

Official Title: A Phase 1, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-3434

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**TITLE PAGE****ORIGINAL STATISTICAL ANALYSIS PLAN**

Study Title	A Phase 1, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-3434
Brief Title	A Study to Evaluate Investigational Therapies in Chronic Hepatitis B Virus Infection
Study Number	VIR-3434-1002
Compound	VIR-3434
Indication	Chronic Hepatitis B Virus (HBV) Infection
Study Phase	1
Study Sponsor	Vir Biotechnology, Inc. 499 Illinois Street, Suite 500 San Francisco, CA 94158, USA
Effective Date	27 March 2023, Version 1.0

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

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VERSION HISTORY

This is the 1st version of statistical analysis plan for the final analysis of Study VIR-3434-1002.

SAP Version	Date	Change	Rationale
1		Not applicable	Original version

1. INTRODUCTION

This statistical analysis plan (SAP) for the final analysis is based on the most recent approved clinical study protocol (amendment 4, version 1.0 dated on 20 January 2022), electronic case report form (eCRF), and eCRF completion guidelines (CCG).

This SAP (Methods) documents the planned statistical analyses of safety, pharmacokinetics (PK), and antiviral activity endpoints for the final analysis of study VIR-3434-1002. It may also document analyses for additional antiviral activity variables not specified in the protocol, which will provide supportive information for the scientific understanding of the study intervention entity.

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VIR Biometrics department or a designated contract research organization (CRO) will perform the statistical analysis of the efficacy and safety data. SAS version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). This SAP will be finalized and approved prior to the final database lock. Any revisions to the approved SAP (Methods) will be documented and approved in an amendment to the SAP.

2. OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

Primary objectives:

- Part A: to evaluate the safety and tolerability of VIR-3434 in healthy adult subjects
- Part B, C, and D: to evaluate the safety and tolerability of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis

Secondary objectives:

- Part A: to characterize the serum PK of VIR-3434 in healthy adult subjects
- Part A: to evaluate the immunogenicity of VIR-3434 (induction of anti-drug antibody [ADA]) in healthy adult subjects
- Part B, C, and D: to characterize the serum PK of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis
- Part B, C, and D: to assess the antiviral activity of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis
- Part B, C, and D: to evaluate the immunogenicity (induction of ADA) of VIR-3434 in adult subjects with chronic HBV infection without cirrhosis

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2.2. Study Endpoints

Primary endpoints (Part A and Part B, C, and D):

- Safety and tolerability assessments determined by treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), clinical laboratory abnormalities, standard 12-lead electrocardiograms (ECGs), vital signs, and physical examination

Secondary endpoints (Part A and Part B, C, and D):

- VIR-3434 serum PK parameters
- Incidence and titers (if applicable) of ADA to VIR-3434
- Maximum reduction of serum HBsAg from baseline
- Maximum change of HBV DNA from baseline (Part D only)

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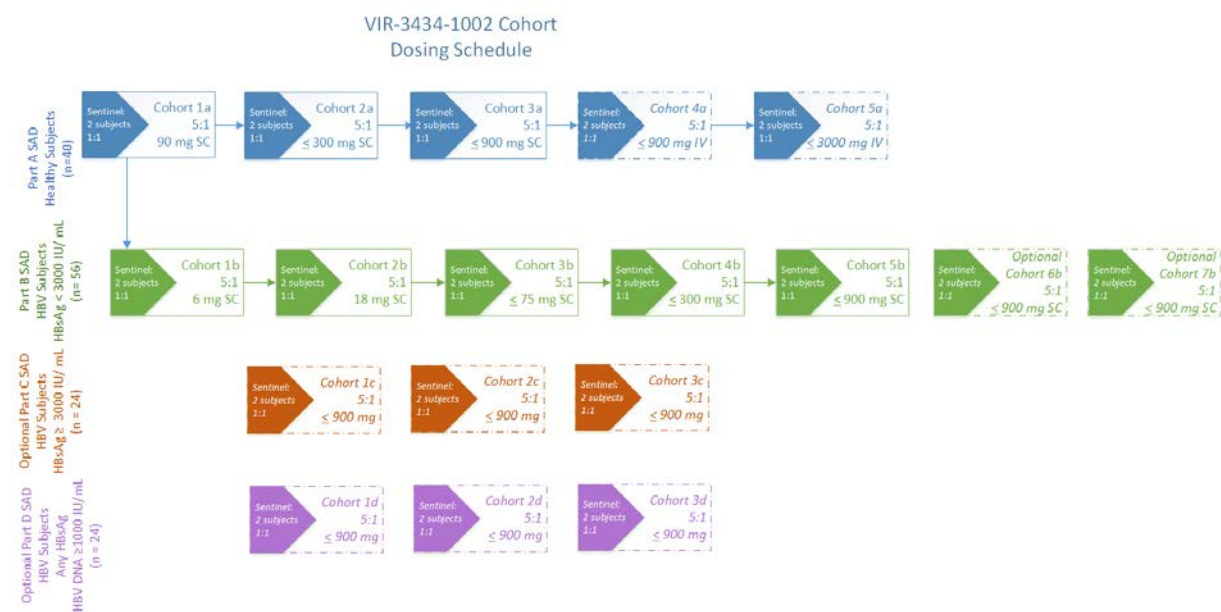
3. STUDY DESIGN

3.1. Overall Design

VIR-3434-1002 is a Phase 1, randomized, double-blind, placebo-controlled, single ascending dose (SAD) study to evaluate the safety, tolerability, PK, and antiviral activity of VIR-3434 administered by subcutaneous (SC) injection or intravenous (IV) infusion in healthy adult subjects and adult subjects with chronic HBV infection without cirrhosis.

