# Official Title: A Phase 1/2, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-2218

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PPD

# STATISTICAL ANALYSIS PLAN

[redacted]

**PROTOCOL NO.:** VIR-2218-1001

**PRODUCT CODE:** VIR-2218

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**SAP APPROVAL**

By my signature, I confirm that this SAP has been reviewed by Vir Biotechnology, Inc. and has been approved for use for the VIR-2218-1001 study:

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**List of Abbreviations**

| Abbreviation | Description |
|---|---|
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| Anti-HBe | Hepatitis B extracellular antibody |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| BUN | Blood urea nitrogen |
| cccDNA | Covalently Closed Circular DNA |
| C-G | Cockroft-Gault |
| CHB | Chronic Hepatitis B |
| CS | Clinically Significant |
| CSR | Clinical Study Report |
| CV | Coefficient of Variation |
| DBP | Diastolic Blood Pressure |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| FU | Follow-up |
| GCP | Good Clinical Practice |
| GGT | Gamma-Glutamyl Transferase |
| CCI | |
| 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 |
| IVRS/IWRS | Interactive Voice/Web Response System |
| LDH | Lactic Acid Dehydrogenase |
| LLOQ | Lower limit of quantification |
| LOD | Limit of Detection |
| MAD | Multiple Ascending Dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N/A | Not Applicable |
| NCS | Not Clinically Significant |
| NK | Not Known |
| NRTI | Nucleos(t)ide Reverse Transcriptase Inhibitor |
| PD | Pharmacodynamic |
| PI | Principal Investigator |
| PK | Pharmacokinetic |

| Abbreviation | Description |
|---|---|
| PT | Preferred Term |
| Q1 | First Quartile |
| Q3 | Third Quartile |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAD | Single Ascending Dose |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| S.I. | International System of Units |
| SRC | Safety Review Committee |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TEAE | Treatment Emergent Adverse Event |
| TSH | Thyroid Stimulating Hormone |
| ULOQ | Upper limit of quantification |
| 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-2218-1001 study [redacted]

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

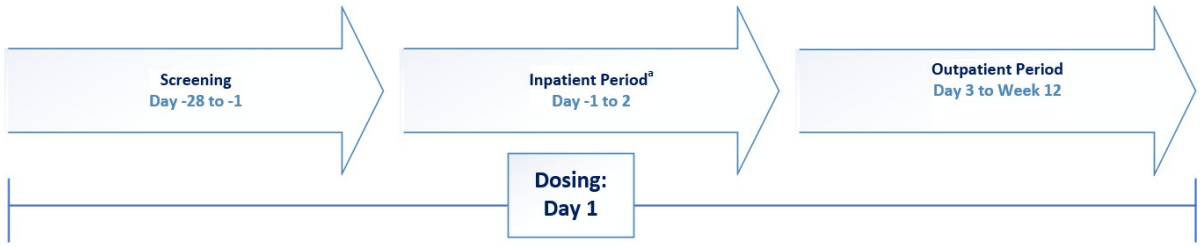
# 2. PROJECT OVERVIEW

## 2.1 Study Design

Part A to C:

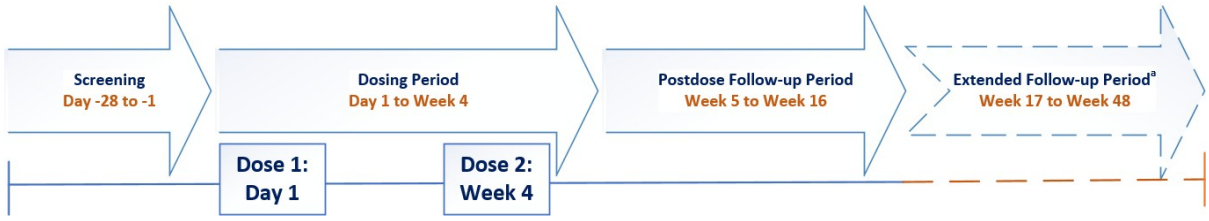
This is a randomized, double-blind, placebo-controlled study of VIR-2218 administered subcutaneously to healthy adult subjects and non-cirrhotic adult subjects with chronic hepatitis B virus (HBV) infection who are on nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy. The study is designed to evaluate the safety, tolerability, Pharmacokinetic (PK), and antiviral activity of VIR-2218. Part A is planned to be conducted at 1 clinical investigative site; Parts B and C are planned to be conducted at multiple clinical investigative sites in the Asia-Pacific region. The study designs for Part A, phase 1 single ascending dose (SAD) and Part B/C, phase 2 multiple ascending dose (MAD) are presented in Figure 1 and Figure 2, respectively.

