STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2a, Open-Label Study to Evaluate the Safety and Efficacy of Selgantolimod (SLGN)-Containing Combination Therapies for the Treatment of Chronic Hepatitis B (CHB)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CK	creatine kinase
COVID-19	coronavirus disease 19
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ddPCR	digital droplet polymerase chain reaction
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
FAS	Full Analysis Set
HBV	hepatitis B virus
HBcrAg	hepatitis B core-related antigen
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HLGT	high-level group term
HLT	high-level term
IRT	interactive response technology
LTT	lower-level term
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NUC	nucleos(t)ide(s)
PT	preferred term
Q1, Q3	first quartile, third quartile
PK	pharmacokinetic(s)
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
siRNA	short interfering RNA
SOC	system organ class

SLGN	selgantolimod
SMQ	Standardized MedDRA Query
TAF	tenofovir alafenamide (Vemlidy®)
TEAE	treatment-emergent adverse event
TE	treatment emergent
TFFU	treatment-free follow-up
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
$AUC_{0–24}$	partial area under the concentration versus time curve from time “0” to time “24”
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where “Dose” is the dose of the drug
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-465-4439. This SAP is based on the study protocol amendment 2 dated 12 April 2023 and the electronic case report form (eCRF). The SAP will be finalized before the Primary Analysis at Follow-up (FU) Week 24 when all participants complete Follow-Up (FU) Week 24 or early terminated from the study prior to FU Week 24, and will be used for both Primary Analysis and Final Analysis. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives and Endpoints

Primary Objective(s)	**Primary Endpoint(s)**
• To evaluate the safety and tolerability of study treatment(s) • To evaluate the efficacy of study treatment(s) as measured by the proportion of participants who achieve functional cure, defined as hepatitis B surface antigen (HBsAg) loss and HBV DNA < LLOQ at FU Week 24	• The proportion of participants who achieve functional cure, defined as HBsAg loss and HBV DNA < LLOQ at FU Week 24
Secondary Objective(s)	**Secondary Endpoint(s)**
• To evaluate the proportion of participants with HBsAg loss with and without anti-HBsAg seroconversion during the study • To evaluate in participants with CHB who are hepatitis B e antigen (HBeAg) positive at baseline, the proportion of participants who achieve HBeAg loss with and without anti-HBeAg seroconversion during the study • To evaluate the proportion of participants who remain off nucleos(t)ide(s) (NUC) treatment during FU • To evaluate the proportion of participants experiencing HBV virologic breakthrough during study treatment(s)	• The proportion of participants with HBsAg loss with and without anti-HBsAg seroconversion during the study • The proportion of participants with HBeAg loss with and without anti-HBeAg seroconversion during the study in participants with CHB who are HBeAg positive at baseline • The proportion of participants who remain off NUC treatment during FU • The proportion of participants experiencing HBV virologic breakthrough during study treatment(s) as defined in protocol Section 2.
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1.2. Study Design

Approximately 40 NUC-suppressed and 60 viremic CHB-infected participants may be enrolled and assigned into a cohort below. Each cohort will enroll a minimum of 20% of HBeAg-positive participants, and up to 20% of participants can have HBsAg ≤ 100 IU/mL.

NUC-suppressed Cohort

Cohort 1 (n = 40):

- TAF 25-mg tablet administered orally once daily for 36 weeks
- VIR-2218 200 mg administered via SC injection once every 4 weeks for 24 weeks (total 6 doses)

At Week 12, add-on and initiate the below treatment:

- SLGN 3 mg (2 × 1.5-mg tablets) administered orally while fasting once a week on the same day for 24 weeks (total 24 doses)
- Nivolumab 0.3 mg/kg administered IV once every 4 weeks for up to 24 weeks (up to 6 doses)

Viremic Cohort

Cohort 2 (n = 60)

Participants will be randomized 2:1 into Cohort 2 (Groups A and B) and stratified by HBsAg > or ≤ 3 $\log_{10}$ IU/mL.

Group A (n = 40):

- VIR-2218 200 mg administered via SC injection once every 4 weeks for 24 weeks (total 6 doses)

At Week 12, add-on and initiate the below treatment:

- SLGN 3 mg (2 × 1.5-mg tablets) administered orally while fasting once a week on the same day for 24 weeks (total 24 doses)
- Nivolumab 0.3 mg/kg administered IV once every 4 weeks for up to 24 weeks (up to 6 doses)

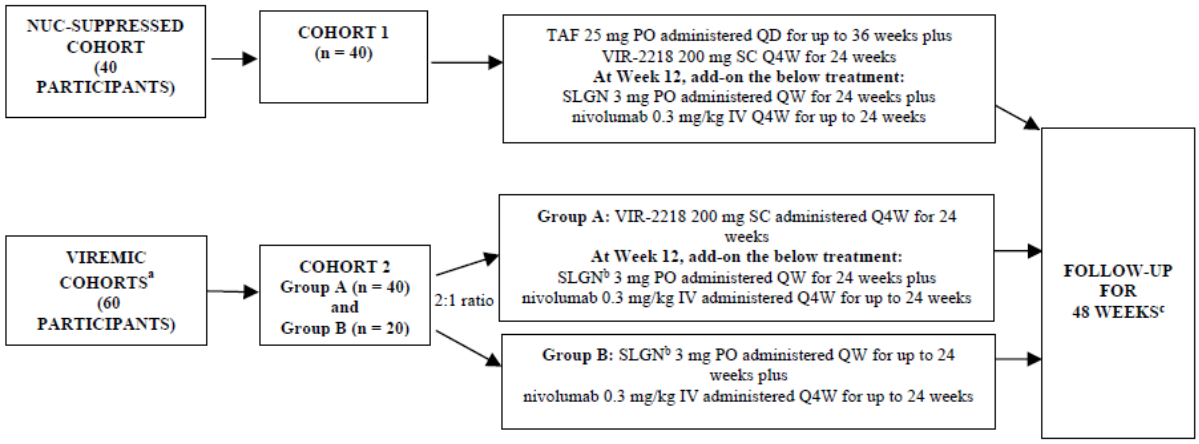
Group B (n = 20):

- SLGN 3 mg (2 × 1.5-mg tablets) administered orally while fasting once a week on the same day for up to 24 weeks (up to 24 doses)
- Nivolumab 0.3 mg/kg administered IV once every 4 weeks for up to 24 weeks (up to 6 doses)

After completing study treatments all participants will enter the FU period.

Figure 1-1 provides the study design schema.

Figure 1-1. Study Design Schema*



IV = intravenous; NUC = nucleos(t)ide(s); PO = oral; Q4W = every 4 weeks; QD = once daily; QW = every week; SLGN = selgantolimod; SC = subcutaneous; TAF = tenofovir alafenamide

a Viremic participants who meet criteria to initiate NUC treatment will receive TAF 25 mg once daily for up to 36 weeks during the study.

b SLGN dosed while fasting once a week, on the same day, for 24 weeks.

c Participants will continue to receive TAF per Protocol Section 3.5.

* NOTE: Nivolumab dosing was stopped in this study and all treatments in Cohort 2 Group B were discontinued. This was a sponsor decision based on a benefit risk assessment on the use of nivolumab in HBV cure. Rationale is provided in Protocol Section 1.3.1.

Additional details regarding study assessments can be found in Appendix 1.

1.2.1. Changes to Study Design

Nivolumab dosing was stopped by Gilead as part of benefit-risk assessment based on emerging safety data from this study, other studies evaluating anti-PD-1/PD-L1 mAbs, and pertinent patient and prescriber insights {Cohen C. 2020}. As the study had completed enrollment and all participants were undergoing study treatment when the decision was made to stop nivolumab administration, the following measures were implemented:

- Stopped further nivolumab administration for all study participants across all cohorts
- Continued treatment with VIR-2218 and SLGN through Week 36 for Cohort 1 and Cohort 2 Group A
- Discontinued all study treatment for Cohort 2 Group B participants
- Stopped all sample collections related to nivolumab
- NUC treatment cessation was no longer required for NUC treated participants (Cohort 1)

1.3. Sample Size and Power

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2. TYPE OF PLANNED ANALYSIS

2.1. Primary Analysis

The Primary Analysis will be conducted after all participants have completed FU Week 24 or early terminated from the study prior to FU Week 24.

2.2. Final Analysis

The final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-participant listings will be presented for all participants in the All Enrolled Analysis Set and sorted by cohort, treatment group if applicable, and participant ID number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within the participant. The cohort, and treatment group if applicable, to which participants were enrolled and/or randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion as well as the number and percentage of participants who were excluded and the reasons for their exclusion, will be summarized by cohort, and treatment group if applicable.

A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all participants in Cohort 1 who received a study participant identification number in the study after screening, or all participants in Cohort 2 who were randomized in the study.

3.1.2. All Randomized Analysis Set

The All Randomized Analysis Set includes all participants in Cohort 2 who were randomized in the study.

3.1.3. Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled participants in Cohort 1, or all randomized participants in Cohort 2 who received at least 1 dose of study drug. This is the primary analysis set for efficacy analyses.

3.1.4. Safety Analysis Set

The Safety Analysis Set includes all participants who received at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.5. Follow-Up (FU) Analysis Set

The FU Analysis Set includes all participants who have at least 1 follow-up visit, after completing or premature discontinued from the study drugs.

