Official Title: A Phase 2 Study Evaluating the Efficacy and Safety of VIR-3434 and/or VIR-2218 Containing Regimens in Participants with Chronic Hepatitis B Infection (STRIVE)

NCT Number: NCT05612581

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STATISTICAL ANALYSIS PLAN AMENDMENT (VERSION 2.0)

Study Title	A Phase 2 Study Evaluating the Efficacy and Safety of VIR-3434 and/or VIR-2218 Containing Regimens in Participants with Chronic Hepatitis B Infection (STRIVE)
Brief Title	A Phase 2 Study to Evaluate VIR-3434 and/or VIR-2218 Containing Regimens for Treatment of Chronic Hepatitis B Infection
Master Study Number	VIR-MHB1-V200
Sub-Study Number	VIR-SHB1-V201
Compound	VIR-3434 (tobevibart), VIR-2218 (elebsiran), tenofovir disoproxil fumarate (TDF) and pegylated interferon alfa-2a (PEG-IFNα)
Indication	Chronic Hepatitis B Infection
Study Phase	2
Study Sponsor	Vir Biotechnology, Inc. 1800 Owens Street, Suite 900 San Francisco, CA 94158, USA
Effective Date	22 July 2024, SAP Original Version 1.0 02 May 2025, SAP Amendment Version 2.0

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

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VERSION HISTORY

This statistical analysis plan (SAP) amendment v2.0 for the sub-study STRIVE is based on the original approved SAP version v1.0. The table below summarizes the main updates.

SAP Version	Date	Section	Change
v1.0	22 July 2024	Original approved version	--
v2.0	02 May 2025	Refer to Section 4.10.2	Refer to Section 4.10.2

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is to describe the planned analyses to be included in the clinical study report (CSR) for VIR-SHB1-V201 (STRIVE). The following documents were reviewed in preparation for this SAP:

- Master Protocol VIR-MHB1-V200 (PREVAIL), Amendment 2, 11Oct2022, Version 3.0
- Sub-study Protocol VIR-SHB1-V201 (STRIVE), Amendment 3, 14Dec2023, Version 1.0
- Electronic case report form (eCRF), Version 5 and eCRF completion guidelines (CCG).

This SAP documents the planned statistical analyses of efficacy, safety and tolerability, pharmacokinetic (PK) endpoints and immunogenicity endpoints for the interim analyses (IAs) and the final analysis of Study VIR-SHB1-V201 (STRIVE) data. In addition, some exploratory endpoint analyses may be documented in this SAP as well to provide supportive information for the scientific understanding of the study intervention entity.

The VIR Biometrics team and a designated contract research organization (CRO) will perform the statistical analysis.

This SAP will be finalized and approved prior to the first Interim Analysis (IA) data cutoff date. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP. Important changes to the SAP after the database lock for the final analysis, along with justifications for the changes, will be described in the CSR. Changes to the protocol will require an SAP amendment ONLY if the changes are to a principal feature of the protocol. Any post hoc or unplanned analyses that are performed and not specifically specified in this SAP will be clearly identified as such if they are included in the CSR.

1.1. Objectives and Endpoints

Table 1: Objectives and Endpoints

Objectives	**Endpoints**
Primary	
• To evaluate the efficacy of VIR-3434 and tenofovir disoproxil fumarate (TDF) with or without VIR-2218, or VIR-2218 and PEG-IFNα	• Proportion of participants achieving suppression of HBV DNA (< lower limit of quantitation [LLOQ]) with HBsAg loss (< 0.05 IU/mL) at the end of treatment
Secondary	
• To evaluate the safety and tolerability of the investigational regimens • To assess the effect of the investigational regimens on serum hepatitis B surface antigen (HBsAg)	1. Proportion of participants with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) 2. Proportion of participants with serum HBsAg ≤ 10 IU/mL at the end of treatment

Objectives	Endpoints
• To assess the effect of the investigational regimens on anti-HBs • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBsAg • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBV DNA • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBeAg and anti-HBe • To assess the immunogenicity of VIR-3434 • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on ALT levels	3. Proportion of participants with serum HBsAg ≤ 10 IU/mL at 24 weeks post-end of treatment 4. Serum HBsAg levels and change from baseline across timepoints in the study 5. Serum HBsAg level at nadir during the study 6. Time to achieve nadir of serum HBsAg during the study 7. Time to achieve serum HBsAg loss (< 0.05 IU/mL) 8. Proportion of participants with HBsAg loss and anti-HBs seroconversion at end of treatment and at 24 weeks post-end of treatment 9. Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) after discontinuation of all treatment a. at 24 weeks b. at the F48 Follow-Up visit 10. Proportion of participants achieving HBsAg loss (< 0.05 IU/mL) a. at end of treatment b. at 24 weeks post-end of treatment 11. Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) after discontinuation of all treatment a. at 24 weeks b. at the F48 Follow-Up visit 12. For HBeAg-positive participants: proportion of participants with HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion 13. Incidence and titers of anti-drug antibodies (ADA; if applicable) to VIR-3434

Objectives	Endpoints
	14. Mean change in serum HBsAg level from baseline across timepoints in the study 15. Proportion of participants achieving HBV DNA < LLOQ across timepoints in the study 16. Proportion of participants achieving ALT ≤ ULN across timepoints in the study
Exploratory	
• To evaluate additional viral parameters associated with HBV and/or study intervention(s) • CCI [redacted] • CCI [redacted] • To evaluate the emergence of viral resistance to study intervention(s) • CCI [redacted] • CCI [redacted] • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBeAg and anti-HBe • To evaluate proportion of participants meeting criteria for nucleos(t)ide reverse	1. Additional viral parameters associated with HBV and/or study intervention(s), including but not limited to HBV RNA and Hepatitis B core-related antigen (HBcrAg) 2. CCI [redacted] 3. CCI [redacted] 4. Emergence of viral resistance to study intervention(s) 5. CCI [redacted] 6. CCI [redacted] 7. For HBeAg-positive participants: time to achieve HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion 8. Proportion of participants meeting criteria for NRTI discontinuation or retreatment in the study

Objectives	Endpoints
transcriptase inhibitor (NRTI) discontinuation or retreatment • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBV DNA • To characterize the pharmacokinetics (PK) of VIR-3434 • To characterize the PK of VIR-2218 (for cohorts with VIR-2218) • To assess the immunogenicity of VIR-2218 (for cohorts with VIR-2218) • To assess the effect of duration of treatment of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα • To assess potential virological relapse	9. HBV DNA levels and change from baseline across timepoints in the study 10. Nadir and maximum change of HBV DNA level from baseline in the study 11. VIR-3434 PK parameters 12. VIR-2218 PK parameters (for cohorts with VIR-2218) 13. Incidence and titers of ADA (if applicable) to VIR-2218 (for cohorts with VIR-2218) 14. Proportion of participants with virological relapse (defined as either (1) an increase of ≥ 1 log10 HBV DNA IU/mL above nadir for at least 2 consecutive visits OR (2) quantifiable HBV DNA of ≥ 1 log10 IU/mL above LLOQ for at least 2 consecutive visits after being < LLOQ)

1.2. Study Design

1.2.1. Overall Design

STRIVE is a Phase 2, multi-center, open-label study designed to evaluate the safety and efficacy of regimens containing VIR-3434, VIR-2218, PEG-IFNα, and NRTI (TDF/TD)[1] in non-cirrhotic adult participants with chronic HBV infection who have not received prior NRTI or PEG-IFNα treatment. The study is planned to be conducted at multiple clinical investigative sites globally.

The STRIVE sub-study is intended to evaluate up to 48-week regimens of VIR-3434 and NRTI, VIR-3434 and NRTI in combination with VIR-2218, and VIR-3434 and NRTI in combination with both VIR-2218 and PEG-IFNα in participants with chronic HBV infection. Study populations II and III in Table 2 as defined in the Master Protocol will be included in this sub-study. Participants who have not received any prior NRTI treatment will be eligible for enrollment into this sub-study.

Table 2: Study Population

Master Protocol Population	HBeAg Status	HBV DNA Level	ALT Level
II	Positive	> 2,000 IU/mL	> ULN and ≤ 5x ULN

[1] In STRIVE, NRTI refers to Tenofovir disoproxil fumarate dose (TDF) or Tenofovir disoproxil (TD). TDF will be supplied in the United States, TD will be supplied outside the United States.

III	Negative	> 2,000 IU/mL	> ULN and ≤ 5x ULN

1.2.2. Number of Participants

Up to 90 participants are planned to be enrolled in this sub-study. Cohorts 1a, 2a, and 3a will each enroll approximately 10 participants. Cohorts 4a and 5a will each enroll approximately 15 participants. Additionally, up to 30 floater participants may be added to any cohort at any time at the Sponsor's discretion.

1.2.3. Intervention Groups and Duration

There are 5 cohorts planned in this sub-study.

Table 3: Intervention Groups

Cohort	Study Drug	Dose	Route	Number of Doses	Frequency of Dosing
1a	VIR-3434	300 mg	SC	12	Every 4 weeks
	TDF	300 mg [b]	Oral	≥ 308 [c]	Every day
2a	VIR-3434	Up to 300 mg [a]	SC	12	Every 4 weeks
	TDF	300 mg [b]	Oral	≥ 308 [c]	Every day
3a	VIR-3434	300 mg	SC	4-6 [d]	Every 8-12 weeks[d]
	TDF	300 mg [b]	Oral	≥ 252 [c]	Every day
4a	VIR-3434	300 mg	SC	12	Every 4 weeks
	VIR-2218	200 mg	SC	12	Every 4 weeks
	TDF	300 mg [b]	Oral	≥ 308 [c]	Every day
5a	VIR-3434	300 mg	SC	13	Every 4 weeks
	VIR-2218	200 mg	SC	13	Every 4 weeks
	PEG-IFNα	180 mcg	SC	48	Every week
	TDF	300 mg [b]	Oral	≥ 336 [c]	Every day

[a] The dose of VIR-3434 will be determined before participants are enrolled in the cohort.
[b] Tenofovir disoproxil fumarate dose (TDF) will be 300 mg as approved by the FDA. Supply outside the United States may be Tenofovir disoproxil (TD) 245 mg.
[c] The minimum number of doses received by participant. Participants will continue receiving additional doses of TDF until they qualify for NRTI discontinuation.
[d] The dosing regimen will be finalized before participants are enrolled in the cohort.

The total duration in the study for participants will be up to 100 weeks in cohorts 1a, 2a, and Cohort 4a, 92-96 weeks for Cohort 3a, and 104 weeks for Cohort 5a. This includes a Screening Period (up to 56 days or 8 weeks), Treatment Period (44 weeks for cohorts 1a and 2a, 36 or

40 weeks for Cohort 3a, 44 weeks for Cohort 4a, and 48 weeks for Cohort 5a) and a Follow-Up Period (up to 48 weeks) for all cohorts.

Once participants complete the Treatment Period per their respective cohort, they will enter the Follow-Up Period. Participants will discontinue the NRTI at the F1 or F12 visit in the Follow-Up Period if they meet the criteria to discontinue NRTI (Section 1.2.4) based on the data available. Additional study visits are required for participants who discontinue NRTI in the Follow-Up Period as indicated in the SOA in the study protocol. Participants who discontinue NRTI at F1 visit will be required to return to the site for additional visits at F2, F6, F10, F28, F32, F40, and F44. Participants who discontinue NRTI at F12 visit will be required to return to the site for additional visits at F14, F18, F22, F28, F32, F40, and F44.