The schema of the study design schema is provided as shown in below Figure 1:

Figure 1: Study Schema

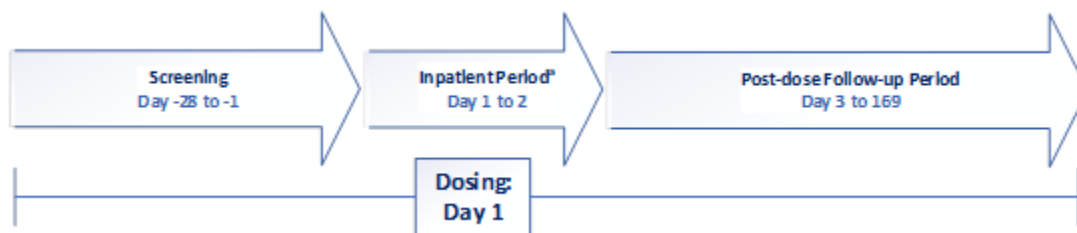


Approximately up to 144 participants are planned to be randomized in Part A and Part B, C, and D.

- **Part A:** approximately 8 participants will be randomized (3:1) to either 1 of up to 5 planned dose-sequential cohorts (VIR-3434) or placebo cohort. The healthy participants will be discharged on Day 2 and will be followed up to 24 weeks, as shown in Figure 2.
- **Part B, C, and D:** approximately 8 participants will be randomized (3:1) to either 1 of VIR-3434 dose-sequential cohorts (up to 7/3/3 planned cohorts for Part B/C/D accordingly) or placebo cohort in Part B, C, and D respectively. Participants will be discharged after all study assessments completed on Day 1 and will be followed up to 8 weeks, as shown in Figure 3.

For participants with > 2-fold HBsAg reduction from baseline at Week 8 will be followed for additional 32 weeks up to Week 40 or until the reduction is < 2-fold relative to baseline at 2 consecutive collections, whichever occurs first.

Figure 2: Part A: SAD in healthy adults



* subjects discharge will occur after all assessments are completed on Day 2

Figure 3: Parts B, C, and D: SAD for adults with chronic HBV infection without cirrhosis



The dose escalation of study intervention and the corresponding cohorts with the enrollment status for Part A and Part B, C, and D are showed in below Table 1 and Table 2 respectively:

Table 1: Dose Escalation Cohorts in Part A

Study Part	Cohort	Route	Dose Level (VIR-3434)	Enrolled
A	1a	SC	90 mg	Yes
A	2a	SC	300 mg	Yes
A	3a	SC	900 mg	Yes
A	4a (optional)	IV	900 mg	Yes
A	5a (optional)	IV	3,000 mg	Yes

Table 2: Dose Escalation Cohorts in Part B, C, and D

Study Part	Cohort	Route	Dose Level (VIR-3434)	Enrolled
B	1b	SC	6 mg	Yes
B	2b	SC	18 mg	Yes
B	3b	SC	75 mg	Yes
B	4b	SC	300 mg	Yes
B	5b	SC	up to 900 mg	No
B	6b (optional)	SC	up to 900 mg	No

Study Part	Cohort	Route	Dose Level (VIR-3434)	Enrolled
B	7b (optional)	SC	up to 900 mg	No
C	1c (optional)	SC	18 mg	Yes
C	2c (optional)	SC	75 mg	Yes
C	3c (optional)	SC	300 mg	Yes
D	1d (optional)	SC	75 mg	Yes
D	2d (optional)	SC	300 mg	Yes
D	3d (optional)	SC	up to 900 mg	No

3.2. Sample Size

The sample size is based on practical consideration, and no formal sample size calculation was performed.

3.3. Randomization

For Part A, in each cohort, 2 sentinel subjects will be randomized 1:1 to receive VIR-3434 or placebo. These subjects will be dosed and monitored for at least 24 hours in an inpatient setting; if the investigator has no safety concerns, the remainder of the subjects in the same cohort will be randomized 5:1 to receive VIR-3434 or placebo.

For Part B, C, and D, in each cohort, 2 sentinel subjects will be randomized 1:1 to receive VIR-3434 or placebo by SC injection. These subjects will be dosed and monitored through at least 72 hours post dose; if the investigator(s) have no safety concerns, the remainder of the subjects in the same cohort will be randomized 5:1 to receive VIR 3434 or placebo by SC injection.

An Interactive Web Response System (IWRS) will be used to assign participants to treatment group. The randomization list will be produced by VIR Biometrics or a qualified randomization vendor.

3.4. Blinding and Unblinding

This is a double-blinded study. Investigators, designated study staff, and participants are blinded to treatment allocation. The Sponsor is not blinded.

An individual cohort will be unblinded when all subjects enrolled in the cohort complete the Week 8 visit. The Sponsor will communicate treatment assignments to investigators, and investigators will share treatment assignment with the subject. Please refer to the VIR-3434-1002 Blinding Plan for more details.

3.5. Planned Analysis

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

4. STATISTICAL HYPOTHESES

There are no formal statistical hypotheses planned for this study.

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

5. ANALYSIS SETS

5.1. All-Randomized Set

The All-Randomized Set includes all participants who were randomized in the study. This analysis set will be used for individual participant data listings and disposition data summary tables, unless otherwise specified.

5.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized participants who received at least 1 dose of study drug. The FAS will be used to summarize participant demographics and baseline characteristics, and analysis for antiviral activity endpoints, unless otherwise specified.

5.3. Safety Analysis Set

The Safety Analysis Set includes all participants who received at least 1 dose of study drug. The Safety Analysis Set will be used for all safety analyses.

5.4. PK Analysis Set

The PK Analysis Set includes all participants in the FAS with at least 1 measurable postdose concentration data to provide interpretable results. The PK Analysis Set will be used for all PK analyses.

5.5. Immunogenicity Analysis Set

The Immunogenicity Analysis Set includes all participants in the FAS who had at least 1 sample that has undergone testing for immunogenicity, including screening, titer, or neutralizing characterization, as applicable. The Immunogenicity Analysis Set will be used for analyses of the immunogenicity endpoints.

6. STATISTICAL ANALYSES

6.1. General Considerations

The study assessments and time points schedule are provided in the study protocol. All individual participant data for those who were randomized to study intervention will be presented in data listings.

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

In general, the precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures, and derived listings. Unless otherwise specified, raw data will be presented with the same number of decimals as collected, and derived data will be presented with an appropriate number of decimals based on general practice, mathematical rationale, or scientific rationale. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

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

Baseline Value: Unless otherwise specified, the baseline value will be defined as the most recent non-missing (scheduled or unscheduled) measurement collected prior to the administration of study intervention.

