Official Title: A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-2218 Alone or in Combination with Pegylated Interferon Alpha-2a

NCT Number: NCT04412863

Document Date: Statistical Analysis Plan, 15 May 2024

ORIGINAL STATISTICAL ANALYSIS PLAN (PARTS D-F)

Study Title	A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-2218 Alone or in Combination with Pegylated Interferon Alpha-2a
Brief Title	A Study to Evaluate Investigational Therapies in Chronic Hepatitis B Virus Infection Parts D-F
Study Number	VIR-2218-1001
Compound	VIR-2218 Peginterferon alfa-2a (PEG-IFNα)
Indication	Chronic Hepatitis B Virus (HBV) Infection
Study Phase	2
Study Sponsor	Vir Biotechnology, Inc. 1800 Owens Street, Suite 900 San Francisco, CA 94158, USA
Effective Date	15 May 2024

This study will be conducted in compliance with the 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) v1.0 for Study VIR-2218-1001(Parts D-F) is based on protocol amendment 8 dated 02DEC2021.

SAP Version	Date	Change	Rationale
0.1	23 Aug, 2021	Not applicable	Original version (based on protocol amendment 7 dated 29APR2021), draft
0.2	10 Nov, 2023	Protocol amendment	Protocol Amendment 8, draft
1.0	15 May, 2024	Original approved version	Protocol Amendment 8, final

1. INTRODUCTION

This statistical analysis plan (SAP) provides the outline of the final statistical analyses for the Parts D-F data collected from the VIR Biotechnology, Inc., protocol number VIR-2218-1001, "A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of VIR-2218 Alone or in Combination with Pegylated Interferon Alpha-2a". The SAP is based on clinical study protocol amendment 8 (dated 02 December 2021), the electronic case report form (eCRF) version 8 (dated on 03 March 2022). The planned analyses in this SAP may be included in clinical study report (CSR), regulatory submission, or future manuscription. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final CSR.

VIR Biometrics team or a designated contract research organization (CRO) will perform the statistical analysis. SAS version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets).

1.1. Objectives

1.1.1. Primary Objective

The primary objective is as follows:

- To evaluate the safety and tolerability of VIR-2218 alone or in combination with PEG-IFNα in non-cirrhotic adult participants with chronic HBV infection on NRTI therapy

1.1.2. Secondary Objective

The secondary objective is as follows:

- To assess the antiviral activity of VIR-2218 alone or in combination with PEG-IFNα in non-cirrhotic adult participants with chronic HBV infection on NRTI therapy

[redacted]

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[redacted]

1.2. Study Design

1.2.1. Overall Design

This is an open-label study of VIR-2218 administered alone or in combination with PEG-IFNα in non-cirrhotic adult participants with chronic HBV infection on NRTI therapy. This portion of the study is designed to evaluate the safety, tolerability, and antiviral activity of VIR-2218 administered alone or in combination with PEG-IFNα. Parts D – F are planned to be conducted at multiple clinical investigative sites in the Asia-Pacific region.

Non-cirrhotic adult participants with chronic HBV infection on NRTI therapy for ≥ 2 months, including both HbeAg-negative and HbeAg-positive, will be enrolled in Parts D – F. Cohorts 1d/e, 2d/e and 3d/e will enroll up to 15 participants each, and Cohorts 1f and 2f will enroll up to 30 participants each. Participants in Cohort 3d that have not completed the Week 12 visit may enter Cohort 2f at their Week 12 visit. Cohort 3f will include participants that qualify to enter from Cohort 2f at their Week 24 visit.

Each cohort will receive multiple doses of VIR-2218 alone or in combination with PEG-IFNα in various regimens. All cohorts within a part will receive the same dose level of VIR-2218 (200 mg for Parts D and F, 50 mg for Part E). Cohorts 2d/e, 3d/e, 1f, 2f and 3f will also receive weekly injections of PEG-IFNα.

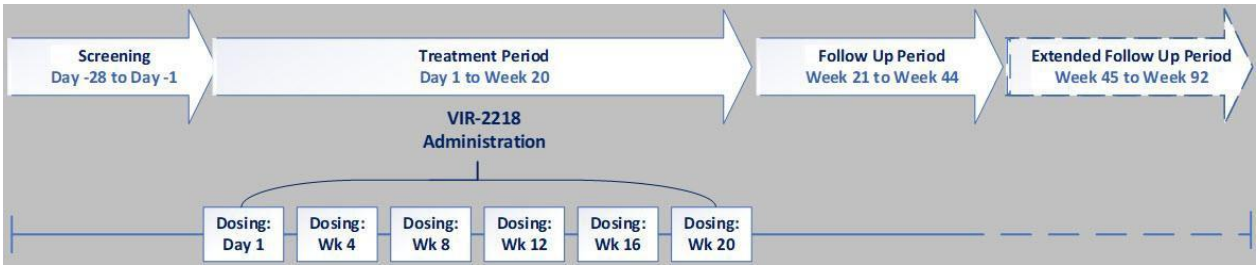
Participants will return to the clinical investigative site on an outpatient basis for safety, tolerability, and antiviral activity monitoring at specified timepoints for up to 24 weeks after the final visit in the Treatment Period. Additional HbsAg monitoring is required for participants with HbsAg decline ≥ 1-log10 relative to the Day 1 Predose level or HbsAg < 1000 IU/mL at the final required follow-up visit or Week 72 visit for Cohorts 2f and 3f. Visits will occur every 8 weeks for an additional 24-48 weeks or until the HbsAg level returns to ≥ 90% of the Day 1 Predose level.Additional HbsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

Participants who are eligible to discontinue from NRTI therapy will discontinue from the Schedule of Assessments for their enrolled cohort and will instead continue into the NRTI Discontinuation Monitoring Period of the study within 2 weeks of the investigator confirming eligibility. Participants who discontinue from NRTI therapy will be followed in the NRTI Discontinuation Monitoring Period for an additional 48 weeks from their day of NRTI discontinuation.