1.2.4. NRTI Discontinuation

Participants will discontinue NRTI at F1 or at F12 Follow-Up visits based on the most recent data available if they meet all of the following criteria:

- HBsAg < LLOQ
- Suppressed HBV DNA (defined as < LLOQ)
- Undetectable HBeAg (based on quantitative HBeAg)
- ALT ≤ 2 times the upper limit of normal (ULN).

Participants who meet the criteria to discontinue NRTI treatment will continue to be followed? per the Follow-Up Period SOA. Participants who meet NRTI discontinuation criteria but are not appropriate for NRTI discontinuation due to other reasons, based on the opinion of the Investigator, may continue on NRTI treatment following discussion with the Sponsor Medical Monitor to document the rationale for continuing NRTI.

Participants who do not qualify for NRTI discontinuation will continue taking the NRTI until the end of the Follow-Up Period. Once a participant has completed the study, long-term care should be determined by the Investigator or primary treating physician based on local clinical guidelines.

1.2.5. NRTI Retreatment

It is recommended that NRTI therapy be reinitiated in participants during the Follow-Up Period if they meet any of the following criteria:

- HBV DNA increase ≥ 2 $\log_{10}$ IU/mL within a 2-week period
- HBV DNA > 100,000 IU/mL at any Follow-Up Period visit (regardless of other biochemical parameters or ALT values)
- Confirmed increase of HBV DNA > 20,000 IU/mL (i.e., at 2 consecutive collections, regardless of other biochemical parameters or ALT values)
  - Note: The repeat HBV DNA test should be performed as soon as possible and no later than 7 calendar days after the initial result is received. Central laboratory testing is preferred, but local laboratory results will be accepted if it is not feasible to collect central laboratory results in time.

- HBV DNA > 2,000 IU/mL concurrent with any of the following criteria at the same visit:
  - Confirmed total bilirubin > 2x ULN and ALT > ULN
  - Any sign of hepatic decompensation (including, but not limited to, confirmed increase in prothrombin time [PT] ≥ 2 or international normalized ratio [INR] ≥ 0.5 from baseline, jaundice, ascites, encephalopathy, etc.)
  - ALT > 10x ULN
  - ALT > 2x ULN persisting for ≥ 12 consecutive weeks
  - ALT > 5x ULN persisting for ≥ 4 consecutive weeks
- Confirmed HBeAg seroreversion (i.e., HBeAg positive after being HBeAg negative at NRTI discontinuation)
- Any other clinically significant event(s) warranting initiation of NRTI therapy in the opinion of the investigator after discussion with the Sponsor

Participants who are retreated with NRTI therapy should continue to be followed per the SOA for the Follow-Up Period through the Week 48 visit. Participants with HBV DNA increase ≥ 2 $\log_{10}$ IU/mL within a 2-week period should:

- return to the site for an unscheduled visit to measure HBV DNA levels and liver function tests as soon as possible after the investigator becomes aware of the HBV DNA increase
- continue returning weekly until HBV DNA levels stabilize (do not increase ≥ 1 $\log_{10}$ IU/mL over a 4-week period or start decreasing for at least 2 consecutive visits), after which they should continue per the SOA for the Follow-Up Period

If any unscheduled visits needed as outlined above coincide with an existing visit per the Follow-Up Period SOA, then the Follow-Up visit assessments should be conducted.

1.2.6. Study Schema

Eligible participants will be assigned via Interactive Response Technology (IRT) to one of the open cohorts. If a participant is ineligible to receive PEG-IFNα (Cohort 5a), they will be assigned to one of the other open cohorts.

The overall study scheme is presented in Figure 1 and the dosing scheme for all the cohorts is shown in Figure 2.

Figure 1: PREVAIL Sub-study STRIVE Study Schema

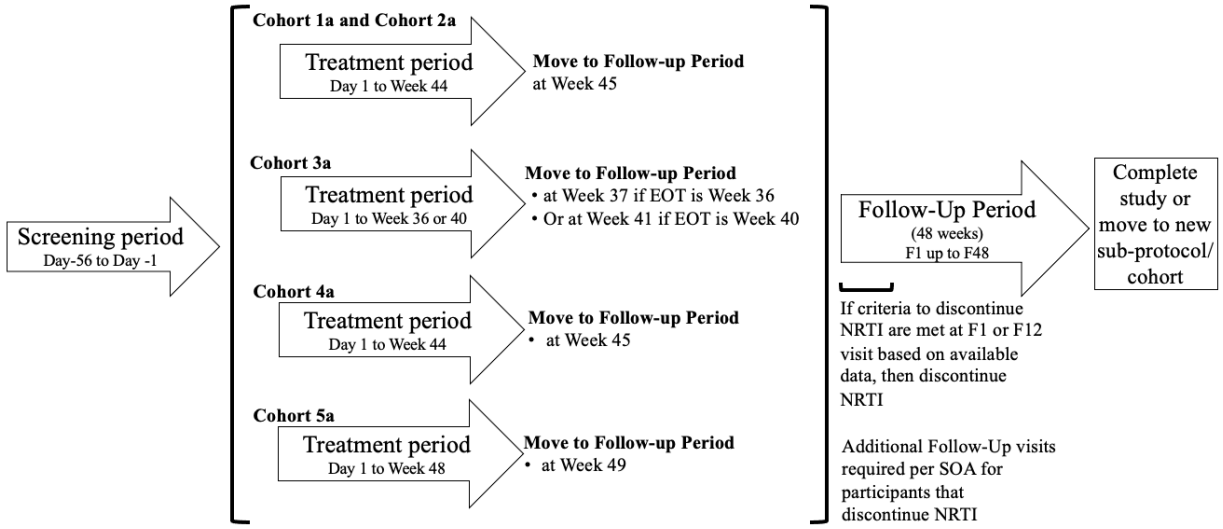
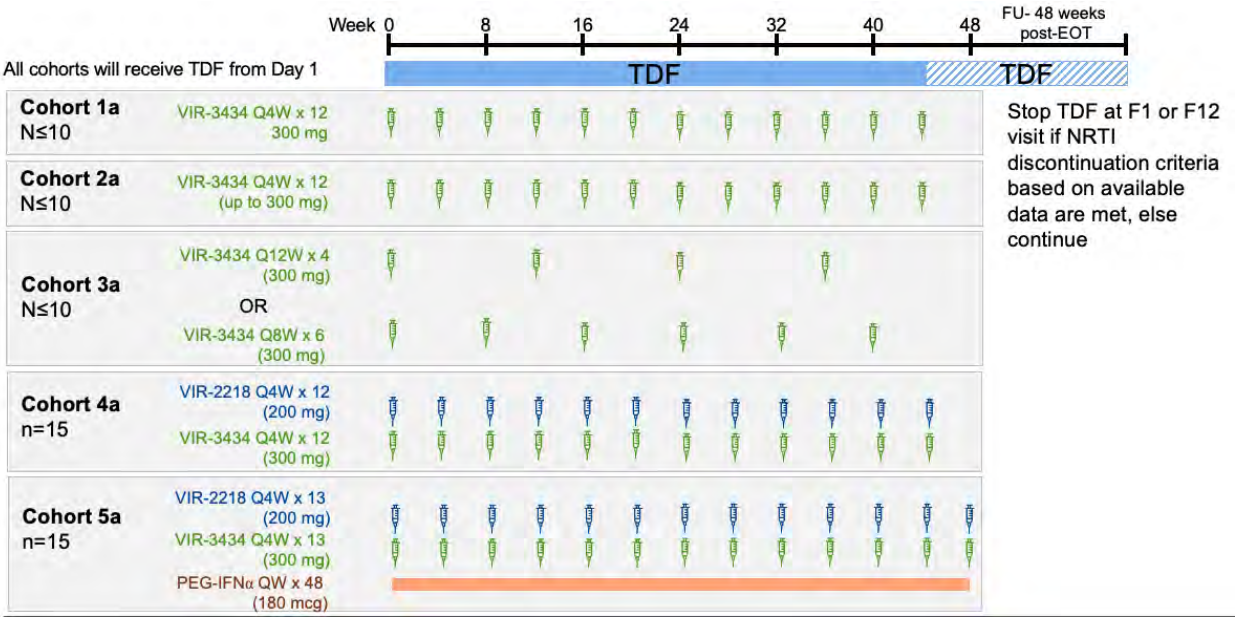


Figure 2: PREVAIL Sub-study STRIVE Dosing Scheme by Cohort



FU = Follow-Up; EOT = end of treatment; QW = every week; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; PEG-IFNα = pegylated interferon alfa-2a; TDF = Tenofovir disoproxil fumarate (or Tenofovir disoproxil where applicable); F1 = Follow-Up Visit 1; F12 = Follow-Up visit 12

2. STATISTICAL HYPOTHESES

This study is exploratory in nature, and no hypothesis testing or multiplicity adjustment will be conducted.

3. ANALYSIS SETS

For the purposes of analysis, the participant analysis sets are defined in **Table 4**.

Table 4: Participant Analysis Set

Participant Analysis Set	Description
All Enrolled Set	The All Enrolled Set includes all participants who signed the informed consent form and were assigned to study intervention. Summaries for disposition, demographics and baseline characteristics will be reported based on the All Enrolled Set.
Full Analysis Set (FAS)	The FAS includes all participants in the All Enrolled Set who received at least one dose of study intervention(s). This set is the primary endpoint analysis set for efficacy and antiviral analyses. Participants will be analyzed according to the study intervention assigned.
Safety Analysis Set	The Safety Analysis Set includes all participants who received any amount of study intervention. All safety analyses will be based on the Safety Analysis Set. Participants will be analyzed according to the study intervention received.
PK Analysis Set	The PK Analysis Set includes all participants in the FAS who had at least one measurable post-dose concentration. The PK Analysis Set will be used for all PK analyses.
Immunogenicity Analysis Set	The Immunogenicity Analysis Set includes all participants in the FAS who had pre-dose and at least one post-dose measurement of immunogenicity, including screening, titers, or neutralizing characterization, as applicable. The Immunogenicity Analysis Set will be used for analyses of the immunogenicity endpoints.

For the efficacy endpoints, no participants in the FAS will be excluded from the efficacy analysis.

Three interim analyses (IAs) will be conducted for each cohort to evaluate the efficacy endpoints at Week 24, EOT, and 24 weeks post-EOT when all participants in the cohort have completed the respective visits. All participants who enrolled or received any amount of study intervention prior to the data cutoff date will be in the scope of the IAs. All data reported on or before the data cutoff date will be included in the IAs. The participant analysis sets for IAs are defined in Table 5.

Table 5: Interim Analysis Set

Participant Analysis Set	Description
Interim Full Analysis Set 1 (iFAS1)	The iFAS1 will include participants in the FAS whose scheduled Week 24 Visit is before or on the IA1 data cutoff date.