If multiple measurements that are prior to dosing are recorded on the same date and with the same time or if time is not available, then the average of these measurements will be considered the baseline value.

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

Treatment-emergent (TE) period: Unless otherwise specified, the TE period will include the time from the administration of study drug until the Week 24 visit (or the Day 169, if the Week 24 visit is unavailable) for Part A, and the Week 8 visit (or the Day 57, if the Week 8 visit is unavailable) for Part B, C, and D.

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

1. In scheduled visit windows per specified visit windowing rules, if applicable
2. In the derivation of baseline and last follow-up measurements
3. In the derivation of maximum and minimum values and/or maximum and minimum change from baseline values during follow-up period or TE period
4. In individual participant data listings as appropriate

Visit Windows: The analysis visit windowing rules for protocol-defined visits are provided in Appendix 2.

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

For virology tests and safety laboratory parameters, the following rules will be applied in calculation of summary statistics and absolute change from baseline values:

- If a data point is missing by reported as “< lower limit of quantification (LLOQ) or < limit of detection (LOD)” with “Target Not Detected (TND)” or reported as the meaning of “Not Detected”, then the missing data point will be imputed as zero.
- If a data point is missing by reported as “< LLOQ or < LOD” with “Target Detected (TD)”, then the missing data point will be imputed as the half of LLOQ value or 1 unit less than the LOD value, respectively. For example, if the LOD values are 0.5 and 0.03, then the imputed values will be 0.4 and 0.02. When the LOD value is 1, it will be imputed as 0.9.

- If a data point is missing by reported as “< LLOQ or < LOD” without knowing “TD or TND”, then the missing data point will be treated as “< LLOQ, TD or < LOD, TND”.
- If a data point is missing by reported as “> upper limit of quantification (ULOQ)” without knowing “ULOQ”, then the missing data point will be imputed as 1 unit greater than the value of ULOQ.
- If a data point is missing by reported as the meaning of “no results obtained”, then it is considered as the missing data and not included in data summary and analysis.

Logarithm transformation will be used for analysis of virological variables. For the \log_{10} transformed data using LOD value, 1) a missing data point due to untransformed value of zero will be imputed as zero, when $\text{LOD} > 1$; and 2) a missing data point due to untransformed value of zero will be imputed as \log_{10} (1 unit less than LOD value), when $\text{LOD} < 1$.

The reported value will be used in individual subject listings for all virology tests and safety laboratory parameters.

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

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

6.2. Background Characteristics

6.2.1. Participant Disposition

A disposition table will be provided with the number of study participants in:

- All-Randomized Set
- FAS
- Safety Analysis Set
- PK Analysis Set
- Immunogenicity Analysis Set

The number and percentage of study participants (based on the FAS) in each of the following disposition categories will be summarized by VIR-3434 treatment cohort, placebo, and overall, for each of Part A, B, C, and D.

- Completed Follow-up (24 weeks or 8 weeks for Part A or Part B, C, and D respectively)
- Completed Study
- Prematurely discontinued study and the primary reason for discontinuation
- Entered extended follow-up (if applicable)

A listing will be provided for subjects who discontinued follow-up or who discontinued study with reason for discontinuation.

6.2.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized based on the FAS by VIR-3434 dosing cohort, placebo, and overall, for each of Part A, B, C, and D.

Demographic data will include the following:

- Age at baseline (in years)
- Age group (< 30, ≥ 30 and < 40, ≥ 40 and < 50, ≥ 50)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not Reported)
- Country

Baseline characteristics will include the following:

For Part A and Part B, C, and D

- Weight (kg)
- Height (cm)
- BMI (kg/m²) and BMI categories (≤ 18.5, >18.5 to ≤ 25, > 25 to ≤ 30, and > 30)
- Creatinine Clearance (mL/min)

For Part B, C, and D only

- HBsAg as a continuous variable (log₁₀ IU/mL) and categories (< 1000 IU/mL, 1000 IU/mL – < 3000 IU/mL, 3000 IU/mL – < 10000 IU/mL, and ≥ 10000 IU/mL)
- HBeAg as categories (HBeAg+ and HBeAg-)
- HBV DNA (part D only)
- HBcrAg
- HBV RNA
- ALT (U/L) as a continuous variable and as categories (≤ ULN, >ULN – 2×ULN, and > 2×ULN)
- Liver stiffness (kPa)
- HBV genotype

In addition, data listings will be provided for:

- Informed consent
- Inclusion/Exclusion criterion for subject with any such violations

6.2.3. Medical History

Medical history will be provided in an individual participant listing.

6.2.4. Prior and Concomitant Medications

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

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

Concomitant medication: medication continued or newly received during the TE period

Post-treatment medication: medication continued or newly received after the TE period

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

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

Both prior and concomitant medications will be summarized descriptively by VIR-3434 treatment cohort, placebo, and overall, with preferred name (PN) based on the FAS, for each of Part A, B, C, and D.

If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the dosing date of study intervention, concomitantly during the TE period, or after the TE period, it will be classified as prior, concomitant, and post-treatment. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix 3.

6.2.5. Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. IPD rules will be developed and finalized prior to database lock and will be used to categorize any of protocol deviation events to be IPDs or not by a sponsor-blinded team.

IPDs (from the deviation log produced by the sponsor or designee) will be summarized descriptively based on the FAS and presented by VIR-3434 treatment cohort, placebo, and overall, for each of Part A, B, C, and D. Additionally, IPDs will be provided in an individual subject data listing.

6.3. Efficacy Analysis

No efficacy analysis will be conducted in this study.

6.4. Safety Analyses

Safety analyses will be based on data from the TE Period for all participants in the Safety Analysis Set, unless otherwise specified. All safety data will be included in the individual participant listings. Participants will be analyzed according to the treatment dose level they received.

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

- TEAEs
- Clinical laboratory
- ECG
- Vital signs
- Physical examination

Only descriptive analysis of safety will be performed, and no statistical testing will be performed.

