, end of study participation) if month is missing. If the end date is entirely missing, assume the AE/medication is ongoing.

Appendix 4: Severity (Toxicity) Grades for Laboratory Abnormalities

The lab abnormality analysis for the selected parameters below will be conducted based on the toxicity grade of the CTCAE v5.0.

Parameter	CTCAE v5.0 Term
Liver Function Test	
Alanine Aminotransferase (ALT)	Alanine aminotransferase increased
Aspartate Aminotransferase (AST)	Aspartate aminotransferase increased
Alkaline Phosphatase (ALP)	Alkaline phosphatase increased
Bilirubin	Blood bilirubin increased
Chemistry	
Albumin	Hypoalbuminemia
Gamma Glutamyl Transferase	GGT increased
Creatinine	Creatinine increased
Calcium	Hypercalcemia
	Hypocalcemia
Lactate dehydrogenase (LDH)	Blood lactate dehydrogenase increased
Sodium	Hypernatremia
	Hyponatremia
Potassium	Hyperkalemia
	Hypokalemia *
Glucose	Hyperglycemia *
	Hypoglycemia
Hematology	
Hemoglobin	Anemia
	Hemoglobin increased
Neutrophil	Neutrophil count decreased
Lymphocytes (absolute)	Lymphocyte count decreased
	Lymphocyte count increased
Platelets	Platelet count decreased
White blood cell (Leukocytes)	Leukocytosis
	White blood cell decreased

Parameter	CTCAE v5.0 Term
Coagulation	
International Normalized Ratio/ Prothrombin time	INR increased

* For low potassium (hypokalemia) and high glucose (hyperglycemia), the grading will be based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events v2.1 due to the lack of clearly defined ranges in CTCAE grading tables.