A Phase 2 Randomized, Placebo-Controlled Study in Mainland China to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of VIR-2218

NCT04507269

Statistical Analysis Plan V1.0

19 November 2021

STATISTICAL ANALYSIS PLAN

A Phase 2 Randomized, Placebo-Controlled Study in Mainland China to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of VIR-2218

PROTOCOL NO.: VIR-2218-1005

PRODUCT CODE: VIR-2218

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SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed by Brii Biosciences, and has been approved for use for the VIR-2218-1005 study:

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List of Abbreviations

Abbreviation	Description
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BUN	Blood urea nitrogen
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
CCI	[redacted]
HBV	Hepatitis B Virus
HBeAg	Hepatitis B e-Antigen
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
INR	International Normalized Ratio
IWRS	Interactive Web Response System
LDH	Lactic Acid Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
NK	Not Known
NrtI	Nucleos(t)ide reverse transcriptase inhibitor
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
S.I.	International System of Units
SRC	Safety Review Committee
SOC	System Organ Class

Abbreviation	Description
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data collected from the VIR-2218-1005 phase 2 study CCI [redacted] focusing on safety, tolerability and antiviral activity of VIR-2218. For PK statistical analysis a separate SAP will be prepared.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts.

2. PROJECT OVERVIEW

2.1 Study Design

This is a phase 2 randomized, double-blind, placebo-controlled study of VIR-2218 administered subcutaneously to adult subjects with chronic Hepatitis B Virus (HBV) infection without cirrhosis on nucleos(t)ide reverse transcriptase inhibitor (NrtI) therapy. The study is designed to evaluate the safety, tolerability, PK and antiviral activity of VIR-2218.

This study will be conducted in close collaboration with an ongoing phase 1/2 regional study being conducted in multiple sites in the Asia-Pacific region.

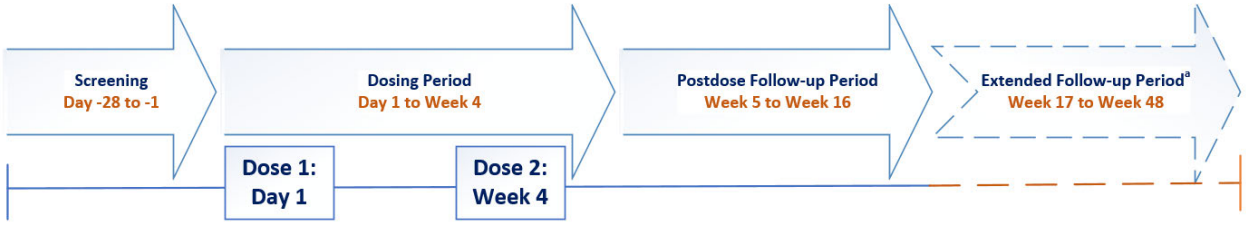
This study will include two Parts:

- Part One: adult subjects with Hepatitis B e-Antigen (HBeAg)-negative chronic HBV infection without cirrhosis on NrtI therapy for ≥ 6 months and HBV DNA < 90 IU/mL at screening (by central laboratory)
- Part Two: adult subjects with HBeAg-positive chronic HBV infection without cirrhosis on NrtI therapy for ≥ 6 months and HBV DNA < 90 IU/mL at screening (by central laboratory)

Each cohort in Part One/Two will be composed of 5 subjects randomized 4:1 to VIR-2218 or placebo, respectively. There are two planned cohorts (50 mg dose-level and 100 mg dose-level) and 1 optional cohort (≤ 200 mg dose-level) for each of Part One and Part Two of the study. Enrollment of the Part One/Two optional cohorts will be according to the same randomization scheme and eligibility criteria as the Part One/Two planned cohorts. The optional cohorts may be initiated after Safety Review Committee (SRC) review of a minimum of 6 weeks of available safety and antiviral activity data from the 200 mg cohorts of the VIR-2218-1001 regional study.

The estimated total duration for each subject is up to 52 weeks, including screening period (4 weeks), dosing period (4 weeks), post-second dose follow-up period (12 weeks) and extended follow-up period (up to 48 weeks) (Figure 1). Additional HBsAg monitoring is required for subjects with a ≥ 1 $\log_{10}$ change from baseline (Day 1 pre-dose level) decrease in HBsAg achieved by the Week 16 visit. Extended follow-up visits will occur every 4 weeks starting at Week 20, and subjects will be followed until the HBsAg level returns to > 90% of the Day 1 pre-dose level or Week 48, whichever comes earlier. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

Figure 1. Study Design for Cohorts



Screening period

Screening will be performed no more than 4 weeks before the Day 1 visit and will include written informed consent, determination of eligibility, collection of demographics and medical history as well as physical examination (including vitals), laboratory tests, 12-lead Electrocardiogram (ECG) and other assessments per the schedule of assessments. To exclude the presence of cirrhosis, screening will include a mandatory noninvasive assessment of liver fibrosis such as a FibroScan evaluation, unless the subject has results from a FibroScan evaluation performed within 6 months prior to screening or a liver biopsy performed within 1 year prior to screening that confirms the absence of Metavir F3 fibrosis or F4 cirrhosis.

Adverse events related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards.

Dosing period

Subjects enrolled will remain outpatient. Subjects will be randomized 4:1 to receive VIR-2218 or placebo within 48 hours prior to study drug administration on Day 1. Subject eligibility must be confirmed prior to study drug administration on Day 1. Subjects will return to the clinical investigative site at Week 4 to receive a second dose of the same study drug administered on Day 1. The decision to administer a second dose will be made based on Week 3 laboratory values in accordance with dose suspension/stopping criteria in Protocol Amendment 2 section 4.6. Additional blood samples for possible analyses to elucidate VIR-2218 antiviral activity and/or host responses to infection and treatment will be collected.

Subjects enrolled into the optional cohorts will receive VIR-2218 or placebo on Day 1 and Week 4 at a maximum dose-level of 200 mg.

Post-dose follow-up period

Subjects will return to the clinical investigative site on an outpatient basis for safety, tolerability, PK, and antiviral activity monitoring at specified timepoints during this Post dose Follow up period (Week 5 to Week 16). Additional HBsAg monitoring is required for subjects with a ≥ 1 $\log_{10}$ change from baseline (Day 1 pre-dose level) decrease in HBsAg achieved by the Week 16 visit.

Extended follow-up period

Subjects who require additional HBsAg monitoring will return to the clinical investigational site for in-person assessments. Extended follow-up visits will occur every 4 weeks starting at Week 20, and subjects will be followed until the HBsAg level returns to > 90% of the Day 1 pre-dose level or Week 48, whichever comes earlier. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

Discontinuations

Subjects who discontinue prematurely will be followed for safety, and under certain circumstances, subjects who discontinue study drug (as described in Protocol Amendment 2 section 4.3) may be replaced. If a subject discontinues from the study post-dose but before completion of the Week 16 visit, an early termination visit should be performed.