1.2.2. Parts D – F Treatment Plan and Regimen

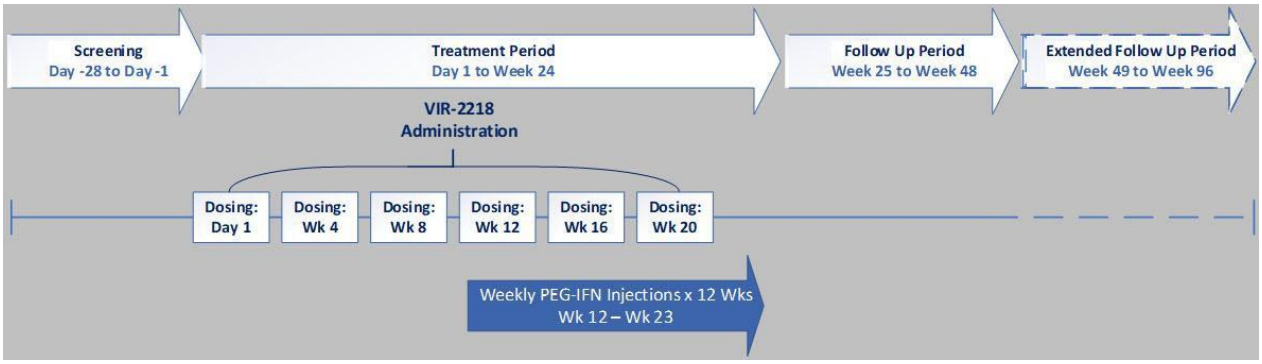
The study designs for Parts D – F are presented in protocol amendment 8 figures 3-8 (see figures 1-6 below). The cohort dosing schedule is provided in protocol amendment 8 Appendix 18. The procedures/assessments performed at each visit are described in Protocol Amendment 8 Appendices 6 to 13, and Appendix 16.

Figure 1: Design for Cohort 1d/1e



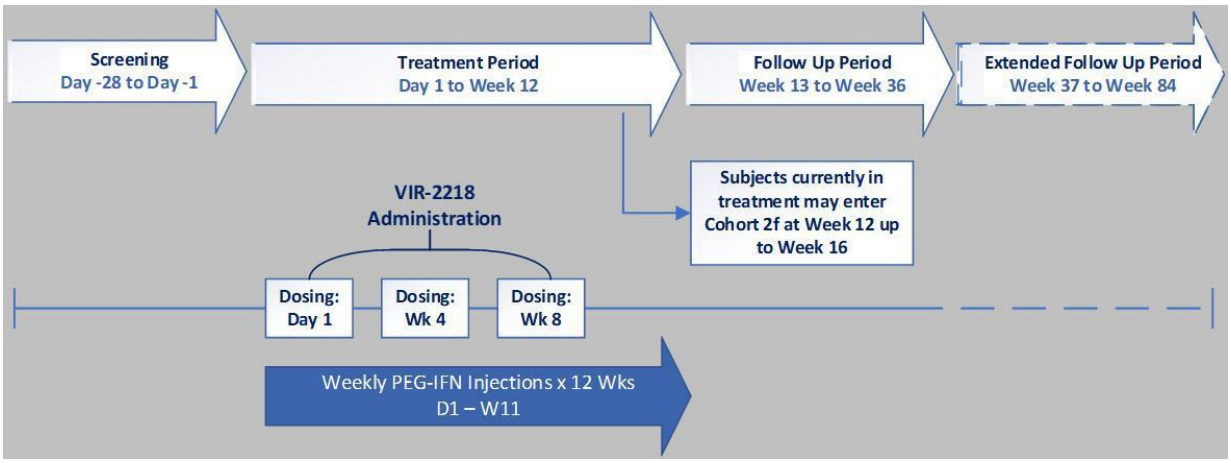
In Cohorts 1d and 1e, participants will receive 6 doses of VIR-2218 at a frequency of every 4 weeks. Each participant will receive a dose of VIR-2218 on Day 1, Week 4, and Week 8, Week 12, Week 16, and Week 20.

Figure 2: Design for Cohort 2d/2e



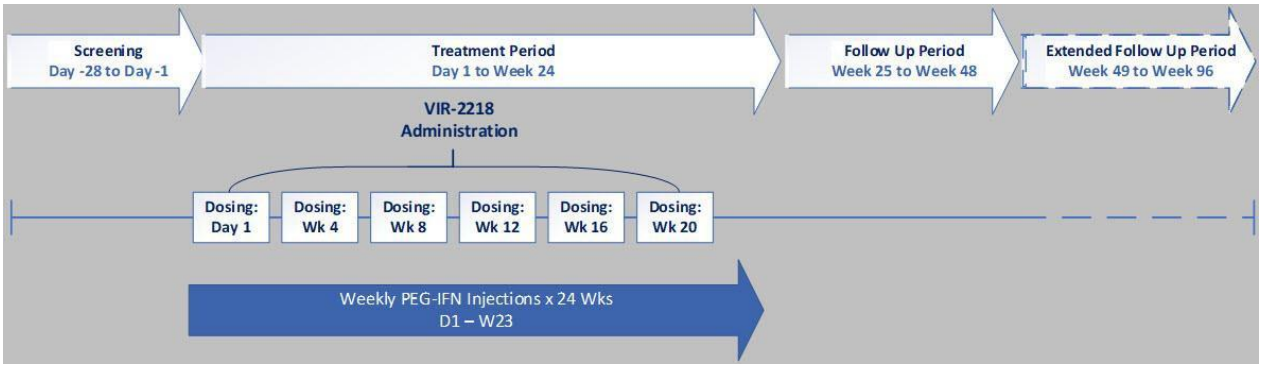
In Cohorts 2d and 2e, participants will receive up to 6 doses of VIR-2218 at a frequency of every 4 weeks. Each participant will receive a dose of VIR-2218 on Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20. Additionally, participants will receive 12 weekly doses of 180 µg PEG-IFNα, administered by SC injection, starting at Week 12 and ending on Week 23.