Figure 1**: SAD Study Design for Part A**




[a]Subject discharge will occur after all assessments are completed on Day 2.

Figure 2**: MAD Study Design for Part B/C**




[a]Additional Hepatitis B Surface Antigen (HBsAg) monitoring is required for subjects with HBsAg levels with a > 10% decrease from the Day 1 predose level at the Week 16 visit. Visits will occur every 4 weeks starting at Week 20 up to Week 48 or until the HBsAg level returns to > 90% of the Day 1 predose level. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

Part A Single Ascending Dose Phase in Healthy Adult Subjects

Healthy adult subjects will be enrolled in 1 of 4 planned ascending dose cohorts. At the start of each cohort, 2 sentinel subjects will be randomized 1:1 to VIR 2218 or placebo. These subjects will be dosed concurrently and monitored for 24 hours; if the investigator has no safety concerns, the remainder of the subjects in the same cohort will be dosed. Vital signs, symptom-directed physical examination(s), and AEs will be reviewed by the investigator prior to dosing any additional subjects. The remaining subjects will be randomized 5:1 to receive a single dose of VIR 2218 or placebo.

Subject screening will occur no more than 4 weeks prior to the Day 1 visit. Eligible subjects will be confined to the clinical investigative site on Day −1 to determine continued eligibility and for predose assessments. Subjects in each cohort will be randomized to receive VIR-

2218 or placebo within 48 hours prior to study drug administration. Subjects will receive a single dose of study drug on Day 1 (VIR 2218 or placebo). Subjects will be discharged from the clinical investigative site after all assessments are completed on Day 2.

Subjects will return to the clinical investigative site on an outpatient basis for safety, tolerability, and PK monitoring at specified timepoints through the last Post-dose Follow-up Visit (Week 12).

Based on review of the accumulated, available data in Part A, the SRC may recommend dosing of 2 optional cohorts. In addition to the optional cohorts, up to 8 “floater” subjects for Part A may be added to any cohort, as determined and approved by the SRC.

Fasting is not required for any study procedure/assessment.

Part B/C Multiple Ascending Dose Phase in Non-Cirrhotic Adult Subjects with Chronic HBV Infection on Nucleoside/Nucleotide Therapy

Non-cirrhotic adult subjects with chronic HBV infection on NRTI therapy for ≥ 6 months will be enrolled in the Part B/C cohorts. Part B will enroll HBeAg negative subjects. Part C will enroll HBeAg positive subjects. Eligible subjects should have HBV DNA < 90 IU/mL. Each cohort in Part B/C will be composed of 4 subjects randomized 3:1 to VIR 2218 or placebo, respectively. There are 3 planned and 2 optional cohorts in Part B. There are 1 planned and 2 optional cohorts in Part C.

Subjects enrolled in Part B/C of the study will remain outpatient. Subject screening will occur no more than 4 weeks prior to the Day 1 visit. Eligible subjects will undergo further assessments on Day 1 to qualify for study drug administration on Day 1. 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.

Subjects in each cohort will be randomized 3:1 to receive VIR 2218 or placebo within 48 hours 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 onDay 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 Section 4.84.6.

Additional blood samples for possible analyses to elucidate VIR 2218 activity and/or host responses to infection and treatment will be collected.

Subjects will return to the clinical investigative site on an outpatient basis for safety, tolerability, PK, and antiviral activity monitoring at specified timepoints through the last Post dose Follow up Visit (Week 16). Additional HBsAg monitoring is required for subjects with HBsAg levels with a > 10% decrease from the Day 1 predose level at the Week 16 visit. Visitswill occur every 4 weeks starting at Week 20 up to Week 48 or until the HBsAg level returnsto > 90% of the Day 1 predose level. Additional HBsAg monitoring may be discontinued at theSponsor’s discretion based on emerging data.

Based on review of the accumulated, available data in Parts A, B, and C, the SRC may recommend dosing of optional cohorts following the same stratification. In addition to the optional cohorts, a combined total of up to 16 “floater” subjects for Part B/C may be added to any cohort, as determined and approved by the SRC.

Fasting is not required for any study procedure/assessment.