Replacement of Subjects

Replacement subjects may be enrolled to ensure that the minimum data requirements for SRC decisions and study progression are met, as described in Protocol Amendment 2 section 4.5. Subjects who do not receive the full planned dose, do not receive a second dose, discontinue due to an Adverse event (AE) that does not meet study progression and dose suspension/stopping rules (Protocol Amendment 2 section 4.6), or who withdraw from the study, may be replaced with confirmation by the SRC. Subjects who are discontinued from treatment for reasons other than experiencing an AE may be replaced following discussion between the Sponsor and investigator.

The replacement subject will be assigned a unique study identification number and will receive the same study drug assignment and dose level as the subject who is being replaced and in the same blinded fashion.

Safety Review Committee

An SRC will perform ongoing reviews of safety, tolerability, and available study data collected throughout the study with the primary purpose of protecting the safety of subjects participating in this clinical study. The SRC will be governed by an SRC Charter that will be finalized prior to screening the first subject.

The SRC will undertake safety data review prior to initiation of dosing the optional cohorts of the study in accordance with the SRC Charter. In addition, ad hoc SRC meetings may take place as needed, e.g., for a significant safety event such as a subject or cohort stopping criterion being reached (Protocol Amendment 2 section 4.6).

Decisions to suspend dosing or discontinue individual subjects from study drug will be made according to predetermined stopping rules (Protocol Amendment 2 section 4.6). Additionally, the SRC may recommend discontinuation of the study to the Sponsor. The SRC membership composition is described in detail in the SRC Charter.

2.2 Objectives

2.2.1 *Primary objective*

The primary objective of this study is:

To evaluate the safety and tolerability of multiple doses of VIR-2218 in subjects with HBeAg-negative and HBeAg-positive chronic HBV infection without cirrhosis on NrtI therapy.

2.2.2 *Secondary objectives*

The secondary objectives of this study are:

- To characterize the PK of VIR-2218 in subjects with chronic HBV infection without cirrhosis on NrtI therapy.
- To assess the antiviral activity of VIR-2218 in subjects with chronic HBV infection without cirrhosis on NrtI therapy.

CCI [redacted]

[redacted]

[redacted]

2.3 Endpoints

2.3.1 *Primary endpoints*

- Incidence of treatment-emergent adverse events (TEAEs).
- Clinical assessments including but not limited to laboratory test results.

2.3.2 *Secondary endpoints*

- PK parameters of VIR-2218 and possible metabolites (may include, but not limited to, maximum plasma concentration, time to reach maximum concentration, area under the concentration versus time curve [to last measurable timepoint and to infinity], percent of area extrapolated, apparent terminal elimination half-life, clearance, and volume of distribution).
- Maximum reduction of serum HBsAg from Day 1 until 12 weeks post last dose.
- Number of subjects with serum HBsAg loss at any timepoint.
- Number of subjects with sustained serum HBsAg loss for greater than or equal to 6 months.
- Number of subjects with anti-HBs seroconversion at any timepoint.
- For HBeAg-positive subjects (Part Two only): number of subjects with HBeAg loss and/or anti-HBe seroconversion at any timepoint.

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[redacted]

[redacted]

2.4 Sample Size

No formal sample size calculation was conducted. Up to 30 subjects with chronic HBV infection are planned to complete the study.

2.5 Randomization

An Interactive Web Response System (IWRS) will be employed to manage subject randomization and treatment assignments.

For each of the planned 50 and 100 mg dose-level cohorts, 5 subjects will be randomized 4:1 to VIR-2218 or placebo administered 4 weeks apart on Day 1 and Week 4.

One optional cohort may be added to each study part (Part One and Part Two), wherein 5 subjects will be randomized 4:1 to VIR-2218 or placebo administered 4 weeks apart on Day 1 and Week 4 at a dose-level of up to 200 mg.

Blinding of study treatment will be managed by the clinical investigative site's pharmacy in accordance with the Pharmacy Manual. In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment for that subject. IWRS should be used as the primary method of breaking the blind. If IWRS cannot be accessed, the investigator should contact the Sponsor medical monitor to break the blind. Treatment assignment should remain blinded unless that knowledge is necessary to guide subject emergency medical care. The investigator is requested to contact the Sponsor medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

The Sponsor or designee may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) as required by regulators.

3. STATISTICAL CONSIDERATIONS

Data will be handled and processed per the sponsor's representative PPD Standard Operating Procedures (SOPs), which are written based on the principles of good clinical practice (GCP).

3.1 General Considerations

All data collected on the electronic case report form (eCRF) will be presented in the data listings and will be listed and sorted by treatment arm, subject number and visit, where applicable. All summaries will be presented by treatment arm.

When reporting descriptive statistics, the following rules will apply:

- Continuous variables: Descriptive statistics for observed data or log10-transformed observed values, where applicable, will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum values. The minimum and maximum are the smallest and largest arithmetic values, respectively, unless specified otherwise.

  The Q1, Q3, minimum and maximum values will be displayed to the same decimal precision as the source data; the arithmetic mean and median values will be displayed to one more decimal than the source data; SD value will be displayed to two more decimal than the source data for the specific variable.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the abovementioned rules.

  n will be an integer. If no subjects have data at a given time point, then only n=0 will be presented.

  All data will be presented to a maximum of 3 decimal places.

- Categorical variables: Descriptive statistics will include counts and percentages per category. The denominator in all percentage calculations will be the number of subjects in the relevant analysis set with non-missing data, unless specifically stated otherwise. Percentages will be displayed to one decimal place.

  Percentage change from baseline values will be calculated and displayed to 1 decimal place in the listings. In the summaries, the mean and median percentage change from baseline values will be presented to 2 decimal places, the minimum and maximum values will be presented to 1 decimal place and the SD value will be presented to 3 decimal places.

  For categories where all subjects fulfill certain criteria, the percentage value will be displayed as 100. For categories where zero subjects fulfill certain criteria, there will be no percentage displayed. All other percentage displays will use 1 decimal place. Data listings will contain all reported and derived data.

Unless otherwise stated, the following methods will be applied:

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. Repeat and unscheduled assessments will be included in the derivation of the baseline values and minimum/maximum values post baseline. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. For screening visits, there are some repeated lab results because the original results may be errors. Then the repeated results will be presented as screening results for these cases. All collected data will be included in the data listings.

- Assessment windows: All assessments will be included in the data listings and no visit windows will be applied to exclude assessments that were performed outside of the protocol specified procedure windows.
- Result display convention: Results will be center aligned in all summary tables and listings. Subject identifiers visit and parameter labels may be left-aligned if required.
- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:
    - Date only: YYYY-MM-DD
    - Date and time: YYYY-MM-DD HH:MM

If only partial information is available, unknown components of the date or time will be presented as 'NK' (not known), i.e., '2016-NK-NK'. Times will be reported in military time.