Figure 3: Design for Cohort 3d/3e



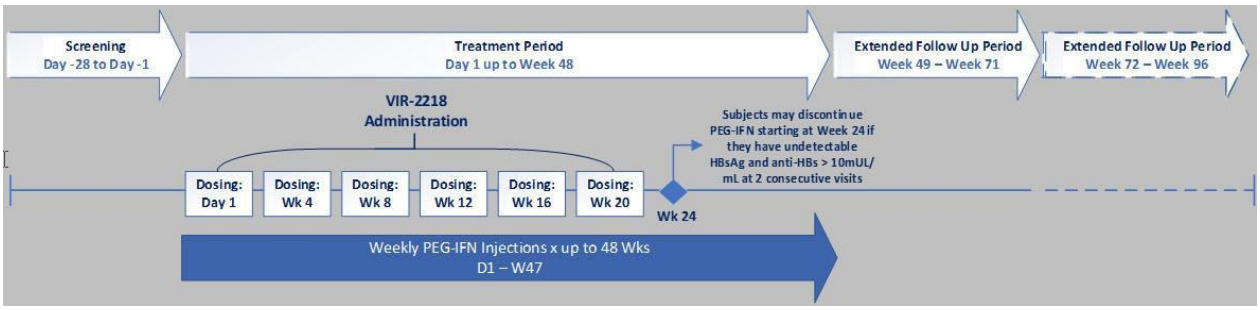
In Cohorts 3d and 3e, participants will receive 3 doses of VIR-2218at a frequency of every 4 weeks. Each participant will receive a dose of VIR-2218 on Day 1,Week 4, and Week 8. Additionally, participants will also receive 12 weekly doses of 180 µg PEG-IFNα, administered by SC injection, starting at Day 1 and ending on Week 11. Participants currently in treatment under the Cohort 3d may enter Cohort 2f at Week 12 or Week 16 as described below.

Figure 4: Design for Cohort 1f



In Cohort 1f, participants will receive up to 6 doses of VIR-2218 at a frequency of every 4 weeks. Each participant will receive a dose of VIR-2218 on Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20. Additionally, participants will receive 24 weekly doses of 180 µg PEGIFNα, administered by SC injection, starting on Day 1 and ending on Week 23.

Figure 5: Design for Cohort 2f

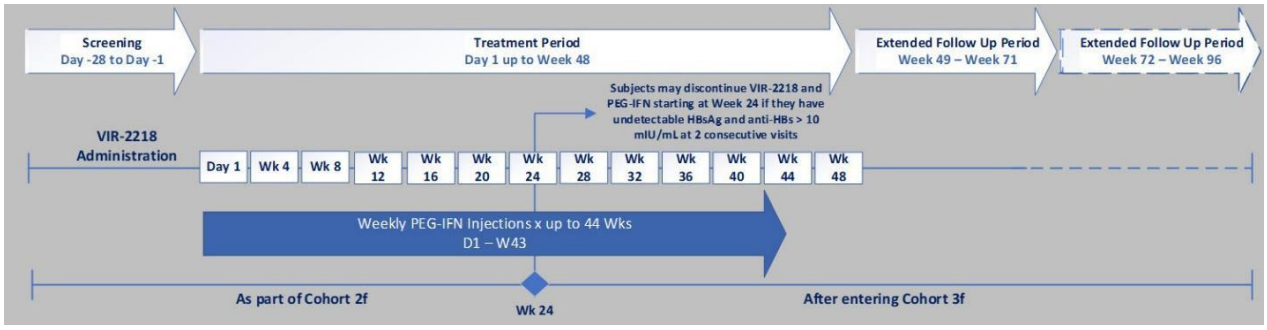


In Cohort 2f, participants will receive up to 6 doses of VIR-2218 at a frequency of every 4 weeks. Each participant will receive a dose of VIR-2218 on Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20. Additionally, participants will receive 24 to 48 weekly doses of 180 µg PEG-IFNα, administered by SC injection, starting on Day 1 and up to Week 48. All participants will receive a minimum of 24 doses of PEG-IFNα. Participants with ≤ 1 log10 IU/mL reduction from predose Day 1 baseline in HbsAg at the Week 20 visit will discontinue PEG- IFNα after 24 weeks. All other participants will continue PEG-IFNα up to Week 47 (ie, the 48th doseof PEG-IFNα) or, until HbsAg is undetectable AND anti-HBs is ≥ 10 mIU/mL for 2 consecutive visits. Participants will receive no more than 48 doses of PEG-IFNα.

Participants from Cohort 3d that are currently in the treatment period may move to Cohort 2f treatment period at their Week 12 visit. At Week 12, participants will receive a 4th dose of VIR-2218 and 13th dose of PEG-IFNα and complete the remaining treatment regimen per Cohort 2f schedule. If participants have already completed their Week 12 visit, they may move to Cohort 2f up to their Week 16 visit. Participants that enter Cohort 2f after their Week 12 but by their Week 16 visit will miss up to 1 dose of VIR-2218 and up to 4 doses of PEG-IFNα but complete the remainder of the treatment period per Cohort 2f schedule. Once participants enter Cohort 2f, they will follow the schedule for Cohort 2f.

Participants from Cohort 2f that have ≥ 1 log10 IU/mL reduction from Predose Day 1 baseline HbsAg at the Week 20 visit and have not completed their Week 24 visit may enter Cohort 3f at their Week 24 visit.

Figure 6: Design for Cohort 3f



In Cohort 3f, starting at Week 24, participants will continue VIR-2218 dosing every 4 weeks until Week 48 (ie, the 13th dose of VIR-2218) and PEG-IFNα weekly up toWeek 43 (ie, the 44th dose of PEG-IFNα) or , until HbsAg is undetectable AND anti-HBs is >=10 mIU/mL for at least 2 consecutive visits.

1.2.3. NRTI Discontinuation

In Parts D-F, the investigator will evaluate whether participants are eligible for discontinuation of NRTI therapy and consider NRTI discontinuation in participants meeting the following criteria:

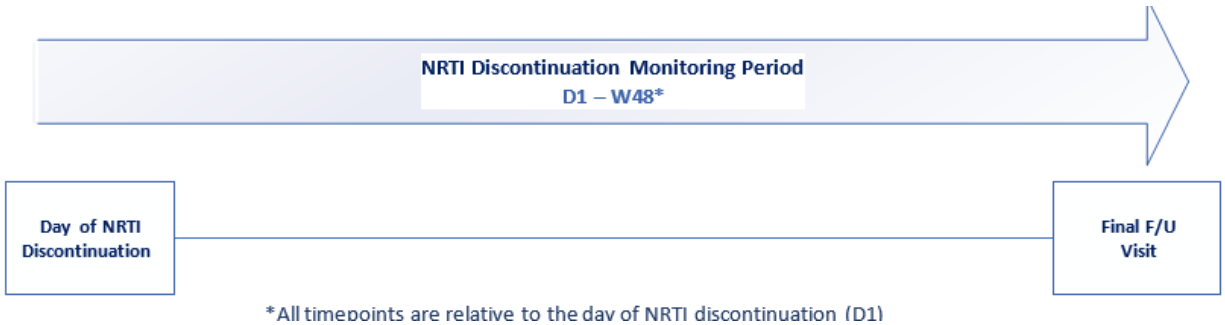
- are HbeAg-negative (defined as undetectable quantitative HbeAg)
- have ALT < 2 x ULN
- have suppression of HBV DNA (defined as < LLOQ)