Safety Review Committee

In Parts A – C, a 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 a new cohort in Parts A, B, and C of the study in accordance with the SRC Charter. 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 (Section 4.8 of the protocol). In Parts D - F of the study, the SRC may meet ad hoc, and/or in the event an unexpected safety concern is identified.

Decisions to suspend dosing or discontinue individual subjects from study drug will be made according to predetermined stopping rules (Section 4.8 of the protocol). 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 objectives of this study are:

- Part A: To evaluate the safety and tolerability of a single dose of VIR-2218 in healthy adult subjects.
- Part B/C: To evaluate the safety and tolerability of multiple doses of VIR-2218 in non-cirrhotic subjects with HBeAg-negative (Part B) and HBeAg-positive (Part C) chronic HBV infection on NRTI therapy.

### 2.2.2 *Secondary objectives*

The secondary objectives of this study are:

- Part A:
  - To characterize the PK of VIR-2218 in healthy adult subjects.
- Part B/C:
  - To characterize the PK of VIR-2218 in non-cirrhotic subjects with chronic HBV infection on NRTI therapy.
  - To assess the antiviral activity of VIR-2218 in non-cirrhotic subjects with chronic HBV infection on NRTI therapy.

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## 2.3 Endpoints

### 2.3.1 *Primary endpoints*

- Part A/B/C:
  - Incidence of AEs
  - Clinical assessments including but not limited to laboratory test results

### 2.3.2 *Secondary endpoints*

- Part A:
  - PK parameters of VIR-2218 and possible metabolites (may include, but not limited to plasma: maximum 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; urine: fraction eliminated in the urine and renal clearance).

- Part B/C:
    - PK parameters of VIR-2218 and possible metabolites (may include, but not limited to plasma: maximum concentration, time to reach maximum concentration, area under the concentration versus time curve [to the last measurable timepoint and to infinity], apparent terminal elimination half-life, clearance, and volume of distribution).
    - Maximum reduction of serum HBsAg from Day 1 until Week 16.
    - Number of subjects with serum HBsAg loss up to all timepoints.
    - Number of subjects with sustained serum HBsAg loss for ≥ 6 months.
    - Number of subjects with anti-HBs seroconversion at any timepoint.
    - For HBeAg-positive subjects (Part C only): number of subjects with HBeAg loss and/or anti-HBe seroconversion at any timepoint.

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[redacted]

### 2.4 Sample Size

No formal sample size calculation was conducted. Up to 104 subjects (up to 56 healthy subjects and up to 48 subjects with chronic HBV infection) are planned to complete the study.The 209 subjects includes “floater” subjects (up to 8 healthy subjects in Part A and up to 16 subjects with chronic HBV infection in Part B and C) that may be added as part of expansion of an existing cohort or cohorts based on SRC recommendations if further data are necessary.

### 2.5 Randomization

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

Four dose-level cohorts are planned for Part A: 50 mg, 100 mg, 200 mg, and 400 mg. Two sentinel subjects will be randomized 1:1 to VIR-2218 or placebo. These subjects will be dosed concurrently and monitored for 24 hours; if the investigator has no safety concerns, the remainder of the subjects in the same cohort will be dosed. The remaining subjects will be randomized 5:1 to VIR-2218 or placebo.

Two optional cohorts in Part A may be added following the same stratification, including sentinel dosing, up to a maximum dose of 900 mg. In addition to the optional cohorts, a totalof 8 “floater” subjects may be added to expand any cohort in Part A. “Floater” subjects are to be added in increments of 4 and randomized 3:1 to VIR-2218 or placebo.

Three dose-level cohorts are planned for Part B: 50 mg, 100 mg, and 200 mg. One dose-level cohort is planned for Part C: 200 mg. Each cohort in Part B/C will be randomized 3:1 to VIR-2218 or placebo.

Two optional cohorts in Part B and 2 optional cohorts in Part C may be added following the same stratification, up to a maximum dose of 450 mg per dose (900 mg cumulative dose). In addition to the optional cohorts, a pool of 16 “floater” subjects may be added to expand any cohort in Part B and/or C if further data are needed. “Floater” subjects are to be added in increments of 4 (3:1) to maintain the randomization ratio.

In Parts A-C, 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 blindedunless 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 trial 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 [redacted] Standard Operating Procedures (SOPs), which are written based on the principles o 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, except for PK concentration data:

- Continuous variables: Descriptive statistics will include the number of non-missingvalues (n), arithmetic mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean, SD, median, Q1 and Q3 values will be displayed to one 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, SD and median percentage change from Baseline values will be presented to 2 decimal places and the minimum and maximum values presented to 1 decimal place.