3.2 Key Definitions

The following definitions will be used:

- Baseline: The baseline value is defined as the last available valid (quantifiable continuous or categorical value), non-missing observation for each subject prior to first study drug administration. Repeat and unscheduled assessments will be included in the derivation of the baseline values.
- Change from Baseline: The change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit/time point and the baseline value.

  The change from baseline value at each post-baseline visit/time point will be calculated for all continuous parameters using the following formula:

  Change from Baseline Value = Result at Visit/Time Point – Baseline Value

  The change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available and will be treated as missing otherwise.
- Study day: The study day of an event is defined as the relative day of the event starting with the date of the first study drug administration (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the first study drug administration will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration)

  For events occurring on or after Day 1, study day will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration) + 1

  Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

  Relative days compared to an alternative reference point will be calculated similarly, but the alternative starting reference start date will be used instead of the date of the first study drug dosing.
- HBsAg loss: quantitative HBsAg < 0.05 IU/mL at two or more consecutive measurements.
- Sustained HBsAg loss: quantitative HBsAg < 0.05 IU/mL at all visits (scheduled and unscheduled) for ≥ 6 months.

- HBsAg Seroconversion: HBsAg loss plus anti-HBs positivity at two or more consecutive measurements
- HBeAg loss (HBeAg+ subjects only): quantitative HBeAg < 0.14 IU/mL at two or more consecutive measurements
- HBeAg Seroconversion (HBeAg+ subjects only): HBeAg loss plus anti-HBe positivity at two or more consecutive measurements

3.3 Hypothesis Testing and Inferential Analyses

Descriptive statistics will be used to summarize all data. No formal hypothesis testing is planned.

3.4 Multiple Comparisons and Multiplicity Adjustments.

Not applicable for this study.

3.5 Coding of Events and Medications

Adverse event verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or the latest version in use. Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analysis.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD, 01MAR2020 Enhanced) or the latest version in use. Medications will be mapped to the full WHO-DD Anatomical Therapeutic Chemical (ATC) class hierarchy, but PTs will be of primary interest in this analysis.

3.6 Cohorts (Treatment Groups)

Part One (HBeAg-):

- VIR-2218 50 mg
- VIR-2218 100 mg
- VIR-2218 optional cohort, up to 200 mg
- VIR-2218 Overall, for safety data
- Placebo
- Overall

Part Two (HBeAg+):

- VIR-2218 50 mg
- VIR-2218 100 mg
- VIR-2218 optional cohort, up to 200 mg
- VIR-2218 Overall, for safety data
- Placebo
- Overall

For summaries using Safety Analysis Set, the VIR-2218 Overall group will be presented.

4. ANALYSIS SETS

In this SAP, 4 analysis sets are defined: The screened, all randomized, safety, and antiviral analysis sets.

Furthermore, any additional exploratory analysis not identified in the SAP will be identified in the final Clinical Study Report (CSR) as exploratory post hoc analyses, including analyses for additional study populations or subgroups of interest.

The number and percentage of subjects in each analysis set will be summarized by cohort and overall by study part.

4.1 Analysis Set Descriptions

4.1.1 *Screened Analysis Set*

The Screened Analysis Set will consist of all subjects that sign the informed consent form. The listing of Eligibility Criteria will be based on this population.

4.1.2 *All Randomized Analysis Set*

The All Randomized Analysis Set will include all randomized subjects, irrespective of whether they received any study treatment. Subjects will be summarized by the treatment to which they were randomized, regardless of treatment actually received.

Important protocol deviations, demographic and baseline characteristics will be summarized by the All Randomized Analysis Set.

4.1.3 *Safety Analysis Set*

The primary analysis set for safety analyses will be the Safety Analysis Set, which includes all randomized subjects who received at least 1 dose of study treatment. The Safety Analysis Set will be based on actual treatment received if different from the treatment to which they were randomized.

All safety analyses will be based on the Safety Analysis Set.

4.1.4 *Antiviral Activity Set*

The primary analysis set for antiviral activity analyses will be the Antiviral Analysis Set, which includes all subjects in the Safety Analysis Set who have at least 1 non-missing data to provide interpretable results for the specific antiviral activity parameters of interest.

5. SUBJECT DISPOSITION AND ANALYSIS SETS

Outcomes will be summarized by cohort, by study part and overall. All outcomes will be listed by study part and cohort.

5.1.1 *Subject Disposition*

Subject disposition will be summarized using counts and percentages and will be based on the Screened Analysis Set. The number and percentage of subjects who completed the study as planned, subjects discontinued early from the study, as well as the primary reason for early discontinuation will be presented.

All disposition information collected will be listed together with the date that the subject provided informed consent and the date and time of study drug administration.

5.1.2 *Analysis Sets*

The number of subjects included in each of the defined analysis sets will be summarized using counts and percentages and will be based on the Screened Analysis Set.

In addition, each subject's inclusion into/exclusion from each of the defined analysis sets will be listed by the Screened Analysis Set.

6. PROTOCOL DEVIATIONS

Important protocol deviations will be presented for each subject in the by-subject data listings by study part and cohort.

Important protocol deviations will be decided prior to database lock, and may include the deviations from the following, depending on the timing and nature of the deviation:

- Informed Consent Criteria
- Eligibility and Entry Criteria
- Concomitant Medication Criteria
- Laboratory Assessment Criteria
- Study Procedures Criteria
- Serious Adverse Event Criteria
- Randomization Criteria
- Visit Schedule Criteria
- Investigation Product (IP) Compliance
- Efficacy Criteria
- Administrative Criteria
- Source Document Criteria
- Regulatory or Ethics Approvals Criteria
- Other Criteria

7. DEMOGRAPHIC AND BASELINE INFORMATION

Demographic and baseline information will be analyzed using the All Randomized Analysis Set. All summarized information will be presented by cohort, by study part and overall. All demographic information will be listed by cohort and study part.

7.1 Demographics

7.1.1 *Definition of variables*

- Age (years)
- Sex
- Childbearing Potential
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)
- HBeAg Baseline Status
- Baseline log10 HBsAg (IU/mL)
- Baseline Alanine Aminotransferase (U/L)
- Baseline HBV DNA Categories (IU/mL) (<10, >=10 and <90, and >=90)

7.1.2 *Biostatistical methods*

Continuous and categorical summaries will be presented for demographic variables as discussed in section 3.1 by cohort, by study part and overall.

7.2 Screening Viral Serology

Viral serology results (Active infection with HIV infection, HCV infection, chronic HBV infection and hepatitis Delta virus infection. Chronic HBV infection is defined as serum HBsAg for > 6 months. In cases of occult HBV, chronic HBV infection is defined as serum HBV DNA positive for > 6 months.) at screening will be listed.

7.3 Medical History

Medical history will be summarized by cohort, by study part and overall if coding using MedDRA® is available. All medical history data will be listed.