6.4.1. Adverse Events

For analysis purposes, AEs will be classified as TEAEs or post-treatment AEs, defined as follows:

Pre-treatment AE: any AE that occurred before the administration of study intervention (which is collected and will be summarized in medical history).

TEAE: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the administration of study intervention through the end of the TE period.

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed after the TE period.

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs are pre-treatment or post-treatment, the AEs will be classified as TEAEs. Details for imputing missing or partial start dates of adverse events are described in Appendix 4.

An overview of all TEAEs by VIR-3434 treatment cohort, placebo, and overall, for each of Part A, B, C, and D, will be summarized in the following categories:

- Number of TEAEs
- Participants with any TEAEs
- Participants with TEAEs by maximum severity (toxicity grade)
- Participants with TEAEs leading to study discontinuation
- Participants with Grade 3/4/5 TEAEs

- Participants with (study intervention) related TEAEs
- Participants with serious TEAEs
- Participants with (study intervention) related serious TEAEs
- Participants with TEAE leading to death

The following summary tables of TEAEs will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts and percentages (i.e., number and percentage of participants with an event), and by VIR-3434 treatment cohort and placebo, for each of Part A, B, C, and D:

- All TEAEs
- Grade 3/4/5 TEAEs
- TEAEs by maximum severity (toxicity grade)
- TEAEs leading to study discontinuation
- Related TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death

In addition, the following TEAEs tables will be also summarized by MedDRA PT only in order of descending incidence by VIR-3434 treatment cohort and placebo:

- All TEAEs
- TEAEs that occurred $\geq 5\%$
- Grade 3/4/5 TEAEs

When summarizing the number and percentages of participants, participants with multiple occurrences of the same adverse event or a continuing adverse event will be counted once, and only the maximum severity (highest grade) level will be presented in the severity summaries, and the study intervention related relationship in the relationship summaries.

All AEs, including TEAEs and post-treatment AEs, will be presented in an individual participant data listing based on the Safety Analysis Set. In addition, a listing containing individual participant adverse event data for TEAEs leading to study discontinuation, Grade 3/4/5 TEAEs, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

6.4.2. Clinical Laboratory

Clinical laboratory data collected (through central laboratories only, unless otherwise specified) will be analyzed using both quantitative and qualitative methods and presented by VIR-3434 treatment cohort and placebo, for each of Part A, B, C, and D. The analysis will be based on values reported in conventional units.

For the treatment-emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology, serum chemistry, and coagulation results will be summarized descriptively (n, mean, SD, median, min, max) at each visit.

For ALT, AST, total bilirubin, lymphocytes, neutrophils, platelets, and INR, mean (\pm SD) of the observed values will be plotted by visit and by each VIR-3434 treatment cohort and placebo for each of Part A, B, C, and D.

The Common Terminology Criteria for Adverse Events (CTCAE, v5.0) will be used as the reference on grading scale to assign severity (toxicity) grades (1 to 4) to abnormal results for the laboratory of interest as shown in Appendix 5. Grade 0 refers to the normal values that do not meet the criteria of laboratory abnormalities.

For treatment-emergent laboratory abnormalities, the number and percentage of participants who met at least 1 threshold criterion of severity grade will be summarized by VIR-3434 treatment cohort and placebo for each of Part A, B, C, and D, based on the most severe postdose abnormality grade during TE period for a given laboratory test. The threshold of severity grade shifted from baseline will also be summarized for selected laboratory tests.

In addition, a separate listing containing individual participants with hematology, chemistry, coagulation, and urinalysis values will be provided based on the Safety Analysis Set by subject ID and visit in chronological order including data collected from both scheduled and unscheduled visits. Values falling out of the relevant normal range (between the value of LLN and ULN) or having the severity grade of 1 or higher on laboratory abnormalities will be flagged as appropriate.

Results of positive urine/serum pregnancy test will be listed in an individual participant data listing only.

6.4.3. Electrocardiogram

An individual listing containing ECG measurements including data from both scheduled and unscheduled visit will be provided based on the Safety Analysis Set and presented by subject ID, visit in chronological order. The abnormal assessment with clinical significance will be flagged as appropriate.

6.4.4. Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each visit by VIR-3434 treatment cohort and placebo, for each of Part A, B, C, and D. The following vital signs parameters will be included: systolic and diastolic blood pressure (mm Hg), body temperature ($^{\circ}$ C), pulse rate (beats per minute [bmp]), and respiratory rate (breaths per minute).

An individual participant listing will be provided using data collected from both scheduled and unscheduled visits.

6.4.5. Physical examination

Physical examination findings will be presented as an individual participant data listing only.

6.5. Pharmacokinetics Analysis

All analyses and summaries of PK serum concentrations and PK parameters will be based on the PK Analysis Set and presented by VIR-3434 treatment cohort and placebo, for each of Part A, B, C, and D. Blood samples of VIR-3434 will be obtained from each participant prior to study drug administration and at selected times after study drug administration as outlined in the study protocol.

Standard non-compartmental methods will be used to estimate PK parameters based on VIR-3434 concentration data using Phoenix WinNonlin® software (Version 8.3.5 or higher). The linear/log trapezoidal rule will be used in conjunction with dosing time, serum concentration, and corresponding real-time values. If the real sampling time will not be recorded or will be missing, the planned time will be used for this time point instead.

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

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

If a missing value is reported due to no valid or missing of sample result in summary of concentration data and PK parameters, it will be presented as not reported “NR” and excluded from PK analyses and not imputed at any time points. The actual reported values will be provided in individual participant listings.