  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. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings. Unscheduled assessments intended as a re-test to replace missing values for scheduled visit will be used as if the results were taken on the scheduled visit for the purpose of summary table reporting.
- 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 thederivation of the baseline values. Multiple pre-dose observations taken on the same date will be averaged as 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
- HBsAg Seroconversion: anti-HBs positivity at two or more consecutive measurements
- HBeAg loss (HBeAg+ subjects only): quantitative HBeAg < 0.11 IU/mL at two or more consecutive measurements
- HBeAg Seroconversion (HBeAg+ subjects only): 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 21.1 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, March 2019 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 A (SAD):

- VIR-2218 50 mg
- VIR-2218 100 mg
- VIR-2218 200 mg
- VIR-2218 400 mg
- VIR-2218 600 mg
- VIR-2218 900 mg
- VIR-2218 Overall
- Placebo
- Overall

Part B (MAD – HBeAg-):

- VIR-2218 20 mg
- VIR-2218 50 mg
- VIR-2218 100 mg
- VIR-2218 200 mg
- VIR-2218 Overall
- Placebo
- Overall

Part C (MAD – HBeAg+):

- VIR-2218 50 mg
- VIR-2218 200 mg
- VIR-2218 Overall
- Placebo

- Overall

# 4. ANALYSIS SETS

In this study 6 analysis sets are defined: The screened, all randomized, full analysis, safety, PK and antiviral analysis sets.

Furthermore, any additional exploratory analysis not identified in the SAP will be identified in the final 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*

All subjects randomized will be included in the All Randomized Analysis Set. The All Randomized Analysis Set will be based on randomized treatment. Disposition data will be summarized by the All Randomized Analysis Set. All data, with the exception of inclusion and exclusion criteria, will be listed by the All Randomized Analysis Set.

### 4.1.3 *Full Analysis Set*

The Full Analysis Set includes all randomized subjects who had at least 1 dose of VIR-2218. Demographics data will be further summarized by this population set.

### 4.1.4 *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 drug. The Safety Analysis Set will be based on actual treatment received if different from randomized treatment.

All safety analyses will be based on the safety analysis set.

### 4.1.5 *PK Analysis Set*

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

### 4.1.6 *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 treatment and overall, by study part. 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 All Randomized Analysis Set for Part A to C. The number and percentage of subjects who completed treatment, completed the study per protocol (this means 16 week or 48 week follow up for the relevant parts), along with primary reason for treatment discontinuation and early termination will be summarized by treatment arm.

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 all randomized set.

In addition, the inclusion of each subject into/from each of the defined analysis sets will be listed by the all screened analysis set.

## 6. PROTOCOL DEVIATIONS

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

Important protocol deviations may include the following, depending on the timing and nature of the deviation:

- Compromises the safety of the subject.
- Creates a potentially unsafe condition for other subjects on the cohort or study.
- Compromises the validity of primary results and secondary endpoints for a cohort or the study.
- Impairs conduct of the study.
- Violates regulatory constraints or guidance.
- Compromises the privacy of a subject.

Summary of major/minor protocol deviations by types will be summarized by treatment groups using descriptive statistics.

# 7. DEMOGRAPHIC AND BASELINE INFORMATION

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

## 7.1 Demographics

### 7.1.1 *Definition of variables*

- Age (years)
- Age, categorized as <30, >=30 and <40, >=40 and <50, >=50
- Sex
- Race
- Ethnicity
- BMI (kg/m$^2$)
- Weight (kg)
- Country of Enrollment
- Estimated Creatine Clearance at Screening (mL/min) by serum-creatinine based Cockroft-Gault (C-G) equation:

$$\frac{[140 - age(years)] \times weight(kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ for\ female\ patients\}$$

For part B/C

  - Baseline HBsAg level (continuous)
  - Baseline HBsAg level, categorized as <10000 IU/mL, >=10000 IU/mL
  - Baseline ALT level (continuous)
  - Baseline ALT level, categorized as <=ULN, >ULN and <=2xULN
  - Cirrhosis status (Fibroscan results and Cirrhosis status)

- 

### 7.1.2 *Biostatistical methods*

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

## 7.2 Viral Serology

Viral serology results (Part A: Active infection with HIV infection, HCV infection, and HBV infection. Part B/C: 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 positivefor > 6 months.) at screening will be listed.