3.1.6. SLGN Pharmacokinetic Analysis Set

The SLGN Pharmacokinetic (PK) Analysis Set will include all enrolled participants who took at least 1 dose of SLGN and have at least 1 nonmissing SLGN concentration value reported by the PK laboratory. This is the primary analysis set for PK analyses associated with SLGN.

3.1.7. SLGN Pharmacokinetic (PK) Substudy Analysis Set

The SLGN PK Substudy Analysis Set will include all enrolled participants who took at least 1 dose of SLGN, participated in the PK substudy, and have at least 1 nonmissing postdose SLGN concentration. This is the primary analysis set for detailed PK analysis of intensive PK sampling associated with SLGN.

3.2. Participant Grouping

For analyses based on the FAS, participants will be grouped according to the treatment group to which they were enrolled for Cohort 1 or to which they were randomized for Cohort 2. For analyses based on the Safety Analysis Set, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the enrolled/randomized treatment group only when their actual treatment differs from enrolled/randomized treatment for the entire treatment duration.

For the PK Analysis Set, participants will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

Cohort 2 participants will be randomized to treatment groups via the interactive voice or web response system (IXRS) in a 2:1 ratio using a stratified randomization schedule. Stratification will be based on the following variable:

- HBsAg > 3 $\log_{10}$ IU/mL or HBsAg ≤ 3 $\log_{10}$ IU/mL

If there are discrepancies in stratification factor values between the IXRS and the clinical database, the values recorded in the clinical database will be used for analyses. However, in the case that stratification factor data is missing in clinical database, values recorded in the IXRS will be used. Additionally, stratification discrepancies will be reviewed and assessed. Based on the assessment of stratification discrepancies, a sensitivity analysis of the primary endpoint may be performed.

Demographics, baseline characteristics, participants disposition and enrollment, and efficacy endpoints will be evaluated by baseline HBsAg status (HBsAg > or ≤ 3 $\log_{10}$ IU/mL).

3.4. Examination of Participant Subgroups

There are no prespecified participant subgroupings for efficacy and safety analyses.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2. The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.4, and for prior HBV and concomitant medications in Section 7.4.

3.6.2. Outliers

Outliers of non-PK data will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the enrollment date for Cohort 1 or randomization date for Cohort 2 will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (e.g., estimates of creatinine clearance, age at date of AE) will be based on age, and derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.

- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ, respectively).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data (eg, $\log_{10}$ transformation may be used for quantitative HBsAg, HBV DNA, HBeAg if applicable, HBV RNA, and HBcrAg) or nonparametric analysis methods may be used, as appropriate.

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

Natural logarithm transformation will be used for analyzing non-BLQ concentrations and PK parameters in intensive PK samples. Concentration values that are BLQ will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose and postdose time points for summary purposes. The number of samples will be summarized to reflect the actual number of samples assessed at that time point.

At predose, if all concentration values are BLQ, then the mean, and order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as 0 and the rest of the summary statistics (ie, SD and CV) will be missing. If any values are non-BLQ, then the number of samples, order statistics, and all summary statistics will be displayed.

At any given postdose time point, if more than one-third of the participants have a concentration value of BLQ, then only the number of samples and order statistics will be displayed; otherwise, order statistics and summary statistics will be displayed.

The following conventions will be used for the presentation of order statistics for postdose time points:

- If at least 1 participant has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the participants have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all participants have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

Concentration related PK parameters (eg, C_{last}, C_{max}, and C_{tau}) that are BLQ will be excluded before log transformation or statistical model fitting and displayed as described above.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of any study drug and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, Study Day 1 is the day of first dose of any study drug administration.

The last dose date of the study drug will be the stop date on the study drug administration eCRF for the record where the "study drug was permanently withdrawn" flag is "Yes".

3.8.2. Analysis Visit Windows

Participant visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows as specified in Table 3-1 to Table 3-12.

Data collected up to the last on-treatment date + 3 days will be considered as on-treatment data, whereas data collected afterwards will be considered as follow-up data.

For each drug, the last on-treatment date is defined as follows:

- Last on-treatment date for VIR-2218 = (last injection date of VIR-2218 + 28 days) – 1
- Last on-treatment date for nivolumab = (last injection date of nivolumab + 28 days) – 1
- Last on-treatment date for selgantolimod = (last dose date of selgantolimod + 7 days) – 1

For Cohort 1 and Cohort 2 Group A, the composite last on-treatment date is the latest date of the last on-treatment date of VIR-2218, nivolumab, or SLGN.

For Cohort 2 Group B, the composite last on-treatment date is the latest date of the last on-treatment date of nivolumab or SLGN.

Participants are allowed to continue taking TAF after the discontinuation of study treatments, hence TAF will not be considered for constructing the analysis windows.

The follow-up day (FU Day) in Posttreatment tables is defined as:

- FU Day = Assessment date – composite last on-treatment date.

A baseline value is defined as the last available value collected on or prior to the date of first dose of any study drug. An unscheduled visit prior to the first dosing of study drug will be included in the calculation of the baseline value, if applicable.

The analysis windows for on-treatment assessments are provided in Table 3-1 to Table 3-9. Table 3-10 to Table 3-12 provide analysis windows for posttreatment assessments.

Table 3-1. Cohort 1 and Cohort 2 Group A: Analysis Visit Windows for On-treatment Vital Signs, Hematology, Chemistry, Coagulation, Quantitative Plasma HBV DNA, Quantitative HBV (serum HBsAg, HBcrAg, HBeAg, and HBV RNA), Qualitative HBV Serology (HBeAg, hepatitis B e antibody (HBeAb), HBsAg, and hepatitis B surface antibody (HBsAb))

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	29	2	43
Week 8	57	44	71
Week 12	85	72	92
Week 14	99	93	106
Week 16	113	107	127
Week 20	141	128	155
Week 24	169	156	183
Week 28	197	184	211
Week 32	225	212	239
Week 36	253	240	≥ 253

Table 3-2. Cohort 1 and Cohort 2 Group A: Analysis Visit Windows for On-treatment Urinalysis

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	29	2	43
Week 8	57	44	71
Week 12	85	72	99
Week 16	113	100	127
Week 20	141	128	155
Week 24	169	156	183
Week 28	197	184	211
Week 32	225	212	239
Week 36	253	240	≥ 253

Table 3-3. Cohort 1 and Cohort 2 Group A: Analysis Visit Windows for On-treatment Body Weight

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	85	2	99
Week 16	113	100	127
Week 20	141	128	155
Week 24	169	156	183
Week 28	197	184	211
Week 32	225	212	239
Week 36	253	240	≥ 253

Table 3-4. Cohort 1 and Cohort 2 Group A: Analysis Visit Windows for On-treatment APRI, FibroTest, ECG, and Estimated Creatinine Clearance (using the Cockcroft-Gault method)

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	85	2	169
Week 36	253	170	≥ 253

Table 3-5. Cohort 1 and Cohort 2 Group A: Analysis Visit Windows for On-treatment Ophthalmologic Examination

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	169	2	211
Week 36	253	212	≥ 253

Table 3-6. Cohort 2 Group B: Analysis Visit Windows for On-treatment Hematology, Chemistry, Coagulation, Quantitative Plasma HBV DNA, Quantitative HBV (serum HBsAg, HBcrAg, HBeAg, and HBV RNA), Qualitative HBV Serology (HBeAg, HBeAb, HBsAg, and HBsAb)

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	29	2	43
Week 8	57	44	71
Week 12	85	72	92
Week 14	99	93	106
Week 16	113	107	127
Week 20	141	128	155
Week 24	169	156	≥ 169

Table 3-7. Cohort 2 Group B: Analysis Visit Windows for On-treatment Vital Signs

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 2	15	2	22
Week 4	29	23	43
Week 8	57	44	71
Week 12	85	72	92
Week 14	99	93	106
Week 16	113	107	127
Week 20	141	128	155
Week 24	169	156	≥ 169

Table 3-8. Cohort 2 Group B: Analysis Visit Windows for On-treatment Urinalysis, and Body Weight

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	29	2	43
Week 8	57	44	71
Week 12	85	72	99
Week 16	113	100	127
Week 20	141	128	155
Week 24	169	156	≥ 169

Table 3-9. Cohort 2 Group B: Analysis Visit Windows for On-treatment APRI, FibroTest, ECG, Estimated Creatinine Clearance (using the Cockcroft-Gault method), and Ophthalmologic Examination

Visit	Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	85	2	127
Week 24	169	128	≥ 169

Table 3-10. Cohort 1, Cohort 2 Groups A and B: Analysis Visit Windows for Posttreatment Hematology, Chemistry, Coagulation, Quantitative Plasma HBV DNA, HBV genotyping, Quantitative HBV Serology (HBsAg, HBcrAg, HBeAg, and HBV RNA), Qualitative HBV Serology (HBeAg, HBeAb, HBsAg, and HBsAb) and Vital Signs

Visit	FU Day	Visit Window FU Day	
		Lower Limit	Upper Limit
FU Week 2*	15	4	22
FU Week 4	29	23	43
FU Week 8	57	44	71
FU Week 12	85	72	127
FU Week 24	169	128	211
FU Week 36	253	212	295
FU Week 48	337	296	≥ 337

* FU Week 2 was defined in protocol amendment 1, but was removed from protocol amendment 2. Since a substantial amount of participants have already completed FU Week 2 per protocol amendment 1, this visit will be kept in analysis.