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

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

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

6.5.1. PK Variables

PK variables include individual concentration measurements for VIR-3434 following the collection times provided in the study protocol, and the estimated PK parameters in evaluation of PK objectives including but not be limited to:

	PK Parameters
Part A	C_{max} , C_{last} , T_{max} , T_{last} , AUC_{inf} , AUC_{last} , $\%AUC_{exp}$, $t_{1/2}$, λ_z , V_z (IV only), CL (IV only), V_z/F (SC only), and CL/F (SC only)

Part B, C, and D	C_{max} , C_{last} , T_{max} , T_{last} , AUC_{inf} , AUC_{last} , $\%AUC_{exp}$, $t_{1/2}$, λ_z , V_z/F , and CL/F
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Definition of selected PK parameters:

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

The apparent terminal-phase elimination rate constant (λ_z) will be estimated by log-linear regression of the concentration-time data associated with this phase. The decision as to which data points describe the terminal elimination phase will be reached by inspecting the semilogarithmic plot of the data, only considering concentrations at time points beyond T_{max} . λ_z is considered to be well-estimated if a minimum of three data points is used, these data points cover a time span of 2 or more elimination half-lives, and the r^2 value of λ_z is ≥ 0.80 . In cases where λ_z is poorly estimated (i.e., a span of < 2 half-lives or $r^2 < 0.80$), λ_z and the related parameters (AUC_{inf} , CL/F , V_z/F , and $t_{1/2}$) will be flagged in the report and may be excluded from the calculation of summary statistics at the discretion of the clinical pharmacologist.

AUC will be computed using the linear up, log down trapezoidal rule. AUC_{inf} is considered to be well-estimated if $\%AUC_{exp} \leq 20\%$. In cases where $\%AUC_{exp} > 20\%$, AUC_{inf} and the related parameters CL/F and V_z/F will be presented in listings but may be excluded from the calculation of summary statistics at the discretion of the clinical pharmacologist. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific

time intervals. The appropriateness of this approach will be assessed by the clinic pharmacologist on a profile-by-profile basis.

6.5.2. Analysis of PK Concentrations

Individual serum concentrations of VIR-3434 will be listed and summarized by nominal sampling time using descriptive statistics (n, mean, SD, coefficient of variation [CV%], median, min, max, geometric mean, and geometric CV% [GeoCV%]). Geometric CV% will be calculated using the following formula where SD is the standard deviation of the log-transformed data:
$$\text{GeoCV\%} = \sqrt{(\exp(\text{SD}^2) - 1)} \times 100.$$

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

Anomalous concentrations identified as sampling errors by the clinical pharmacologist will be excluded from summaries but flagged in the listings.

Individual and aggregate mean (\pm SD) of serum VIR-3434 free and total concentrations data (as applicable) will be displayed graphically in linear and semi-logarithmic plots of concentration versus time by treatment cohort, for Part A and Part B, C, and D. Time will be displayed in units of days of time elapsed relative to dosing, with dosing at time zero (clinical Day 1). The nominal sample collection timepoints will be used for plots of mean concentrations. The number of participants with quantifiable concentrations per timepoint will be displayed in each plot. Mean postdose concentration values that are BQL will not be displayed in the figures and remaining points connected. Natural logarithm transformation will be used for serum concentrations.

6.5.3. Analysis of PK Parameters

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

Individual participant PK parameters for VIR-3434 will be listed and summarized using descriptive statistics (n, mean, SD, CV%, median, min, max, geometric mean, and GeoCV%). Selected summary statistics (e.g., mean with %CV or median with Q1 and Q3) of PK parameters will also be presented by treatment cohort, for Part A and Part B, C, and D.

6.5.4. Analysis of Dose Proportionality for PK parameters

Dose proportionality will be evaluated for healthy subjects in Part A who were administered VIR-3434 SC. Dose proportionality may also be evaluated for participants in Part B, C, and D. PK parameters from subjects with dosing deviation will be excluded from the analysis.

To assess dose proportionality, the natural log transformed PK parameters, including AUC_{inf} (AUC_{last} and/or AUC_{0-t} will be used if AUC_{inf} is poorly estimated) and C_{max} , will be analyzed using power model [1], with VIR-3434 log transformed dose level as the independent variable, in form of $\ln(y) = \beta_0 + \beta_1 * \ln(\text{VIR-3434 dose})$, where y = the PK parameter of interest.

Dose proportionality is concluded if 90% CI for the β_1 falls within the critical interval of (0.7, 1.43), which is less than 30% difference between doses for a given PK parameter.

6.6. Immunogenicity Analysis

All immunogenicity analyses described in this section will be based on the Immunogenicity Analysis Set and presented by treatment cohort, treatment total, and placebo, for Part A and Part B, C, and D separately, unless specified otherwise.

6.6.1. Definition of Variables

The immunogenicity analysis will be analyzed through the following antidrug antibodies (ADA) to VIR-3434 variables:

- Binding ADA: binding ADA is defined as any antibodies (neutralizing and non-neutralizing) binding biologic drug, which is determined by the positive results from both screening and confirmed test using an *in vitro* test method. Any positive screening result followed by a confirmed negative result, will be treated as negative response.
- Titers: the presence and quasi-quantitative expression of the level of ADA, which is determined by serially diluting the serum fraction of blood and assaying (testing) each dilution for the antibody of interest
- Treatment-induced ADA: is defined as a baseline sample negative for ADA (or missing) and a post-baseline sample confirmed positive for ADA.
- Treatment-boosted ADA: is defined as pre-existing ADA (confirmed positive at baseline) that is boosted to >4x baseline ADA titer at any post-baseline measures.
- Treatment-unaffected ADA: is defined as pre-existing ADA (confirmed positive at baseline) that is changed to native or increased to $\leq 4x$ baseline ADA titer at all post-baseline measures.
- Transient ADA: ADA is defined as transient if the last ADA result for a participant is negative but there is treatment-induced ADA at only one time point (excluding the last non-missing result) or there are ≥ 2 samples with treatment-induced ADA with fewer than 16 weeks between the first and last samples that are positive for ADA (irrespective of negative samples in between).
- Persistent ADA: ADA is defined as persistent if there are ≥ 2 samples at different timepoints with treatment-induced ADA with 16 or more weeks between the first and the last samples that are positive for ADA or there is treatment-induced ADA at the final timepoint.

6.6.2. Analysis Methods

The incidence rate of participants who had samples of negative, screened positive, and confirmed positive for binding ADA to VIR-3434 will be summarized using frequency counts and percentage at baseline and each post-baseline visit up to Week 24 (Part A) or Week 8 (Part B, C, and D). Titers for participants confirmed positive for ADA to VIR-3434 will be summarized descriptively (n, median, min, max).