## 7.3 Medical History

Medical history will be coded using MedDRA® and 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 listed.

## 8. TREATMENT EXPOSURE

Treatment exposure information will be described using the All Randomized Analysis Set. All exposure information will be listed by cohort and study part. Counts and percentages of patients who received full planned doses will be tabulated by cohort and study part.

# 9. PHARMACOKINETICS (PK)

All PK analyses will be conducted on the plasma and urine concentration data of VIR-2218 and its metabolite in the PK analysis set. VIR-2218 and metabolite plasma,urineconcentrations and PK parameter data will be listed and used for the descriptive statistics.

Immunogenicity analysis is not in the scope of this SAP.

## 9.1 DATA HANDLING FOR PK DATA

Plasma and urine concentration values not collected or not determined will be treated as missing. Concentrations below the limit of quantifiable (BLQ) values will be treated as 0 prior to the first quantifiable concentration. BLQ values at all other timepoints will be treated as missing.

## 9.2 SUMMARY STATISTICS FOR PK DATA

### 9.2.1 *Summary statistics for plasma and urine concentration data*

The units of concentration with amount or concentration in the 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 metabolites (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 summarised by treatment group for healthy subjects (part A) and CHB subjects (part B andC), 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 metabolite plasma and urine and 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 or 1 additional significant figure – depending on the reporting format of the original data with a maximum of 3 significant figures - 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.

### 9.2.2 *Summary statistics for plasma and urine PK parameters*

Calculated PK parameters will be listed and summarized descriptively, including n, arithmetic mean, SD, minimum, median, maximum, coefficient of variation [CV(%)], geometric mean

(GM), geometric SD, geometric CV%; For $t_{max}$, only n, minimum, median, and maximum will be reported.

When reporting individual values and descriptive statistics for PK plasma and urine for VIR-2218 and its metabolites, 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.

## 9.1 9.3 CONCENTRATION-TIME PROFILES

Individual (for each subject) and mean plasma VIR-2218 and metabolite concentrations will be displayed graphically in linear and semi-logarithmic plots of concentration versus time (hour)by treatment group separately for healthy subjects (part A) and CHB subjects (part B and C). 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.

Individual (for each subject) and mean urine VIR-2218 and metabolite concentrations will be displayed graphically in linear and semi-logarithmic plots of concentration versus time (hour), by treatment group separately for healthy subjects in part A and CHB subjects (part B and C). 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.

## 9.2 Plasma PK Parameters

Pharmacokinetic analysis will be performed on the plasma PK concentration data to determine PK parameters by non-compartmental analysis using Phoenix WinNonlin® software (version 8.1 or higher).

Actual sampling times will be used for the PK analysis and if the actual sampling time is not recorded, the nominal sampling time will be used.

PK parameters (applicable for single dose cohorts in part A, day 1-dose and day-29 dose of multiple dose cohorts in part B and C):

Due to the short plasma half-life of VIR-2218 and metabolite, pharmacokinetic analysis will be performed separately for day-1 dose and day-29 dose in patients in parts B/C.

The following PK parameters of VIR-2218 and its metabolites to be determined at defined timepoints include:

- **$C_{max}$:** Individual maximum concentration ($C_{max}$) values are directly determined from the plasma concentration time profiles for each subject.
- **$t_{max}$:** The time to attain $C_{max}$. If the same $C_{max}$ concentration occurs at different time points, $t_{max}$ is assigned to the first occurrence of $C_{max}$.
- **$t_{last}$:** Time of last measurable (positive) observed concentration

- **$C_{last}$:** Observed concentration corresponding to $t_{last}$.
- **$AUC_{0-t}$:** 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 ($t_1$, $C_1$) and ($t_2$, $C_2$) where $C_2 \geq C_1$ 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 ($t_1$, $C_1$) and ($t_2$, $C_2$) where $C_2 < C_1$ will be computed by:
  $$AUC_{t1-t2} = \frac{\left((t2 - t1)(C1 - C2)\right)}{lnC1 - lnC2}$$

- **$AUC_{0-12hr}$:** 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.

- **$AUC_{0-24hr}$:** 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.

- **$AUC_{0-\infty}$:** 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 $\lambda_z$ is given below.

