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: Amendment 8, 02 December 2021

CLINICAL STUDY PROTOCOL

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
Sponsor:	Vir Biotechnology, Inc. 499 Illinois Street, Suite 500 San Francisco, CA 94158, USA
Investigational Product:	VIR-2218
Clinicaltrials.gov ID:	Parts A-C: NCT03672188 Parts D-F: NCT04412863
Indication:	Chronic Hepatitis B Virus (HBV) Infection
Protocol ID:	VIR-2218-1001
Vir Study Director:	PPD [redacted]
Protocol Version/Date:	Amendment 8: 02 Dec 2021

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PROTOCOL SYNOPSIS

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
Clinical Investigative Sites Planned:	Part A is planned to be conducted at 1 clinical investigative site. Parts B-F are planned to be conducted at multiple clinical investigative sites in the Asia-Pacific region.
Phase	**Part A:** Phase 1 Single Ascending Dose (SAD) **Part B/C:** Phase 2 Multiple Ascending Dose (MAD) **Parts D - F**: Phase 2
Number of Subjects Planned:	**Parts A – C**: Up to 104 subjects **Part D**: Up to 45 subjects **Optional Part E:** Up to 45 subjects **Optional Part F:** Up to 60 subjects
Target Population:	**Part A:** Up to 56 healthy adult subjects **Part B/C:** Up to 48 non-cirrhotic adult subjects with chronic hepatitis B virus (HBV) infection on nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy **Part D – F:** Up to 150 non-cirrhotic adult subjects with chronic HBV infection on NRTI therapy. A target of 5 HBeAg-positive subjects will be enrolled per cohort. The target for each cohort will be to enroll approximately 10% of subjects with screening HBsAg level >10,000 IU/mL.
Diagnosis and Main Eligibility Criteria	**Part A**: healthy adult subjects **Part B/C**: non-cirrhotic adult subjects with chronic HBV infection **Part D – F:** non-cirrhotic adult subjects with chronic HBV infection

Duration of Study Participation:	**Part A:** The estimated total time on study, inclusive of screening and follow-up, for each subject is up to 16 weeks. The duration of treatment is a single dose, which can consist of up to 3 subcutaneous (SC) injections based on the assigned dose level. **Part B/C:** The estimated total time on study, inclusive of screening and follow-up, for each subject is up to 20 weeks. For subjects requiring additional HBsAg monitoring, subjects will continue into the Extended Follow Up period and the estimated total time on study is up to 52 weeks. The duration of treatment is 2 doses 4 weeks apart, consisting of up to 2 SC injections per dose based on the assigned dose level. **Part D and E** **Cohort 1d and optional Cohort 1e:** The estimated total time on study, inclusive of screening and follow-up, for each subject is up to 48 weeks. The duration of VIR-2218 treatment is 6 doses, each given 4 weeks apart. The duration of follow-up is 24 weeks after the last visit in the Treatment Period. For subjects requiring additional HBsAg monitoring, subjects will continue into the Extended Follow Up period and the estimated total time on study is up to 96 weeks. For subjects who discontinue NRTI therapy, the estimated total time on study is up to 144 weeks. **Cohort 2d and optional Cohort 2e:** The estimated total time on study, inclusive of screening and follow-up, for each subject is up to 52 weeks. The duration of VIR-2218 treatment is 6 doses, each given 4 weeks apart. The duration of PEG-IFNα therapy is 12 doses, each given 1 week apart. PEG-IFNα will be initiated 12 weeks after the first dose of VIR-2218. The duration of follow-up is 24 weeks after the last visit in the Treatment Period. For subjects requiring additional HBsAg monitoring, subjects will continue into the Extended Follow Up period and the estimated total time on study is up to 100 weeks. For subjects who discontinue NRTI therapy, the estimated total time on study is up to 148 weeks. **Cohort 3d and optional Cohort 3e:** The estimated total time on study, inclusive of screening and follow-up, for each subject is up to 40 weeks. The duration of VIR-2218 treatment is 3 doses, each given 4 weeks apart. The duration of PEG-IFNα therapy is 12 doses, each given 1 week apart. The duration of follow-up is 24 weeks after the last visit in the Treatment Period. For subjects requiring additional HBsAg monitoring, subjects will continue into the Extended Follow Up period and the estimated total time on study is up to 88 weeks. For subjects who discontinue NRTI therapy, the estimated total time on study is up to 136 weeks. Some subjects may move to Cohort 2f at their Week 12 or up to Week 16 visit. These subjects will subsequently follow the schedule for Cohort 2f. **Optional Part F** **Optional Cohort 1f:** The estimated total time on study, inclusive of screening and follow-up, for each subject is up to 52 weeks. The duration of VIR-2218 treatment is 6 doses, each given 4 weeks apart. The duration of PEG-IFNα therapy is 24 doses, each given 1 week apart. The duration of follow-up is 24 weeks after the last visit in the Treatment Period. For subjects requiring additional HBsAg monitoring, subjects will continue into the Extended Follow Up period and the estimated total time on study up to 100 weeks. For subjects who discontinue NRTI therapy, the estimated total time on study is up to 148 weeks. **Optional Cohort 2f:** The estimated total time on study, inclusive of screening and initial Extended Follow-Up, for each subject is up to 76 weeks. The duration of VIR-2218 treatment is 6 doses, each given 4 weeks apart. The duration of PEG-IFNα therapy is a minimum of 24 doses and up to a total of 48 doses, each given 1 week apart. All subjects will continue per treatment period schedule up to Week 48, including subjects that discontinue PEG-IFNα prior to Week 48. All subjects will continue into the Extended Follow Up period after Week 48 visit to Week 72 visit. Subjects requiring additional HBsAg monitoring will continue in the Extended Follow Up period up to the Week 96 visit, with the estimated total time on study up to 100 weeks. For subjects who discontinue NRTI therapy, the estimated total time on study is up to 148 weeks. Subjects may enter Cohort 3f if they have not completed their Week 24 visit. These subjects will subsequently follow the schedule for Cohort 3f.