A summary table of immunogenicity results will be provided including the number of study participants with:

- Any ADA result
- Both baseline and post-baseline ADA
- Any baseline ADA
- Any post-baseline ADA

The number and percentage of participants (based on the participants with any post-baseline ADA) in each of the following ADA type category will be provided. In addition, titers for participants with ADA to VIR-3434 will also be summarized descriptively (n, median, min, max) for ADA types, including treatment-induced ADA, treatment-boosted ADA, and treatment-unaffected ADA.

- Treatment-emergent ADA (treatment-induced or treatment-boosted)
- Treatment-induced ADA
- Treatment-boosted ADA
- Treatment-unaffected ADA

For transient or persistent ADA to VIR-3434, the number and percentage of participants (based on the participants with any post-baseline ADA) will be summarized. Titers for participants with transient or persistent ADA to VIR-3434 will also be summarized descriptively (n, median, min, max).

An individual participant listing will be provided by subject ID, visit in chronological order.

6.7. Antiviral Activity Analysis

All antiviral activity analyses described in this section will be based on the FAS and applied for Part B, C, and D only, unless specified otherwise.

6.7.1. Definition of Variables

Selected antiviral activities will be analyzed through the following variables:

- HBV viral parameters (quantitative): HBsAg, HBV RNA, HBcrAg, and HBV DNA (Part D only)
- HBeAg loss: HBeAg changing from positive at baseline to negative at any post-baseline visit (up to Week 8), which will be only applied for participants from Part C and D with qualitative positive HBeAg at baseline.
- HBsAg loss: HBsAg changing from positive (\geq LLOQ) at baseline to negative ($<$ LLOQ) at 2 separate, consecutive, post-baseline visits during the follow-up period (up to Week 8) with at least 2 weeks apart
- Anti-HBs seroconversion: HBsAb changing from negative or missing at baseline to positive (\geq LLOQ) at any post-baseline visit (up to Week 8), which will be only applied for participants with negative or missing Anti-HBs at baseline.

- Anti-HBe seroconversion: HBeAb changing from negative or missing at baseline to positive at any post-baseline visit (up to Week 8), which will be only applied for participants with negative or missing Anti-HBe at baseline.

6.7.2. Analysis Methods

HBV viral parameters (quantitative), the raw values and the absolute change from baseline at each post-baseline visit up to Week 8 visit will be summarized descriptively (n, mean, SD, median, Q1, Q3, min, max) by VIR-3434 treatment cohort and placebo.

Similarly, the raw values and the change from baseline at nadir during the follow-up period up to Week 8 in HBsAg and HBV DNA (Part D only) will be summarized descriptively (n, mean, SD, median, Q1, Q3, min, max) by VIR-3434 treatment cohort and placebo.

In addition, mean (\pm SD) of change from baseline in HBsAg (Part B, C, and D) and HBV DNA (Part D only) will be plotted at each post-baseline visit up to Week 8 by VIR-3434 treatment cohort and placebo.

HBeAg loss, HBsAg loss, Anti-HBs seroconversion, and Anti-HBe seroconversion: the percentage and number of participants who ever met each of the variables during the follow-up period up to Week 8 will be summarized and presented by VIR-3434 treatment cohort and placebo.

6.8. Modifications

6.8.1. Modifications to the Approved Study protocol

Change and Rationale	Affected Sections
Team decided to use the All-Randomized Set for disposition data summary to cover other analysis sets in this summary table	Section 6.2.1
Team decided to change the name of “Antiviral Analysis Set” to “Full Analysis Set (FAS)” to be consistent with the industry convention. The FAS will be also used in summary of demographics and baseline characteristics as well as analysis of antiviral activities	Section 6.2 and Section 6.7
Team decided to change the PK Analysis Set by including all participants in the FAS with at least 1 measurable postdose concentration data to provide interpretable results	Section 6.5
Team decided to change the Immunogenicity Analysis Set by including all participants in the FAS who had at least 1 sample that has undergone testing for immunogenicity, including screening, titer, or neutralizing characterization, as applicable.	Section 6.6
Team decided to modify the definition of TEAE as any AE occurred during the TE period, which includes the time from the administration of study drug until the Week 24 visit (or the Day 169,	Section 6.4

if the Week 24 visit is unavailable) for Part A, and the Week 8 visit (or the Day 57, if the Week 8 visit is unavailable) for Part B, C, and D to ensure a consistent reporting period across study cohorts	
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6.8.2. Modifications to the Approved Statistical Analysis Plan

Not Applicable. This is the first version of the SAP.

7. SUPPORTING DOCUMENTATION

Appendix 1: List of Abbreviations and Definitions of Terms

AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index (kg/m ²)
CI	confidence interval
CLDQ-HBV	Chronic Liver Disease Questionnaire-Hepatitis B Virus
CPT	Child-Pugh-Turcotte
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ECI	Events of Clinical Interest
FAS	full analysis set
HBcrAg	hepatitis B core-related antigen
HBV	hepatitis B virus
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HDV	hepatitis Delta virus
ICF	informed consent form
LOD	limit of detection
LLOQ	lower limit of quantitation
ISR	injection site reaction
MAR	missing at random
Max	maximum value

MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
METAVIR	Meta-Analysis of Histological Data in Viral Hepatitis
Min	minimum value
PD	pharmacodynamic/pharmacodynamics
PK	pharmacokinetic/pharmacokinetics
PR	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex
PT	preferred term
QRS	Q, R, and S-wave define the QRS-complex in an ECG
QT	QT interval represents the duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
T(N)D	target (not) detected
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary
WPAI - GH	Work Productivity and Activity Impairment Questionnaire – General Health

Appendix 2: Analysis Visit Windows for Safety, Efficacy, and Immunogenicity Assessment