Table 3-11. Cohort 1, Cohort 2 Groups A and B: Analysis Visit Windows for Posttreatment APRI and FibroTest

Visit	FU Day	Visit Window FU Day	
		Lower Limit	Upper Limit
FU Week 12	85	4	211
FU Week 48	337	212	≥ 337

Table 3-12. Cohort 1, Cohort 2 Groups A and B: Analysis Visit Windows for Posttreatment Body Weight, ECG, Estimated Creatinine Clearance (using the Cockcroft-Gault method)

Visit	FU Day	Visit Window FU Day	
		Lower Limit	Upper Limit
FU Week 48	337	4	≥ 337

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug will be selected, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be considered as the baseline value. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of these measurements.
- For postbaseline values (except for alanine aminotransferase [ALT]):
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken except for qHBsAg (IU/mL), HBV DNA (IU/mL), and quantitative HBeAg (IU/mL), for which the geometric mean will be taken.

- For postbaseline ALT values:
  - The record with the largest value within the same analysis window will be selected.
  - If there is more than 1 record with the largest value, the latest record will be selected.
  - If there are multiple largest records with the same time or no time recorded on the same day, any one of these measurements can be selected as the analysis value.

If multiple valid, nonmissing, categorical measurements exist in an analysis window, and a single value is needed, records will be chosen based on the following rules:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected for safety data (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings), and the most conservative value will be selected for efficacy data (eg, negative will be selected over positive for HBeAg and HBsAg, whereas positive will be selected over negative for HBeAb and HBsAb).
- For postbaseline values:
  - The most conservative value (eg, abnormal will be selected over normal for safety ECG) within the analysis window will be selected, except for HBV serology (HBsAg, HBsAb, HBeAg, and HBeAb), for which the most favorable value (ie, negative will be selected over positive for HBsAg and HBeAg, whereas positive will be selected over negative for HBsAb and HBeAb) will be selected.
  - In the event that more than 1 value within an analysis window are equal, the value collected closest to the nominal day will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the latest record will be selected; if these measurements were recorded at the same time or no time recorded, any one of these measurements can be selected as the analysis value.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

Key study dates (ie, first participant screened, first participant enrolled, last participant enrolled, last participant last visit for the primary endpoint, and last participant last visit for the clinical study report) will be provided.

A summary of participant enrollment will be provided by cohort for each country or region, investigator within a country or region, and study overall. Within Cohort 2, the summary will be presented by treatment group (Group A or Group B) and stratification group (HBsAg > 3 or HBsAg ≤ 3 $\log_{10}$ IU/mL). The summary will present the number and percentage of participants enrolled/randomized. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column. For Cohort 2, if there are discrepancies in the value used for stratification assignment between the IXRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of participants with discrepancies in the value used for stratification assignment between the IXRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for Cohort 2 will be provided as an appendix to the CSR.

A summary of participant disposition will be provided by cohort and study overall. Within Cohort 2, the summary will be presented by treatment group (Group A or Group B) and stratification group (HBsAg > 3 or HBsAg ≤ 3 $\log_{10}$ IU/mL). This summary will present the number of participants screened, the number of participants who met all eligibility criteria but were not enrolled/randomized with reasons participants not enrolled/randomized, and the number of participants in each of the categories listed below:

- All Enrolled Analysis Set
- All Randomized Analysis Set
- Full Analysis Set
- Safety Analysis Set
- FU Analysis Set
- SLGN PK Analysis Set
- SLGN PK Substudy Analysis Set
- SLGN completion status
  - Completed SLGN
  - Prematurely discontinued SLGN

- Reasons for premature discontinuation of SLGN
- Nivolumab completion status
  - Nivolumab not initiated
  - Completed nivolumab
  - Prematurely discontinued nivolumab
- Reasons for premature discontinuation of nivolumab
- VIR-2218 completion status
  - Completed VIR-2218
  - Prematurely discontinued VIR-2218
- Reasons for premature discontinuation of VIR-2218
- TAF completion status (for Cohort 1 during treatment phase only)
  - Completed TAF
  - Prematurely discontinued TAF
- Reasons for premature discontinuation of TAF
- FU Completion Status
  - Continuing FU (for FU Week 24 Analysis)
  - Completed FU
  - Prematurely discontinued FU
- Study completion status
  - Continuing study (for FU Week 24 Analysis)
  - Completed study
  - Premature discontinued study
- Reasons for premature discontinuation of study

For the status of study drugs, FU completion, and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

The following by-participant listings will be provided by cohort (and by treatment group for Cohort 2), and participant identification (ID) number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation
- Lot number and kit ID

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to a study drug during treatment period will be defined as follows:

- Duration of exposure to TAF = last dosing date of TAF for the treatment period − first dosing date of TAF for the treatment period + 1 day
- Duration of exposure to SLGN = last dosing date of SLGN − first dosing date of SLGN + 7 days
- Duration of exposure to VIR-2218 = last injection date of VIR-2218 − first injection date of VIR-2218 + 28 days
- Duration of exposure to nivolumab = last injection date of nivolumab − first injection date of nivolumab + 28 days

The calculations for duration of exposure to study drugs are made regardless of any temporary interruptions in study drug administration and will be expressed in weeks using up to 1 decimal place (e.g., 4.5 weeks). If the last study drug dosing date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used for participants included in the Final Analyses or the last available date in the database snapshot for FU Week 24 Analysis. If month and year of the last dose are known, and the last study drug dosing date imputed above is different from the month collected, the last date of that month will be used. If only year of the last dose is known, and the last study drug dosing date imputed above is after the year collected, the last date of that year will be used; if the last study drug dosing date imputed above is before the year collected, the first date of that year will be used.

The total duration of exposure to each of the study drugs will be summarized using descriptive statistics and using the number (ie, cumulative duration of exposure by weeks) and percentage of participants exposed through the following time periods: 1 day, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 28 weeks, 32 weeks, and 36 weeks, where applicable. Summaries will be drug specific and be provided by cohort (and by treatment group for Cohort 2) for the Safety Analysis Set.

For nivolumab, number of doses administered (ie, 6 doses, 5 doses, 4 doses, 3 doses, 2 doses, and 1 dose) will be summarized by cohort (and by treatment group for Cohort 2) for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

4.2.2.1. On-Treatment Adherence for TAF (Cohort 1 Only)

The level of on-treatment adherence to TAF will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a participant's actual on-treatment period (ie, by Week 36) based on the study drug regimen.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{Adherence (\%)} = \left(\frac{\text{Total number of tablets taken}}{\text{Total number of tablets prescribed}}\right) \times 100$$

$$= \frac{\sum \text{No. of tablets taken at each dispensing period [1]}}{\sum \text{No. of tablets prescribed at each dispensing period [2]}} \times 100$$

[1] Number of tablets taken during a distinct dispensing period for TAF is calculated as the minimum of (a) the daily number of tablets prescribed for the study drug multiplied by the **duration of treatment** at the dispensing period of the same dispensing date, and (b) the number of tablets taken for the study drug (number of tablets dispensed minus the number of tablets returned). Total number of tablets taken is determined by summing the number of tablets taken from all evaluable dispensing periods.

[2] Number of tablets prescribed at a distinct dispensing period for TAF is calculated as the daily number of tablets prescribed for the study drug multiplied by the **duration of treatment** at the dispensing period of the same dispensing date. Total number of tablets prescribed is determined by summing the number of tablets prescribed from all evaluable dispensing periods.

The **duration of treatment** (in days) at a dispensing period for TAF is calculated as the minimum of (a) the last returned date of the same dispensing period for the study drug, (b) date of premature discontinuation of the study drug, and (c) **next dispensing date** of the study drug, minus dispensing date of the study drug.

The **next dispensing date** is the following dispensing date of the study drug regardless of the bottle return date.

For a record where the number of tablets returned was missing (with "Yes" answered for "Was bottle returned?" question), then this record will be excluded from both denominator and numerator calculation. If the number of tablets dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown for the same dispensing date, then all records for the same dispensing date for that study drug will be excluded from both denominator and numerator calculation.

Adherence up to end of treatment will be calculated for each participant in Cohort 1.

The number and percentage of participants who return at least 1 bottle and have calculable adherence during the study, descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) for adherence up to end of treatment visit (ie, Week 36) along with the number and percentage of participants belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be summarized for Cohort 1 participants based on the Safety Analysis Set.

4.2.2.2. On-Treatment Adherence for SLGN

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a participant's actual on-treatment period based on the study drug regimen.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{Adherence (\%)} = \left(\frac{\text{Total Amount of SLGN Administered [1]}}{\text{Total Amount of SLGN Expected to be Administered on Treatment [2]}}\right) \times 100$$

[1] The total amount of SLGN administered to a participant will be determined by $\sum$ No. of tablets dispensed $-$ $\sum$ No. of tablets returned based on the study drug accountability CRF.

[2] The total amount of SLGN expected to be Administered on treatment is determined as follows:

a For participants who completed SLGN, the amount of SLGN expected to be administered will be the 6×8 tablets;

b For participants who did not complete SLGN, the total amount of SLGN expected to be administered is the sum of number of tablets expected to be taken at each dispensing period, which is calculated as the number of on-treatment weeks on or before the last dosing date for SLGN multiplied by the number of tablets expected to be taken at each dispensing period (ie, 8 tablets). If there are more than 6 dispensing visits for a participant, 6 visits will be used for calculation.

Descriptive statistics for the level of on-treatment adherence with the number and percentage of participants belonging to adherence categories (< 95%, ≥ 95%) will be provided by cohort (and by treatment group for Cohort 2) for the Safety Analysis Set.