AND one of the following criteria:

- have HbsAg loss (defined as undetectable HbsAg) sustained for at least 24 weeks after the final visit in the Treatment Period **OR**
- have positive anti-HBs result sustained for at least 24 weeks after the final visit in theTreatment Period **OR**
- have confirmed HbsAg levels < 100 IU/mL at the two consecutive visits at the end of the Extended Follow-Up Period

The investigator should assess participant eligibility for NRTI discontinuation. Participants who are eligible to discontinue from NRTI therapy may discontinue from the Schedule of Assessments for their enrolled cohort and instead continue into the NRTI Discontinuation Monitoring Period of the study within 2 weeks of the investigator confirming eligibility. These participants will follow the Schedule of Assessments for participants who have discontinued from NRTI therapy (Protocol Appendix 16). Participants who discontinue from NRTI therapy will be followed in the NRTI Discontinuation Monitoring Period for an additional 48 weeks from their day of NRTI discontinuation. (defined as their first day off NRTI therapy).

Figure 7: NRTI Discontinuation Monitoring Period



1.2.4. NRTI Retreatment

It is recommended that the investigator should consider retreatment with NRTI therapy during the NRTI Discontinuation Monitoring Period if participants have HBV DNA > 2,000 IU/mL concurrent with any of the following criteria at the same visit:

- Confirmed bilirubin > 2x ULN and ALT > ULN
- Any sign of hepatic decompensation (including, but not limited to, confirmed

increase in PT ≥ 2 or INR ≥ 0.5 from baseline, jaundice, ascites, encephalopathy, etc.)

- ALT > 10x ULN
- ALT > 2x ULN and ≤ 5x ULN persisting for ≥ 12 consecutive weeks
- ALT > 5x ULN and ≤ 10x ULN persisting for ≥ 4 consecutive weeks

Participants who are retreated with NRTI therapy should continue to be followed per the Schedule of Assessments for the NRTI Discontinuation Monitoring Period (Protocol Appendix 16) through the Week 48 visit.

2. STATISTICAL HYPOTHESES

All analyses are descriptive only. No hypothesis test will be performed.

3. ANALYSIS SETS

For Parts D-F of this study, analysis sets are defined as below:

Participant Analysis Set	Description
All Participant Set	All Participant Set is defined as all participants who enrolled or received any amount of study drug.
Safety Analysis Set	The Safety Analysis Set will include all participants who receive at least 1 dose of study drug of any amount. This Safety Analysis Set will be used for all safety analyses in which participants will be analyzed according to the treatments they receive, unless otherwise specified.
Antiviral Analysis Set	The Antiviral Analysis Set will include all participants in the Safety Analysis Set who have at least 1 non-missing post-baseline HBsAg to provide interpretable results for the specific antiviral activity parameters of interest.
Pharmacokinetic (PK) Analysis Set	The PK Analysis Set will include all participants in the Safety Analysis Set who have at least 1 measurable post-dose concentration data to provide interpretable results for the specific parameters of interest for the analyte under evaluation

4. STATISTICAL ANALYSES

4.1. General Considerations

The study assessments and time points schedule are provided in protocol amendment 8. All individual participant data will be presented in data listings. Data listings will contain all reported and derived data.

Continuous variable will be summarized using the following descriptive summary statistics: the number of participants (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max), unless otherwise specified (for example Geometric mean and geometric covariance will be reported for PK concentrations). 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 listings (for derived variables). Minimum and maximum values will be reported with the same precision as the units of measure. The mean, median, Q1 and Q3 values 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. The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the above-mentioned rules.

Categorical variable will be summarized using counts and percentages. Percentages will be presented to 1 decimal place. The denominator in all percentage calculations will be the number of participants in the relevant analysis set with non-missing data, unless missing category is also presented.

For categories where all participants fulfill certain criteria, the percentage value will be displayed as 100. For categories where zero participants fulfill certain criteria, there will be no percentage displayed.

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 drug. A missing baseline result will be replaced with a screening result, if available.

Change from Baseline will be calculated as post-baseline value – baseline value.

The change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available and will be treated as missing otherwise.

Study Day: The study day of an event/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, study day will be calculated as:

Study Day = (Date of Event/measurement – Date of First Study Drug Administration) + 1

Study Periods: This study includes five study periods, specifically screening period, Treatment Period, Follow-up Period, Extended Follow-up Period and NRTI Discontinuation Monitoring Period. Details of each period for specific cohort can be found in the Figures 1 to 6, or the Protocol Amendment 8 Appendices 6 to 13, and Appendix 16.

End of Treatment Date: Defined as last date a participant is given any study drug (VIR 2218 or PEG-IFNα).

Treatment Completion: Participant completed scheduled administration of study drugs (VIR-2218 or PEG-IFNα). The treatment completion for VIR-2218 and PEG-IFNα are defined separately. The information of treatment completion is collected in eCRF.

Completed Follow-up Period: Participant completed 24-week follow-up after the last visit in the treatment period, regardless of missed visits in between.

Completed Extended Follow-up Period: Participants completed extended follow-up that occur every 8 weeks for up to 48 weeks, regardless of missed visits in between.

Treatment-emergent (TE) Period: Unless otherwise specified, the TE period is defined as the time period from the first dose date of study drug (VIR 2218 or PEG-IFNα) to last dose date of VIR-2218 +30 days (or PEG-IFNα +7 days, whichever later).

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

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

Analysis Visit Window:

The analysis visit windows will be used to derive protocol defined visits (scheduled visits).

First, Baseline visit is set as target study day 1 with analysis visit window of ≤1 study day Pre-dose.

For any subsequent analysis visit, the analysis visit window can be derived based on study day as follows:

(1): First get the target study day for this analysis visit, which is "Study Week Number*7 +1", for example, for cohort 1d Week 8, the target day is 8x7+1= Day 57

(2): Get the gap between this analysis visit and previous scheduled visit, the start study day (lower bound) for this analysis visit window will be half the gap before target day. For Week 8 of cohort 1d, the previous schedule visit is "Week 6", the gap between Week 6 and Week 8 is 14 days, then the start study day for Week 8 will be half the gap before target day, which is Day 57-7= Day 50 (not include day 50).

(3): Get the gap between this visit and next scheduled visit, the end study day (upper bound) for this analysis visit window will be the half gap after the target day. For Week 8 of cohort 1d, the

next scheduled visit is Week 10, the gap between Week 8 and Week 10 is also 14 days, then the end study day for Week 8 will be Day 57+7=Day 64.