	Optional Cohort 3f: The estimated total time on study, inclusive of screening and initial Extended Follow-Up, for each subject is up to 76 weeks. Subjects will enter from Cohort 2f at their Week 24 visit. Inclusive of the dosing in Cohort 2f, the total duration VIR-2218 treatment is a minimum of 6 doses and up to a total of 13 doses, each given 4 weeks apart. Inclusive of the dosing in Cohort 2f, the duration of PEG-IFNα therapy is a minimum of 24 doses and up to a total of 44 doses, each given 1 week apart. All subjects will continue per treatment period schedule up to Week 48, including subjects that discontinue VIR-2218 and PEG-IFNα prior to Week 48. All subjects will continue into the Extended Follow Up period after Week 48 visit to Week 72 visit. Subjects requiring additional HBsAg monitoring will continue in the Extended Follow Up period up to the Week 96 visit, with the estimated total time on study up to 100 weeks. For subjects who discontinue NRTI therapy, the estimated total time on study is up to 148 weeks.

Duration of Follow-up:	**Part A**: 12 weeks after study drug administration **Part B/C:** All subjects should be followed until Week 16. This period is referred to as the Follow-Up Period. Additional HBsAg monitoring (Extended Follow Up) is required for subjects with HBsAg levels with a > 10% decrease from the Day 1 predose level at the Week 16 visit. Visits will occur every 4 weeks starting at Week 20 up to Week 48 or until the HBsAg level returns to ≥ 90% of the Day 1 predose level. This period is referred to as the Extended Follow-Up period. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data. **Parts D-F:** All subjects should be followed for 24 weeks after the last visit in the Treatment Period. This period is referred to as the Follow-Up period. Additional HBsAg monitoring is required for subjects with HBsAg decline ≥ 1-log relative to the Day 1 predose level or HBsAg < 1000 IU/mL at the final required follow-up visit or Week 72 visit for Cohort 2f. Visits will occur every 8 weeks for up to 48 weeks or until the HBsAg level returns to ≥ 90% of the Day 1 predose level. This period is referred to as the Extended Follow-Up period. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data. In Parts D-F, the investigator will evaluate whether subjects are eligible for discontinuation of NRTI therapy and consider NRTI discontinuation in subjects meeting the following criteria: • are HBeAg-negative (undetectable quantitative HBeAg) • have ALT ≤ 2 x ULN • have suppression of HBV DNA (< LLOQ) **AND** one of the following criteria: • have HBsAg loss (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 the Treatment 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 subject eligibility for NRTI discontinuation. Subjects 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. These subjects will follow the Schedule of Assessments for the NRTI Discontinuation Monitoring Period (Appendix 16). Subjects 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 the first day they do not take NRTI therapy).

Objective(s):	**Part A** The primary objective is: • To evaluate the safety and tolerability of a single dose of VIR-2218 in healthy adult subjects The secondary objective is: • To characterize the pharmacokinetics (PK) of VIR-2218 in healthy adult subjects **Part B/C** The primary objective is: • To evaluate the safety and tolerability of multiple doses of VIR-2218 in non-cirrhotic subjects with HBeAg negative (Part B) and HBeAg positive (Part C) chronic HBV infection on NRTI therapy The secondary objectives are: • To characterize the PK of VIR-2218 in non-cirrhotic subjects with chronic HBV infection on NRTI therapy • To assess the antiviral activity of VIR-2218 in non-cirrhotic subjects with chronic HBV infection on NRTI therapy CCI [redacted] **Parts D-F** The primary objective is: • To evaluate the safety and tolerability of VIR-2218 alone or in combination with PEG-IFNα in non-cirrhotic adult subjects with chronic HBV infection on NRTI therapy The secondary objective is: • To assess the antiviral activity of VIR-2218 alone or in combination with PEG-IFNα in non-cirrhotic adult subjects with chronic HBV infection on NRTI therapy CCI [redacted]