HBV Genotype data will be listed.

7.4 Urine Drug Test

Urine drug test results obtained at screening will be listed.

7.5 Cirrhosis Status

Cirrhosis status (FibroScan results and Cirrhosis status) at screening will be summarized by cohort, by study part and overall, and all cirrhosis data collected will be listed.

8. TREATMENT EXPOSURE

Treatment exposure information will be summarized by cohort, by study part and overall using safety population. Duration of Treatment (Days) is calculated as Date of Last Dose - Date of First Dose + 1.

All exposure information will be listed by cohort and study part.

9. PHARMACOKINETICS (PK)

Pharmacokinetic analysis falls outside the scope of the SAP. There will be a sperate SAP for PK analyses.

10. PHARMACODYNAMICS (PD)

No PD analysis is planned for this study.

11. EFFICACY

No efficacy analysis is planned for this study.

12. SAFETY

Safety endpoints will be analyzed using the safety analysis set. All information will be presented by cohort, by study part and overall, unless otherwise specified. All safety data will be listed by cohort and study part.

12.1 Adverse Events

12.1.1 *Definition of variables*

- AE
- Serious adverse event (SAE)
- Treatment emergent adverse event (TEAE)

AEs and SAEs are defined in the study protocol. TEAEs are defined as any AEs with an onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug. If a subject experiences an AE before dosing and after dosing, this AE will be considered as TEAE only if it has worsened in severity. Adverse events that have missing onset dates will be considered treatment-emergent, unless the stop date is known to be prior to the first administration of the study medication. Related AEs are adverse events with relationship as “Related” collected in CRF or missing relationship.

Please refer to section 14 for handling of partial dates for AEs.

12.1.2 *Biostatistical methods*

All AEs will be coded using MedDRA.

AE summary tables will be provided. Summary tables will include the number of subjects (%) experiencing an event and the number of events. Subjects will be counted only once at each SOC and PT level of summary.

The AE, SAE and TEAE summaries will include:

- Overall Summary of all AEs including SAEs
- Overall Summary of TEAEs
- TEAE summary by SOC and PT
- TEAE of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 summary by SOC and PT
- Drug related TEAE summary by SOC and PT
- TEAE leading to study withdrawal summary by SOC and PT
- TEAE leading to treatment withdrawal summary by SOC and PT
- Serious TEAE summary by SOC and PT
- Serious TEAE of CTCAE Grade ≥ 3 summary by SOC and PT
- Drug related serious TEAE summary by SOC and PT
- Serious TEAE leading to study withdrawal summary by SOC and PT
- Serious TEAE leading to treatment withdrawal summary by SOC and PT
- SAE summary by SOC and PT
- SAE of CTCAE Grade ≥ 3 summary by SOC and PT
- Drug related SAE summary by SOC and PT

- SAE leading to study withdrawal summary by SOC and PT
- SAE leading to treatment withdrawal summary by SOC and PT
- TEAE leading to death summary by SOC and PT
- Death
- TEAE summary by CTCAE Grade, SOC and PT
- Serious TEAE summary by CTCAE Grade, SOC and PT
- SAE summary by CTCAE Grade, SOC and PT

All AEs will be listed and will include verbatim term, PT, SOC, treatment, severity, causal relationship to the study drug, seriousness, outcome, and action taken with regards to the study drug. Separate listings will be created for AEs leading to study withdrawal and SAEs.

12.2 Safety Laboratory Assessments

Blood and urine samples will be collected at the time points specified in the Schedule of Assessments (refer to the protocol) to conduct hematology, chemistry, liver function tests, coagulation, urinalysis, pregnancy testing, and serology analyses.

The following tests will be performed within each of the specified test panels:

Hematology:

- Complete blood count with differential

Chemistry:

- Albumin
- Creatinine clearance
- Blood urea nitrogen (BUN)
- Gamma glutamyl transferase (GGT)
- Calcium
- Glucose
- Carbon dioxide/bicarbonate
- Lactate dehydrogenase (LDH)
- Chloride
- Potassium
- Creatine kinase
- Sodium
- Creatinine
- Uric acid

Liver Function Tests:

- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Bilirubin (total and direct)

Coagulation:

- International normalized ratio (INR) time
- Prothrombin

Urinalysis & Microscopic Urinalysis:

- Bilirubin
- Proteins
- Glucose
- Red Blood Cells
- Ketones
- Screen for drugs of abuse
- Leukocytes
- Specific gravity
- Microscopy (if clinically indicated)
- Urobilinogen
- Nitrite
- Visual inspection for appearance and color
- pH

Pregnancy Testing:

- Beta-human chorionic gonadotropin (WOCBP)
- Urine pregnancy test

Serology

- Hepatitis B, C, and Delta
- Human immunodeficiency virus I and II

12.2.1 *Biostatistical Methods*

All laboratory data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables. Repeated and unscheduled assessments will be included in the derivation of the baseline values and minimum/maximum values post baseline. All information will be presented by cohort and study part.

Results for individual parameters may be reported in different units depending on the analyzing laboratory. If required, the results (and the corresponding normal range cut-off values) for individual parameters may be converted to International System of Units (S.I.) units to summarize the data.

For all the parameters where a unit value has been reported, the parameter names that will be used in the outputs will comprise the test name and the unit of measure, for example, ‘Albumin (g/L)’. Parameters will be sorted alphabetically within tables and listings.

For all parameters where a normal range limit value is reported, the normal range will be derived based on the available lower and upper limit values and any reported mathematical symbols. If both a lower and upper limit value is available, the normal range will be presented as ‘(Lower, Upper)’.

The reported results for each parameter with a defined normal range will be classified ('Low', 'Normal' or 'High') in relation to the defined normal range limits. If a result is equal to the normal range cut-off value, the result will be considered normal.

The change from baseline values at each post-baseline visit will be calculated for all parameters with continuous results.

The minimum/maximum post baseline value will be the minimum/maximum non-missing value after baseline and during the reference period. Scheduled visits, unscheduled visits, and repeated measurements will be included to derive the minimum/maximum post baseline values.

The decimal precision to which the summaries for each parameter will be based on the maximum number of decimals to which the reported result or the normal range limits are presented to in the raw data. The results and normal ranges will be displayed to the same decimal precision in the listings.

The hematology and chemistry results tables will present summary statistics for each laboratory parameter within the specific test panel. For each parameter, summaries will be presented for the baseline and each scheduled post-baseline visit. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit.

The incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any postbaseline timepoint will be summarized by cohort.

The worst post baseline value will be the worst non-missing value after baseline and during the reference period. Scheduled visits, unscheduled visits, and repeat measurements will be included to derive the worst post baseline values.

Additionally, shift tables from baseline in CTCAE grade (version 5) by visit plus worst post-baseline will be summarized by counts and percentages.

The urinalysis table will present counts and percentages for the reported results at baseline and each post-baseline visit within each test parameter. Result categories will be order alphabetically, or in ascending order.