4.2.2.3. On-treatment Adherence for VIR-2218 (Cohort 1 and Cohort 2 Group A only)

The level of on-treatment adherence to VIR-2218 will be determined by the total amount of VIR-2218 administered relative to the total amount of VIR-2218 expected to be administered during a participant's actual on-treatment period based on the study drug regimen.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{Adherence (\%)} = \left(\frac{\text{Total Amount of VIR} - 2218 \text{ Administered [1]}}{\text{Total Amount of VIR} - 2218 \text{ Expected to be Administered on Treatment [2]}}\right) \times 100$$

[1] The total amount of VIR-2218 administered to a participant will be determined by $(\sum \text{No. of vials dispensed}) - (\sum \text{No. of vials returned})$ based on the drug accountability CRF

[2] The total amount of VIR-2218 expected to be administered on treatment is determined as follows:

a For participants who completed VIR-2218, the amount of VIR-2218 expected to be administered will be the 6 × 2 vials;

b For participants who did not complete VIR-2218, the number of VIR-2218 expected to be administered is determined by the last on-treatment visit. For example, if the last on-treatment visit is Week 12, the number of VIR-2218 expected to be administered for this participant will be 4 × 2 vials.

Descriptive statistics for the level of on-treatment adherence with the number and percentage of participants belonging to adherence categories (< 100%, 100%) will be provided by cohort for the Safety Analysis Set.

4.2.2.4. On-Treatment Adherence for Nivolumab

The level of on-treatment adherence to nivolumab will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a participant's actual on-treatment period based on the study drug regimen.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{Adherence (\%)} = \left(\frac{\text{Total No. of Nivolumab Administered [1]}}{\text{Total No. of Nivolumab Expected to be Administered on Treatment [2]}}\right) \times 100$$

[1] The total number of nivolumab administered to a participant will be determined by the number of doses administered based on the study drug administration CRF.

[2] The total number of nivolumab expected to be administered on treatment is determined as follows:

a For participants who completed nivolumab, the number of nivolumab expected to be administered will be set to 6;

b For participants who did not complete nivolumab, the number of nivolumab expected to be administered is determined by the last administration visit (for example, for a participant in Cohort 1 and Cohort 2 Group A, if the last administration visit is Week 16, the number of nivolumab expected to be administered will be 2; for a participant in Cohort 2 Group B, if the last administration visit is Week 16, the number of nivolumab expected to be administered will be 5).

For participants who never initiate nivolumab, adherence will not be calculated.

Descriptive statistics for the level of on-treatment adherence with the number and percentage of participants belonging to adherence categories (< 50%, 50% to < 75%, 75% to < 100%, 100%) will be provided by cohort (and by treatment group for Cohort 2) for the Safety Analysis Set.

4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry but enrolled in the study, will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of participants who did not meet at least 1 eligibility criterion and the number of participants who did not meet specific criteria by treatment group based on the All Enrolled/Randomized Analysis Set. A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations (e.g., at least 1, with 1, 2, 3 or more important protocol deviations), and the total number of important protocol deviations by deviation category (e.g., eligibility criteria, informed consent) will be summarized by cohort (and by treatment group for Cohort 2) for the Enrolled/Randomized Analysis Set. A by-participant listing will be provided for those participants with important protocol deviation.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis. Please refer to Appendix 3 for data collection and determination of COVID-19 Data.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A by-participant listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided if applicable.

4.4.2. Protocol Deviations Due to COVID-19

A by-participant listing will be provided for participants with important protocol deviations related to COVID-19 if applicable. A separate listing will be provided for participants with non-important protocol deviations related to COVID-19 if applicable.

4.4.3. Missed and Virtual Visits due to COVID-19

A by-participant listing of participants with missed or virtual visits due to COVID-19 will be provided by participant ID number in ascending order.

Missed or virtual visits due to COVID-19 will be collected on the visit date CRF page.

4.4.4. Adverse Events Due to COVID-19

AEs of COVID-19 will be included in analyses of AEs if applicable, which will be determined through MedDRA COVID-19 SMQ narrow search. A by-participant listing of AEs of COVID-19 will be provided if applicable.

4.4.5. Overall Assessment of COVID-19 Pandemic Impact

For participants affected by COVID-19 infection and/or pandemic while participating in the study, a listing of the following individual COVID-19 related outcome categories will be provided:

- Death due to COVID-19
- Adverse event of COVID-19, as determined by COVID-19 SMQ narrow search
- Specific adverse event directly associated with the pathogen causing COVID-19, as determined by MST
- Hospitalization (using data from AE eCRF) due to adverse event of COVID-19 as defined above
- Study drug discontinuation due to COVID-19
- Study discontinuation due to COVID-19
- Missed visits due to COVID-19
- Missed key assessments due to COVID-19 (Key assessments are the assessments contributing to primary endpoint, ie, FU Week 24 assessments related to qualitative HBsAg and quantitative HBV DNA)

In addition, composite broad COVID-19 impact indicator will be derived based on the following individual categories defined above: death, adverse event, hospitalization, study drug discontinuation, study discontinuation, missed visits, and missed key assessments. Composite specific COVID-19 impact indicator will be derived based on death and specific adverse event.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be displayed by cohort and study overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. Within Cohort 2, the summary will be presented by treatment group (Group A or Group B) and HBsAg category (HBsAg > 3 and ≤ 3 $\log_{10}$ IU/mL). The summary of demographic data will be provided for the Safety Analysis Set.

A by-participant demographic listing, including the informed consent date, and stratification group (for Cohort 2 only), will be provided by cohort (and by treatment group for Cohort 2), and participant ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- HBsAg ($\log_{10}$ IU/mL) as a continuous variable
- HBsAg ($\log_{10}$ IU/mL) as categories (< 2, 2 to < 3, 3 to < 4, ≥ 4)
- HBV DNA ($\log_{10}$ IU/mL) as a continuous variable
- HBV DNA ($\log_{10}$ IU/mL) as categories (< LLOQ, LLOQ to < 3.3, 3.3 to < 4.3, ≥ 4.3)
- HBeAg/HBeAb status (negative, positive)
- HBV genotype
- ALT (U/L) as a continuous variable
- ALT level as categories based on central laboratory normal range (≤ upper limit of normal [ULN], > ULN to 5 × ULN, > 5 × ULN to 10 × ULN, > 10 × ULN)
- FibroTest Score as a continuous variable
- Fibrosis Stage by FibroTest Score as categories (0.00 to 0.48, 0.49 to 0.74, 0.75 to 1.00)
- APRI (≤ 1, > 1)
- Current oral nucleoside/nucleotide treatment

- Previous interferon experience to treat HBV (yes, no)
- Duration of being HBV positive (in years) as a continuous variable
- Mode of HBV infection
- Estimated glomerular filtration rate using the Cockcroft-Gault equation ($eGFR_{CG}$) (mL/min), which will be calculated as follows:

  $eGFR_{CG}$ (mL/min) = [(140 – age [years]) × weight (kg) × (0.85 if female)] / (serum creatinine [mg/dL] × 72), where weight is actual body weight in kilograms

These baseline characteristics will be summarized by cohort and study overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. Within Cohort 2, the summary will be presented by treatment group (Group A or Group B) and HBsAg category (HBsAg > 3 and ≤ 3 $\log_{10}$ IU/mL). The summary of these baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

A by-participant listing of other baseline characteristics, including HBsAg category for Cohort 2, will be provided by cohort (and by treatment group for Cohort 2), and participant ID number in ascending order.

5.3. Medical History

General medical history data will be collected at screening and listed only.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definitions of Primary Efficacy Endpoint

The primary efficacy endpoint of this study is defined as the proportion of participants who achieve functional cure, defined as HBsAg loss and HBV DNA < LLOQ at FU Week 24.

6.1.2. Statistical Hypothesis for Primary Efficacy Endpoint

No statistical hypothesis testing will be performed.

6.1.3. Analysis of Primary Efficacy Endpoint

The primary efficacy analysis will be performed for the FAS after the last participant has completed FU Week 24 assessments or prematurely discontinued study drug.

Analysis for Cohort 1:

The point estimates and the 2-sided 95% exact confidence interval (CI) of the primary efficacy endpoint will be provided. The CIs of the proportion point estimates will be constructed based on the Clopper-Pearson method {Clopper 1934}.

Analysis for Cohort 2:

To compare Group A and Group B for HBsAg categories(> 3 and ≤ 3 $\log_{10}$ IU/mL) separately, point estimates and the 2-sided 95% exact confidence intervals (CIs) of the primary efficacy endpoint will be provided based on the Clopper-Pearson method {Clopper 1934} by HBsAg status and overall for each treatment group.

In addition, point estimates and the 2-sided 95% exact CIs of the proportion difference between Group A and Group B will be displayed separately by HBsAg category for each treatment group. CIs for the proportion differences will be constructed based on the standardized statistic and inverting two 1-sided tests {Chan 1999}.