Study Design:	The study will be conducted in 6 Parts: **Parts A – C:** This is a randomized, double-blind, placebo-controlled study of VIR-2218 administered subcutaneously to healthy adult subjects and non-cirrhotic adult subjects with chronic HBV infection who are on NRTI therapy. The study is designed to evaluate the safety, tolerability, PK, and antiviral activity of VIR-2218. • **Part A:** SAD phase in healthy adult subjects • **Part B:** MAD phase in non-cirrhotic adult subjects with HBeAg-negative chronic HBV infection on NRTI therapy for ≥ 6 months and serum HBV DNA < 90 IU/mL • **Part C:** MAD phase in non-cirrhotic adult subjects with HBeAg-positive chronic HBV infection on NRTI therapy for ≥ 6 months and serum HBV DNA < 90 IU/mL A Safety Review Committee (SRC) will perform ongoing reviews of safety and tolerability based on available study data collected throughout the study. Four dose-level cohorts are planned for Part A: 50 mg, 100 mg, 200 mg, and 400 mg. Two sentinel subjects will be randomized 1:1 to VIR-2218 or placebo. These subjects will be dosed concurrently and monitored for 24 hours; if the investigator has no safety concerns, the remainder of the subjects in the same cohort will be dosed. The remaining subjects will be randomized 5:1 to VIR-2218 or placebo. Two optional cohorts in Part A may be added following the same stratification, including sentinel dosing, up to a maximum dose of 900 mg. In addition to the optional cohorts, a total of 8 "floater" subjects may be added to expand any cohort in Part A. "Floater" subjects are to be added in increments of 4 and randomized 3:1 to VIR-2218 or placebo. Three dose-level cohorts are planned for Part B: 50 mg, 100 mg, and 200 mg. One dose-level cohort is planned for Part C: 200 mg. These planned dose levels will be administered twice, with each subject receiving a dose on Day 1, and a second dose at Week 4, such that the cumulative dose received for these subjects will be 100 mg, 200 mg, and 400 mg (Part B) and 400 mg (Part C). Each cohort in Part B/C will be randomized 3:1 to VIR-2218 or placebo. Two optional cohorts in Part B and 2 optional cohorts in Part C may be added following the same stratification, up to a maximum dose of 450 mg per dose (900 mg cumulative dose). In addition to the optional cohorts, a pool of 16 "floater" subjects may be added to expand any cohort in Part B and/or C if further data are needed. "Floater" subjects are to be added in increments of 4 (3:1) to maintain the randomization ratio. All dose levels explored in Part B/C must first be completed in Part A with data reviewed by the SRC prior to initiating the dose-level cohort in subjects with chronic HBV infection. The cohort dosing strategy for Part B/C of this study is staggered; 2 dose levels in Part A (1a: 50 mg and 2a: 100 mg) must be completed and data must be reviewed by the SRC to begin dosing at the starting dose in Part B (1b: 50 mg). Part C will be initiated at the Part C starting dose (3c: 200 mg) at the same time that the equivalent Part B dose level cohort is initiated (3b: 200 mg).

Study Design continued:	**Parts D-F:** This is an open-label study of VIR-2218 administered alone or in combination with PEG-IFNα in non-cirrhotic adult subjects with chronic HBV infection on NRTI therapy for > 2 months with HBV DNA < 90 IU/mL. The study is designed to evaluate the safety, tolerability, and antiviral activity of VIR-2218 administered alone or in combination with PEG-IFNα. In Part D, a total of up to 45 subjects with chronic HBV infection will be enrolled to one of 3 planned cohorts (1d, 2d, or 3d). Optional Parts E and F may be enrolled at Sponsor discretion based on emerging data, at any point during the conduct of Parts D - F. Each cohort within Parts E and F is considered optional and may be opened at any time. In Part E, a total of up to 45 subjects with chronic HBV infection may be enrolled to one of 3 possible cohorts (1e, 2e, or 3e). In Part F, a total of up to 60 subjects may be enrolled to Cohorts 1f or 2f. The dose levels of VIR-2218 in Parts D, E, and F were determined based on safety, tolerability and pharmacokinetics (PK) of VIR-2218 in Parts A-C, as well as analysis of antiviral activity and PK of VIR-2218 in Parts B and C. The dose levels explored in Parts D – F are indicated below: • The dose level in Part D is 200 mg • The dose level in Part E is 50 mg • The dose level in Part F is ≤ 200 mg In Cohort 1d and optional Cohort 1e, subjects will receive 6 doses of VIR-2218 at a frequency of every 4 weeks. Each subject will receive a dose of VIR-2218 on Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20. In Cohort 2d and optional Cohort 2e, subjects will receive 6 doses of VIR-2218 at a frequency of every 4 weeks. Each subject will receive a dose of VIR-2218 on Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20. Additionally, subjects will receive 12 weekly doses of 180 µg PEG-IFNα, administered by SC injection, starting at Week 12 and ending on Week 23. In Cohort 3d and optional Cohort 3e, subjects will receive 3 doses of VIR-2218 at a frequency of every 4 weeks. Each subject will receive a dose of VIR-2218 on Day 1, Week 4, and Week 8. Additionally, subjects will receive 12 weekly doses of 180 µg PEG-IFNα, administered by SC injection, starting at Day 1 and ending on Week 11. Subjects currently in the Cohort 3d that have not completed the Week 12 visit may enter Cohort 2f at their Week 12 visit. At Week 12, subjects 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 subjects have completed their Week 12 visit, they may enter Cohort 2f up to their Week 16 visit. Subjects that move from Cohort 3d to Cohort 2f will receive a total of 6 doses of VIR-2218, at a frequency of every 4 weeks, and up to 48 weekly doses of PEG-IFNα as specified below. Subjects that enter Cohort 2f after the Week 12 visit, may miss up to 1 dose of VIR-2218 and up to 4 doses of PEG-IFNα. In optional Cohort 1f, subjects will receive 6 doses of VIR-2218 at a frequency of every 4 weeks. Each subject will receive a dose of VIR-2218 on Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20. Additionally, subjects will receive 24 weekly doses of 180 µg PEG-IFNα, administered by SC injection, starting on Day 1 and ending on Week 23. In optional Cohort 2f, subjects will receive 6 doses of VIR-2218 at a frequency of every 4 weeks. Each subject will receive a dose of VIR-2218 on Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20. Additionally, subjects 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. Subjects with ≤ 1 $\log_{10}$ IU/mL reduction in HBsAg from pre-dose D1 at the Week 20 visit will discontinue PEG-IFNα after 24 doses. All other subjects will continue PEG-IFNα up to Week 47 (ie, the 48th dose of PEG-IFNα) or, until HBsAg is undetectable AND anti-HBs is ≥10 mIU/mL for 2 consecutive visits. Subjects will receive no more than 48 doses of PEG-IFNα. Subjects that are enrolled in Cohort 2f, have ≥ 1 $\log_{10}$ IU/mL reduction in HBsAg from pre-dose D1 at their Week 20 visit and have not completed their