Table 7-1 Analysis Visit Windows for Safety and Antiviral Assessments			
Assessment	Analysis Visit¹	Target Study Day	Analysis Visit Window (in study days)^{2, 3, 4, 5}
Part A: <ul style="list-style-type: none"> Serum Chemistry Liver function tests Hematology Vital signs 	Day 1 (Baseline)	1	≤1 Pre-dose/post-dose
	Day 2	2	[1, 2]
	Day 4	4	(2, 6]
	Week 1	8	(6, 11]
	Week 2	15	(11, 22]
	Week 4	29	(22, 43]
	Week 8	57	(43, 71]
	Week 12	85	(71, 106]
	Week 18	127	(106, 148]
Week 24	169	(148, ≥176]	
Part A: <ul style="list-style-type: none"> Local tolerability 	Day 1 (Baseline)	1	≤1 Pre-dose
	Day 2	2	[1, 2]
	Day 4	4	(2, 6]
	Week 1	8	(6, ≥176]
Part A: <ul style="list-style-type: none"> Immunogenicity 	Day 1 (Baseline)	1	≤1 Pre-dose
	Week 2	15	[1, 22]
	Week 4	29	(22, 43]
	Week 8	57	(43, 71]
	Week 12	85	(71, 106]
	Week 18	127	(106, 148]
Week 24	169	(148, ≥176]	
Part A: <ul style="list-style-type: none"> Pregnancy test 	Day 1 (Baseline)	1	≤1 Pre-dose
	Week 4	29	[1, 43]
	Week 8	57	(43, 71]
	Week 12	85	(71, 106]
	Week 18	127	(106, 148]
	Week 24	169	(148, ≥176]
Part B, C, and D: <ul style="list-style-type: none"> Serum Chemistry Liver function tests Hematology Coagulation Vital signs 	Day 1 (Baseline)	1	≤1 Pre-dose/post-dose
	Day 2	2	[1, 2]
	Day 4	4	(2, 6]
	Week 1	8	(6, 11]
	Week 2	15	(11, 22]
	Week 4	29	(22, 43]
	Week 8	57	(43, min(≥64, Ext FU Day 1)]
Part B, C, and D: <ul style="list-style-type: none"> HBsAg HBV DNA (Part D) 	Day 1 (Baseline)	1	≤1 Pre-dose
	Day 2	2	[1, 2]
	Day 4	4	(2, 6]
	Week 1	8	(6, 9]
	Day 11	11	(9, 13]
	Week 2	15	(13, 22]
	Week 4	29	(22, 43]
	Week 8	57	(43, min(≥64, Ext FU Day 1)]

Table 7-1 Analysis Visit Windows for Safety and Antiviral Assessments			
Assessment	Analysis Visit¹	Target Study Day	Analysis Visit Window (in study days)^{2, 3, 4, 5}
Part B, C, and D: • Anti-HBs • HBV DNA (Part B and C)	Screening (Baseline) Week 1 Week 2 Week 4 Week 8	<1 8 15 29 57	<1 Pre-dose [1, 11] (11, 22] (22, 43] (43, min(≥64, Ext FU Day 1)]
Part B, C, and D: • HBeAg • HBV RNA • HBcrAg • Pregnancy test	Day 1 (Baseline) Week 4 Week 8	1 29 57	≤1 Pre-dose [1, 43] (43, min(≥64, Ext FU Day 1)]
Part B, C, and D: • Anti-HBe	Day 1 (Baseline) Week 8	1 57	≤1 Pre-dose [1, min(≥64, Ext FU Day 1)]
Part B, C, and D: • Immunogenicity	Day 1 (Baseline) Week 2 Week 4 Week 8	1 15 29 57	≤1 Pre-dose [1, 22] (22, 43] (43, min(≥64, Ext FU Day 1)]
Part B, C, and D: • Urinalysis	Day 1 (Baseline) Week 1 Week 2	1 8 15	≤1 Pre-dose [1, 11] (11, min(≥64, Ext FU Day 1)]
Part B, C, and D: • Local tolerability	Day 1 (Baseline) Day 2 Day 4 Week 1	1 2 4 8	≤1 Pre-dose [1, 3] (3, 6] (6, min(≥64, Ext FU Day 1)]
Part B, C, and D: • Physical examination	Screening (Baseline) Day 4 Week 8	<1 4 57	<1 Pre-dose [1, 30] (30, min(≥64, Ext FU Day 1)]
CCI			
Extended Follow-Up Period (Part B, C, and D)			
• Pregnancy test • Liver function test • Serum chemistry • Immunogenicity • HBsAg and Anti-HBS • HBV DNA (Part D)	Ext Week 12 Ext Week 16 Ext Week 24 Ext Week 32 Ext Week 40	85 113 169 225 281	(Ext FU Day 1, 99] (99, 141] (141, 197] (197, 253] (253, ≥288]

Table 7-1 Analysis Visit Windows for Safety and Antiviral Assessments			
Assessment	Analysis Visit¹	Target Study Day	Analysis Visit Window (in study days)^{2, 3, 4, 5}
Part B, C, and D: <ul style="list-style-type: none"> • HBV RNA • HBcrAg 	Ext Week 12 Ext Week 24 Ext Week 32 Ext Week 40	85 169 225 281	(Ext FU Day 1, 113] (113, 197] (197, 253] (253, ≥288]
CCI			
Part B, C, and D: <ul style="list-style-type: none"> • HBeAg and Anti-HBe 	Ext Week 40	281	(Ext FU Day 1, ≥288]
Notes: <p>¹ Visit name for analysis purpose is used to report data in tables and figures.</p> <p>² The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:</p> <ol style="list-style-type: none"> a. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit. b. If there is more than 1 numerical measurement available within a visit window, use the following rules: <ol style="list-style-type: none"> i. If the scheduled visit measurement will be used if it is available ii. If not, the unscheduled visit measurement closest to the target day will be used; or iii. If there are multiple unscheduled visit measurements with the same distance from the target day, the latest measurement will be used. <p>³ For an assessment, e.g., laboratory, ECG and vital sign measurement collected on the date of first dose of study drug, if it cannot be determined whether the measurement is before or after the first dose:</p> <ol style="list-style-type: none"> a. Scheduled measurement will be treated as pre-dose observation. b. Unscheduled measurement will be treated as post-dose observation. <p>⁴ For vital signs, Day 1 will be included in the Day 1 visit window to account for the post-dose assessments on Day 1, .</p> <p>⁵ PK analysis window will follow the protocol-defined assessment visit window.</p>			

Appendix 3: Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
 - a. If only DAY is missing, use the first day of the month.
 - b. If DAY and Month are both missing, use the first day of the year.
 - c. If DAY, Month and Year are all missing, use a date before the first dose date (in practical, use the informed consent date to impute).
2. Missing or partial medication stop date:
 - a. If only DAY is missing, use the last day of the month.
 - b. If DAY and Month are both missing, use the last day of the year.
 - c. If DAY, Month and year are all missing, assign ‘continuing’ status to stop date (in practical, use the end of study date to impute).