To compare Group A and Group B for pooled HBsAg > 3 and ≤ 3 $\log_{10}$ IU/mL participants, the proportion differences and the corresponding 95% CIs will be calculated using the stratum-adjusted Mantel-Haenszel (MH) method {Koch 1989}, stratified by HBsAg category(> 3 and ≤ 3 $\log_{10}$ IU/mL), as follows:

$$P_1 - P_2 \pm Z_{(1-\alpha/2)} \times SE(P_1 - P_2)$$

where

- $(P_1 - P_2) = \frac{\sum w_h d_h}{\sum w_h}$ is the stratum-adjusted MH proportion difference, where $d_h = P_{1h} - P_{1h}$ is the proportion difference of group 1 and group 2 in stratum h (h = 1 and 2).
- $w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$ is the weight based on the harmonic mean of sample size for stratum h, where n_{1h} and n_{2h} are the sample sizes of groups 1 and 2 in stratum h.
- $SE(P_1 - P_2) = \sqrt{\frac{\sum w_h^2 \left[\frac{p_{1h}(1-p_{1h}^*)}{n_{1h}-1} + \frac{p_{2h}^*(1-p_2^*)}{n_{2h}-1}\right]}{(\sum w_h{}^2)}}$, where $p_{1h}^* = \frac{m_{1h} + 0.5}{n_{1h} + 1}$ and $p_{2h}^* = \frac{m_{2h} + 0.5}{n_{2h} + 1}$, and m_{1h} and m_{2h} are the number of participants who achieve the primary efficacy endpoint in groups 1 and 2 respectively in stratum h.
- Groups 1 and 2 (in the equations above) represent Group A and Group B from Cohort 2 respectively.
- $\alpha = 0.05$ for this study.
- $Z_{(1-\alpha/2)} = Z_{0.975} = 1.96$ is the 97.5th percentile of the normal distribution.

If the computed lower confidence bound is less than –1, the lower bound is defined as –1. If the computed upper confidence bound is greater than 1, then the upper bound is defined as 1.

6.1.4. Subgroup Analysis of Primary Efficacy Endpoint

No subgroup analyses will be performed.

6.2. Secondary Efficacy Endpoints

6.2.1. Definitions of Secondary Efficacy Endpoints

- The proportion of participants with HBsAg loss with and without anti-HBsAg seroconversion during the study
- The proportion of participants with HBeAg loss with and without anti-HBeAg seroconversion during the study in participants with CHB who are HBeAg positive at baseline
- The proportion of participants who remain off NUC treatment during FU
- The proportion of participants experiencing HBV virologic breakthrough (defined as confirmed HBV DNA ≥ LLOQ after 2 consecutive HBV DNA < LLOQ in participants who are complying with NUC therapy OR confirmed HBV DNA ≥ 1 $\log_{10}$ IU/mL increase from nadir on treatment) during study treatment(s)

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

The secondary efficacy analyses will be performed on FAS.

- The proportions of participants with HBsAg loss with and without anti-HBsAg seroconversion will be summarized by cohort and visit.

- The proportion of participants with HBeAg loss with and without anti-HBeAg seroconversion will be summarized by cohort and visit for participants who are HBeAg positive at baseline.

- The proportion of participants who remain off NUC treatment during FU will be summarized by cohort and FU visit.

Data collected on Visit Date CRF will be used to identify participants who entered FU phase. If a participant had any follow-up visit with nonmissing visit date, then this participant will be considered as entered FU phase.

For participants who entered the FU phase, if NUC treatment was ended no later than FU Week 1 visit, and there is no NUC treatment re-initiation during the FU phase, then this participant is considered as remaining off NUC treatment during FU phase. If partial start/stop dates are entered, any NUC treatment with the month and year (if day is missing) or year (if day and month are missing) of either start or stop date after FU Week 1 will be considered as using NUC treatments. Participants with completely missing NUC treatment start and stop dates will be considered as using NUC treatments, unless otherwise specified.

A list of NUC treatments can be found in Appendix 3.

- The proportion of participants experiencing HBV virologic breakthrough during study treatment(s) will be summarized by cohort.

The HBV virologic breakthrough is defined as confirmed HBV DNA ≥ LLOQ after 2 consecutive HBV DNA < LLOQ in participants who are complying with NUC therapy OR confirmed HBV DNA ≥ 1 log10 IU/mL increase from nadir during study treatments.

In addition, a summary table will be provided for HBsAg-related serology results. The proportion of participants who have ever had HBsAg loss, confirmed HBsAg loss, on-treatment HBsAg loss, posttreatment HBsAg loss (for participants with positive HBsAg at the end of the on-treatment period), HBsAg loss with HBsAb seroconversion, HBsAg loss with HBsAb seroreversion, and HBsAg loss reversion with or without HBsAb seroconversion will be summarized.

For all the above summaries, within Cohort 2, the summary will be presented by treatment group (Group A or Group B) and HBsAg category (HBsAg > 3 and ≤ 3 log10 IU/mL).

HBV serology definitions:

- **HBsAg loss**: HBsAg changing from positive at baseline to negative at any postbaseline visit.
- **Confirmed HBsAg loss**: HBsAg loss confirmed by any 2 consecutive results.
- **HBsAg loss reversion**: Any postbaseline HBsAg positive result following HBsAg loss.
- **HBsAb seroconversion**: HBsAb changing from negative or missing at baseline to positive at any postbaseline visit.
- **Confirmed HBsAb seroconversion**: HBsAb changing from negative or missing at baseline to positive at any postbaseline visit confirmed by any 2 consecutive results.
- **HBsAb seroreversion**: Any postbaseline HBsAb negative result following HBsAb seroconversion.

Both baseline and postbaseline borderline results for HBeAg, HBeAb, HBsAg, and HBsAb will be imputed as follows:

- HBsAb/HBeAb borderline/equivocal → HBsAb/HBeAb negative
- HBsAg/HBeAg borderline/equivocal → HBsAg/HBeAg positive

Missing data will be treated as a nonevent unless otherwise specified (eg, no HBsAg loss, no seroconversion, etc.)

HBeAg-related terminology is defined similarly.

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7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Adverse events (AEs) will be coded using the current version of the MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, or 4 according to toxicity criteria specified by Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities Version 01 April 2015, with the exception of infusion-related reactions (IRRs). For grading of IRRs, the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 are used.

The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" in the eCRF in response to the question for the relatedness to each study treatment, ie, SLGN, TAF, nivolumab, or VIR-2218.

Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Relationship of Adverse Events to Study Procedures

Study procedure related AEs are those for which the investigator selected "Yes" on the AE case report form (CRF) to the question of "Related to Study Procedures." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationships to study procedure will be considered related to study procedure for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.5. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with SAEs on the Gilead global safety database before data finalization.

7.1.6. Treatment-Emergent (TE) Adverse Events (AEs), Non-TEAEs, and AEs Through FU Week 24

7.1.6.1. Definition of TEAEs

TEAEs are defined as 1 or both of the following:

- Any AEs with an onset date on or after the start date of any study drug and on or before the composite last on-treatment date + 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of any study drug

7.1.6.2. Definition of Non-TEAEs

Non-TEAEs are defined as defined as any AEs with an onset date after the composite last on-treatment date + 30 days after permanent discontinuation of study drug through the end of the study.

7.1.6.3. Definition of AEs through FU Week 24

AEs through FU Week 24 are defined as any AEs with an onset date on or after the start date of any study drug and on or before the composite last on-treatment date + 24 weeks after permanent discontinuation of study drug.

Definitions of the composite last on-treatment date for each cohort can be found in Section 3.8.2.

7.1.6.4. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of any study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent.

The event is considered as TE if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of any study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to the cutoff day in Section 7.1.6.1.

The event is considered as non-TE if the AE onset date is after the month and year (or year) of the date corresponding to the cutoff day in Section 7.1.6.2.

The event is considered as AEs through FU Week 24 if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of any study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to the cutoff day in Section 7.1.6.3.

7.1.7. Summaries of Adverse Events and Deaths

7.1.7.1. Summaries of TEAEs

TEAEs will be summarized based on the Safety Analysis Set.

The analysis in this section regarding treatment-related TEAEs will be study drug specific (ie, SLGN, nivolumab, or VIR-2218) in the summaries.

A brief, high-level summary of the number and percentage of participants who experienced the following will be provided for each cohort: any TEAE, any TEAE of Grade 3 or above, any TEAE of Grade 2 or above, any treatment-related TEAE, any treatment-related TEAE of Grade 3 or above, any treatment-related TEAE of Grade 2 or above, any TE SAE, any treatment-related TE SAE, any potential immune-related AEs (irAEs), any potential uveitis, any AE leading to premature discontinuation of any study drug, any AE leading to temporary interruption of any study drug. All deaths (including those that are treatment-emergent and those that are not treatment-emergent) observed in the study will also be included in this summary. Within Cohort 2, the summary will be presented by treatment group (Group A or Group B).

Adverse event summaries with the number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC and PT for each cohort, and within Cohort 2, the summary will be presented by treatment group (Group A or Group B), as follows:

- TEAEs
- TEAEs with Grade 3 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of any study drug
- TEAEs leading to temporary interruption of any study drug

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC, and then by PT in descending order of total frequency within each SOC.

A summary by SOC and PT by severity grade will be provided for TEAEs, TEAEs with Grade 3 or higher, and TEAEs related to study drug(s), and the most severe grade will be used for those TEAEs that occurred more than once in an individual participant during the study.

TEAEs, TEAEs with Grade 3 or higher, TEAEs with Grade 2 or higher, TE SAEs, TE treatment-related AEs, TE treatment-related AEs with Grade 3 or higher, TE treatment-related AEs with Grade 2 or higher, and TE treatment-related SAEs will be summarized by PT only, in descending order of total frequency.

7.1.7.2. Summaries of Non-TEAEs

A brief, high-level summary will be provided for non-TEAEs.