	Week 24 visit may enter Cohort 3f at their Week 24 visit. At Week 24, subjects will receive their next dose of VIR-2218 (ie, 7th dose) and PEG-IFNα (ie, 24th dose) and complete their remaining treatment regimen per Cohort 3f schedule. In optional Cohort 3f, subjects will enter from Cohort 2f at their Week 24 visit and continue VIR-2218 dosing every 4 weeks up to Week 48 (ie, the 13th dose of VIR-2218 and weekly PEG-IFNα up to Week 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.

Study Procedures:	**Part A** Screening • Screening will be performed no more than 4 weeks prior to the Day 1 visit and will include written informed consent, determination of eligibility, collection of demographics and medical history as well as physical examination (including vitals), laboratory tests, 12-lead electrocardiogram (ECG) and other assessments per the schedule of assessments (SoA). Adverse events (AEs) related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All serious adverse events (SAEs) must be collected from the time of consent onwards. Inpatient Period (Day −1 to Day 2) • Subjects will be admitted into the clinical investigative site on Day −1. Eligible subjects will be randomized to receive VIR-2218 or placebo within 48 hours prior to study drug administration on Day 1. Subjects will be discharged after all study assessments are performed on Day 2. Outpatient/Follow-Up Period • Subjects will return to the clinical investigative site for in-person assessments per the SoA including but not limited to physical examination (including vitals), laboratory testing (including safety), 12-lead ECG and review of AEs and concomitant medication for 12 weeks after study drug administration. **Part B/C** Screening • Screening will be performed no more than 4 weeks prior to the Day 1 visit and will include written informed consent, determination of eligibility, collection of demographics and medical history as well as physical examination (including vitals), laboratory tests, 12-lead ECG and other assessments per the SoA. Adverse events related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards. Treatment Period (Day 1 to Week 4) • The Treatment Period for Part B/C is outpatient. Eligible subjects will be randomized to receive VIR-2218 or placebo within 48 hours prior to study drug administration on Day 1. Subjects will return to the clinical investigative site at Week 4 to receive a second dose of the same study drug administered on Day 1. Follow-Up Period • Subjects will return to the clinical investigative site for in-person assessments per the SoA including but not limited to physical examination (including vitals), laboratory testing (including safety), 12-lead ECG and review of AEs and concomitant medication until Week 16. Extended Follow-Up Period • Subjects that require additional HBsAg monitoring will return to the clinical investigative site for in-person assessments per the SoA. Visits will occur every 4 weeks starting at Week 20 for a maximum of 48 weeks from the first study drug administration.

Study Procedures continued:	**Part D/Optional Part E** Screening • Screening will be performed no more than 4 weeks prior to the Day 1 visit and will include written informed consent, determination of eligibility, collection of demographics and medical history as well as physical examination (including vitals), laboratory tests, and other assessments per the SoA. Adverse events related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards. Treatment Period • The Treatment Period for Part D/optional Part E is outpatient. Eligible subjects will be assigned to a cohort within 48 hours prior to study drug administration on Day 1. Subjects will return to the clinical investigative site on scheduled days per the SoA. Cohort 1d/optional Cohort 1e: The Treatment Period will extend from Day 1 up to Week 20. Subjects will receive the first dose of VIR-2218 at the clinical investigative site on Day 1 and subsequent doses at Week 4, Week 8, Week 12, Week 16, and Week 20. Cohort 2d/optional Cohort 2e: The Treatment Period extends from Day 1 to Week 24. Subjects will receive the first dose of VIR-2218 at the clinical investigative site on Day 1 and subsequent doses at Week 4 and Week 8, Week 12, Week 16, and Week 20. Subjects will also receive 12 weekly doses of 180 µg PEG-IFNα starting at Week 12 and through Week 23. Cohort 3d/optional Cohort 3e: The Treatment Period extends from Day 1 to Week 12. Subjects will receive the first dose of VIR-2218 at the clinical investigative site on Day 1 and subsequent doses at Week 4 and Week 8. Subjects will also receive 12 weekly doses of 180 µg PEG-IFNα starting at Day 1 and through Week 11. Subjects currently in treatment may move to Cohort 2f between their Week 12 and Week 16 visits. Follow-Up Period • Subjects will return to the clinical investigative site for in-person assessments per the SoA including but not limited to physical examination (including vitals), laboratory testing (including safety), and review of AEs and concomitant medication until 24 weeks after the final visit in the Treatment Period. Extended Follow-up Period • Subjects who require additional HBsAg monitoring will return to the clinical investigative site for in person assessments per the SoA. Visits will occur every 8 weeks for an additional 48 weeks. NRTI Discontinuation Monitoring Period • Subjects who discontinue NRTI therapy will discontinue from the SoA for their enrolled cohort and will instead continue into the NRTI Discontinuation Monitoring Period of the study. These subjects will follow the SoA for the NRTI Discontinuation Monitoring Period (Appendix 16). Subjects who discontinue from NRTI therapy will be followed for an additional 48 weeks from the day of NRTI discontinuation (defined as the first day off of NRTI therapy).