- **$AUC_{\%extrap}$:** The percentage of the AUC that has been extrapolated beyond the last observed data point, calculated as:
  $$AUC_{\%extrap} = \left(\frac{\mathrm{AUC}_{0-\infty} - \mathrm{AUC}_{0-t}}{\mathrm{AUC}_{0-\infty}}\right) * 100$$
- **$\lambda_z$**: The apparent terminal rate constant $\lambda_z$ 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, $\lambda_z$ 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 $\lambda_z$ 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 $\lambda_z$ is not determinable (for example, adjusted-$r^2$ value <0.8) then consequently only parameters not requiring $\lambda_z$ 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 $\lambda_z$ will be listed.

- **$t_{1/2}$**: The terminal half-life will be calculated from the terminal rate constant using the equation:

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

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

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

where *D* is dose.

- **Vz/F:** The apparent volume of distribution based on terminal phase will be calculated according to the following equation:

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

### *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 $AUC_{0-\infty}$ willbe 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 (**$\lambda_z$**, $AUC_{0-\infty}$, $t_{1/2}$, CL/F or $CL/F_{,ss}$, and Vz/F or $Vz/F_{,ss}$) 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 $AUC_{0\text{-}24hr}$ were included in the calculation of summary statistics.

- If $t_{last}$<12hr, $AUC_{0\text{-}12hr}$ will only be reported when $AUC\%_{extrap}$ <20%; It will be presented in the listing with footnote to indicate that $AUC_{0\text{-}12hr}$ was extrapolated. In the summary tables, the cohort will be footnoted to indicate that subjects with extrapolated $AUC_{0\text{-}12hr}$ were included in the calculation of summary statistics.

## 9.5 Urine PK Parameters

The following urine PK parameters of VIR-2218 and its metabolites will be determined for all single dose and multiple dose cohorts/parts:

- **$Ae_{t1\text{-}t2}$**: Total amount of drug excreted in urine from time t1 to t2 hours (cumulative and for each specific urine time intervals)

- **CLr:** Renal clearance of drug (cumulative) calculated as:

$$\mathrm{CLr} = \frac{\mathrm{Ae}_{t1-t2}}{Plasma\ AUC_{t1-t2}}$$

- **fe**- Fraction of the administered drug excreted into the urine (cumulative and for each specific urine time intervals)

$$fe = \left(\frac{Urinary\ excreted\ amount(mg)}{Dose(mg)}\right) * 100$$

## 9.6 DOSE PROPORTIONALITY FOR PK PARAMETERS

Dose proportionality will be evaluated separately for healthy subjects (part A) and day-1 dose of CHB subjects (part B and C) based on subjects without dosing deviations.

To assess dose proportionality, the natural log transformed, dose normalized $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}12'}$ $AUC_{0\text{-}24}$ and $C_{max}$ parameters will be evaluated using power model [2], with VIR-2218 dose level as the independent variable.

The power model for assessment of dose proportionality has the form of $\log(y)=\log(\beta_0)+\beta_1\log(\mathrm{Dose})$ where y represents the PK parameter of interest. Dose proportionality is concluded if 90% CI for the $\beta_1$ falls within 0.7 to 1.43, which is less than 30% difference between doses for a given PK parameter.

# 10. PHARMACODYNAMICS (PD)

No PD analysis is planned for this study.

Pharmacokinetic/Pharmacodynamic analysis falls outside the scope of the SAP.

# 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 and overall, by study part. 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. 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.

### 12.1.2 *Biostatistical methods*

All AEs including will be coded using MedDRA.

All AE summaries will be restricted to TEAEs only. 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 TEAE summaries will include:

- Overall Summary of TEAEs
- TEAE summary by SOC and PT
- TEAE summary of serious events by SOC and PT
- TEAE summary by causality to study drug by SOC and PT
- TEAE summary by maximum toxicity
- TEAE summary by SOC, PT and maximum toxicity

All SOC by PT tables will be sorted by PT in descending order of total occurrence for each part.

All AEs will be listed and will include verbatim term, PT, SOC, treatment, severity, relationship, seriousness, outcome, and action taken with regards to the study drug. Separatelistings 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 events (refer to the Protocol) to conduct hematology, coagulation, chemistry and urinalysis 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
- Urea
- Uric acid
- Liver Function Tests
    - Alkaline phosphatase (ALP)
    - AST
    - ALT
    - Bilirubin (total and direct)

Coagulation:

- International normalized ratio (INR) time
- Prothrombin

Urinalysis & Microscopic Urinalysis:

- Specific gravity
- pH
- Glucose
- Proteins
- Red Blood Cells
- Ketones
- Bilirubin
- Urobilinogen
- Nitrite
- Leukocytes
- Visual inspection for appearance and color

- Microscopy (if clinically indicated)

### 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.

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 of 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', '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 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 willbe presented for the change from baseline values at each scheduled post-baseline visit.