- Non-TEAEs
- Non-TEAEs with Grade 3 or higher
- Non-TE SAEs

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC, and then by PT in descending order of total frequency within each SOC.

7.1.7.3. Summaries of AEs Through FU Week 24

A brief, high-level summary will be provided for AEs through FU Week 24.

In addition, AEs through FU Week 24 for the following summaries will be provided:

- AEs through FU Week 24
- AEs with Grade 3 or higher through FU Week 24
- SAEs through FU Week 24

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC, and then by PT in descending order of total frequency within each SOC.

7.1.7.4. Listings of AEs and Deaths

Data listings will be provided for the following:

- All AEs
- All Non-TEAEs
- All AEs with Grade 3 or higher
- All SAEs
- All Deaths
- All AEs leading to premature discontinuation of any study drug
- All AEs leading to temporary interruption of any study drug

7.1.8. Additional Analysis of Adverse Events – Potential irAEs

Potential irAEs will be analyzed based on a broad (all PTs) search from MedDRA SMQs of Hypersensitivity and Immune-mediated/Autoimmune Disorders.

The number and percentage of participants who experienced any of the above events will be summarized by PT and treatment group for 1) TE potential irAE events, 1) non-TE potential irAE events, and 3) potential irAE events through FU Week 24.

A by-participant listing of identified potential events will be provided.

7.1.9. Additional Analysis of Adverse Events – Potential Uveitis

A predefined MedDRA Search Terms (MST) list consisting of ocular PTs reviewed by an external ophthalmologist and maintained by Patient Safety through MedDRA upversioning for safety monitoring of uveitis in clinical trials will be used for this analysis.

The number and percentage of participants who experienced potential uveitis will be summarized by PT and cohort, and by treatment group within Cohort 2 for 1) TE potential uveitis events, 2) non-TE potential uveitis events, and 3) potential uveitis events through FU Week 24.

A by-participant listing of identified potential events will be provided.

The analysis for potential uveitis will be performed for Final Analysis only.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-participant listing for laboratory test results will be provided by cohort (and treatment group for Cohort 2), participant ID number and visit in chronological order. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities Version April 1, 2015 (or CTCAE Version 5.0 severity grade for infusion-related AEs) will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided for each cohort (and for each treatment group for Cohort 2) for chemistry (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, alkaline phosphatase [ALP], creatine kinase [CK], fasting total cholesterol, fasting glucose, international normalized ratio [INR], lactate dehydrogenase [LDH]), creatinine, and $eGFR_{CG}$ as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date of first dose of any study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values for ALT will be plotted using a line plot by treatment group and visit.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities Version April 1, 2015, will be used to assign toxicity grades to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent (TE) Laboratory Abnormalities

TE laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the composite last on-treatment date plus 30 days. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Non-TE Laboratory Abnormalities

Non-TE laboratory abnormalities are defined as values that increase at least 1 toxicity grade from the last TE laboratory abnormality after the composite last on-treatment date plus 30 days. If the relevant TE laboratory abnormality for a participant is missing, any abnormality of at least Grade 1 observed after the composite last on-treatment date plus 30 days until the end of the study will be consider as non-TE.

7.2.2.3. Laboratory Abnormalities Through FU Week 24

Laboratory abnormalities through FU Week 24 are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the composite last on-treatment date plus 24 weeks. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered as within FU Week 24.

Definitions of the composite last on-treatment date for each cohort can be found in Section 3.8.2.

7.2.2.4. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

The following summaries (number and percentage of participants) will be provided by lab test and cohort; within cohort 2, the summary will be presented by treatment group (Group A or Group B). Participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values.

The above summaries will be provided for 1) TE laboratory abnormalities, 2) non-TE laboratory abnormalities, and 3) laboratory abnormalities through FU W24.

By-participant listings of all laboratory abnormalities, and Grade 3 or 4 laboratory abnormalities will be provided by cohort, participant ID number and visit in chronological order. The listings will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades or abnormal flags displayed.

7.2.3. Liver-related Laboratory Evaluations

The following liver-related laboratory abnormalities will be summarized using the number and percentage of participants for any postbaseline measurements as follows:

- Confirmed ALT flare: ALT > 2 × baseline and ≥ 5 × ULN
- Confirmed ALT elevation: ≥ 10 × ULN

- Confirmed ALT elevation with evidence of hepatic toxicity: ALT > 2 × nadir and one of the following confirmed laboratory abnormalities:

  — Total bilirubin > 2 × ULN

  — Elevated INR > 0.5 above baseline and > ULN

  — Abnormal serum ALB > 1 g/dL decrease from baseline

Central Lab ULNs will be used for all liver-related laboratory evaluations.

For individual laboratory tests, participants will be counted once based on the most severe postbaseline values during the analysis period. For the composite criteria of ALT and total bilirubin, INR or ALB, participants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of participants in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date.

ALT flare and confirmed ALT elevations will be summarized by cohort; within Cohort 2, the summary will be presented by treatment group (Group A or Group B).

The above summaries will be provided for 1) TE laboratory abnormalities, 2) non-TE laboratory abnormalities; 3) laboratory abnormalities through FU Week 24.

Listings of participants who met at least 1 of the above criteria for ALT flares and elevations will be provided. For the listings of ALT flares and elevations, AST (U/L), ALB (g/dL), total bilirubin (mg/dL), INR, HBsAg (log_{10} IU/mL) and HBV DNA (log_{10} IU/mL) will also be provided.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided by cohort (and by treatment group for Cohort 2) for body weight, height, BMI, and vital signs as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and vital signs measured at unscheduled visits will be included for the baseline value selection.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-participant listing of vital signs will be provided by participant ID number and visit in chronological order. Body weight, height, and BMI will be included in the vital signs listing if space permits. If not, they will be provided separately.

7.4. Prior HBV and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior HBV Medications

Prior HBV medications are defined as any medications taken before a participant took any of the study drugs.

Prior HBV medications will be summarized by preferred name using the number and percentage of participants by cohort (and by treatment group for Cohort 2). A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred term in order of descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a participant took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of participants for each treatment group. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date, or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any

medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

7.5. Electrocardiogram Results

Electrocardiogram (ECG) analysis results are intended to identify meaningful abnormalities. If potential abnormalities of interest are identified, further analyses may be conducted.

A shift table of the investigators' assessment of ECG results at Weeks 12 and 36 for Cohort 1 and Cohort 2 Group A, or Weeks 12 and 24 for Cohort 2 Group B compared with baseline values will be presented by cohort (and by treatment group for Cohort 2) using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-participant listing for ECG assessment results will be provided by participant ID number and visit in chronological order.

7.6. Other Safety Measures

For Cohort 1 and Cohort 2 Group A, ophthalmic examinations will be performed at Screening, Week 24, and Week 36. For Cohort 2 Group B, ophthalmic examinations will be performed at Screening, Week 12, and Week 24.

A shift table of the overall assessment of ophthalmology results at each visit compared with baseline values will be presented for each cohort (and for each treatment group for Cohort 2) using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing/unknown. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

By-participant listings for ophthalmology assessment results will be provided by participant ID number and visit in chronological order.

8. PHARMACOKINETIC (PK) ANALYSES

Only SLGN PK Analysis will be performed for this study.

8.1. PK Sample Collection

For Cohort 1 and Cohort 2 Group A, sparse (timed) blood PK samples will be obtained at Baseline/Day1 (predose and postdose), Weeks 12 and 20 at any time between 1 to 5 hours postdose relative to SLGN administration unless otherwise indicated.

For Cohort 2 Group B, sparse (timed) blood PK samples will be obtained at Baseline/Day1, Weeks 12 and 20 at any time between 1 to 5 hours postdose relative to SLGN administration unless otherwise indicated.

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8.2. PK Analyses Related to Intensive PK Sampling

8.2.1. Estimation of PK Parameters

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

All predose sample times before time-zero will be converted to 0.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event 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 PK scientist on a profile-by-profile basis.

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

8.2.2. PK Parameters

PK parameters will be generated for all participants for whom parameters can be derived. The analyte presented in Table 8-1 will be evaluated if data are available

Table 8-1. Study Treatments and Associated Analyte

Treatment Group	Analyte
Cohort 1, Cohort 2 Group A, and Cohort 2 Group B	SLGN

The analyte and parameters presented in Table 8-2 will be used to evaluate the PK objectives of the study. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-2. PK Parameters for Each Analyte

Analyte	Parameters
SLGN	AUC_{last}, $AUC_{0-24,}$ AUC_{inf}, $\%AUC_{exp}$, C_{max}, T_{max}, C_{last}, T_{last}, λz, CL/F, and $t_{1/2,}$ as appropriate

Individual participant concentration data and individual participant PK parameters, as appropriate, for SLGN will be listed and summarized using descriptive statistics by cohort (and by treatment group for Cohort 2). Summary statistics (number of participants, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual participant concentration data by time point and individual participant PK parameters by cohort (and by treatment group for Cohort 2). Moreover, the geometric mean, 95% CI, %Geometric CV [%GCV], and the mean and SD of the natural log-transformed values will be presented for individual participant PK parameter data.

Individual concentration data listings and summaries will include all participants with concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ, as well as an indicator if more than one-third of the participants are BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as zero at predose and postdose time points. If more than one-third of the values at a postdose time point are BLQ then the mean and SD will not be presented at that time point. Concentration values will be presented as received from the bioanalytical lab and summary statistics will be presented to three significant digits.