The listings of laboratory parameters will include all the information (fields) collected (including CTCAE derived values). In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each post-baseline visit will be presented.

12.3 Vital Signs Measurements

The following vital signs measurements will be taken at the time points specified in the Schedule of Assessments (refer to the protocol):

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Pulse rate (beats/min)
- Respiratory rate (breaths/min)
- Temperature (ºC)

12.3.1 *Biostatistical Methods*

All vital signs data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables. Repeated and unscheduled assessments will be included in the derivation of the baseline values and

minimum/maximum values post baseline. All information will be presented by cohort and study part.

The parameter names that will be used in the outputs will comprise the test name and the unit of measure, for example, 'Systolic Blood Pressure (mmHg)'. Parameters will be sorted in the order that the measurements were collected in on the Vital Signs eCRF page within the tables and listings: Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate, Respiratory Rate, and Temperature.

The change from baseline to the pre-dose assessment at each post-baseline visit will be calculated for all parameters. If unscheduled pre-dose assessments are recorded on Day 1, the average of the pre-dose Day 1 and unscheduled pre-dose assessments will be used as baseline for all change from baseline calculations.

The minimum/maximum post baseline value will be the minimum/maximum non-missing value after baseline and during the reference period. Scheduled visits, unscheduled visits, and repeat measurements will be included to derive the minimum/maximum post baseline values.

The decimal precision to which the summaries for each parameter will presented will be based on the maximum number of decimals to which the results were reported on the eCRF.

Vital signs measurements will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit.

The listings of vital signs measurements will include all the information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each post-baseline visit will be presented.

12.4 12-Lead Safety Electrocardiogram (ECG)

12-lead safety ECGs interpretations will be recorded and reviewed on-site by the investigator as outlined in the Schedule of Assessments (refer to the protocol). This 12-lead safety ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes.

12.4.1 *Biostatistical Methods*

All ECG data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables. All information will be presented by cohort and study part.

The summary of overall interpretation findings table will present counts and percentages for the reported results at baseline and each post-baseline visit/time point. Result categories will be ordered as 'Normal', 'Abnormal - Not Clinically Significant (NCS)' and 'Abnormal - Clinically Significant (CS)'.

The worst post baseline value will be the worst non-missing value after baseline and during the reference period. Scheduled visits, unscheduled visits, and repeat measurements will be included to derive the worst post baseline values (Abnormal CS is the worst, Abnormal NCS is next, then normal).

Additionally, shift tables from baseline in categories as 'Normal', 'Abnormal - Not Clinically Significant (NCS)', 'Abnormal - Clinically Significant (CS)' and 'Missing', will be summarized by counts and percentages.

The listings of ECG measurements will include all the information collected. In addition, the observations that are used as the baseline record (value) for each parameter will be flagged, and the change from baseline values at each post-baseline visit will be presented.

12.5 Physical Examinations

Physical Examination assessments will be listed for all time points.

12.6 Substance Use

Alcohol intake during the study will be recorded.

12.6.1 *Biostatistical Methods*

All alcohol intake data collected at scheduled and unscheduled visits will be included in the listings.

The parameter names that will be used in the outputs will comprise the test name and the unit of measure, for example, 'Amount of alcohol consumed (unit)'.

The listings of alcohol intake assessment will include all the information collected.

12.7 Pregnancy Test Results

Pregnancy testing are performed per Schedule of Assessments (refer to the protocol) and any time pregnancy is suspected. A serum pregnancy test is performed at screening and urine pregnancy tests are to be performed thereafter.

All information related to pregnancy testing (urine and serum based - beta-human chorionic gonadotropin) will be listed. This listing will include all pregnancy test results collected during the study.

12.8 Prior and Concomitant Medications

Prior medications are defined as any medication which started and stopped prior to the first dose of study medication.

Concomitant medications are defined as any medication (other than the study drug) that was used at least once after the first administration of the study medication and before end of study. Medications that were stopped on the same date as the first study drug administration will be analyzed as concomitant medications. If a clear determination cannot be made (partial medication end dates) the medication will be classified as concomitant.

Please refer to section 14 for handling of partial dates for medications.

12.8.1 *Biostatistical Methods*

Concomitant medications will be summarized by ATC class Level 3 and PT. Within each category, the number of subjects who used the medication (count and percentage) will be presented. Subject who used the same medication on multiple occasions will only be counted once in the specific category (PT). PTs will be sorted alphabetically. In addition to the summaries by the coded terms, the number of subjects who used at least one concomitant medication during the study will be presented.

Prior medications will be summarized similarly with concomitant medications.

All information that was collected on the Concomitant Medication eCRF as well as the coded WHO-DD terms will be included in the listings.

All prior and concomitant medications will be listed.

13. ANTIVIRAL ACTIVITY

Antiviral activity endpoints will be analyzed using the Antiviral Analysis Set. All information will be presented by cohort, by study part and overall. All antiviral activity data will be listed by cohort and study part.

13.1 Definition of variables

- Maximum reduction of serum HBsAg from Day 1 until Week 16.
    - Serum log_{10} HBsAg levels by timepoint
    - Serum log_{10} HBsAg Nadir level per subject
- Number of subjects with serum HBsAg loss.
- Number of subjects with sustained serum HBsAg loss for ≥ 6 months.
- Number of subjects with anti-HBs seroconversion.
- For HBeAg-positive subjects (Part Two only): number of subjects with HBeAg loss and/or anti-HBe seroconversion.

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13.2 Biostatistical methods

All antiviral data collected at scheduled and unscheduled visits will be included in the listings. The results collected as scheduled visits will be included in the summary tables.

The parameter names that will be used in the outputs will comprise the test name and the unit of measure, for example, HBsAg (IU/mL). Parameters will be sorted within parameter class (if present) in alphabetical order within the tables and listings.

Measurements will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline of the antiviral measure to that assessed at baseline values at each scheduled post-baseline visit. See section 3.1 for more detail with regards continuous data representation. Spaghetti plots of log10-transformed observed values and change from baseline values in HBsAg, HBeAg (Part Two only), CCI HBV DNA and CCI will be provided.

Categorical summaries (% of subjects) will present counts and percentages for the reported results at baseline and each post-baseline time point.

14. HANDLING OF MISSING DATA

All data will be analyzed as collected and missing values will not be imputed nor replaced.

Laboratory data that are continuous in nature but are less than the 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).

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE If start date >= study med start date and start date <= study med end date + 30, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of study, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of study, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of study, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of study, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of study, assign as concomitant
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of study, assign as concomitant
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	Assign as concomitant

Imputed dates will not be presented in the listings.

15. CHANGES TO THE PLANNED ANALYSIS

Not applicable.

16. INTERIM AND FINAL ANALYSIS

16.1 Interim Analysis

No planned interim analysis for this study.