Study Procedures continued:	**Optional Part F** Screening • Screening will be performed no more than 4 weeks prior to the Day 1 visit and will include written informed consent, determination of eligibility, collection of demographics and medical history as well as physical examination (including vitals), laboratory tests, and other assessments per the SoA. Adverse events related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards. Treatment Period • The Treatment Period in optional Part F is outpatient. <u>Cohort 1f</u> The Treatment Period extends from Day 1 to Week 24. Subjects will receive the first dose of VIR-2218 at the clinical investigative site on Day 1 and subsequent doses at Week 4, Week 8, Week 12, Week 16, and Week 20. Subjects will also receive 24 weekly doses of 180 µg PEG-IFNα starting on Day 1 and through Week 23. <u>Cohort 2f</u> The Treatment Period extends from Day 1 to Week 48 for all subjects. Subjects will receive the first dose of VIR-2218 at the clinical investigative site on Day 1 and subsequent doses at Week 4, Week 8, Week 12, Week 16, and Week 20. Subjects will also receive up to 48 weekly doses of 180 µg PEG-IFNα starting on Day 1 and up to Week 47. Subjects with ≥ 1 log decline in HBsAg from predose D1 level at Week 20 will continue weekly PEG-IFNα doses up to Week 47 or, until subjects achieve undetectable HBsAg AND anti-HBs ≥ 10 mIU/mLat 2 study visits taken at least 4 weeks apart. Subjects that meet criteria to discontinue PEG-IFNα treatment will continue in the Treatment Period per schedule. <u>Cohort 3f</u> The Treatment Period extends from Day 1 to Week 48 for all subjects. As part of Cohort 2f, subjects will have received the first dose of VIR-2218 and at the clinical investigative site on Day 1 and subsequent doses every 4 weeks up to Week 20. Subjects will have also received weekly doses of PEG-IFNα up to Week 23. Once subjects enter Cohort 3f at Week 24, subjects will continue receiving VIR-2218 doses every 4 weeks up to Week 48 and weekly PEG-IFNα doses up to Week 43 or, until subjects achieve undetectable HBsAg AND anti-HBs ≥10 mIU/mL at 2 study visits taken at least 4 weeks apart. Subjects that meet criteria to discontinue VIR-2218 and PEG-IFNα treatment will continue in the Treatment Period per Cohort 3f schedule. Follow-Up Period (Cohort 1f only) • Subjects will return to the clinical investigative site for in-person assessments per the SoA including but not limited to physical examination (including vitals), laboratory testing (including safety), and review of AEs and concomitant medication up to 24 weeks after the final visit in the Treatment Period. Extended Follow-up Period <u>Cohort 1f</u> Subjects who require additional HBsAg monitoring will return to the clinical investigative site for in-person assessments per the SoA after the follow up period. Visits will occur every 8 weeks for an additional 48 weeks. <u>Cohort 2f/3f</u> All subjects will return to the clinical investigative site for in-person assessments per the SoA up to the Week 72 visit. Subjects who require additional HBsAg monitoring will return to the clinical investigative site for in-person assessments

	per the SoA up to Week 96. Visits will occur every 8 weeks for an additional 24-48 weeks. NRTI Discontinuation Monitoring Period • Subjects who are eligible to discontinue 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. These subjects will follow the Schedule of Assessments for the NRTI Discontinuation Monitoring Period (Appendix 16). Subjects 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).
Investigational Product, Dose, and Mode of Administration:	VIR-2218 is a synthetic, chemically modified small interfering RNA (siRNA) targeting HBV RNA with a covalently attached triantennary N-acetylgalactosamine (GalNAc) ligand that allows for specific uptake by hepatocytes. VIR-2218 will be supplied as a sterile solution for SC injection at a free acid concentration of 200 mg/mL. The starting dose for Parts A and B is 50 mg. The starting dose for Part C is 200 mg. The dose levels in Parts A, B, and C will not exceed the defined maximum administered dose of 900 mg (single or cumulative). The dose level in Part D is 200 mg. The dose level in Part E is 50 mg. The dose level in Part F will be chosen by the Sponsor, based on emerging data, and will be ≤ 200 mg. PEG-IFNα is an alpha interferon product with broad immunomodulatory and direct antiviral effects against HBV that is approved for the treatment of adults with HBeAg-positive and HBeAg-negative chronic HBV infection who have compensated liver disease and evidence of viral replication and liver inflammation. In Cohorts 2d and 3d, optional Cohorts 2e and 3e, optional Cohorts 1f, 2f and 3f, subjects will receive 180 µg PEG-IFNα administered by SC injection.
Reference Therapy (Parts A – C Only):	Subjects randomized to placebo in Parts A – C will be administered sterile, preservative-free normal saline 0.9% solution for SC injection.
Criteria for Evaluation:	**Part A** Primary Endpoints • Incidence of AEs • Clinical assessments including but not limited to laboratory test results Secondary Endpoints • PK parameters of VIR-2218 and possible metabolites (may include, but not be limited to, plasma: maximum concentration, time to reach maximum concentration, area under the concentration versus time curve [to last measurable timepoint and to infinity], percent of area extrapolated, apparent terminal elimination half-life, clearance, and volume of distribution; urine: fraction eliminated in the urine and renal clearance)