Individual PK parameter data listings and summaries will include all participants for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of participants with nonmissing data for that PK parameter. Data and summary statistics will be presented to three significant digits.

The following tables will be provided by cohort (and by treatment group for Cohort 2):

- Individual participant concentration data and summary statistics
- Individual participant plasma PK parameters and summary statistics

The following figures may be provided by cohort (and by treatment group for Cohort 2):

- Individual participant concentration data versus time (on linear and semilogarithmic scales). Values of BLQ will be displayed as 0 on the linear scale and missing on the semi-logarithmic scale.
- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales). If more than one-third of the values at a postdose time point are BLQ then the mean and SD will not be presented at that time point and remaining points connected. If lower error bar (mean-SD) is < 0 at a timepoint then it will not be presented at that timepoint.
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales). If more than one-half of the values at a timepoint are BLQ then the median and quartile values will not be presented at that timepoint, and remaining points connected. If lower error bar (Q1) is BLQ at a timepoint then it will be presented as lower LOQ at that timepoint.

The following listings will be provided:

- PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age from the combined intensive and sparse PK samples.
- Individual data on determination of plasma half-life and corresponding regression correlation coefficient

8.3. PK Analyses Related to Sparse PK Sampling

For PK Analysis Set, sparse (*timed*) PK data will be summarized by visit and time point, if appropriate. Individual participant concentration data will be listed and summarized using descriptive statistics by cohort. Summary statistics (n, mean, SD, percent coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for individual participant concentration data by visit and by cohort (and by treatment group for Cohort 2).

Individual concentration data listings and summaries will include all participants with concentration data. The sample size for each visit will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and postdose time points.

The following tables will be provided for SLGN by cohort (and by treatment group for Cohort 2):

- Individual participant concentration data and summary statistics

The following listing will be provided for SLGN:

PK sampling details by participant (using concentration data from all sparse and intensive plasma PK sampling), including procedures, differences in scheduled and actual draw times, and sample age.

8.4. Changes From Protocol-Specified PK Analyses

For summary statistics, PK concentration values below the limit of quantitation will be treated as zero at predose and postdose time points, rather than being treated as zero at predose and one-half of the LLOQ for postdose time points.

9. REFERENCES

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10. SOFTWARE

SAS® Software Version 9.X. SAS Institute Inc., Cary, NC, USA.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Schedule of Assessments

Appendix Table 1. Study Procedures Table for NUC-Suppressed Cohort 1

	Screening (45 days)	Baseline Day 1	Treatment Cycles Week (± 2 days) [a]										EOT (−5 days)		Follow-up Weeks[b]							
			4	8	12	13[c]	14	16	20	24	28	32	36/EOT	ED[d]	1[c]	4	8[c]	12	16[c]	24	36	48
Written Informed Consent[e]	X																					
Review of Inclusion/Exclusion Criteria	X																					
Medical History	X																					
AEs & Concomitant Medications[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X	X			X								X	X								
Symptom-directed physical examination			X	X			X	X	X	X	X	X				X		X		X	X	X
Vital signs	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Height	X																					
Body weight	X	X			X			X	X	X	X	X	X	X								X
12-lead ECG[g]	X	X			X								X	X								X
Chest x-ray	X													X[h]								
Ophthalmologic examination[i]	X									X			X	X[h]								
Symptom-directed ophthalmologic examination		X	X	X			X	X	X		X	X				X		X		X	X	X
Safety laboratory tests (hematology & chemistry; coagulation)	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
APRI	X	X			X								X	X				X				X

	Screening (45 days)	Baseline Day 1	Treatment Cycles Week (± 2 days) [a]										EOT (−5 days)		Follow-up Weeks[b]							
			4	8	12	13[c]	14	16	20	24	28	32	36/EOT	ED[d]	1[c]	4	8[c]	12	16[c]	24	36	48
FibroTest	X	X			X								X	X				X				X
FibroScan[j]	X																					
α-fetoprotein (HCC imaging [eg, CT scan] is required for participants with α-fetoprotein ≥ 50 ng/mL at screening)	X																					
Serology testing to exclude HCV, HDV, and HIV infection[k]	X																					
Quantitative plasma HBV DNA	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Serum sample for HBV viral sequencing (resistance surveillance) and ddPCR	X																					
Serum sample for HBV viral sequencing (resistance surveillance) and genotyping sample		X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Quantitative HBV Serum HBsAg, HBcrAg, HBeAg, and HBV RNA	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Qualitative HBV serology HBeAg, HBeAb, and HBsAg, HBsAb	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X

	Screening (45 days)	Baseline Day 1	Treatment Cycles Week (± 2 days) [a]										EOT (−5 days)		Follow-up Weeks[b]							
			4	8	12	13[c]	14	16	20	24	28	32	36/EOT	ED[d]	1[c]	4	8[c]	12	16[c]	24	36	48
Biomarker Samples: Collection of PBMC, whole blood, serum, and plasma samples for biomarker analysis[l, m]		X			X[l]		X					X[m]								X		
Sparse PK for VIR-2218[n]		X			X				X													
Sparse PK for SLGN[n]					X				X			X										
Estimated creatinine clearance (using the Cockcroft-Gault method)	X	X			X								X	X								X
Urinalysis	X	X	X	X	X			X	X	X	X	X	X	X								
Urine Drug and Alcohol Screen	X																					
Autoantibodies	X																					
TSH	X									X			X	X								
FSH[o]	X																					
Serum Pregnancy Test[p]	X													X								
Urine Pregnancy Test[p]		X	X	X	X			X	X	X	X	X	X			X	X[p]	X	X[p]	X	X	X
Enrollment		X																				
Dispense and Administer TAF as appropriate		Tenofovir alafenamide (TAF) 25-mg tablet administered orally daily for up to 84 weeks																				

	Screening (45 days)	Baseline Day 1	Treatment Cycles Week (± 2 days) [a]										EOT (−5 days)	ED[d]	Follow-up Weeks[b]							
			4	8	12	13[c]	14	16	20	24	28	32	36/EOT		1[c]	4	8[c]	12	16[c]	24	36	48
Dispense & Administer VIR-2218 SC as appropriate		X	X	X	X			X	X													
Dispense & Administer SLGN[q] as appropriate					X	X	X	X	X	X	X	X										
Study Drug Accountability			X	X	X		X	X	X	X	X	X	X									
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AE = adverse event; APRI = AST to Platelet Ratio Index; CT = computed tomography; ddPCR = digital droplet polymerase chain reaction; ECG = electrocardiogram; ED = early discontinuation; EOT = end of treatment; FSH = follicle-stimulating hormone; FU = follow-up; HBcrAg = hepatitis B core-related antigen; HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus;
IV = intravenous; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous; SLGN = selgantolimod; TAF = tenofovir alafenamide;
TSH = thyroid-stimulating hormone

a All study visits except for Weeks 13 and 14.
b FU Week 1 will have a visit window of + 3 days, FU Weeks 4 through FU Week 16 will have a visit window of ± 5 days, and FU Weeks 24 through FU Week 48 will have a visit window of ± 14 days.
c Week 13, FU Week 1, FU Week 8, and FU Week 16 will be conducted as a virtual/telephonic visit to review AEs, concomitant medications, and overall health of the participant by investigator.
d The ED visit should be performed within 14 days from notification of study discontinuation. If ED is done in FU period, all of these procedures should be performed.
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f Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the informed consent form. After drug administration, report all AEs and SAEs.
g Participants must rest quietly in the supine position for a minimum of 5 minutes prior to the recording.

h At ED visit, these procedures are optional and to be done as needed.
i Ophthalmologic examination at screening should be performed during the screening window, ie, within 45 days of randomization. Ophthalmologic examinations post-Day 1 should occur within −4
j to +10 days of visit.
k FibroScan testing where applicable for liver disease staging.
l In the event of a positive result for serology and/or antigen testing for HIV, HDV, or HCV, reflex tests will be performed as necessary.
m Collect pre-SLGN dose administration on Week 12, 4 hours and 24-72 hours postdose.
n Collect pre-SLGN dose administration on Week 32, 4 hours, and 24-72 hours postdose.
o The sparse PK collection for VIR-2218 at baseline/Day 1 should occur predose and postdose. Postdose sparse PK collection should occur any time between 1 and 5 hours postdose relative to VIR-2218, and/or SLGN administration.
p FSH test is required for female participants who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of
q ovarian hormonal failure.

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s SLGN tablets will be administered while fasting once a week, on the same day.