In summary, the prior, concomitant, or post categorization of a medication is described below.

Table 7-2 Prior, Concomitant, and Post Categorization of a Medication

Medication Start Date	Medication Stop Date		
	< First Dose Date of Study Drug	≥ First Dose Date and ≤ End Date of TE Period	> End Date of TE Period
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of TE period	-	C	CA
> End date of TE period	-	-	A

P: Prior; C: Concomitant; A: Post

Imputation rules for missing and/or partial dates of non-pharmacological treatment/procedure will follow the same imputation rule.

Appendix 4: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below. If the imputed AE start date is before the study informed consent date, the AE start date will be imputed using the study informed consent date.

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

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

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

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

- If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing, then query site and

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

Imputation rules for partial AE end date are defined below:

- Impute the AE end date as min (the last day of the month, end of study participation) if day is missing, or min (Dec, end of study participation) if month is missing.

Appendix 5: Severity (Toxicity) Grades for Laboratory Abnormalities

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Liver Function Tests				
ALT	>ULN - 3xULN	>3x - 5xULN	>5x - 20xULN	>20xULN
AST	>ULN - 3xULN	>3x - 5xULN	>5x - 20xULN	>20xULN
Alkaline Phosphatase	>ULN - 2.5xULN	>2.5x - 5xULN	>5x - 20xULN	>20xULN
Total Bilirubin	>ULN - 1.5xULN	>1.5x - 3xULN	>3x - 10xULN	>10xULN
Chemistry				
Albumin	<LLN - 3.0 g/dL	<3.0 - 2.0 g/dL	<2.0 g/dL	-
GGT	>ULN - 2.5xULN	>2.5x - 5.0xULN	>5.0x - 20.0xULN	>20.0xULN
Creatinine	>ULN - 1.5 x ULN	1.5x - 3.0xULN	>3.0x - 6.0xULN	>6.0xULN
Creatinine clearance	<LLN - 60 mL/min	<60 - 30 mL/min	<30 - 15 mL/min	<15 mL/min
Calcium (hypocalcemia)	<LLN - 8.0 mg/dL	<8.0 - 7.0 mg/dL	<7.0 - 6.0 mg/dL	<6.0 mg/dL
Calcium (hypercalcemia)	>ULN - 11.5 mg/dL	>11.5 - 12.5 mg/dL	>12.5 - 13.5 mg/dL	>13.5 mg/dL
Bicarbonate	<LLN - 16.0 mEq/L	<16.0 - 11.0 mEq/L	<11.0 - 8.0 mEq/L	□<8.0 mEq/L
Sodium (hyponatremia)	<LLN - 130 mEq/L	<130 - 125 mEq/L	<125 - 120 mEq/L	<120 mEq/L
Sodium (hypernatremia)	>ULN - 150 mEq/L	>150 - 155 mEq/L	>155 - 160 mEq/L	>160 mEq/L
Potassium (hypokalemia)	<LLN - 3.0 mEq/L	2.5 - <3.0 mEq/L	2.0 - <2.5 mEq/L	<2.0 mEq/L
Potassium (hyperkalemia)	>ULN - 5.5 mEq/L	>6.0 - 6.5 mEq/L	>6.0 - 7.0 mEq/L	>7.0 mEq/L
Glucose (hypoglycemia)	<LLN - 55 mg/dL	<55 - 40 mg/dL	<40 - 30 mg/dL	<30 mg/dL
Glucose (hyperglycemia)	>ULN - 160 mg/dL	>160 - 250 mg/dL	>250 - 500 mg/dL	>500 mg/dL
Hematology				
Hemoglobin (anemia)	<LLN - 10.0 g/dL	<10.0 - 8.0 g/dL	<8.0 g/dL	-
WBC (leukocytes)	<LLN - 3.0 x 10 ⁹ /L	<3.0 - 2.0 x 10 ⁹ /L	<2.0 - 1.0 x 10 ⁹ /L	<1.0 x 10 ⁹ /L
Neutrophil (absolute) dec	<LLN - 1.5 x 10 ⁹ /L	<1.5 - 1.0 x 10 ⁹ /L	<1.0 - 0.5 x 10 ⁹ /L	<0.5 x 10 ⁹ /L
Lymphocytes (absolute) dec	<LLN - 0.8 x 10 ⁹ /L	<0.8 - 0.5 x 10 ⁹ /L	<0.5 - 0.2 x 10 ⁹ /L	<0.2 x 10 ⁹ /L
Platelets dec	<LLN - 75.0 x 10 ⁹ /L	<75.0 - 50.0 x 10 ⁹ /L	<50.0 - 25.0 x 10 ⁹ /L	<25.0 x 10 ⁹ /L
Coagulation				
Activated partial thromboplastin time (aPTT)	>ULN - 1.66xULN	>1.66 - 2.33xULN	>2.33 - 3.00xULN	>3.00xULN
Prothrombin time (PT)	>ULN - 1.25xULN	>1.25 - ≤1.50xULN	>1.50 - 3.00x ULN	>3.00xULN
International Normalized Ratio (INR)	>ULN - 1.5xULN	>1.5 - 2.0xULN	>2.0 - 3.0xULN	>3.0xULN

8. REFERENCES

¹ Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharm Res.* 2000; 17(10):1278-1283.