16.2 Final Analysis (End of Study)

After all subjects have completed the study, outstanding data queries have been resolved/closed, and the data have been cleaned and finalized, and database has been locked, the sponsor will authorize breaking of the study blind and the final analysis of the data will be performed.

The final SAP and analysis sets must be approved and signed by the sponsor before the database is locked and treatment assignment unblinded. Any deviations from the planned analysis will be documented in the CSR.

17. SOFTWARE

- The following software will be used to perform the statistical analyses: SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

18. REFERENCES

1) VIR-2218-1005 protocol amendment 2 dated 23 September 2020.
2) VIR-2218-1001, ClinicalTrials.gov Identifier: NCT03672188.

STATISTICAL ANALYSIS PLAN for PHARMACOKINETICS

A Phase 2 Randomized, Placebo-Controlled Study in Mainland China to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of VIR-2218

PROTOCOL NO.: VIR-2218-1005

PRODUCT CODE: VIR-2218

DATE OF ISSUE: 12 NOV 2021

VERSION/STATUS: Fina Version 1

SPONSER: Brii Biosciences Ltd.
Room 301, 3/F,
Building 7,
No. 1 Yongtaizhuang North Street,
Haidian District, Beijing 100192, China

PPD [redacted]

SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed and has been approved for use for the VIR-2218-1005 study:

Table of contents

List of Abbreviations

Abbreviation	Description
HBV	Hepatitis B Virus
HBeAg	Hepatitis B e-Antigen
HBsAg	Hepatitis B Surface Antigen
PK	Pharmacokinetic
Q1	First Quartile
Q3	Third Quartile
SAP	Statistical Analysis Plan
SD	Standard Deviation

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the pharmacokinetic data collected from the VIR-2218-1005 phase 2 study CCI [redacted] should be used in conjunction with the separate SAP focusing on safety, tolerability, and antiviral activity of VIR-2218.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts.

2. PROJECT OVERVIEW

2.1 Study Design

This is a phase 2 randomized, double-blind, placebo-controlled study of VIR-2218 administered subcutaneously to adult subjects with chronic Hepatitis B Virus (HBV) infection without cirrhosis on nucleos(t)ide reverse transcriptase inhibitor (NrtI) therapy. The study is designed to evaluate the safety, tolerability, PK and antiviral activity of VIR-2218.

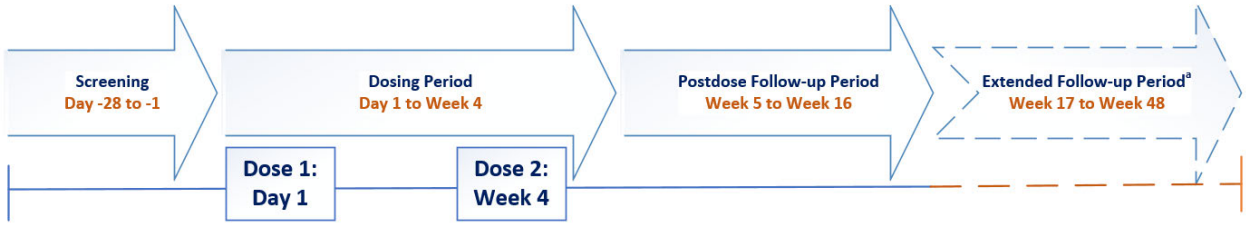
This study will include two Parts:

- Part One: adult subjects with Hepatitis B e-Antigen (HBeAg)-negative chronic HBV infection without cirrhosis on NrtI therapy for ≥ 6 months and HBV DNA < 90 IU/mL at screening (by central laboratory)
- Part Two: adult subjects with HBeAg-positive chronic HBV infection without cirrhosis on NrtI therapy for ≥ 6 months and HBV DNA < 90 IU/mL at screening (by central laboratory)

Each cohort in Part One/Two will be composed of 5 subjects randomized 4:1 to VIR-2218 or placebo, respectively. There are two planned cohorts (50 mg dose-level and 100 mg dose-level) and 1 optional cohort (≤ 200 mg dose-level) for each of Part One and Part Two of the study. Enrollment of the Part One/Two optional cohorts will be according to the same randomization scheme and eligibility criteria as the Part One/Two planned cohorts. The optional cohorts may be initiated after Safety Review Committee (SRC) review of a minimum of 6 weeks of available safety and antiviral activity data from the 200 mg cohorts of the VIR-2218-1001 regional study.

The estimated total duration for each subject is up to 52 weeks, including screening period (4 weeks), dosing period (4 weeks), post-second dose follow-up period (12 weeks) and extended follow-up period (up to 48 weeks) (Figure 1).

Figure 1. Study Design for Cohorts



2.2 Pharmacokinetic Assessments

Blood samples will be collected to assess concentrations of VIR-2218 and its metabolite (A-312327) , as applicable. Timepoints for the collection of samples for VIR-2218 PK analysis of the study are provided Table 1.

Table 1: Part One/Two Pharmacokinetic Assessment Timepoints

Study Day/Week	Protocol Time (Time Window)	PK Blood
Screening		
Day 1	Predose	X[a]
	Dose	
	1 hour ± 5 minutes	X
	2 hours ± 10 minutes	X
	4 hours ± 30 minutes	X
	8 hours ± 30 minutes	X
Day 2	24 hours ± 2 hours	X
Week 1		X
Week 4	Predose	X[a]
	Dose	
	1 hour ± 5 minutes	X
	2 hours ± 10 minutes	X
	4 hours ± 30 minutes	X
	8 hours ± 30 minutes	X
	24 hours ± 2 hours	X
Week 5		X
Week 8		X
Week 16		X
Week 24[b]		X

[a] At ≤ 15 minutes prior to dosing

[b] Collected only from subjects in extended follow up.

2.3 Pharmacokinetic Objective

- To characterize the PK of VIR-2218 in subjects with chronic HBV infection without cirrhosis on NrtI therapy.

3. PHARMACOKINETIC EVALUATION/ANALYSIS

3.1 Pharmacokinetic Concentration Population

The pharmacokinetic (PK) concentration population is defined as all randomized subjects who have at least 1 dose of VIR-2218 and at least 1 measurable (>LLOQ) concentration value.

3.2 Pharmacokinetic Analysis Population

The PK Analysis Set includes all randomized subjects who have at least 1 dose of VIR-2218 and 1 post-baseline PK parameter of interests.

3.3 Summary Statistics for PK Data

3.3.1 *General Consideration*

Due to the short plasma half-life of VIR-2218 and its metabolite (A-312327), pharmacokinetic parameters will be generated separately for day-1 dose and day-29 dose for patients in PK analysis population.

All analyses, including summary for plasma concentration data, summary for plasma PK parameter data, and concentration vs. time plots, will be summarized by Part, Dose Level, and Dosing Day as listed below. In addition, subjects received the same dose level (ie, VIR-2218 50 mg or VIR-2218 100 mg) from Parts One and Two will be pooled together for summary purpose.