	This set also includes the FAS participants who prematurely discontinued the study intervention prior to the IA1 data cutoff date.
Interim Safety Analysis Set 1 (iSAS1)	The iSAS1 will include participants in the Safety Analysis Set whose scheduled Week 24 Visit is before or on the IA1 data cutoff date. This set also includes the Safety Analysis Set participants who prematurely discontinued the study intervention prior to the IA1 data cutoff date.
Interim Full Analysis Set 2 (iFAS2)	The iFAS2 will include participants in the FAS whose scheduled EOT Visit is before or on the IA2 data cutoff date. This set also includes the FAS participants who prematurely discontinued the study intervention prior to the IA2 data cutoff date.
Interim Safety Analysis Set 2 (iSAS2)	The iSAS2 will include participants in the Safety Analysis Set whose scheduled EOT Visit is before or on the IA2 data cutoff date. This set also includes the Safety Analysis Set participants who prematurely discontinued the study intervention prior to the IA2 data cutoff date.
Interim Full Analysis Set 3 (iFAS3)	The iFAS3 will include participants in the FAS who complete the 24 weeks post-EOT Visit before or on the IA3 data cutoff date. This set also includes the FAS participants who prematurely discontinued the study prior to the IA3 data cutoff date.
Interim Safety Analysis Set 3 (iSAS3)	The iSAS3 will include participants in the Safety Analysis Set who complete the 24 weeks post-EOT Visit before or on the IA3 data cutoff date. This set also includes the Safety Analysis Set participants who prematurely discontinued the study prior to the IA3 data cutoff date.

All Enrolled Set will be used for participant disposition, demographics, and baseline characteristics, and iFAS1/2/3 will be used for all efficacy and antiviral analyses, if applicable, at IA, in which participants will be analyzed according to their study intervention assigned. The iSAS1/2/3 will be used for all safety analyses at IA, in which participants will be analyzed according to the study intervention they received.

4. STATISTICAL ANALYSES

4.1. General Considerations

All analyses will use SAS version 9.4 or higher. The schedule of study assessments and time points are provided in the current PREVAIL master protocol and STRIVE sub-study.

Data will be provided in by-participant listings for the All Enrolled Set, unless otherwise specified.

Efficacy endpoints will be summarized by TDF/TD discontinued (participants who discontinued TDF/TD when the TDF/TD discontinuation criteria were met in the Follow-up period) and overall for each cohort.

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, Q1 (first quartile), Q3 (third quartile), minimum value (min), and maximum value (max), unless otherwise specified. In general, the precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures, and derived listings. Minimum and maximum values will be reported with the same precision as the units of measure. The mean and median will be reported to 1 additional decimal place, and the SD will be reported to 2 additional decimal places. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

Categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places, and percentages will not be displayed for zero counts.

Baseline value: Unless otherwise specified, the baseline value will be defined as the most recent non-missing (scheduled or unscheduled) measurement collected prior to the initial administration of study intervention. If baseline cannot be determined due to missing data, no derivation will be performed, and baseline will be set to missing.

Change (absolute change) from baseline will be calculated as post-baseline value – baseline value.

Study day: The study day of an event/measurement is defined as the relative day of the event/measurement starting with the date of the first study drug administration (reference date) as Day 1 (there will be no Day 0).

The study day of event/measurement occurring before the first study drug administration will be calculated as:

Study Day = (Date of event/measurement – Date of first study drug administration)

For event/measurement occurring on or after Day 1, the study day will be calculated as:

Study Day = (Date of event/measurement – Date of first study drug administration) + 1.

End of treatment (EOT) date: EOT date is the date of the last dose of VIR-2218, VIR-3434 and PEG-IFNa.

EOT assessment: The earliest available assessment on or after EOT date.

EOT + 24 weeks assessment: The earliest available assessment on or after EOT + 161 days.

Treatment Period and Follow-Up Period: Treatment Period and Follow-Up Period are defined in the protocol.

Treatment-emergent (TE) Period: The TE Period is defined as the time period on or from the start of study intervention(s) until the last dose of VIR-2218 + 30 days, or VIR-3434 + 24 weeks, or PEG-IFNα + 30 days, or TDF/TD + 30 days, whichever is later. The TE Period will be used for safety analysis.

Post-TE Period: The Post-TE Period is defined as the time period after the TE Period through the end of Follow-Up Period.

Analysis windows: The analysis window rules for protocol-defined visits are provided in Appendix 2.

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

1. In planned visit windows as specified, the analysis window rules described in Appendix 2, if applicable.
2. In the derivation of the baseline.
3. In the derivation of maximum and minimum values, or maximum and minimum change from baseline values during the Treatment Period and Follow-Up Period for efficacy analyses, or worst values/grades during the TE Period for safety analyses.
4. In individual participant data listings as appropriate.

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

If there are multiple records at a single assessment date, regardless of whether scheduled or unscheduled visit, the latest record will be used for the analysis.

Missing data handling conventions:

- Missing data can occur due to study withdrawal or participants lost to follow-up before the completion of the study or due to intermittent missing values (i.e., data between two non-missing assessments).
- Missing data in the by-participant data listings will be presented as missing.
- For efficacy response variables, the missing equals failure (MEF) approach will be used for the analysis, except for the sensitivity analysis for the primary endpoint described in Section **Error! Reference source not found.**. The sensitivity analysis will be conducted to evaluate the impact of missing data, in which missing data will be imputed.
- Missing data will not be imputed, and will be considered as missing data that will not be included in the data summary statistics and analysis. Qualitative data will be imputed as follows:

  1. HBV DNA, for the analysis of the primary endpoint:

a. If the missing data is reported as "Target Not Detected (TND)", then the missing data point will be imputed as 0.
b. If the missing data is reported as "< LLOQ", then the missing data point will be imputed 1 unit less than the LLOQ value. That's the LLOQ for HBV DNA is 20 IU/mL, so 19 IU/mL will be imputed.

2. HBs(e)Ag and Anti-HBs(e), for the analyses of primary and secondary efficacy endpoints:

   If the missing data is reported as "Not Detected" or "Nonactive", then the missing data point will be imputed as 0.

3. HBV RNA, for the analysis of an exploratory endpoint:

   a. If the missing data is reported as "Not Detected", then the missing data point will be imputed as 0.
   b. If the missing data is reported as "< LLOQ", then the missing data point will be imputed 1 unit less than the LLOQ value. That's the LLOQ for HBV RNA is 0.49 log U/mL, so 0.48 log U/mL will be imputed.
   c. If the missing data is reported as "> upper limit of quantification (ULOQ)", then the missing data point will be imputed as 1 unit greater than the value of ULOQ. E.g., The ULOQ for HBV RNA is 6.0 log U/mL, so 6.1 log U/mL will be imputed.
   d. If the missing data is reported as "Invalid" or "Quantity Not Sufficient (QNS)", then the missing data will not be imputed and considered as missing data.

4. HBcrAg, for the analysis of an exploratory endpoint:

   a. If the missing data is reported as "TND", then the missing data point will be imputed as 0.
   b. If the missing data is reported as "Target Detected (TD)", then the missing data point will be imputed as 1 unit less than the LLOQ. That's the LLOQ is 3.0 $\log_{10}$ U/mL, so 2.9 $\log_{10}$ U/mL will be imputed.
   c. If the missing data is reported as "> ULOQ", then the missing data point will be imputed as 1 unit greater than the value of ULOQ. That's, the ULOQ for HBcrAg, depending on whether the dilution could be performed, is either 7.0 $\log_{10}$ U/mL or 9.0 $\log_{10}$ U/mL, then 7.1 $\log_{10}$ U/mL or 9.1 $\log_{10}$ U/mL will be imputed, respectively.
   d. If the missing data is reported as "QNS" or "Results pending", then the missing data point will not be imputed, and it is considered as a missing.

5. In case other viral parameters are reported in a similar way, the same rule is applied if applicable.

6. For laboratory parameters, the below imputation rule will be applied: if any laboratory parameters are reported outside the reportable range (i.e. "< minimum reportable value (minRV)" or "> maximum reportable value (maxRV)"), one unit less than the minimum reportable value and one unit greater than the maximum reportable value will be imputed, respectively. For example, if the reported results is "< 0.05", then 0.04 will be imputed; if the reported results is "> 0.3", then 0.4 will be imputed. For special reported values, e.g. < 1 or < 0.1 will be imputed as < 0.9 or < 0.09, respectively. The lab data with a value of ≤ x.x / ≥ x.x will be imputed by x.x.

7. For the summary of medication and adverse event, no imputation will be performed except for missing/partial dates. The imputation rules for missing/partial dates of medication and adverse event are specified in Section 4.2.4 and Section 4.7.3, respectively.

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

Laboratory data analysis scope: For laboratory parameters, only data from the central lab will be analyzed and summarized. Local laboratory data will not be analyzed or summarized but will be provided in a by-participant laboratory data listing, with a flag indicating the data is from the local lab.

Multicenter considerations: Data from different sites will be pooled for analysis.

4.2. Background Characteristics

4.2.1. Participant Disposition

A disposition table will be provided with the number of study participants for each cohort and overall, in:

- Participants signed informed consent form
- Participants screened
- All Enrolled Set
- FAS
- Safety Analysis Set
- PK Analysis Set
- Immunogenicity Analysis Set

The number and percentage of study participants in each of the following disposition categories will be summarized by cohort and overall. Percentages will be calculated relative to the number of participants in the All Enrolled Set.

- Participants who completed all study intervention
- Participants who completed study
- Participants who met NRTI (TDF/TD) discontinuation criteria
- Participants who met NRTI (TDF/TD) retreatment criteria
- Participants prematurely discontinued VIR-3434
  - Primary reason for premature discontinuation of VIR-3434
- Participants prematurely discontinued VIR-2218
  - Primary reason for premature discontinuation of VIR-2218
- Participants prematurely discontinued PEG-IFNα

  - Primary reason for premature discontinuation of PEG-IFNα
- Participants prematurely discontinued TDF/TD
  - Primary reason for premature discontinuation of TDF/TD
- Participants early withdrawal from the study
  - Primary reason for early withdrawal from the study
- Roll over from/to other study/sub-study

A by-participant listing will be provided for the disposition of all participants.

4.2.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by cohort and overall based on the All Enrolled Set using descriptive statistics, including n, mean, SD, median, Q1, Q3, min, and max for continuous variables and numbers and percentages of participants for categorical variables. The number of participants with any missing demographics or baseline characteristics will be summarized for each categorical variable.

Demographic data will be summarized as follows:

- Age at baseline, in years
- Age group (<18, 18 – < 30, 30 – < 40, 40 – < 50, 50 – < 66)
- Sex at birth (Male, Female, Female with child-bearing potential)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)
- Country

Baseline characteristics will be summarized as follows:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Disease baseline characteristics will be summarized as follows:

- HBeAg status (Positive, Negative)
- Values of HBsAg (IU/mL) and HBsAg (log_{10} IU/mL)
- HBsAg categories (< 3000 IU/mL, and ≥ 3000 IU/mL)
- Values of HBV DNA (IU/mL) and HBV DNA (log_{10} IU/mL)
- Values of ALT (U/L)

Demographics and baseline characteristics data will be presented in a by-participant listing. In addition, liver elastography results (kPa) and fibrosis/cirrhosis status will also be listed.

4.2.3. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later.

Medical history will be summarized descriptively by system organ class (SOC) and preferred term (PT) by cohort and overall based on the FAS. All medical history data will be presented in a listing.

4.2.4. Prior, Concomitant Medications and Concomitant Procedure

Prior and concomitant medications used will be coded using the World Health Organization Drug Dictionary (WHODD) version Global B3 March 2022 or later and summarized by anatomic therapeutic chemical (ATC) classification level 2, ATC classification level 3, preferred name, and by cohort and overall based on the FAS.