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u Intensive PK sample to be drawn at any one visit at Week 20, 24, 28 or 32 **relative to SLGN** dosing in clinic on the morning of the intensive PK visit. Collection will occur at predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, 10, 12 and 24 hours postdose CCI
v Intensive PK sample to be drawn on Baseline/Day 1 and at Week 20 **relative to VIR-2218** dosing in clinic on the morning of the intensive PK visit. Collection will occur at predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, 10, 12 and 24 hours postdose CCI

Appendix Table 2. Study Procedures Table for NUC-Suppressed Cohort 2

			Treatment Cycles Week (± 2 days)[a]												EOT (−5 days)		Follow-up Weeks[b]							
			Cohort 2 Group B only									Cohort 2 Group A only												
	Screening (45 days)	BL Day 1	1[c]	2[d]	4	8	12	13[c]	14	16	20	24	28	32	24 (Cohort 2 Group B) / 36 (Cohort 2 Group A)	EDe	1[b,c]	4	8[c]	12	16	24	36	48
Written Informed consent[f]	X																							
Review of Inclusion/ Exclusion Criteria	X																							
Medical History	X																							
AEs & Concomitant Medications[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X	X					X								X	X								
Symptom- directed physical examination					X	X			X	X	X	X	X	X		X		X	X	X		X	X	X
Vital signs	X	X		X (Cohort 2 Group B)	X	X	X		X	X	X	X	X	X	X	X		X	X	X		X	X	X
Height	X																							
Body weight	X	X			X (Cohort 2 Group B)	X (Cohort 2 Group B)	X			X	X	X	X	X	X	X								X
12-lead ECG[h]	X	X					X								X	X								X
Chest x-ray	X															X[i]								
Ophthalmologic examination[j]	X						X (Cohort 2 Group B)					X			X	X[i]								
Symptom-directed ophthalmologic examination		X			X	X			X	X	X		X	X				X		X		X	X	X

			Treatment Cycles Week (± 2 days)[a]												EOT (−5 days)		Follow-up Weeks[b]							
			Cohort 2 Group B only									Cohort 2 Group A only			24 (Cohort 2 Group B) / 36 (Cohort 2 Group A)									
	Screening (45 days)	BL Day 1	1[c]	2[d]	4	8	12	13[c]	14	16	20	24	28	32		EDe	1[b,c]	4	8[c]	12	16	24	36	48
Safety laboratory tests (hematology & chemistry; coagulation)	X	X			X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
APRI	X	X					X								X	X				X				X
FibroTest	X	X					X								X	X				X				X
FibroScan[k]	X																							
α-fetoprotein (HCC imaging [eg, CT scan] is required for participants with α-fetoprotein ≥ 50 ng/mL at screening)	X																							
Serology testing to exclude HCV, HDV, and HIV infection[l]	X																							
Quantitative plasma HBV DNA	X	X			X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Serum sample for HBV viral sequencing (resistance surveillance) and ddPCR	X																							
Serum sample for HBV viral sequencing (resistance surveillance) and genotyping sample		X			X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X

			Treatment Cycles Week (± 2 days)[a]												EOT (−5 days)		Follow-up Weeks[b]							
			Cohort 2 Group B only									Cohort 2 Group A only			24 (Cohort 2 Group B) / 36 (Cohort 2 Group A)									
	Screening (45 days)	BL Day 1	1[c]	2[d]	4	8	12	13[c]	14	16	20	24	28	32		EDe	1[b,c]	4	8[c]	12	16	24	36	48
Quantitative HBV Serum HBsAg, HBcrAg, HBeAg, and HBV RNA	X	X			X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Qualitative HBV serology HBeAg, HBeAb, and HBsAg, HBsAb	X	X			X	X	X		X	X	X	X	X	X	X	X		X		X		X	X	X
Biomarker Samples: Collection of PBMC, whole blood, serum and plasma samples for biomarker analysis[m,n]		X[m,n]		X[n]			X[m]		X[m]		X[n]			X[m]								X		
Sparse PK for VIR-2218[o]		X					X				X													
Sparse PK for SLGN[p]		X[p]					X				X			X[p]										
Estimated creatinine clearance (using the Cockcroft-Gault method)	X	X					X								X	X								X
Urinalysis	X	X			X	X	X			X	X	X	X	X	X	X								
Urine Drug and Alcohol Screen	X																							
Autoantibodies	X																							
TSH	X						X (Cohort 2 Group B)					X			X	X								
FSH[q]	X																							

	Screening (45 days)	BL Day 1	Treatment Cycles Week (± 2 days)[a]												EOT (−5 days)		Follow-up Weeks[b]							
			Cohort 2 Group B only								Cohort 2 Group A only				24 (Cohort 2 Group B) / 36 (Cohort 2 Group A)	EDe								
			1[c]	2[d]	4	8	12	13[c]	14	16	20	24	28	32			1[b,c]	4	8[c]	12	16	24	36	48
Serum Pregnancy Test[r]	X															X								
Urine Pregnancy Test[r]		X			X	X	X			X	X	X	X	X	X			X	X[r]	X	X	X	X	X
Enrollment		X																						
Dispense & Administer VIR-2218 SC as appropriate (Group A only)		X			X	X	X			X	X													
Dispense & Administer SLGN[s] as appropriate (Group A only)							X	X	X	X	X	X	X	X										
Dispense & Administer SLGN[s] as appropriate (Group B only)		X	X	X	X	X	X	X	X	X	X													
Study Drug Accountability					X	X	X		X	X	X	X	X	X	X	X								

[redacted]

AE = adverse event; APRI = AST to Platelet Ratio Index; BL = baseline; CT = computed tomography; ddPCR = digital droplet polymerase chain reaction; ECG = electrocardiogram; ED = early discontinuation; EOT = end of treatment; FSH = follicle-stimulating hormone; FU = follow-up; HBcrAg = hepatitis B core-related antigen; HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus; IV = intravenous; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; SAE = serious adverse event; SC = subcutaneous; SLGN = selgantolimod; TAF = tenofovir alafenamide; TSH = thyroid-stimulating hormone

a All study visits (± 2 days), except for Weeks 1, 2, 13, and 14.
b FU Week 1 will have a visit window of ± 2 days, FU Weeks 4 through FU Week 16 will have a visit window of ± 5 days, and FU Weeks 24 through FU Week 48 will have a visit window of ± 14 days.
c Week 1 (Cohort 2 Group B only), Week 13 (Cohort 2 Group A only), and FU Week 1, Week 8, and Week 16 will be conducted as a virtual/telephonic visit to review AEs, concomitant medications, and overall health of the participant by investigator.
d Week 2 visit is only applicable for Cohort 2 Group B.
e The ED visit should be performed within 14 days from notification of study discontinuation.
f Obtain written informed consent, including Main Informed Consent, CCI
g Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form. After drug administration, report all AEs and SAEs.
h Participants must rest quietly in the supine position for a minimum of 5 minutes prior to the recording.
i At ED visit, these procedures are optional and to be done as needed.
j Ophthalmologic examination at screening should be performed during the screening window, ie, within 45 days of randomization. Ophthalmologic examinations post-Day 1
k should occur within −4 to +10 days of visit.
l FibroScan testing where applicable for liver disease staging.
m In the event of a positive result for serology and/or antigen testing for HIV, HDV, or HCV, reflex tests will be performed as necessary.
n Cohort 2 Group A biomarker collection. Collect pre-SLGN dose administration at Baseline/Day 1, Week 12, 4 hours and 24-72 hours postdose. Collect at Week 14, predose.
o Collect pre-SLGN dose administration at Week 32, 4 hours and 24-72 hours postdose.
p Cohort 2 Group B biomarker collection. Collect pre-SLGN dose administration on Baseline/Day 1, 4 hours and 24-72 hours postdose. Collect at Week 2, pre-dose. Collect pre-SLGN dose administration at Week 20, 4 hours and 24-72 hours postdose.
q The sparse PK collection for VIR-2218 at baseline/Day 1 should occur predose and postdose. Postdose sparse PK collection for VIR-2218 should occur any time between 1 and 5 hours postdose relative to VIR-2218 administration.
r Sparse PK collection for SLGN should occur any time between 1 and 5 hours postdose relative to SLGN administration. The collection at Baseline/Day 1 is only applicable to Cohort 2 Group B. The collection at Week 32 is only applicable to Cohort 2 Group A.

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x For Group A, intensive PK sample to be drawn at any one visit at Week 20, 24, 28 or 32 **relative to SLGN** dosing in clinic on the morning of the intensive PK visit. For Group B, sample will be collected Week 12 or later **relative to SLGN** dosing in clinic on the morning of the intensive PK visit.
y Group A and B: Collection will occur at Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, 10, 12 and 24 hours postdose CCI
z For Group A only, intensive PK sample to be drawn on Baseline/Day 1 and at Week 20 **relative to VIR-2218** dosing in clinic on the morning of the intensive PK visit.

Appendix 2. Data Collection and Determination of COVID-19 Data

This appendix describes the clinical trial site collection of COVID-19 data and the data processing algorithm that will be used to determine COVID-19 related information from CRF comment fields.

12.1. Data Collection

Missed or virtual visits due to COVID-19 will be collected through the visit date CRF page. However, some COVID-19 related information will be collected via CRF comment fields (eg. comments related to study drug or study discontinuation due to COVID-19, missed key assessment due to COVID-19).

12.2. Determination of COVID-19 Related Information from CRF Comment

Natural Language Processing (NLP) will be used to search the CRF comment fields to identify instances of "COVID-19", "Virtual", or synonyms (see Appendix Table 3). The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. If COVID-19 and Virtual terms are identified through NLP, it will help the determination of study drug or study discontinuation due to COVID-19 for certain reasons (eg. participant decision, withdrew consent, or investigator discretion), and provide supplemental information to determine missed key assessments due to COVID-19.

Appendix Table 3. Example Search Terms for "COVID-19" and "Virtual"

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

Appendix 3. List of Nucleos(t)ide (NUC) Therapy

ENTECAVIR
TELBIVUDINE
TENOFOVIR
TENOFOVIR ALAFENAMIDE
TENOFOVIR ALAFENAMIDE FUMARATE
TENOFOVIR DISOPROXIL FUMARATE
LAMIVUDINE

GS-US-465-4439-SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Global Development Lead (GDL) eSigned	18-Apr-2024 21:44:05
PPD	Biostatistics eSigned	19-Apr-2024 13:44:34