- Part One: VIR-2218 50 mg, Day X
- Part One: VIR-2218 100 mg, Day X
- Part Two: VIR-2218 50 mg, Day X
- Part Two: VIR-2218 100 mg, Day X
- Part One & Two: VIR-2218 50 mg, Day X
- Part One & Two: VIR-2218 100 mg, Day X

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3.3.2 *Summary statistics for plasma concentration data*

The concentration and associated unit will be presented as they are received from the analytical laboratories.

The actual sampling date and time and elapsed time relative to dosing time for plasma and urine data will be listed by subject and nominal sampling time, with time deviation (difference in minutes between nominal and actual sampling times) calculated, for all subjects with available concentration data, including subjects excluded from the PK analysis set.

Summary statistics of PK concentration data of VIR-2218 and its metabolite (A-312327) (n, arithmetic mean, standard deviation [SD], coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum and maximum) will be calculated for each time point and summarized by dose day and dose level from each part and in combination (ie, subjects received the same dose level from part one and two will be pooled together), respectively. Geometric CV% calculated as the square root of the exponentiated SD of the natural log transformed data (SQRT(exp(sln^2)-1), where appropriate.

When reporting individual values and descriptive statistics for VIR-2218 and its metabolite (A-312327) plasma concentration data, the following rules will apply regarding rounding and precision:

- Descriptive statistics for PK concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place - for the mean (arithmetic and geometric), median and standard deviation.
- Between-subject CV% and geometric CV% will be reported as a percentage to 1 decimal place.
- Subjects with dosing deviations will be listed but excluded from the summary tables.

3.3.3 *Summary statistics for plasma PK parameters*

MR (metabolite to parent ratio) for a selected PK parameter is defined as the ratio of VIR-2218 metabolite(A-312327) PK parameter divided by the corresponding VIR-2218 PK parameter, for example MR of AUC_{inf} (%) = AUC_{inf} of A-312327 / AUC_{inf} of VIR-2218 * 100%. Summary tables with MR in PK parameters of AUC_{0-8}, AUC_{0-12}, AUC_{inf} and C_{max} will be tabulated.

Calculated PK parameters will be listed and summarized descriptively, including n, arithmetic mean, SD, minimum, median, maximum, coefficient of variation [CV(%)], geometric mean, geometric SD, geometric CV%; For time-related PK parameters (ie., $T_{max,}$ T_{last} and $t_{1/2}$) only n, minimum, median, and maximum will be reported. When reporting individual values and descriptive statistics for PK parameters of VIR-2218 and its metabolite (A-312327), the following rules will apply to rounding and precision:

- Individual values for PK parameters will be reported to 3 significant figures.
- Descriptive statistics for PK parameters will be reported to 3 significant figures.
- Between-subject CV% and geometric CV% will be reported as a percentage to 1 decimal place.
- Data listings containing all documented data and all derived data will be generated. Missing data will not be imputed.
- Subjects with dosing deviations will be reported in the listings but excluded from the summary tables.

3.4 CONCENTRATION-TIME PROFILES

Individual (for each subject) and mean plasma VIR-2218 and metabolite (A-312327) concentrations will be displayed graphically in linear and semi-logarithmic plots versus time (hour) Part, Dose Level, and Dosing Day l and Day 29. The actual collection time will be used for plots of individual plasma concentrations and nominal time will be used for plots of mean plasma concentrations. Below the plots, the number of quantifiable concentrations per timepoint will be displayed. Subjects with dosing deviations will be excluded from the mean plots. They will be displayed in the individual plots with footnote.

3.5 Estimation of Pharmacokinetic Parameters

Pharmacokinetic (PK) parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, PK concentration, and corresponding real time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to zero.

For area under the curve (AUC), samples below the limit of quantitation (BLQ) of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of zero to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event (e.g., plasma collection) or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals.

Pharmacokinetic parameters such as AUC_{inf}, λ_z, and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

The following parameters will be used to evaluate the PK objectives of the study: T_{max}, C_{max}, T_{last}, C_{last}, $t_{1/2}$, AUC_{0-t}, AUC_{0-8hr}, AUC_{0-12hr}, AUC_{0-24hr}, AUC_{inf}, λ_z, CL/F, V_z/F.

- T_{max}: The time to attain C_{max}. If the same C_{max} concentration occurs at different time points, tmax is assigned to the first occurrence of C_{max}.
- C_{max}: Individual maximum concentration (C_{max}) values are directly determined from the plasma concentration time profiles for each subject.
- T_{last}: Time of last measurable (positive) observed concentration.
- C_{last}: Observed concentration corresponding to T_{last}.
- $t_{1/2}$: The terminal half-life will be calculated from the terminal rate constant using the equation:

$$t_{1/2} = \frac{Ln(2)}{\lambda_z}$$

- AUC_{0-t}: The areas under the curve spanning time interval from 0 to t (up to the last time point with measurable concentration. AUC_{0-t} will be calculated using the linear-up /logarithmic-down trapezoidal rule. Linear trapezoidal rule: The area of the trapezoid between the two data points (t1, C1) and (t2, C2) where C2≥C1 will be computed by:

$$AUC_{t1-t2} = 0.5(t2 - t1)(C1 + C2)$$

Logarithmic trapezoidal rule: The area of the trapezoid between the two data points (t1, C1) and (t2, C2) where C2<C1 will be computed by

$$AUC_{t1-t2} = \frac{((t2 - t1)(C1 - C2))}{lnC1 - lnC2}$$

- When a partial AUC(e.g. $AUC_{0\text{-}12hr}$) is requested at time points not included in the scheduled measurements scheme, Interpolation will be used to estimate the concentration of these time points.
  1) Additional point before last observed data point
     Depending on the choice of the "Integral method" setting, this can be done using a linear or log formula to find the added concentration C* at requested time t*, given that the previous and following measurements are C1 at t1 and C2 at t2.
     Linear interpolation formula:

$$C^* = C_1 + \left|\frac{t^* - t_1}{t_2 - t_1}\right| \times (C_2 - C_1)$$

     Logarithmic interpolation formula:

$$C^* = exp\left(ln(C_1) + \left|\frac{t^* - t_1}{t_2 - t_1}\right| \times \left(ln(C_2) - \ln(C_1)\right)\right)$$

     If the logarithmic interpolation rule fails in an interval because C1 or C2 are null or negative, then the linear interpolation rule will apply for that interval.