Prior medication: Any medication started prior to administration of the study intervention, regardless of when it ended. If the medication end date is before the date of first dosing of the study intervention, then the medication will be summarized as prior medication, regardless of whether the medication start date is missing or not.

Concomitant medication: Any medication received on or after administration of the study intervention or received prior to administration of the study intervention and continued after administration of the study intervention. If medication start date is on or after administration of the study intervention, then medication will be summarized as concomitant medication regardless of whether the medication end date is missing or not.

Note that any medication that started prior to and continued after administration of the study intervention will be summarized as prior medication and concomitant medication, separately.

If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken prior to administration of the study intervention, it will be classified as both prior and concomitant medications. Details for handling missing or partial missing dates of medication are described in Appendix 3.

All medications will be provided in a by-participant listing along with a column indicating whether the medication was prior, concomitant, or both. The imputed date will not be presented in the listing.

Concomitant procedure: Any procedure or surgery received on or after administration of the study intervention. The procedure used in this study will be coded using MedDRA version 25.0 or later. All concomitant procedures will be summarized descriptively by SOC and PT, and by cohort and overall based on the FAS.

All concomitant procedures/surgeries will be provided in a by-participant listing.

Missing and/or partial dates of concomitant procedure/surgery will not be imputed.

4.2.5. Protocol Deviations

Protocol deviations (PDs) will be regularly reviewed by Vir, particularly before database cutoff dates for IAs. A final review of PDs will be conducted prior to the study database lock. Any PDs identified after the database lock will be included in the analyses and identified as such in the CSR.

An important PD is a PD that may significantly impact the completeness, accuracy, and/or reliability of study data or that may significantly affect a participant's rights, safety, or well-being.

A by-participant listing of all important PDs and COVID-19 related PDs will be provided with columns identifying the date of the deviation, deviation category, and the verbatim description of the deviation.

4.3. Primary Endpoint Analysis

The primary efficacy endpoint analyses will be based on the FAS.

4.3.1. Primary Endpoint

The primary efficacy endpoint is the proportion of participants achieving suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at EOT. The LLOQ for HBV DNA is 20 IU/mL.

The number and proportion of participants achieving the combined response variable – the suppression of HBV DNA (<LLOQ) with HBsAg loss (<0.05 IU/mL) – at EOT will be summarized, and the two-sided 95% exact Clopper-Pearson confidence interval (CI) will be calculated for each cohort.

If a participant misses HBV DNA or HBsAg at EOT, then this participant will be considered not meeting the primary endpoint.

HBV DNA and HBsAg values will be provided in a by-participant listing.

4.3.2. Supplementary Analysis

Two supplementary analyses will be performed for the primary efficacy analysis.

For the first supplementary analysis, the number and percentage of the participants meeting the primary efficacy endpoint – achieving suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at EOT – will be summarized based on the FAS excluding those participants who have prematurely discontinued all interventions during the Treatment Period before the planned EOT.

For the second supplementary analysis, the number and percentage of the participants meeting the primary efficacy endpoint – achieving suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at EOT – will be summarized based on the FAS excluding those participants who have missed or discontinued any dose of study intervention before the planned EOT.

The two-sided 95% exact Clopper-Pearson CI by cohort will also be calculated for each supplementary analysis.

4.3.3. Subgroup Analysis

Not applicable.

4.4. Secondary Endpoints Analysis

4.4.1. Secondary Efficacy Endpoints

The analysis of the following secondary endpoints will be conducted based on the FAS, unless otherwise specified. The numbering in the table below is consistent with the numbering of the endpoints in Table 1. HBeAg, anti-HBsAg, and anti-HBeAg values will be provided in a by-participant listing.

Secondary Endpoints	Analysis Methods
2. Proportion of participants with serum HBsAg ≤ 10 IU/mL at the EOT 3. Proportion of participants with serum HBsAg ≤ 10 IU/mL at 24 weeks post-EOT 8. Proportion of participants with HBsAg loss with anti-HBs seroconversion at EOT and at 24 weeks post-EOT 10. Proportion of participants achieving HBsAg loss (< 0.05 IU/mL) a. at EOT b. at 24 weeks post-EOT	The number and proportion of participants for each endpoint will be summarized at each visit by cohort, and the two-sided 95% Clopper-Pearson CI will be calculated for each cohort.
4. Serum HBsAg levels and change from baseline across timepoints in the study 5. Serum HBsAg level at nadir during the study 14. Mean change in serum HBsAg level from baseline across timepoints in the study	The observed values and the absolute change from baseline values in both IU/mL and $\log_{10}$ IU/mL of HBsAg at each visit up to end of study (EOS) at nadir during the study will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) by cohort. In addition, the change from baseline in $\log_{10}$ IU/mL at each visit will be plotted for each participant by cohort. Absolute value in $\log_{10}$ IU/mL at each visit will be plotted for each participant by cohort. Mean change from baseline in $\log_{10}$ IU/mL at each visit will be plotted for each cohort.

6. Time to achieve nadir of serum HBsAg during the study 7. Time to achieve serum HBsAg loss (< 0.05 IU/mL)	Time-to-nadir of serum HBsAg during the study period (up to EOS) will be summarized as a continuous variable by cohort. Time-to-HBsAg loss will be summarized as a continuous variable by cohort.
9. Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) after discontinuation of all treatment: a. at 24 weeks b. at the F48 Follow-Up visit 11. Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) after discontinuation of all treatment: a. at 24 weeks b. at the F48 Follow-Up visit	Due to early study termination, modification to timepoints of a. and b. as below: a) at 24 weeks after discontinuation of all treatments (an analysis window of 168 ± 14 days will be applied to capture data around the 24 weeks timepoint, following the rules in Appendix 2 for data selection) b) at the last Follow-Up visit, for participants who have > 24 weeks of discontinuation, after discontinuation of all treatments c) at the last Follow-Up visit after discontinuation of all treatments (all participants will be included in the denominator) Specifically, for a) and b), the denominator used in the percentage calculation will exclude participants with uncertain NRTI discontinuation status due to early study termination (e.g., no Follow-Up 12 visit). The number and percentage of participants achieving • sustained suppression of HBV DNA (< LLOQ) • sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) will be summarized by cohort with the two-sided 95% Clopper-Pearson CI. In addition, the number and percentage of participants achieving • sustained suppression of HBV DNA (< LLOQ), allowing transient viremia

	• sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL), allowing transient viremia where transient viremia is defined as HBV DNA ≥ LLOQ or HBsAg ≥ LLOQ for ≤ 35 days, adapted from the 2022 American Association for the Study of Liver Diseases (AASLD) – The European Association for the Study of the Liver (EASL) functional cure definition (AASLD-EASL, 2022), will be analyzed similarly. Similarly, the analyses above will be repeated after replacing "HBsAg loss (<0.05 IU/mL) with "HBsAg < 100 IU/mL". Accordingly, the transient viremia is defined as HBV DNA ≥ LLOQ or HBsAg ≥ 100 IU/mL for ≤ 35 days, adapted from the 2022 AASLD-EASL partial functional cure definition (AASLD-EASL, 2022).
12. For HBeAg-positive participants: proportion of participants with HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion	The number and percentage of participants achieving • HBeAg loss (undetectable HBeAg) will be summarized at each visit up to EOS by cohort for each visit; and • Anti-HBe seroconversion • HBeAg loss (undetectable HBeAg) and anti-HBe seroconversion will be summarized at each follow-up visit by cohort up to EOS. The two-sided 95% Clopper-Pearson CI will also be calculated at each follow-up visit for each cohort. The percentage will be based on those participants who have HBeAg tested positive at baseline in the FAS.
15. Proportion of participants achieving HBV DNA < LLOQ across timepoints in the study	The number and percentage of participants with • HBV DNA < LLOQ ALT ≤ ULN

16. Proportion of participants achieving ALT ≤ ULN across timepoints in the study	will be summarized at each visit by cohort. The two-sided 95% Clopper-Pearson CI will also be calculated across visits for each cohort. In addition, the individual ALT (U/L) value at each visit will be plotted for each participant by cohort.

- The LLOQ for HBV DNA is 20 IU/mL.
- HBsAg loss is defined as HBsAg < 0.05 IU/mL.
- Anti-HBs seroconversion: Anti-HBs change from baseline negative to post-baseline positive. The quantitative results will be used. The definition of negative, indeterminate, and positive is < 8.50 mIU/mL, ≥ 8.50 mIU/mL and < 11.50 mIU/mL, and ≥ 11.50 mIU/mL, respectively. If a result is "indeterminate", a further assessment or judgement will be performed to determine positive or negative.
- HBeAg-positive participants: the qualitative results at Screening will be used to determine if a participant is HBeAg-positive. In case a participant has a missing qualitative result in screening, the most recent non-missing qualitative result before the first dose of the study intervention will be used. If the qualitative result is not available, then the most recent non-missing quantitative value before the first dose of the study intervention will be used.
- Undetectable HBeAg/HBeAg loss: HBeAg < 0.06 IU/mL.
- Anti-HBe seroconversion: Anti-HBe changes from baseline negative to post-baseline positive. Anti-HBe qualitative data at Screening will be used for baseline assessment. Anti-HBe qualitative data collected during the Follow-Up Period will be used for post-baseline assessment.
- Nadir of HBsAg (or HBV DNA): Nadir is defined as the lowest HBsAg (or HBV DNA) value among all scheduled and unscheduled post-baseline HBsAg (or HBV DNA) values.

4.4.2. Secondary Endpoints for Safety

The analysis of the following secondary endpoints for safety will be conducted based on the Safety Analysis Set, unless otherwise specified:

Secondary Endpoints	Analysis Methods
1. Proportion of participants with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)	The number and percentage of participants with • TEAEs • SAEs will be summarized by cohort.

For a complete description of safety analyses for adverse events, please see Section 4.7.3.

All safety analyses, including but not limited to Exposure, Study Intervention Compliance, Safety Laboratory tests, Event of Clinical Interest (ECI), Vital Signs, please see Section 4.7.

4.4.3. Secondary Endpoints for Immunogenicity

The analysis of the following immunogenicity secondary endpoints will be conducted based on the Immunogenicity Analysis Set, unless otherwise specified:

Secondary Endpoints	Analysis Methods
13. Incidence and titers of ADA (if applicable) to VIR-3434	For a complete description of Immunogenicity Analysis, please see Section 4.8.2.

4.4.4. Sensitivity Analysis

Not applicable.

4.4.5. Supplementary Analysis

Not applicable.

4.4.6. Subgroup Analysis

Not applicable.

4.5. Exploratory Endpoints Analysis

4.5.1. Exploratory Efficacy Analysis

The analyses of the following exploratory efficacy endpoints will be conducted based on the FAS, unless otherwise specified. The numbering in the table below is consistent with the numbering of the endpoints in Table 1. HBV RNA and HBcrAg values will be provided in a by-participant listing.