Criteria for Evaluation continued:	**Part B/C** Primary Endpoints • Incidence of AEs • Clinical assessments including but not limited to laboratory test results Secondary Endpoints • PK parameters of VIR-2218 and possible metabolites (may include, but not be limited to, plasma: maximum concentration, time to reach maximum concentration, area under the concentration versus time curve [to last measurable timepoint and to infinity], percent of area extrapolated, apparent terminal elimination half-life, clearance, and volume of distribution) • Maximum reduction of serum HBsAg from Day 1 until Week 16 • Number of subjects with serum HBsAg loss at any timepoint • Number of subjects with sustained serum HBsAg loss for ≥ 6 months • Number of subjects with anti-HBs seroconversion at any timepoint • For HBeAg-positive subjects (Part C only): number of subjects with HBeAg loss and/or anti-HBe seroconversion at any timepoint CCI [redacted]

Criteria for Evaluation continued:	**Parts D – F** Primary Endpoints • Incidence of AEs • Clinical assessments including but not limited to laboratory test results Secondary Endpoints • Mean maximum reduction of serum HBsAg at any timepoint • Proportion of subjects with serum HBsAg loss (undetectable HBsAg) at any timepoint • Proportion of subjects with sustained serum HBsAg loss (undetectable HBsAg) for greater than 6 months • Proportion of subjects with anti-HBs seroconversion at any timepoint • For HBeAg-positive patients: proportion of subjects with HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion at any timepoint CCI [redacted]
Statistical Methods:	Statistical analyses will be primarily descriptive. All study data will be presented by subject data listings. For Parts A – C, summary tables will present results by cohort for each VIR-2218 dose and placebo, where the placebo subjects will be combined across dose cohorts. For Parts D – F, summary tables will present results by analysis grouping, which will be defined in SAP Descriptive statistics will be presented for continuous variables, and frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of non-missing values in a dose group. Details will be provided in the Statistical Analysis Plan.

This study will be conducted in accordance in compliance with the protocol, International Conference on Harmonisation Good Clinical Practices (ICH GCP) and applicable state, local, and federal regulatory requirements including archiving of essential documents.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBe	hepatitis B extracellular antibody
anti-HBs	hepatitis B surface antibody
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
BLQ	below the limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
cccDNA	covalently closed circular DNA
CL_{cr}	creatinine clearance
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
ECI	event(s) of clinical interest
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
GalNAc	N-acetyl-galactosamine
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
GNA	glycol nucleic acid
HBcrAg	hepatitis B core-related antigen
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e-antigen

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBx	hepatitis B protein X
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
HLGT	High-Level Group Term
HLT	High-Level Term
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	interactive web response system
LDH	lactate dehydrogenase
LFAC	Liver Flare Adjudication Committee
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LLT	Lowest Level Term
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
NRTI	nucleos(t)ide reverse transcriptase inhibitor
OTC	over-the-counter
PEG-IFNα	pegylated interferon alpha
PK	pharmacokinetics
pgRNA	pregenomic RNA
PT	Preferred Term
Q1	first quartile

Q3	third quartile
RBC	red blood cell (count)
RT	reverse transcriptase
rcDNA	relaxed-circular DNA
SAD	single ascending dose
SADR	serious adverse drug reaction
SAE	serious adverse event
SC	Subcutaneous
SD	standard deviation
siRNA	small interfering RNA
SoA	schedule of assessments
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
US	United States
ULN	upper limit of normal
WBC	white blood cell (count)
WHO	World Health Organization
WOCBP	women of child-bearing potential

1. INTRODUCTION

1.1. Background

VIR-2218 is a synthetic small interfering RNA (siRNA) therapeutic being developed for the treatment of chronic hepatitis B virus (HBV) infection. Chronic HBV infection remains an important global public health problem with significant morbidity and mortality (Trepo 2014). According to the World Health Organization (WHO 2017) an estimated 257 million people are living with chronic HBV infection worldwide (WHO 2017; Schweitzer 2015). Over time, chronic HBV infection leads to serious sequelae including cirrhosis, liver failure, hepatocellular carcinoma (HCC), and death. Almost 800,000 people are estimated to die annually due to sequelae associated with chronic HBV infection (Stanaway 2016).

HBV prevalence varies geographically, with a range of less than 2% in low to greater than 8% in high prevalence countries (Schweitzer 2015). In high prevalence countries, such as those in sub-Saharan Africa and East Asia, transmission occurs predominantly in infants and children by perinatal and horizontal routes. In more industrialized countries, new infections are highest among young adults and transmission occurs predominantly via injection drug use and high-risk sexual behaviors. The risk of developing chronic HBV infection depends on the age at the time of infection. While only ~10% of people infected as adults develop chronic HBV infection, 90% of infants infected perinatally or during the first 6 months of life, and 20–60% of children infected between 6 months and 5 years of age remain chronically infected. Twenty-five percent of people who acquire HBV during infancy and childhood will develop primary liver cancer or cirrhosis during adulthood.

HBV is a DNA virus that infects, replicates, and persists in human hepatocytes (Protzer 2012). The small viral genome (3.2 kb), consists of partially double-stranded, relaxed-circular DNA (rcDNA) and has 4 open reading frames encoding 7 proteins: HBcAg (HBV core antigen, viral capsid protein), HBeAg (hepatitis B e-antigen), HBV Pol/RT (polymerase, reverse transcriptase), PreS1/PreS2/HBsAg (large, medium, and small surface envelope glycoproteins), and HBx (HBV × antigen, regulator of transcription required for the initiation of infection) (Seeger 2015; Tong 2016).