(4): Therefore, we get the analysis visit window for Week 8 of cohort 1d as study day (50, 64].

The analysis visit windows for other scheduled visits can be derived similarly.

For the last visit, the end study day will be derived that the study window symmetrical around the target study day. For example, for cohort 1d, the last scheduled visit is Week 92 (target day 645) and previous scheduled visit is Week 84, the lower bound for analysis window for Week 92 is Day 645-4x7=Day 617, then we set the upper bound symmetric at target day as: Day 645+4x7= Day 673. As Week 92 is the end of extended follow up period, the participant generally will terminate the study earlier than Day 673, therefore the analysis visit window for Week 92 can be set as (617, min (673, end of Extended FU).

Table 1 below shows the example for analysis visit windows for Cohort 1d. The same logic applies to other cohorts.

Table 1: Analysis Visit Window for Efficacy and Safety Analysis in Cohort 1d (Standard)

Assessment	Scheduled Visit	Target Day	Analysis Window
Cohort 1d (Standard): • Serum Chemistry • Liver Function Tests • Hematology • Coagulation • HBsAg quantitative • Anti-HBs quantitative and qualitative (no week 2, week 4 windows set as [2,36]) • Vital signs (up to week 44) • Symptom- directed physical examination (up to week 40)	Day 1 (Baseline)	1	≤1 Pre-dose
	Week 2	15	[2,22]
	Week 4	29	(22, 36]
	Week 6	43	(36, 50]
	Week 8	57	(50, 64]
	Week 10	71	(64, 78]
	Week 12	85	(78, 92]
	Week 14	99	(92, 106]
	Week 16	113	(106, 120]
	Week 18	127	(120, 134]
	Week 20	141	(134, 155]
	Week 24	169	(155, 183]
	Week 28	197	(183, 211]
	Week 32	225	(211, 239]
	Week 36	253	(239, 267]
	Week 40	281	(267, 295]
	Week 44	309	(295, 337]
	Week 52	365	(337, 393]
	Week 60	421	(393, 449]
	Week 68	477	(449,505]
	Week 76	533	(505,561]
	Week 84	589	(561,617]
	Week 92	645	(617, min (673, end of Extended FU)

The table above provides the analysis windows for tests or measurements scheduled to be collected at all protocol defined visits, such as laboratory assessments (Serum Chemistry, Liver Function Tests, Hematology, Coagulation, HBsAg quantitative, and Anti-HBs quantitative and qualitative (no week 2, week 4 windows set as [2,36]), or assessments collected at visits continuously up to specific week (like vital signs up to week 44).

For lab tests or measurements scheduled to be done less frequently (for example HBeAg or Anti-HBe), the analysis windows for the corresponding visits can be derived similarly, as shown in Table 2

Table 2: Analysis Visit Window for HBeAg and Anti-HBe in Cohort 1d (Non-Standard)

Assessment	Scheduled Visit	Target Day	Analysis Window
Cohort 1d (non-standard)			
• HBeAg quantitative • Anti-HBe (no day 1, use screening as baseline)	Day 1 (Baseline)	1	≤1 Pre-dose
	Week 4	29	(2, 43]
	Week 8	57	(43, 71]
	Week 12	85	(71, 99]
	Week 16	113	(99, 127]
	Week 20	141	(127, 155]
	Week 24	169	(155, 197]
	Week 32	225	(197, 267]
	Week 44	309	(267, 351]
	Week 52	365	(351, 393]
	Week 60	421	(393, 449]
	Week 68	477	(449,505]
	Week 76	533	(505,561]
	Week 84	589	(561,617]
	Week 92	645	(617, min (673, End of Extended FU)]

For participants with unscheduled or early termination lab visits, if the endpoint is based on scheduled measurement(s), then unscheduled and early termination measurements will be included only if a scheduled measurement is not available and the unscheduled and early termination measurement falls within the visit window for the scheduled visit.

For simplicity of programming, we will map all lab visits (scheduled, unscheduled or early termination) to analysis visits, then choose scheduled visit lab over unscheduled/early termination if they fall into same analysis window.

If two or more measurements mapped to the same analysis visit, the rule of "scheduled visit >> closest to the target day" will be used to select the appropriate measurement for the analysis visit. The analysis windows for other cohorts and other laboratory measurements will be derived similarly.

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

Incomplete/Missing data: In general, missing data will not be imputed, unless specified otherwise. For efficacy response variables, the missing equals failure (MEF) approach will be used for the primary analysis.

Laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 30, a value of 29 will be assigned; if the result of a continuous laboratory test is < 30.0, a value of 29.9 will be assigned).

Specifically, for summary reports of virology tests, the results of <LLOQ will be imputed as 0.04 IU/mL for HBsAg (reported as <0.05IU/mL), 4.99 mIU/mL for anti-HBs (reported as <5.00 mIU/mL), 0.10 IU/mL for HBeAg (reported as <0.11 IU/mL) and 9 IU/mL for HBV DNA (reported as <10 IU/mL).

No imputation will be used in individual participant listings for all virology tests and safety laboratory parameters.

For missing or partial missing of AE and concomitant treatment dates, the imputation rule is included in Appendix 2.

Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:

- Date only: YYYY-MM-DD
- Date and time: YYYY-MM-DD HH:MM

If only partial information is available, unknown components of the date or time will be presented as 'UN' (unknown), i.e., '2016-UN-UN'. Times will be reported in military time.

4.2. Background Characteristics

4.2.1. Participant Disposition

Participant disposition will be summarized using counts and percentages by Parts D-F cohorts based on All Participant Set. The number of participants of analysis sets, the number and percentage of participants who completed treatment, completed the study per protocol, along with primary reason for treatment discontinuation and early termination from the study will be summarized in the disposition table. Number and percentage of participants who meet NRTI discontinuation criteria, number and percentage of participants who meet NRTI retreatment criteria will also be summarized.

Subject-level listings for disposition information collected will be presented.

4.2.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by cohort using descriptive statistics including n, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous variables and number and percentage for categorical variables. All summaries will be based on Safety Analysis Set. No baseline subgroup comparison will be performed.
Demographic data will include baseline age (years), age category, sex, ethnicity, race, country of enrolment.

Baseline characteristics will include baseline weight (kg), height (cm), BMI (kg/m^2). BMI also categorized as <25, >=25 and <30, >=30.