Exploratory Endpoints	Analysis Methods
1. Additional viral parameters associated with HBV and/or study intervention(s), including but not limited to HBV RNA and HBcrAg	The observed values and the absolute change from baseline values at each visit up to End of Follow-up will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) by cohort for the following HBV viral parameters: • HBV RNA in $\log_{10}$ U/mL • HBcrAg in log10 U/mL

Exploratory Endpoints	Analysis Methods
2. CCI [redacted]	CCI [redacted]
3. CCI [redacted]	CCI [redacted]
4. Emergence of viral resistance to study intervention(s)	Not covered by this SAP, will be analyzed separately.
7. For HBeAg-positive participants: time to achieve HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion	Time to HBeAg loss and/or anti-HBe seroconversion will be summarized as a continuous variable. Participants with HBeAg loss with or without anti-HBe seroconversion will be listed.
8. Proportion of participants meeting criteria for NRTI discontinuation or retreatment in the study	The number and percentage of participants who meet NRTI discontinuation criteria NRTI retreatment criteria will be summarized by cohort. A by-participant listing will be provided for participants who met NRTI discontinuation criteria and retreatment criteria.
9. HBV DNA levels and change from baseline across timepoints in the study 10. Nadir and maximum change of HBV DNA level from baseline in the study	The observed values and the absolute change from baseline values of HBV DNA in both log IU/mL and IU/mL: a. at each visit b. at nadir up to EOS, will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) by cohort. In addition, the change from baseline in log_{10} IU/mL and absolute value in log_{10} IU/mL at

Exploratory Endpoints	Analysis Methods
	each visit will be plotted for each participant by cohort.
14. Proportion of participants with virological relapse (defined as either (1) an increase of ≥ 1 $\log_{10}$ HBV DNA IU/mL above nadir for at least 2 consecutive visits OR (2) quantifiable HBV DNA of ≥ 1 $\log_{10}$ IU/mL above LLOQ for at least 2 consecutive visits after being < LLOQ)	The number and percentage of participants with virological relapse will be summarized during the study.

CCI

4.5.3. Exploratory Endpoints for Immunogenicity

The analyses of the immunogenicity exploratory endpoints will be conducted using the Immunogenicity Analysis Set and by cohort, unless otherwise specified.

Exploratory Endpoints	Analysis Methods
13. Incidence and titers of ADA (if applicable) to VIR-2218 (for cohorts with VIR-2218)	Not covered by this SAP, will be analyzed separately.

4.5.4. Exploratory Endpoints for Pharmacokinetics

The analysis of the PK exploratory endpoints will be conducted using the PK Analysis Set, unless otherwise specified.

Exploratory Endpoints	Analysis Methods

11. VIR-3434 PK parameters 12. VIR-2218 PK parameters (for cohorts with VIR-2218)	For a complete description of Pharmacokinetics Analysis, please see Section 4.8.1.

4.6. Multiplicity Adjustment

Not applicable. This study is exploratory in nature, and no multiplicity adjustment will be made.

4.7. Safety Analyses

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

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

- TEAEs
- Clinical laboratory
- Laboratory Events of Clinical Interest (ECIs)

Only descriptive analysis of safety will be performed.

4.7.1. Extent of Exposure

Exposure summaries will be based on the Safety Analysis Set and presented by study intervention and by cohort and overall. Duration of exposure and the amount of dosage will be summarized.

Duration of exposure (weeks) of study intervention administration will be estimated as: (last dose date – first dose date + DoseFreq days) /7, regardless of dose interruption. DoseFreq will be 28 and 7 when the dosing frequency is every 4 weeks (Q4W) and once weekly (QW), respectively. DoseFreq for Cohort 3a will be either 56 or 84 when the VIR-3434 dosing is administered either every 8 weeks (Q8W) or every 12 weeks (Q12W), respectively. DoseFreq for TDF/TD that is administered daily will be 1 day. For an exposure duration involving more than one treatment, DoseFreq is the longest dosing frequency.

Duration of exposure will be summarized for all study interventions, including VIR-3434, VIR-2218, TDF/TD, and PEG-IFNα. Duration of exposure will be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) by study intervention and cohort. The number and percentage of participants who received the full dose, dose interruption, dose reduction and study intervention discontinuation will be summarized as appropriate by study intervention and cohort.

The amount of dosage will be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) by study intervention and cohort. All data related to exposure of study drug will be provided in a by-participant listing.

4.7.2. Study Intervention Compliance

Study intervention compliance will be assessed by the compliance rate. The compliance rate is defined as (total amount of drug dosage injected or taken) / (total amount of drug dosage planned to be injected or taken during the study). The compliance rate will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) by study intervention and cohort based on the FAS.

4.7.3. Adverse Events (AEs)

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

- Pre-treatment AE: defined as any AEs that started after informed consent was signed and prior to the administration of the study intervention.
- TEAE: defined as any AEs reported with an onset date on or after the first dose of study intervention(s) until the end of TE Period.
- Post-TE AE: defined as any AEs with onset after the TE Period through the end of Follow-Up Period.

All AEs will be coded using MedDRA version 25.0 and later.

For AEs with completely missing or partially missing start/stop dates, if it can't be decided whether the AE is TEAE due to the missing dates, the AE will be classified as TEAE. Imputation rules for missing or partial missing dates of AEs are described in Appendix 4.

An overview table of all TEAEs by cohort and overall will be summarized in the following categories:

- Number of TEAEs (total number of TEAEs only)
- Participants with any TEAEs
- Participants with TEAEs by strongest relationship to study intervention(s)
- Participants with TEAEs by maximum severity
- Participants with TEAEs leading to any study intervention discontinuation
- Participants with TEAEs leading to any study intervention interruption
- Participants with TEAEs leading to PEG-IFNa and TDF/TD dose reduction
- Participants with study intervention-related TEAEs
- Participants with Grade 3/4/5 TEAEs
- Participants with serious TEAEs
- Participants with study intervention-related serious TEAEs
- Participants with TEAE leading to death

The following summary tables of TEAEs will be presented by MedDRA SOC and PT using the number and percentage of participants by cohort and overall:

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

In addition, the following TEAE tables will also be summarized by MedDRA PT only for each cohort and overall:

- TEAEs
- Study intervention related TEAEs
- Serious TEAEs

A participant with multiple occurrences of the same AE will be counted only once, at the maximum severity (toxicity grade) or strongest relationship to study intervention.

A TEAE table of injection site reactions will be summarized by MedDRA PT for each cohort and overall in order of descending incidence.

The following table-listings will be presented per cohort based on the All Enrolled Set:

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

All AEs will be presented in a by-participant listing based on the All Enrolled Set. In addition, the local tolerability of VIR-3434 will also be listed.

4.7.4. Clinical Laboratory

All statistical analyses of laboratory values will be performed using conventional units. Clinical laboratory data collected will be summarized using quantitative methods.

4.7.4.1. Summaries of Laboratory Results

For the laboratory measurements, the observed values and change from baseline values of the continuous variables of liver function tests, hematology, serum chemistry, and coagulation will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) by cohort at each scheduled visit until EOS.

Separate listings containing individual participant liver function tests, hematology, chemistry, coagulation, and urinalysis values will be provided by participant ID and visit in chronological order, including data collected from both scheduled and unscheduled visits. Values falling out of the relevant normal range (between the value of lower limit of normal (LLN) and upper limit of normal (ULN)) and having a severity grade of 1 or higher on laboratory abnormalities will be flagged as appropriate. Local lab data will be presented only in a by-participant listing and will be flagged accordingly.

In addition, results of positive urine/serum pregnancy test will be listed in the individual participant data listing only.

4.7.4.2. Summaries of Laboratory Abnormalities

The Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (CTCAE 5.0 2017) will be used as the reference on the grading scale to assign severity (toxicity) grades (1 to 4) to abnormal results for the laboratory parameters of interest, as shown in Appendix 5. Grade 0 refers to the normal values that do not meet the criteria of laboratory abnormalities. Grade 5 refers to death related to an adverse event, if any.

For the laboratory abnormalities, the number and percentage of participants who met at least 1 threshold criterion of severity grade during the TE Period will be summarized by cohort based on the most severe post-baseline abnormality for selected laboratory parameters in Appendix 5.

4.7.5. Summaries of Events of Clinical Interest

The TE laboratory events of clinical interest (ECI) are defined as instances of:

- ALT > 5 x ULN and > 2 x baseline.

The number and percentage of participants with ECI will be summarized for each scheduled visit until EOS by cohort. If any participant has multiple ECIs, they will only be counted once. An ECI is considered resolved when ALT returns to ≤ Day 1 baseline value.

A listing including individual participant ECI data will be provided.

If a participant has at least one ECI, the related data – substance use, exercise, and travel history – will be collected, and the corresponding listings will be presented. Otherwise, if no participant meets the ECI criteria, the three listings will not be provided, as no data will have been collected.

4.7.6. Safety ECG Measurements, Physical Examinations, Vital Signs, Pregnancy Testing

Safety ECG Measurements, Physical Examinations, Vital Signs, and Pregnancy Testing will be provided as by-participant listings.

4.8. Other Analyses

4.8.1. Pharmacokinetics Analysis

PK concentrations and PK parameters will be summarized descriptively based on the PK Analysis Set and presented by treatment and cohort. Other PK analyses will not be covered by this SAP.

For PK concentration data, values reported below the quantitation limit (BQL) will not be imputed in summary statistics with only the number of participants who have non-missing quantifiable results included at each time point. Any positive concentration (i.e., greater than LLOQ) is excluded from the summary statistics at the Day 1 pre-dose visit only.

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

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

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

4.8.1.1. PK Variables

PK variables include individual concentration measurements for VIR-2218, its metabolite AS(N-1)3'VIR-2218, and VIR-3434 following the collection times provided in the protocol, and the estimated PK parameters in evaluation of PK objectives including but not be limited to, C_{max} (maximum observed concentration of drug following a dose), C_{tau} (concentration at dosing time plus T_{au}), AUC_{tau} (area under the concentration-time curve during the dose interval), and $t_{1/2}$ (terminal elimination half-life).

Participants' data collected from the VIR-3434 PK sub-study will be included in all analysis. The details of the VIR-3434 PK sub-study can be found in the Protocol.

4.8.1.2. Analysis of PK Concentrations

Plasma concentrations of VIR-2218 and its metabolite AS(N-1)3'VIR-2218 and serum concentrations of VIR-3434 will be listed and summarized by the nominal sampling time using descriptive statistics (n, mean, SD, coefficient of variation [CV%], median, min, max, geometric mean, and Geometric CV% [GeoCV%]). Geometric CV% will be calculated using the following formula where SD is the standard deviation of the log-transformed data: GeoCV% = sqrt[(exp (SD^2) – 1)] x 100. Participants' data collected from the VIR-3434 PK sub-study will be marked.

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

Both individual and aggregate mean (± SD) of the serum concentrations of free VIR-3434 will be displayed graphically in linear and semi-logarithmic plots of concentration versus time. Time will be displayed in units of days of time elapsed relative to dosing, with dosing at time zero (clinical Day 1). The nominal sample collection timepoints will be used for plots. The number of participants with quantifiable concentrations per timepoint will be displayed in each plot of mean concentrations. Mean post-dose concentration values that are BQL will not be displayed in the figures and the remaining points will be connected.

4.8.1.3. Analysis of PK Parameters

PK parameter summaries for free VIR-3434 serum concentrations will include all participants for whom PK parameters can be derived. The sample size for each PK parameter will be based on the number of participants with non-missing data for that PK parameter.

Individual participant PK parameters for VIR-3434 will be listed and summarized using descriptive statistics (n, mean, SD, CV%, median, min, max, geometric mean, and GeoCV%).

Selected summary statistics (e.g., geometric mean with GeoCV% or median with min and max) for PK parameters will be presented by cohort.