In hepatocytes, rcDNA, the form of HBV nucleic acid that is introduced by the infection virion, is converted into a covalently closed circular DNA (cccDNA), which persists in the host cell's nucleus as an episomal chromatinized structure (Allweiss 2017). cccDNA serves as a transcription template for all viral transcripts (Lucifora 2016). Pregenomic RNA (pgRNA) transcripts are reverse transcribed into new rcDNA for new virions, which are secreted without causing cytotoxicity. In addition to infectious virions, infected hepatocytes secrete large amounts of genome-free subviral particles, that may exceed the number of secreted virions by 10,000-fold (Seeger 2015). Random integration of the virus into the host genome can occur as well, a mechanism that contributes to hepatocyte transformation (Levrero 2016).

In acute resolving infections, the virus is cleared by effective innate and adaptive immune responses that include cytotoxic T cells leading to death of infected hepatocytes, and induction of B cells producing neutralizing antibodies that prevent the spread of the virus (Bertoletti 2016; Maini 2016; Li 2016). In contrast, chronic infection is associated with T and B cell dysfunction, mediated by multiple regulatory mechanisms including presentation of viral epitopes on hepatocytes and secretion of subviral particles (Bertoletti 2016; Burton 2018; Maini 2016). Thus,

the continued expression and secretion of viral proteins due to cccDNA persistence in hepatocytes is considered a key step in the inability of the host to clear the infection.

Chronic HBV infection is a dynamic process reflecting the interaction between HBV replication and host immune responses. The laboratory hallmark of chronic HBV infection is persistence of HBsAg in the blood for greater than 6 months, and a lack of detectable anti-HBs. Chronic infection is divided into 4 stages based on HBV markers in blood (HBsAg, HBeAg/anti-HBe, HBV DNA), and liver disease based on biochemical parameters (ALT), as well as fibrosis markers (noninvasive or based on liver biopsy) (EASL 2017). Overall, across the various phases of chronic HBV infection, only a minority of patients (less than 1% per year) clear the disease as measured by HBsAg seroclearance.

Currently, there are 2 main treatment options for patients with chronic HBV infection: treatment with nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and pegylated interferon-alpha (PEG-IFNα) (Liang 2015). NRTIs inhibit the production of infectious virions, and often reduce serum HBV DNA to below the limit of quantification. However, NRTIs do not directly eliminate cccDNA, and therefore, transcription and translation of viral proteins continues. Consequently, expression of viral epitopes on hepatocytes, secretion of subviral particles, and immune dysfunction remain largely unaffected by NRTI therapy. In turn, this necessitates prolonged, often lifelong therapy; furthermore, while NRTI therapy reduces the incidence of HCC, it does not eliminate the increased risk of HCC that HBV infection confers. In contrast to NRTIs, PEG-IFNα can induce long-term viral control with finite treatment duration, but only in a small percentage of patients (≤ 10%) after 48 weeks of therapy (Konerman 2016). While the exact mechanism of action of PEG-IFNα treatment is unknown, interferon induces multiple innate immune mechanisms and exerts antiproliferative and antiviral effects at various points of the HBV lifecycle in vitro (PEGASYS® Prescribing Information; Rijckborst 2010a). The low response rate coupled with limited tolerability and a long treatment course preclude treatment of most patients with PEG-IFNα monotherapy (PEGASYS® Prescribing Information).

The failure of NRTI therapy to eradicate the virus, and the limitations of PEG-IFNα therapy highlight the clinical need for new HBV therapies that are effective, well tolerated, and do not require lifelong administration. To address this unmet need, Vir is developing an investigational agent, VIR-2218, for the treatment of chronic HBV infection. In preclinical models, VIR-2218 inhibits viral replication, translation, and secretion of HBsAg. Therefore, VIR-2218 has the potential, alone or in combination with other therapies, to achieve a functional cure of chronic HBV infection.

Parts D – F of this study are designed to determine whether the combination of VIR-2218 with PEG-IFNα can lead to clinically meaningful rates of functional cure (defined as undetectable HBsAg and sustained suppression of HBV DNA [< LLOQ] for more than 6 months after discontinuation of all treatment, including NRTIs) with an acceptable safety and tolerability profile. PEG-IFNα monotherapy will not be studied given the significant side effects associated with this therapy and the low likelihood of benefit when given as a single agent (Marcellin 2016).

1.2. VIR-2218

1.2.1. VIR-2218 Description

VIR-2218 is an siRNA targeting a region of the HBV genome that is common to all HBV viral transcripts. The siRNA is chemically modified using Enhanced Stabilization Chemistry Plus (ESC+) consisting of 2'-fluoro (2'F), 2'-O-methoxy (2'OMe) ribose sugar modifications, phosphorothioate backbone modifications, glycol nucleic acid (GNA) modification, and conjugation to a triantennary N-acetyl-galactosamine ligand (GalNAc) at the 3' end of the sense strand, to facilitate delivery to hepatocytes through the asialoglycoprotein receptor (ASGPR). The drug product, VIR-2218, is the drug substance VIR-2218 formulated in water for subcutaneous (SC) injection. VIR-2218 is pharmacologically active against HBV genotypes A through J; see the Investigator's Brochure for additional information on VIR-2218.

1.2.2. Rationale for VIR-2218 for the Treatment of HBV Infection

The use of siRNA offers a novel strategy for the treatment of chronic HBV infection. siRNAs are 19-21 base-pair RNA duplexes that exploit the endogenous RNA-interference pathway to enable sequence-specific RNA cleavage and degradation. One siRNA can have multiple antiviral effects, including degradation of the pgRNA, thus inhibiting viral replication, and degradation of all viral messenger RNA (mRNA) transcripts, thereby preventing expression of viral proteins. This may result in the return of a functional immune response directed against HBV, either alone or in combination with other therapies, in particular, immune modulatory agents.