Baseline disease characteristics will include the following:

- HBsAg (IU/mL) and HBsAg (Log_{10} IU/mL) at baseline (continuous)
- Baseline HBsAg level (IU/mL), categorized as follows:
  - – <100
  - ≥ 100 – <1000
  - ≥ 1000 – <3000
  - ≥ 3000 – <10000

- – <1000
- ≥ 1000

- – <1500
- ≥ 1500

- – <3000
- ≥ 3000

- – <10000
- ≥ 10000

- HBV DNA (IU/mL) and HBV DNA (log10 IU/mL) at baseline
- Baseline Estimated Creatinine Clearance (mL/min) by serum-creatinine based Cockroft-Gault (C-G) equation:

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

- Baseline HBeAg status (categorized as HBeAg positive and HBeAg negative)
- Baseline ALT level (U/L) (continuous)
- Baseline ALT level (U/L), categorized as <=ULN, >ULN and <=2xULN, >2xULN
- Fibroscan result (kPa) at screening
- Cirrhosis status at screening

Subject-level demographics and baseline characteristics will be listed.

4.2.3. Viral Serology at Screening

Viral serology results at screening will be listed, including Active infection with HIV infection, HCV infection, confirmation of chronic HBV infection and hepatitis Delta virus infection. Chronic HBV infection as defined by a positive serum HBsAg for ≥ 6 months.

4.2.4. Urine Drug Test

Urine drug test results obtained at screening will be presented in the listing.

4.2.5. Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 or later. Medical history will be presented in the listing.

4.2.6. Prior and Concomitant Medications

Prior and concomitant medications used in this study will be coded by the World Health Organization Drug Dictionary (WHODD) version 202009 or later and summarized (number and percentage) by preferred name and by treatment cohort based on Safety Analysis Set.

Prior medication: any medication that started prior to the first dose of study drug (Study Day 1), regardless of when it ended.

Concomitant medication (CM): medication continued or newly received after Study Day 1.

If medication start date is at or after date of first dosing of study drug, then medication will be summarized as concomitant medication regardless of whether the medication end date is missing or not. If the medication end date is before the date of first dosing of study drug, then the medication will be counted as prior medication regardless of whether the medication start date is missing or not. Note that medication that started prior to first dosing of study drug and continued after dosing will be summarized as both prior and concomitant medications.

For medications with partial start dates, missing month will be imputed with January and missing day will be imputed with 1. For medications with partial stop dates, missing month will be imputed with December and missing day will be imputed with the last day of the month. More details can be referred in Appendix 2.

Both prior and concomitant medications will be summarized by treatment cohort based on Safety analysis Set. Prior medications (including prescription medications, over the counter medications, natural remedies, herbal remedies, vitamins, and supplements) taken by the participant from 30 days prior to the screening visit and up to the last study visit will be recorded and reported.

Medications will be summarized (number and percentage) by ATC class Level 3 and preferred names. Participants who used the same medication on multiple occasions will only be counted once in the specific category. Preferred names will be sorted alphabetically. In addition, the number of participants who used at least one prior/concomitant medication during the study will be presented.

Subject-level prior medications and concomitant medications will be listed separately.

4.2.7. Protocol Deviations

An important protocol deviation is a protocol deviation 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.

Important protocol deviation, COVID-19 protocol deviation and COVID-19 important protocol deviation will be identified during the study and finalized before final database lock and will be summarized by category and by treatment cohort using descriptive statistics.

Important protocol deviations will also be provided in an individual participant data listing. COVID-19 protocol deviations and COVID-19 important protocol deviations will also be listed.

4.3. Primary Endpoint Analysis

The primary endpoints for Parts D-F will be based on Safety Analysis Set. Details will be described in the safety analyses section.

4.3.1. Primary Endpoints

Primary endpoints for Parts D-F are:

- Incidence of AEs
- Clinical assessments include but not limited to laboratory test results (such as liver functional lab tests, hematology lab tests, vital signs, physical examination, etc.).

4.3.2. Sensitivity Analysis

Sensitivity Analysis is not planned for Parts D-F.

4.4. Secondary Endpoint Analysis

4.4.1. Secondary Endpoints

The Secondary Endpoints are:

- Change from baseline in serum HBsAg at any timepoint
- Proportion of participants with serum HBsAg loss (undetectable HBsAg) at any timepoint
- Proportion of participants with sustained serum HBsAg loss (undetectable HBsAg) for at least 24 weeks
- Proportion of participants with anti-HBs seroconversion at any timepoint
- For HBeAg-positive participants: proportion of participants with HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion at any timepoint

4.4.2. Secondary Endpoints Analysis

All secondary endpoint analysis will be based on Antiviral Analysis Set.

HBsAg (log10 IU/mL) value and change from baseline will be summarized as continuous and categorical variables by visit and treatment cohort. Mean change from baseline in HBsAg will be plotted by visit and treatment cohort. The proportion of HBsAg categories at Baseline, EOT and 24 weeks post-EOT will be plotted by treatment cohort.

The lowest HBsAg post-baseline value (nadir) and change from baseline at nadir will also be summarized by treatment cohort.

HBsAg loss is defined as undetectable HBsAg or HBsAg <LLOQ (0.05 IU/mL).

The number and percentage of participants with serum HBsAg loss at any time, EOT, 24 weeks post-EOT and by scheduled visit will be summarized by treatment cohort along with 95% Clopper-Pearson confidence intervals (CI). The number and percentage of participants with HBsAg loss and anti-HBs >=10 mIU/mL at any time, EOT, 24 weeks post-EOT and by scheduled visit will be summarized by treatment cohort along with 95% Clopper-Pearson CI.

The number and percentage of participants with serum HBsAg loss sustained for at least 24 weeks will be summarized by treatment cohort along with 95% Clopper-Pearson CI.

The number and percentage of participants with serum HBsAg loss sustained for at least 24 weeks and with anti-HBs >=10 mIU/mL will be summarized by treatment cohort along with 95% Clopper-Pearson CI.

Anti-HBs seroconversion is defined as anti-HBs quantitative value changed from baseline <LLOQ (5 mIU/mL) to post-baseline >=LLOQ. The number and percentage of participants with anti-HBs

seroconversion at any time, at EOT, 24 weeks post-EOT and by scheduled visit will be summarized by treatment cohort along with 95% Clopper-Pearson CI. Participants with anti-HBs >=LLOQ at baseline will be excluded from the analysis.