4.8.2. Immunogenicity Analysis

All immunogenicity analyses described in this section will be based on the Immunogenicity Analysis Set and presented by cohort.

4.8.2.1. Definition of Variables

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

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

4.8.2.2. Analysis Methods

The incidence rate of participants who had samples of negative, screened positive, and confirmed positive for binding ADA to VIR-3434 will be summarized using frequency counts and percentages at baseline and each post-baseline visit up to EOS. Titers for participants confirmed positive for ADA to VIR-3434 will be summarized descriptively (n, median, min, max).

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

- Any ADA result

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

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

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

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

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

4.9. Interim Analyses

4.9.1. Introduction

CCI [redacted]

4.9.2. General Consideration

For each planned IA, the VIR Biometrics team and a designated CRO will prepare the analysis package and conduct the analysis using cleaned data up to the IA data cutoff date. All data reported on or before the data cutoff date will be included in the IA. General considerations, reporting conventions, and analysis methods specified for the final analysis apply to IA, unless otherwise specified.

CCI [redacted]

4.9.3. Interim Analysis 1

4.9.3.1. Subject Disposition

The number of participants in the following categories will be summarized:

- All Enrolled Set
- iFAS1
- iSAS1

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

- Participants completed Week 24 visit
- Participants early withdrawn from the study
  - Primary reason for early withdrawal from study
- Roll over from/to other study/sub-study

A by-participant listing will be provided for disposition, including primary reasons for premature discontinuation of VIR-3434/ TDF/TD/ VIR-2218/ PEG-IFNα.

4.9.3.2. Demographics and Baseline Characteristics

The same demographics and baseline characteristics specified in Section 4.2.2 will be summarized based on the All Enrolled Set.

4.9.3.3. Medical History, Prior/Concomitant Medications and Concomitant Procedure

Medical History, Prior/Concomitant Medications and Concomitant Procedure specified in Section 4.2.3 and Section 4.2.4 will be summarized based on the iFAS1.

4.9.3.4. Extent of Exposure and Study Intervention Compliance

For the IA1 purpose, the study drug exposure and study intervention compliance will be calculated using the same approach specified in Section 4.7.1 based on the iSAS1 and Section 4.7.2 based on the iFAS1, respectively. For other cohorts, if participants are still on a study intervention at the IA1 data cutoff date, the IA1 data cutoff date will be used as the last exposure date for the exposure calculation.

4.9.3.5. Efficacy Analysis

All efficacy analyses described in this section will be based on the iFAS1.

4.9.3.5.1. Primary Endpoint Analysis

No primary endpoint(s) analysis will be conducted for IA1.

The observed values of the parameters related to the primary endpoint, i.e., HBV DNA and HBsAg and the absolute changes from baseline values in both IU/mL and $\log_{10}$ IU/mL at each visit up to the IA1 data cutoff date will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) by cohort. The observed value at the nadir of HBsAg and the maximum change from baseline will be included in the HBsAg descriptive statistics summary table.

4.9.3.5.2. Secondary Endpoints Analysis

For IA1, the secondary endpoints analysis will be performed as described in Section 4.4.1, including the endpoints below:

- Serum HBsAg levels and change from baseline across timepoints in the study
- Serum HBsAg level at nadir during the study
- Time to achieve serum HBsAg loss
- For HBeAg-positive participants: proportion of participants with HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion
- Mean change in serum HBsAg level from baseline across timepoints in the study
- Proportion of participants achieving HBV DNA < LLOQ across timepoints in the study
- Incidence and titers of ADA (if applicable) to VIR-3434
- Proportion of participants achieving ALT ≤ ULN across timepoints in the study

4.9.3.5.3. Exploratory Endpoints Analysis

For IA1, the following Exploratory Endpoints will be analyzed as described in Section 4.5.1:

- HBV RNA and HBcrAg levels and change from baseline across timepoints in the study
- HBV DNA levels and change from baseline across timepoints in the study
- Nadir and maximum change of HBV DNA level from baseline in the study

4.9.3.6. Safety Analysis

For IA1, the safety analyses specified in Section 4.7.3 to Section 4.7.6 will be performed based on the iSAS1.

4.9.4. Interim Analysis 2

CCI [redacted]

CCI

4.9.4.1. Subject Disposition

The number of participants in the following categories will be summarized:

- All Enrolled Set
- iFAS2
- iSAS2

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

- Participants completed EOT visit
- Participants early withdrawn from the study
  - Primary reason for early withdrawal from study
- Roll over from/to other study/sub-study

A by-participant listing will be provided for disposition, including primary reasons for premature discontinuation of VIR-3434/ TDF/TD/ VIR-2218/ PEG-IFNα.

4.9.4.2. Demographics and Baseline Characteristics

The same demographics and baseline characteristics specified in Section 4.2.2 will be summarized based on the All Enrolled Set.

4.9.4.3. Medical History, Prior/Concomitant Medications and Concomitant Procedure

Medical History, Prior/Concomitant Medications and Concomitant Procedure specified in Section 4.2.3 and Section 4.2.4 will be summarized based on the iFAS2.

4.9.4.4. Extent of Exposure and Study Intervention Compliance

For the IA2 purpose, the study drug exposure and study intervention compliance will be calculated using the same approach specified in Section 4.7.1 based on the iSAS2 and Section 4.7.2 based on the iFAS2, respectively. For other cohorts, if participants are still on a study intervention at the IA2 data cutoff date, the IA2 data cutoff date will be used as the last exposure date for the exposure calculation.

4.9.4.5. Efficacy Analysis

All efficacy analyses described in this section will be based on the iFAS2.

4.9.4.5.1. Primary Endpoint Analysis

For IA2, the proportion of participants achieving suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at EOT will be summarized, and the two-sided 95% exact Clopper-Pearson CIs will be calculated for each cohort.

4.9.4.5.2. Secondary Endpoints Analysis

For IA2, the secondary endpoints analysis will be performed as described in Section 4.4.1, including the endpoints below:

- Proportion of participants with serum HBsAg ≤ 10 IU/mL at EOT
- Proportion of participants with HBsAg loss with anti-HBs seroconversion at EOT
- Proportion of participants achieving HBsAg loss (< 0.05 IU/mL) at EOT
- Serum HBsAg levels and change from baseline across timepoints in the study
- Serum HBsAg level at nadir during the study
- Mean change in serum HBsAg level from baseline across timepoints in the study
- Time to achieve nadir of serum HBsAg during the study
- Time to achieve serum HBsAg loss (< 0.05 IU/mL)
- For HBeAg-positive participants: proportion of participants with HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion
- Proportion of participants achieving HBV DNA < LLOQ across timepoints in the study
- Proportion of participants achieving ALT ≤ ULN across timepoints in the study

4.9.4.5.3. Exploratory Endpoints Analysis

Data collected based on CLDQ-HBV and WPAI questionnaires will be analyzed as described in Section 4.5.2 based on iFAS2:

- Change from baseline in health-related quality of life as measured by the CLDQ-HBV questionnaire
- Change from baseline in work productivity and daily activities as measured by the WPAI questionnaire

4.9.4.6. Safety Analysis

Safety analyses specified in Section 4.7.3 to Section 4.7.6 will be performed based on the iSAS2.

4.9.5. Interim Analysis 3

CCI [redacted]

4.9.5.1. Subject Disposition

The number of participants in the following categories will be summarized:

- All Enrolled Set
- iFAS3
- iSAS3

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

- Participants who completed all study interventions
- Participants who met NRTI (TDF/TD) discontinuation criteria
- Participants who met NRTI (TDF/TD) retreatment criteria
- Participants early withdrawn from the study
  - Primary reason for early withdrawal from study
- Roll over from/to other study/sub-study

A by-participant listing will be provided for disposition, including primary reasons for premature discontinuation of VIR-3434/ TDF/TD/ VIR-2218/ PEG-IFNα.

4.9.5.2. Demographics and Baseline Characteristics

The same demographics and baseline characteristics specified in Section 4.2.2 will be summarized based on the All Enrolled Set.

4.9.5.3. Medical History, Prior/Concomitant Medications and Concomitant Procedure

Medical History, Prior/Concomitant Medications and Concomitant Procedure specified in Section 4.2.3 and Section 4.2.4 will be summarized based on the iFAS3.

4.9.5.4. Extent of Exposure and Study Intervention Compliance

For the IA3 purpose, the study drug exposure and study intervention compliance will be calculated using the same approach specified in Section 4.7.1 based on the iSAS3 and Section 4.7.2 based on the iFAS3, respectively. For other cohorts, if participants are still on a study intervention at the IA3 data cutoff date, the IA3 data cutoff date will be used as the last exposure date for the exposure calculation.

4.9.5.5. Efficacy Analysis

All efficacy analyses described in this section will be based on iFAS3.

4.9.5.5.1. Secondary Endpoints Analysis

For IA3, the secondary endpoints analysis will be performed as described in Section 4.4.1, including the endpoints below:

- Proportion of participants with serum HBsAg ≤ 10 IU/mL at 24 weeks post-EOT
- Proportion of participants with HBsAg loss with anti-HBs seroconversion at 24 weeks post-EOT

- Proportion of participants achieving HBsAg loss (< 0.05 IU/mL) at 24 weeks post-EOT
- Serum HBsAg levels and change from baseline across timepoints in the study
- Serum HBsAg level at nadir during the study
- Mean change in serum HBsAg level from baseline across timepoints in the study
- For HBeAg-positive participants: proportion of participants with HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion
- Proportion of participants achieving HBV DNA (< LLOQ) across timepoints in the study
- Proportion of participants achieving ALT ≤ ULN across timepoints in the study
- Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at 24 weeks after discontinuation of all treatment
- Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) at 24 weeks after discontinuation of all treatment

4.9.5.6. Safety Analysis

Safety analyses specified in Section 4.7.3 to Section 4.7.6 will be performed based on iSAS3.

4.10. Modifications

Not applicable.

4.10.1. Modifications to the Approved Study Protocol

Protocol	SAP v2.0
Section 3: secondary endpoints: 9. Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) after discontinuation of all treatment: a. at 24 weeks b. at the F48 Follow-Up visit 11. Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) after discontinuation of all treatment: a. at 24 weeks b. at the F48 Follow-Up visit	A modification to the timepoint is below due to early study termination: a. at 24 weeks post-stopping all treatments b. at the last Follow-Up visit, for participants who have > 24 weeks of discontinuation post-stopping all treatments c. at the last Follow-Up visit Add additional analysis below: In addition, the number and percentage of participants achieving

	• sustained suppression of HBV DNA (< LLOQ), allowing transient viremia after discontinuation of all treatment • sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL), allowing transient viremia after discontinuation of all treatment where transient viremia is defined as HBV DNA ≥ LLOQ or HBsAg ≥ LLOQ for ≤ 35 days, adapted from the 2022 American Association for the Study of Liver Diseases (AASLD) – The European Association for the Study of the Liver (EASL) functional cure definition (AASLD-EASL, 2022), will be analyzed similarly. The analyses above will be repeated after replacing "HBsAg loss (<0.05 IU/mL) with "HBsAg < 100 IU/mL". Accordingly, the transient viremia is defined as HBV DNA ≥ LLOQ or HBsAg ≥ 100 IU/mL for ≤ 35 days.
Master protocol Section 9.3: All Screened Set includes all participants who signed the informed consent form.	All Screened Set will not be included in this SAP. Because the All Screened Set will not be used in the analysis. Instead, the number of participants screened will be provided in the disposition table.
Section 9.4.1: TEAE definition for this sub-protocol: An AE that is reported with an onset date on or after the start of study intervention(s) until end of Follow-Up Period.	TEAE is defined as any AEs reported with an onset date on or after the first dose of study intervention(s) until the end of TE Period. The TE Period is defined as the time period on or from the start of study intervention(s) until the last dose of VIR-2218 + 30 days, or VIR-3434 + 24 weeks, or PEG-IFNα + 30 days, or TDF/TD + 30 days, whichever is later.
Protocol Section 9.5: Three interim analyses will be conducted for each cohort to evaluate the efficacy endpoints at Week 24, EOT, and 24 weeks post-EOT when all participants in the cohort completed the respective visits.	The Sponsor has decided to combine IA1 and IA2. As the study will be terminated earlier, the Sponsor also plans to merge IA3 with the final analysis.