Additionally, shift tables from baseline in CTCAE grade (version 5) from baseline will be summarized by counts and percentages along with a summary of maximum CTCAE Gradefor post treatment lab assessments The summary for the maximum CTCAE will be based on both scheduled and unscheduled visits.

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 baselinerecord (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 Events (refer to the Protocol):

- Pulse Rate (beats/min)
- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)

- 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.

The parameter names that will be used in the outputs will comprise of 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.

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

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 protocol scheduled of event in Appendix 2 and Appendix 3. Specified collection timepoints for each visit are provided in the protocol: Appendix 4 and Appendix 5.

Holter ECG analysis falls outside the scope of the study.

### 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.

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 listings of ECG measurements will include all the information collected data. 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 consumption within 7 days prior to each visit will be listed.

## 12.7 Pregnancy Test Results

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

## 12.8 Concomitant Medications

Prior medications are defined as any medication where the use was stopped prior to the first administration of the 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. 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.

### 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.

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

Prior medications will be listed only.

## 13. ANTIVIRAL ACTIVITY

Antiviral activity endpoints will be analyzed using the antiviral analysis set. All information will be presented by treatment group, overall by study part (Parts B & C). 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 levels < 10000 IU/mL, <1000 IU/mL and < 100 IU/mL by timepoint
  - Serum $\log_{10}$ HBsAg Nadir level per subject, summarize as continuous and categories of < 10000 IU/mL, <1000 IU/mL and < 100 IU/mL
  - Time to Nadir, Nadir value and Nadir change from baseline value
- Number of subjects with serum HBsAg loss at any timepoint.
- Number of subjects with sustained serum HBsAg loss for ≥ 6 months.
- Number of subjects with anti-HBs seroconversion at any timepoint.
- For HBeAg-positive subjects (Part C only): number of subjects with HBeAg loss and/or anti-HBe seroconversion at any timepoint.

CCI [redacted]

### 13.2 Biostatistical methods

All antiviral 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.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, HBsAg (IU/mL). For HBV DNA both IU/mL and copies/mL CCI [redacted] will be presented. For HBV DNA, undetected and <LOQ will be imputed as 9 U mL. Parameters will be sorted within parameter class (if present) in alphabetical order within the tables and listings.

Summary for serum $\log_{10}$ HBsAg nadir level and time to nadir will be based on all scheduled and un-scheduled post-baseline visits. 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. Categorical summaries (% of subjects) will present counts and percentages for the reported results at baseline and each post-baseline time point. Additionally, HBV DNA CCI [redacted] will be summarized into TND, <LOQ, and >LOQ categories.

## 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 LOD) or above the upper limit of quantitation, will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (e.g., if the result of a continuous laboratory test is < 30, a value of 29 will be assigned; if the result of a continuous laboratory test is <30.0, a value of 29.9 will be assigned). If the results of continuous lab test is <1, the imputed value should be 0.9; If the results of the lab test is <0.1, the imputed value should be 0.09. The actual reported values will be provided in by-subject listings.

## 15. CHANGES TO THE PLANNED ANALYSIS

Not applicable.

# 16. INTERIM AND FINAL ANALYSIS

## 16.1 Interim Analysis 1

The first interim analysis for the study will be based on all data captured up to the time of the data freeze for the analysis.

After data cleaning and database soft lock, the study will be unblinded by treatment group at a subject level. The following outputs will be included as part of the interim analysis:

CCI

CCI

### 16.2 Final Analysis (End of Study)

The final analysis will be conducted after all subjects have completed the study, the clinical database has been locked and the analysis sets have been approved.

The final analysis will be based on the final version of the SAP. 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 9.2 or higher (SAS Institute, Cary, North Carolina, USA).

## 18. TABLES, LISTINGS AND FIGURES

CCI

## 19. REFERENCES

1) Clinical Study Amendment 2.0 dated 27 March 2019.

2) Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharm Res*. 2000;17(10):1278-1283. doi:10.1023/a:1026451721686

3) National Cancer Institute (USA) Common Terminology Criteria for Adverse Events (CTCAE) v5.0