Among participants who are HBeAg-positive at baseline, the number and percentage of participants with HBeAg loss (undetectable HBeAg or < LLOQ (0.11 IU/mL)) at any time, EOT, 24 weeks post-EOT and by scheduled visit, will be summarized by treatment cohort along with 95% Clopper-Pearson CI. Similarly, the number and percentage of participants with HBeAg loss and anti-HBe seroconversion (defined as qualitative anti-HBe changed from baseline negative to post-baseline positive) will be summarized.

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4.6. Multiplicity Adjustment

Not applicable for this study.

4.7. Safety Analyses

All safety analyses will be based on Safety Analysis Set. Participants will be analyzed according to the treatment they received in the Treatment Period.

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

- TEAEs
- Clinical laboratory
- Vital signs
- Physical Examinations
- Alcohol Assessment

Only descriptive analysis will be performed. Summary tables will be presented by the treatment cohort. Vital signs, physical examinations and alcohol assessment will be listed only.

4.7.1. Extent of Exposure

Exposure summaries will be based on Safety Analysis Set.

Study participants are to be treated every 4 weeks for VIR-2218 and weekly for PEG-IFNα. Details for the planned total duration of treatment for each study drug are described in Section 1.2.2. Actual total treatment days may be slightly different from the targeted days due to visit windowing over the course of the study.

The number and percentage of participants who received the full dose of treatment, as well as the number of participants with interruption, dose reduction (PEG-IFNa only), treatment discontinuation will be summarized.

Exposure duration will be summarized descriptively (n, mean, SD, median, min, max) by study treatment and cohort. Exposure duration (week) will be calculated by (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. For an exposure duration involving more than one treatment, DoseFreq will be the longest dosing frequency.

The number and percentage of participants with exposure duration category will also be summarized by study treatment and cohort.

The exposure duration is categorized as below:

- ≤ 8 weeks
- 8 - ≤ 12 weeks
- 12 - ≤ 20 weeks
- 20 - ≤ 24 weeks
- 24 - ≤ 48 weeks

- 48 - < 53 weeks

4.7.1.1. Treatment Compliance

Study treatment compliance is calculated as:

Treatment compliance (%) = [total amount (mg/μg) of study drug injected or taken] / [total amount (mg/μg) of study drug planned to be injected or taken] x 100%.

Treatment compliance will be summarized by study treatment and cohort based on Safety Analysis Set.

The treatment compliance of VIR-2218 and PEG-IFNα will be summarized by cohort with the following categories:

- >90% - <=100%
- >80% - <=90%
- >70% - <=80%
- <=70%

The planned dose for each treatment cohort is calculated as follows:

Cohort	VIR-2218 Full Dose	PEG-IFNα Full Dose
1d	1200 mg	-
2d	1200 mg	2160 μg
3d	600 mg	2160 μg
1f	1200 mg	4320 μg
2f	1200 mg	8640 μg
3f	2600 mg	7920 μg

4.7.2. Adverse Events (AEs)

Adverse events will be analyzed based on Safety Analysis Set. For analysis purposes, AEs will be classified as pre-treatment AEs, TEAEs or post-treatment AEs.

Pre-treatment AEs will be defined as AEs that started after informed consent up to the first dose of study drug.

Treatment-emergent AE (TEAE) is defined as any AE that increased in severity or that was newly developed on or after the date of the first dose of study treatment through the end of TE period.

Post-treatment AEs will be defined as AEs that started after 30 days post the last dose of study drug. All adverse events will be coded using MedDRA version 23.1 or later and graded using Common Terminology Criteria for Adverse Events (CTCAE v5.0)

Adverse event summary tables will be presented for TEAEs only. Summaries will be presented using number and percentage of participants by treatment cohort and overall, sorted by descending order of counts in the total column. An additional column for VIR-2218+PEG-IFNa combination therapies (2d, 3d, 1f, 2f, and 3f) will also be included in all TEAE tables. All AEs will be listed by the treatment cohort.

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

- Participants with any TEAEs
- Participants with TEAEs by maximum severity (*or toxicity grade*)
- Participants with TEAEs by strongest relationship to study treatment
- Participants with Grade 3/4/5 TEAEs
- Participants with TEAEs leading to treatment discontinuation
- Participants with TEAEs leading to treatment interruption
- Participants with study treatment related TEAEs
- Participants with serious TEAEs
- Participants with study treatment related serious TEAEs
- Participants with TEAEs leading to death

The following summary tables of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) using frequency count and percentage (i.e., number and percentage of participants with an event), and by treatment cohort:

- TEAEs
- Study treatment related TEAEs
- TEAEs by maximum severity
- TEAEs by strongest relationship
- Grade 3/4/5 TEAEs
- Serious TEAEs
- Treatment related serious TEAEs
- TEAEs leading to treatment discontinuation.

The following summary tables of TEAEs will be presented by PT and by treatment cohort:

- TEAEs
- Serious TEAEs

For AEs with completely missing or partially missing start date, if there is no clear evidence that the AEs are pre-treatment or post-treatment, the AEs will be classified as TEAEs.

Adverse events that have missing onset dates will be considered treatment-emergent unless the stop date is known to be prior to the first administration of the study drug.

Details for imputing missing or partial start/stop dates of adverse events are described in Appendix 2.

Participants with multiple occurrences of the same adverse event or a continuing adverse event will be counted once, and only the maximum severity (highest grade) level will be presented in the severity summaries, and the strongest relationship to study treatment will be presented in the relationship summaries.

The following TEAEs will be listed:

- SAEs
- Grade 3/4/5 TEAEs
- TEAEs leading to death
- TEAEs leading to study treatment interruption
- TEAEs leading to study treatment discontinuation

4.7.3. Additional Safety Assessments

Additional safety assessments include clinical laboratory, vital signs, physical examinations, and alcohol intake.

4.7.3.1. Clinical Laboratory

Clinical laboratory data will be summarized by lab parameter, treatment cohort and by visit. The analysis will be based on values reported in conventional unit.

The observed value and change from baseline will be summarized by lab parameter, treatment cohort and visit.

Individual participant hematology, chemistry, coagulation, and urinalysis data will be listed by treatment cohort, subject ID and visit in chronological order including data collected from both scheduled and unscheduled visits. Values falling out of the relevant normal range (between the values of LLN and ULN) will be flagged as appropriate.

In addition, results of urine/serum pregnancy test will be listed.