4.10.2. Modifications to the Approved Statistical Analysis Plan

Section (SAP v1.0)	Update (SAP Amendment v2.0)
Section 4.1 General considerations.	○ To update the imputation rule for viral parameters by removing "LOD" and imputing TND as 0. ○ To add the definitions of EOT, EOT assessment and EOT+24 weeks assessment. ○ To add the efficacy endpoint summary for participants who qualified to discontinue the TDF/TD.
Section 4.2.1 Participant disposition	To add the number of participants who signed the informed consent form, and the number of participants screened.
Section 4.2.5 Protocol deviations	To remove the summary of the PD table.
Section 4.3 Primary endpoint analysis	To update the sensitivity analysis.
Sections 4.4.1 and 4.5.1 Secondary and exploratory endpoints analysis	○ To update the timepoints due to study early termination, and add additional analysis for sustained suppression of HBV DNA, and sustained suppression of HBV DNA with HBsAg loss. ○ To update the analysis of "time to xx". ○ To update HBeAg and anti-HBe timepoints for the summary. ○ To update the virological relapse summary. ○ To add the plots for ALT and HBV DNA.
Sections 4.5.3 and 4.8.2 Exploratory endpoints for immunogenicity and immunogenicity analysis	○ To exclude the analysis of ADA to VIR-2218. ○ To remove the analysis visit (with analysis window) for the ADA data.
Section 4.7.1 Extend of exposure	To update the analysis of exposure.
Section 4.7.3 Adverse event	○ To move the local tolerability of VIR-3434 from Section 4.7.6 to Section 4.7.3. ○ To add the table of study intervention related TEAEs.
Section 4.8.1 Pharmacokinetics analysis	To remove the PK listing for the PK sampling time deviation.

Sections 4.9 and 4.10.1 Interim analysis and modifications to the approved study protocol	To update the changes of the interim analyses.
Appendix 2. Analysis windows for study assessment	To update the EOT date for the analysis window and address the typo in the analysis window for the Follow-up tables 11, 12 and 13.
Others: words/sentences, format, etc.	Other minor edits, updates, etc.

5. SAMPLE SIZE DETERMINATION

Sample size calculation for the initial assessment of an investigational regimen is based on HBsAg loss rate as described below (FDA 2018; Terrault 2018).

- An investigational regimen will initially be evaluated in an open-label single-arm study, without a concurrent control arm. If the true HBsAg loss rate ranges from 25% to 40%, at least 10 participants will be required to provide > 70% statistical power to detect a 23% difference in HBsAg loss rate, using a 1-sided exact binomial test with a significance level of 0.025 (Table 6).

Table 6: Power and Sample Size Calculation for Single-Arm Efficacy

Null Hypothesis: Response rate is ≤2%, which is the assumed rate in NRTI-suppressed participants. **Assumptions:** Use exact binomial test with 1-sided significance level of 0.025.		
Sample Size	Power to detect a 23% difference in HBsAg loss rate, if the true HBsAg loss rate is 25%	Power to detect a 38% difference in HBsAg rate, if the true HBsAg loss rate is 40%
10	75.6%	95.4%
15	76.4%	97.3%
25	96.8%	> 99%
30	98.9%	> 99%

This study is exploratory in nature, and there is no hypothesis testing. The sample size of the study is estimated, referring to the calculation above and based on practical considerations. A sample size of 10 or 15 will be initially enrolled in each cohort.

Up to 60 participants will be enrolled in this sub-study initially. Additionally, up to 30 floater participants may be added to the cohorts. As described in Section 9.5 of the Protocol, this addition may be based on data from an interim analysis. No more than 90 participants will be enrolled.

6. SUPPORTING DOCUMENTATION

APPENDIX 1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AASLD	American Association for the Study of Liver Diseases
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine transaminase
Anti-HBe	hepatitis B e antibody
Anti-HBs	hepatitis B surface antibody
AST	aspartate transaminase
BMI	body mass index (kg/m2)
BQL	below limit of quantification
CI	confidence interval
CLDQ-HBV	Chronic Liver Disease Questionnaire-Hepatitis B
CM	concomitant medication
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
EASL	The European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
ECI	Events of Clinical Interest
EOS	End of Study
HBcrAg	hepatitis B core-related antigen
HBV	hepatitis B virus
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
INR	international normalized ratio
LLN	lower limit of normal
LLOQ	lower limit of quantitation
Max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum value

PDs	protocol deviations
PK	pharmacokinetic/pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
T(N)D	target (not) detected
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary
CCI	[redacted]

APPENDIX 2. ANALYSIS WINDOWS FOR STUDY ASSESSMENT

Notes:

- The analysis windows will be applied using the following rules for both scheduled and unscheduled visits:
  a. If no numerical measurement is available within an analysis window, the measurement will be considered missing for the visit.
  b. If there is more than 1 numerical measurement available within an analysis window, use the following rules:
     i. The scheduled visit measurement will be used if it is available;
     ii. The unscheduled visit measurement closest to the target day will be used unless the scheduled visit is available; or
     iii. If there are multiple unscheduled visit measurements at the same distance from the target day, the latest measurement will be used.
- For the study assessments, e.g., laboratory, ECG, and vital sign measurements, collected on the date of the first dose of study drug, the following rules will be applied if it cannot be determined whether the measurement is before or after the first dose:
  a. Scheduled measurement will be treated as a pre-dose observation.
  b. Unscheduled measurement will be treated as a post-dose observation.
- Analysis Visits: The visit name for analysis purpose is used to report data in tables and figures.
- The Analysis Window is continuous, without leaving any date gaps between visits (no gap date). The Analysis Window boundaries are left exclusive, right inclusive, except specified otherwise.

Table 7: Analysis Windows for Safety, Efficacy, and other Assessments: Treatment Period for Cohort 1a/2a

Study Stage	**Screening**	**Treatment Period**												
Visit Week		**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44/ EOT**
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**D29±2**	**D57±2**	**D85±2**	**D113±2**	**D141±2**	**D169±2**	**D197±2**	**D225±2**	**D253±2**	**D281±2**	**D309±2**
Analysis Visit	**Week 1 Day 1 (Baseline)**		**Week 1 Day 8**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44 /EOT**
Analysis Window	**< D1 dose time**		**≥D1 dose time, +7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, EOT Date**
HBsAg quantitative, HBV DNA quantification, Liver function tests, Serum chemistry, Hematology, Coagulation parameters.														
Analysis Visit	**Week 1 Day 1 (Baseline)**			**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44 /EOT**
Analysis Window	**< D1 dose time**			**≥D1 dose time, +14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, EOT Date**
Anti-HBs quantitative, HBeAg quantitative, HBcrAg, HBV RNA.														
Analysis Visit	**Week 1 Day 1 (Baseline)**			**Week 4**		**Week 12**		**Week 20**			**Week 32**			**Week 44 /EOT**
Analysis Window	**< D1 dose time**			**≥D1 dose time, +28**		**±28**		**-28, +42**			**±42**			**-42, EOT DATE**
CLDQ-HBV, WPAI:GH.														

Table 8: Analysis Windows for Safety, Efficacy, and other Assessments: Treatment Period for Cohort 3a

Study Stage	**Screening**	**Treatment Period**											
Visit Week		**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36/ EOT[a]**	**W40/ EOT[a]**
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**D29±2**	**D57±2**	**D85±2**	**D113±2**	**D141±2**	**D169±2**	**D197±2**	**D225±2**	**D253±2**	**D281±2**
Analysis Visit	**Week 1 Day 1 (Baseline)**		**Week 1 Day 8**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36 /EOT[b]**	**Week 40 /EOT[c]**
Analysis Window	**< D1 dose time**		**≥D1 dose time, D8+7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, EOT DATE**
HBV DNA quantification, HBsAg quantitative, Liver function tests, Serum chemistry, Hematology, Coagulation parameters.													
Analysis Visit	**Week 1 Day 1 (Baseline)**			**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36 /EOT[b]**	**Week 40 /EOT[c]**
Analysis Window	**< D1 dose time**			**≥D1 dose time, +14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, EOT DATE**
Anti-HBs quantitative, HBeAg quantitative, HBcrAg, HBV RNA.													
Analysis Visit	**Week 1 Day 1 (Baseline)**			**Week 4**		**Week 12**		**Week 20**			**Week 32**	**Week 36 /EOT[b]**	**Week 40 /EOT[c]**
Analysis Window	**< D1 dose time**			**≥D1 dose time, +28**		**±28**		**-28, +42**			**-42, +14**	**±14**	**-14, EOT DATE**
CLDQ-HBV, WPAI:GH.													

[a] If Q8W dosing regimen is chosen, then W40 will be the EOT visit and assessments for EOT should be done at W40. Similarly, if Q12W dosing regimen is chosen then W36 will be the EOT and assessments for EOT should be done at W36.

[b] To be conducted if W36 will be EOT (Q12W dosing regimen).

[c] To be conducted if W40 will be EOT (Q8W dosing regimen).

Table 9: Analysis Windows for Safety, Efficacy, and other Assessments: Treatment Period for Cohort 4a

Study Stage	**Screening**	**Treatment Period**												
Visit Week		**W1**			**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44/ EOT**
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D2**	**D8 ±2**	**D29 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±2**	**D225 ±2**	**D253 ±2**	**D281 ±2**	**D309 ±2**
Analysis Visit	**Week 1 Day 1 (Baseline)**		**Week 1 Day 2**	**Week 1 Day 8**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44 /EOT**
Analysis Window	**< D1 dose time**		**≥D1 dose time, +2**	**-4, +7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, EOT DATE**
HBV DNA quantification, HBsAg quantitative, Liver function tests, Serum chemistry, Hematology, Coagulation parameters.															
Analysis Visit	**Week 1 Day 1 (Baseline)**		**Week 1 Day 2**		**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44 /EOT**
Analysis Window	**< D1 dose time**		**≥D1 dose time, +13**		**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, EOT DATE**
Anti-HBs quantitative, HBeAg quantitative.															
Analysis Visit	**Week 1 Day 1 (Baseline)**				**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44 /EOT**
Analysis Window	**< D1 dose time**				**≥D1 dose time, +14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, EOT DATE**
HBcrAg, HBV RNA.															
Analysis Visit	**Week 1 Day 1 (Baseline)**				**Week 4**		**Week 12**		**Week 20**			**Week 32**			**Week 44 /EOT**
Analysis Window	**< D1 dose time**				**≥D1 dose time, +28**		**±28**		**-28, +42**			**±42**			**-42, EOT DATE**
CLDQ-HBV, WPAI:GH.															