  2) Additional point after last observed data point
     If λ_z is not estimable, the partial area will not be calculated. Otherwise, λ_z is used to calculate the additional Concentration C*

$$C^*=\exp(\text{Lambda\_z\_intercept} - \lambda_z \times t_{last})$$

     Where Lambda_z_intercept is the intercept on log scale estimated via linear regression of time vs. log concentration in estimating λ_z

- $AUC_{0\text{-}8hr}$: The area under the plasma concentration-time curve over the time interval from 0 to 8 hr using the linear-up /logarithmic-down trapezoidal rule.
- $AUC_{0\text{-}12hr}$: The area under the plasma concentration-time curve over the time interval from 0 to 12 hr using the linear-up /logarithmic-down trapezoidal rule. $AUC_{0\text{-}24hr}$: The area under the plasma concentration-time curve over the time interval from 0 to 24 hr using the linear-up /logarithmic-down trapezoidal rule.
- AUC_{inf}: The area under the plasma concentration-time curve over the time interval from 0 extrapolated to infinity will be calculated according to the following equation:

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_t'}{\lambda_z}$$

  where C't is the predicted concentration at the time t (last time point with a measurable plasma concentration above the quantification limit) at which quantification was still possible, the calculation of λ_z is given below.

- $AUC_{\%extrap}$: The percentage of the AUC that has been extrapolated beyond the last observed data point, calculated as:

$$AUC_{\%extrap} = \left(\frac{AUC_{0-\infty} - AUC_{0-t}}{AUC_{0-\infty}}\right) * 100$$

- λ_z: The apparent terminal rate constant λ_z will be estimated from a regression of ln(C) versus time over the terminal log-linear drug disposition portion of the concentration-time profiles. To calculate the elimination rate constant, the terminal data from a concentration-time curve will be used. Starting with the final non-BLQ data point and moving backwards, toward time zero, at least 3 data points not included C_{max} are fit to a linear regression. The number of data points used can be determined by maximizing the value adjusted-r^2 which defines the "best-fit" of the data. The first order rate constant associated with the terminal (log-linear) portion of the curve will be estimated via linear regression of time vs. log concentration. The rules are that a minimum of three points is needed to define the terminal (log-linear) portion of the curve, λ_z must be positive, and the selection is based on the best adjusted square coefficient of regression (r^2). Additionally, if the adjusted r^2 does not improve, but is within 0.0001 of the largest adjusted R^2 value, the regression with the larger number of points is used. The "adjusted" r^2 is calculated using the following equation:

$$Adjusted\ r^2 = 1 - (1 - r^2) * \frac{(n-1)}{(n-2)}$$

  where n = the number of data points used in the regression. The slope of the line is equal to $-\lambda_z$ (i.e., the slope will be negative, but λ_z is a positive value).

  If terminal concentration-time point(s) increases, this time point may be included if the $t_{1/2}$ estimate is reasonable. If λ_z is not determinable (for example, adjusted-r^2 value <0.8) then consequently only parameters not requiring λ_z will be reported. In addition, the lower (R_{start}) and upper (R_{end}) limit on time (h) for values to be included in the calculation of λ_z will be listed.

- CL/F: The total clearance will be calculated as following:

$$CL/F = \frac{D}{AUC_{0-\infty}}$$

  where D is dose

  V_z/F: The apparent volume of distribution based on terminal phase will be calculated according to the follow equation:

$$V_z/_F = \frac{CL/_F}{\lambda_z}$$

3.6 Other important PK considerations

- The value of $AUC_{\%extrap}$ will be less than or equal to 20% for the $AUC_{0-\infty}$ to be considered well estimated. If this proportion is > 20%, then the values of $AUC_{0-\infty}$ will be treated with caution, and emphasis will be placed on AUC_{0-t} values (i.e. in subsequent statistical analyses).
- If $AUC_{\%extrap}$ >20%, all elimination related parameters (λ_z, $AUC_{0-\infty}$, $t_{1/2}$, CL/F or CL/F,ss, and V_z/F or V_z/F,$_{ss}$) will be presented in the listings but excluded from the calculation of summary statistics. All values excluded from the summaries should be flagged in the individual listings with an explanation for the exclusion.
- If data permits, the other PK parameters may be reported.
- If $t_{last} = t_{max}$; C_{max} will not be reported for that subject in the listings. It will be footnoted to indicate that sampling timepoints were not appropriate for that subject.

- If t_{last}<24hr, AUC_{0-24hr} will only be reported when AUC%extrap<20%; it will be presented in the listing with footnote to indicate that AUC_{0-24hr} was extrapolated. In the summary tables, the cohort will be footnoted to indicate that subjects with extrapolated AUC_{0-24hr} were included in the calculation of summary statistics.
- If t_{last}<8hr, AUC_{0-8hr} will only be reported when $AUC_{\%extrap}$ <20%; it will be presented in the listing with footnote to indicate that AUC_{0-8hr} was extrapolated. In the summary tables the cohort will be footnoted to indicate that subjects with extrapolated AUC_{0-8hr} were included in the calculation of summary statistics.

4. SOFTWARE

- The following software will be used to perform the statistical analyses: SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA). Phoenix WinNonlin® software (version 8.1 or higher).

5. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

6. PROPOSED TABLES, FIGURES, AND LISTINGS

6.1 Tables

	Title	Analysis Set	Notes
1.1.1	Individual and Summary of VIR-2218 and A-312327 Plasma Concentrations by Timepoint, Dosing Day, and Dose Level	PK Analysis Population	
1.1.2	Individual and Summary of VIR-2218 Plasma Pharmacokinetic Parameter by Dosing Day and Dose Level	PK Analysis Population	
1.1.3	Individual and Summary of A-312327 Plasma Pharmacokinetic Parameter by Dosing Day and Dose Level	PK Analysis Population	
1.1.4	Individual and Summary of MR metabolite to parent ratio by Dosing Day and Dose Level	PK Analysis Population	

6.2 Figures

	Title	Analysis Set	Notes
1.1.1.1	Individual VIR-2218 Plasma PK Concentration vs Time by Dosing Day and Dose Level (Linear)	PK Concentration Population	
2.2.2.1	Individual A-312327 Plasma PK Concentrations vs Time by Dosing Day and Dose Level (Linear)	PK Concentration Population	
2.2.2.2	Individual VIR-2218 Plasma Concentration vs Time by Dosing Day and Dose Level (Semi-Logarithmic)	PK Concentration Population	
2.2.3.1	Individual A-312327 Plasma PK Concentrations vs Time by Dosing Day and Dose Level (Semi-Logarithmic)	PK Concentration Population	
3.2.1.1	Mean VIR-2218 Plasma Concentration vs time by Dose Day and Dose Level (Linear)	PK Concentration Population	
3.2.1.2	Mean A-312327 Plasma Concentration vs time by Dose Day and Dose Level (Linear)	PK Concentration Population	
3.2.1.1	Mean VIR-2218 Plasma Concentration vs time by Dose Day and Dose Level (Semi-Logarithmic)	PK Concentration Population	
3.2.1.2	Mean A-312327 Plasma Concentration vs time by Dose Day and Dose Level (Semi-Logarithmic)	PK Concentration Population	

6.3 Listings

	Title	Analysis Set	Notes
11	Plasma Concentrations of VIR-2218 and A-312327	PK Concentration Population	