For selected clinical laboratory assessments (Appendix 3), the number and percentage of participants who meet threshold criteria based on the most severe post-baseline abnormality (including both increased and decreased abnormality, if applicable) will be summarized by cohort during the TE period. The threshold criteria to grade laboratory abnormalities will refer to the standard toxicity grading according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, including severity (toxicity) grades 1 to 4 (Grade 5 death related to AE will not be presented but will be included in the "Any grade" category in the table). The normal values that do not meet the criteria will be grade 0. The treatment-emergent laboratory Events of Clinical Interest (ECI) related to ALT abnormalities are defined as:

- ALT > 3x ULN, if Day 1 pre-dose ALT ≤ ULN
- ALT > 2x baseline, if Day 1 pre-dose ALT > ULN

Laboratory ECI is considered resolved when the ALT levels return to ≤ baseline or ≤ ULN, whichever is higher.

Number and percentage of participants with ECI will be summarized by treatment cohort and by visit. Number and percentage of participants with ECI resolved will be summarized by treatment cohort and by visit.

Participant with ECI and the ECI resolution will be listed.

4.7.3.2. Vital Signs

Vital signs parameters include:

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

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

4.7.3.3. Physical Examination

Physical examination results will be listed by treatment cohort and by visit.

4.7.3.4. Alcohol Assessment

Alcohol intake will be listed by treatment cohort and by visit.

4.8. Pharmacokinetic Analysis

Individual VIR-2218 and its metabolite concentrations in plasma and urine, when applicable, will be listed and summarized by nominal sampling time, treatment cohort, and study part using descriptive statistics (n, mean, SD, coefficient of variation [CV%], median, min, max, geometric mean, and geometric CV%).

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

Amount of individual VIR-2218 and its metabolite in urine will be listed and summarized by nominal sampling time, treatment cohort, and study part using descriptive statistics. Urine volume will also be listed. Amount is calculated based on concentration in urine and urine volume.

4.9. Interim Analysis

Interim analysis is not planned in this study.

4.10. Modifications

4.10.1. Modifications to the Approved Study Protocol

An additional analysis set (All Participant Set) is defined for the summary of participant disposition and associated listings.

The secondary endpoint of "Mean maximum reduction of serum HBsAg at any timepoint" is changed to "Change from baseline in serum HBsAg at any timepoint", in the meantime, summaries of HBsAg at Nadir and HBsAg change from baseline at Nadir are added.

Due to the characteristics of the study and limited sample size, the hypothesis test described in protocol amendment 8 section 9.9 will not be performed.

4.10.2. Modifications to the Approved Statistical Analysis Plan

Not applicable.

5. SAMPLE SIZE DETERMINATION

In total, Parts D - F are planned to enroll 150 participants.

For Parts D and E, no formal sample size calculation was conducted. The sample size is up to 15 participants per cohort in Cohorts 1d/e, 2d/e and 3d/e (up to 90 participants in total). For Part F, up to 30 participants in Cohort 1f and up to 30 participants between Cohort 2f and 3f (up to 60 participants in total) are planned to complete the study, including participants rolled over from Cohort 3d into Cohort 2f and participants rolled over from Cohort 2f into Cohort 3f.

The maximum sample size of 30 participants will provide 84% statistical power to detect a difference of 22% in HBsAg loss rate, when comparing to 8% HBsAg loss rate for patients assessed 24 weeks after completing a 1-year course of PEG-IFNα therapy (Wong 1993; Konerman 2016), using a two-sided binomial distribution exact test with a significance level of 0.05.

6. SUPPORTING DOCUMENTATION

APPENDIX 1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index (kg/m2)
BQL	below quantitation limit
CI	confidence interval
CM	concomitant medication
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
eCRF	electronic case report form
ECI	Events of Clinical Interest
HBV	hepatitis B virus
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
ICF	informed consent form
LOD	limit of detection
LLOQ	lower limit of quantitation
ISR	injection site reaction
Max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum value
PK	pharmacokinetic/pharmacokinetics
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation

SOC	system organ class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary

APPENDIX 2. IMPUTATION RULE FOR PARTIAL AE AND CM DATES

Imputation Rules for Partial or Missing Stop Dates for AE and CM:

- If the month and year are presented, impute the day by the last day of that month.
- If only the year is presented, impute by December 31st of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

Imputation Rules for Partial or Missing Start Dates for AE and CM:

- If the month and year are presented, impute the day by the first day of that month. If the month and year are the same as those of the date of first dose, impute the day with the day of first dose.
- If only the year is presented, impute by January 1st. If the year is the same as the year of the date of first dose, impute by the date of the first dose.
- If the start date is entirely missing, impute by the date of the first dose.

AE/Medication with a missing start time occurring on the day of the first dose will be set to a TEAE/CM, unless the end time of the AE/medication is before the first dose time.

APPENDIX 3. SELECTED CLINICAL LABORATORY PARAMETERS FOR LAB ABNORMALITY ANALYSIS

The lab abnormality analysis for the parameters below will be conducted based on the toxicity grade of the CTCAE v5.0.

Parameter	CTCAE 5.0 Term for toxicity
Liver Function Test	
Alanine Aminotransferase (ALT)	Alanine aminotransferase increased
Aspartate Aminotransferase (AST))	Aspartate aminotransferase increased
Alkaline Phosphatase (ALP)	Alkaline phosphatase increased
Bilirubin	Blood bilirubin increased
Chemistry	
Albumin	Hypoalbuminemia
Gamma Glutamyl Transferase (GGT)	GGT increased
Carbon dioxide/Bicarbonate	Blood bicarbonate decreased
Creatinine	Creatinine increased
Creatinine clearance	Chronic kidney disease (Creatinine clearance decreased)
Calcium	Hypercalcemia
	Hypocalcemia
Lactate dehydrogenase (LDH)	Blood lactate dehydrogenase increased
Lipase	Lipase increased
Sodium	Hypernatremia
	Hyponatremia
Potassium	Hyperkalemia
	Hypokalemia
Glucose	Hypoglycemia
Uric acid	Hyperuricemia
Hematology	
Hemoglobin	Anemia
	Hemoglobin increased
Neutrophil	Neutrophil count decreased
Lymphocytes (absolute)	Lymphocyte count decreased

Parameter	CTCAE 5.0 Term for toxicity
	Lymphocyte count increased
Platelets decrease	Platelet count decreased
White blood cell (Leukocytes)	Leukocytosis
	White blood cell decreased
Coagulation	
International Normalized Ratio/ Prothrombin time	INR increased

REFERENCES

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