Table 10: Analysis Windows for Safety, Efficacy, and other Assessments: Treatment Period for Cohort 5a

Study Stage	**Screening**	**Treatment Period**														
Visit Week		**W1**			**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48/ EOT**
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D2**	**D8 ±2**	**D29 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±2**	**D225 ±2**	**D253 ±2**	**D281 ±2**	**D309 ±2**	**D337 ±2**
Analysis Visit	**Week 1 Day 1 (Baseline)**		**Week 1 Day 2**	**Week 1 Day 8**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48 /EOT**
Analysis Window	**< D1 dose time**		**≥D1 dose time, +2**	**-4, +7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, EOT DATE**
HBV DNA quantification, HBsAg quantitative, Liver function tests, Serum chemistry, Hematology, Coagulation parameters.																
Analysis Visit	**Week 1 Day 1 (Baseline)**		**Week 1 Day 2**		**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48 /EOT**
Analysis Window	**< D1 dose time**		**≥D1 dose time, +13**		**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, EOT DATE**
Anti-HBs quantitative, HBeAg quantitative.																
Analysis Visit	**Week 1 Day 1 (Baseline)**		**Week 1 Day 2**		**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48 /EOT**
Analysis Window	**< D1 dose time**		**≥D1 dose time, +13**		**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, EOT DATE**
HBcrAg, HBV RNA.																
Analysis Visit	**Week 1 Day 1 (Baseline)**				**Week 4**		**Week 12**		**Week 20**			**Week 32**			**Week 44**	**Week 48 /EOT**
Analysis Window	**< D1 dose time**				**≥D1 dose time, +28**		**±28**		**-28, +42**			**±42**			**-42, +14**	**-14, EOT Date**
CLDQ-HBV, WPAI:GH.																

Table 11: Analysis Windows for Safety, Efficacy, and other Assessments: Follow-Up Period for Participants Who Never Discontinue NRTI during Follow-Up Period

Study Stage	**Follow-Up Period**								
Follow up Visit	**F1**	**F4**	**F8**	**F12**	**F16**	**F20**	**F24**	**F36**	**F48/ EOFU**
Visit Day ± Visit Window	**D8 ±2**	**D29 ±7**	**D57 ±7**	**D85 ±7**	**D113 ±7**	**D141 ±7**	**D169 ±7**	**D253 ±7**	**D337 ±7**
Analysis Visit	**FU Week 1**	**FU Week 4**	**FU Week 8**	**FU Week 12**	**FU Week 16**	**FU Week 20**	**FU Week 24**	**FU Week 36**	**FU Week 48/EOFU**
Analysis Window	**EOT DATE , +7**	**±14**	**±14**	**±14**	**±14**	**±14**	**-14, +42**	**±42**	**-42, +14**
HBV DNA quantification, HBsAg quantitative, Liver function tests, Serum chemistry, Hematology, Coagulation parameters, Anti-HBs quantitative, HBeAg quantitative, Anti-HBe qualitative.									
Analysis Visit	**FU Week 1**	**FU Week 4**		**FU Week 12**			**FU Week 24**		**FU Week 48/EOFU**
Analysis Window	**EOT DATE , +7**	**-14, +28**		**-28, +42**			**-42, +84**		**-84, +14**
HBcrAg, HBV RNA.									
Analysis Visit	**FU Week 1**			**FU Week 12**			**FU Week 24**		**FU Week 48/EOFU**
Analysis Window	**EOT DATE , +35**			**±42**			**-42, +84**		**-84, +14**
CLDQ-HBV, WPAI:GH.									

Table 12: Analysis Windows for Safety, Efficacy, and other Assessments: Follow-Up Period for Participants Who Discontinue NRTI at F1

Study Stage	**Follow-Up Period**															
Follow up Visit	**F1**	**F2**	**F4**	**F6**	**F8**	**F10**	**F12**	**F16**	**F20**	**F24**	**F28**	**F32**	**F36**	**F40**	**F44**	**F48/ EOFU**

Visit Day ± Visit Window	D8 ±2	D15 ±2	D29 ±7	D43 ±7	D57 ±7	D71 ±7	D85 ±7	D113 ±7	D141 ±7	D169 ±7	D197 ±7	D225 ±7	D253 ±7	D281 ±7	D309 ±7	D337 ±7
Analysis Visit	**FU Week 1**	**FU Week 2**	**FU Week 4**	**FU Week 6**	**FU Week 8**	**FU Week 10**	**FU Week 12**	**FU Week 16**	**FU Week 20**	**FU Week 24**	**FU Week 28**	**FU Week 32**	**FU Week 36**	**FU Week 40**	**FU Week 44**	**FU Week 48/EOFU**
Analysis Window	**EOT DATE, +2**	**-5, +7**	**±7**	**±7**	**±7**	**±7**	**-7, +14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**
HBV DNA quantification, HBsAg quantitative, Liver function tests, Serum chemistry, Hematology, Coagulation parameters, Anti-HBs quantitative, HBeAg quantitative, Anti-HBe qualitative.																
Analysis Visit	**FU Week 1**		**FU Week 4**				**FU Week 12**			**FU Week 24**						**FU Week 48/EOFU**
Analysis Window	**EOT DATE, +7**		**-14, +28**				**-28, +42**			**-42, +84**						**-84, +14**
HBcrAg, HBV RNA.																
Analysis Visit	**FU Week 1**						**FU Week 12**			**FU Week 24**						**FU Week 48/EOFU**
Analysis Window	**EOT DATE, +35**						**±42**			**-42, +84**						**-84, +14**
CLDQ-HBV, WPAI:GH.																

Table 13: Analysis Windows for Safety, Efficacy, and other Assessments: Follow-Up Period for Participants Who Discontinue NRTI at F12

Study Stage	Follow-Up Period															
Follow up Visit	**F1**	**F4**	**F8**	**F12**	**F14**	**F16**	**F18**	**F20**	**F22**	**F24**	**F28**	**F32**	**F36**	**F40**	**F44**	**F48/ EOFU**
Visit Day ± Visit Window	**D8 ±2**	**D29 ±7**	**D57 ±7**	**D85 ±7**	**D99 ±7**	**D113 ±7**	**D127 ±7**	**D141 ±7**	**D155 ±7**	**D169 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D281 ±7**	**D309 ±7**	**D337 ±7**
Analysis Visit	**FU Week 1**	**FU Week 4**	**FU Week 8**	**FU Week 12**	**FU Week 14**	**FU Week 16**	**FU Week 18**	**FU Week 20**	**FU Week 22**	**FU Week 24**	**FU Week 28**	**FU Week 32**	**FU Week 36**	**FU Week 40**	**FU Week 44**	**FU Week 48/EOFU**
Analysis Window	**EOT DATE, +7**	**±14**	**±14**	**-14, +7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-7, +14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**

HBV DNA quantification, HBsAg quantitative, Liver function tests, Serum chemistry, Hematology, Coagulation parameters, Anti-HBs quantitative, HBeAg quantitative, Anti-HBe qualitative.

Analysis Visit	**FU Week 1**	**FU Week 4**		**FU Week 12**						**FU Week 24**						**FU Week 48/EOFU**
Analysis Window	**EOT DATE , +7**	**-14, +28**		**-28, +42**						**-42, +84**						**-84, +14**

HBcrAg, HBV RNA.

Analysis Visit	**FU Week 1**			**FU Week 12**						**FU Week 24**						**FU Week 48/EOFU**
Analysis Window	**EOT DATE , +35**			**±42**						**-42, +84**						**-84, +14**

CLDQ-HBV, WPAI:GH.

APPENDIX 3. IMPUTATION RULE FOR MISSING/PARTIAL PRIOR/CONCOMITANT MEDICATION DATES

In principle, if a medication cannot be determined as prior, concomitant, or both, it will be classified as both and summarized in both prior medication and concomitant medication. Imputation rules for partial medication dates (D = day, M = month, Y = year):

1. Missing or partial medication start date:
    a. If only D is missing, use the first day of the month.
    b. If D and M are both missing, use the first day of the year.
    c. If D, M and Y are all missing, use the informed consent date.
2. Missing or partial medication stop date:
    a. If only D is missing, use the last day of the month.
    b. If D and M are both missing, use the last day of the year.
    c. If D, M and year are all missing, assign 'ongoing' status to stop date.

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

Table 14: Prior and Concomitant Categorization of Medication

	Medication Stop Date	
Medication Start Date	**< First Dose Date of Study Drug**	**≥ First Dose Date**
< First dose date of study drug	P	PC
≥ First dose date	-	C

P: Prior; C: Concomitant

APPENDIX 4. IMPUTATION RULE FOR MISSING/PARTIAL AE DATES

In principle, if an AE contains a missing date so that it cannot be categorized as a pre-treatment AE or TEAE, it will be categorized as a TEAE.

Table 15: Imputation Rules for Partial/Missing AE Dates (D = day, M = month, Y = year)

Procedure	Missing	Additional Conditions	Imputation
1. First, impute the missing Stop date	D		Last day of the month
	D and M		Dec.31
	D, M, Y		No imputation, but assume ongoing
2. Then, compare the Stop date with the first dosing date			
a. If the stop date is before the dosing date, impute the missing start date	D		1st day of the month
	D and M		Jan.1
	D, M, Y		Jan.1 of the Y of the stop date
b. If the stop date is on or after the dosing date, impute the missing start date	D	MY same as MY of the first dosing date	D of the first dosing date
		M or Y not the same as the first dosing date	1st day of the month
	D and M	Y same as Y of the first dosing date	DM of the first dosing date
		Y is not the same as Y of the first dosing date	Jan.1
	D, M, Y		DMY of the first dosing date

APPENDIX 5. SEVERITY (TOXICITY) GRADES FOR LABORATORY ABNORMALITIES

Below parameters' toxicity grades will be assessed and based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (CTCAE 5.0 2017).

Parameter	Parameter Code	CTCAE 5.0 Term
Liver Function Tests		
Alanine Aminotransferase	ALT	Alanine aminotransferase increased
Aspartate Aminotransferase	AST	Aspartate aminotransferase increased
Alkaline Phosphatase	ALP	Alkaline phosphatase increased
Total Bilirubin	BILI	Blood bilirubin increased
Chemistry		
Albumin	ALB	Hypoalbuminemia
Gamma Glutamyl Transferase	GGT	GGT increased
Creatinine	CREAT	Creatinine increased
Calcium	CA	Hypercalcemia
		Hypocalcemia
Bicarbonate	BICARB	Blood bicarbonate decreased
Sodium	SODIUM	Hypernatremia
		Hyponatremia
Lactate dehydrogenase	LDH	Blood lactate dehydrogenase increased
Potassium	K	Hyperkalemia
		Hypokalemia
Glucose	GLUC	Hyperglycemia
		Hypoglycemia
Hematology		
Hemoglobin	HCB1	Anemia
		Hemoglobin increased
Neutrophil	NEUT	Neutrophil count decreased
Lymphocytes (absolute)	LYM	Lymphocyte count decreased
		Lymphocyte count increased
Platelets decrease	PLAT1	Platelet count decreased
Coagulation		
International Normalized Ratio/ Prothrombin time	INR	INR increased

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