By contrast, NRTIs act at a distinct part of the viral life cycle and have a different mechanism of action than VIR-2218. NRTIs inhibit the action of HBV RNA polymerase, blocking the reverse transcription of the viral pgRNA to viral DNA and preventing the production of infectious virions. NRTIs, however, do not directly impact the production of viral proteins such as HBsAg. Reduction of HBsAg-containing noninfectious subviral particles by VIR-2218 is considered an important differentiator from current treatments.

Subjects randomized to active treatment in Part B/C of this study will receive VIR-2218 added to their ongoing NRTI therapy. Such subjects have already been determined by their physician to require treatment. Based on the known mechanisms of action there is a low risk for pharmacodynamic drug-drug interactions or overlapping toxicities between NRTIs and siRNA.

1.2.3. Nonclinical Data

Refer to the Investigator's Brochure for VIR-2218 Nonclinical data.

1.2.4. Summary of Clinical Experience

The safety and tolerability of VIR-2218 has been evaluated in Parts A-C of the study, evaluating doses of VIR-2218 up to 900 mg administered subcutaneously in healthy subjects (Part A) and a regimen of 2 doses administered 4 weeks apart at doses up to 200 mg in subjects with CHB (Part B/C).

In Part A (healthy subjects), 59.5% of VIR-2218 subjects (22 of 37) and 50% of placebo subjects (6 of 12) had at least 1 AE, each of which was Grade 1 or 2 in severity with the exception of a single Grade 3 AE of respiratory tract infection (considered not related to study drug). The most common AEs in VIR-2218 subjects were headache (24.3%; 9 of 37 subjects), and upper respiratory tract infection, contact dermatitis, injection site bruising, and injection site pain

(8.1% each; 3 of 37 subjects). Three VIR-2218 subjects (8.1%) had AEs considered related to study drug by the investigator, including headache, injection site pain, and abdominal pain, each of which was Grade 1 in severity. Seven VIR-2218 subjects (18.9%) had injection site reactions (ISRs), including injection site bruising, injection site pain, catheter site pain, and injection site discomfort. All ISRs were Grade 1 in severity and resolved within 12 days of onset. Injection site reactions were reported in the 200 mg, 400 mg, 600 mg, and 900 mg dose cohorts. No placebo subjects had an ISR.

In Part B/C (subjects with chronic HBV infection), 54.2% of VIR-2218 subjects (13 of 24) and 25% of placebo subjects (2 of 8) had at least 1 AE, each of which was Grade 1 or 2 in severity with the exception of 1 Grade 3 nonserious AE of hypophosphatemia (considered not related to study drug), a known adverse reaction of tenofovir disoproxil fumarate with which the subject was receiving treatment. The most common AEs in VIR-2218 subjects were headache (25.0%; 6 of 24 subjects), and dizziness, fatigue, and myalgia (8.3% each; 2 of 24 subjects). Five subjects (20.8%) had AEs considered related to study drug by the investigator, including headache, injection site pain, and pyrexia, each of which was Grade 1 or 2 in severity. Two VIR-2218 subjects (8.3%) each had 1 ISR: injection site bruising and injection site pain. All ISRs were Grade 1 in severity and resolved within 3 days of onset. Injection site reactions were reported in the 50 mg and 100 mg dose cohorts. No placebo subjects had an ISR.

One treatment-emergent SAE was reported in Study VIR-2218-1001 in a subject administered 100 mg VIR-2218. The SAE of headache was Grade 2 in severity and considered related to study drug by the investigator, but the Sponsor determined that the constellation of concurrent symptoms (fever, headache, nausea, vomiting, and dehydration) were more consistent with a viral syndrome than a drug reaction and assessed the event as not related to study drug.
Two subjects had a non-treatment-emergent SAE considered not related to study drug by the investigator; 1 subject had depression and 1 subject committed suicide (outcome of death). The death (suicide) occurred approximately 9 months after last study drug administration.

No clinically significant laboratory, ECG, or vital sign abnormalities were observed. In Part A, most laboratory abnormalities were Grade 1 or 2 in severity. In Part B/C, no Grade 3 or 4 laboratory abnormalities were reported. Regarding hepatic laboratory evaluation for Parts A to C, no clinically significant hyperbilirubinemia, changes in functional status of the liver (eg, albumin, coagulation parameters), or clinical signs/symptoms of hepatic dysfunction were observed.

In Part A, asymptomatic Grade 1 ALT elevations were observed in 18.9% of VIR-2218 subjects (7 of 37) with none observed in placebo subjects. Five of the 7 VIR-2218 subjects with Grade 1 ALT elevations were in the 900-mg dose cohort, which, suggests a potential dose relationship of ALT elevations with the highest single dose administered in this study. None of the ALT elevations were reported as an AE.

In Part B/C, asymptomatic Grade 1 ALT elevations were observed in 20.8% of VIR-2218 subjects (5 of 24) and 12.5% of placebo subjects (1 of 8). Four of the 5 VIR-2218 subjects and the placebo subject with Grade 1 ALT elevations were HBeAg positive. There were no apparent trends in ALT elevation onset time or relationship to dose, and none of the elevations were reported as an AE.

The antiviral activity of VIR-2218 was evaluated in subjects with chronic HBV infection (Part B/C) to assess the effect on HBsAg following VIR-2218 administration. Part B enrolled HBeAg-negative subjects and Part C enrolled HBeAg-positive subjects. Reductions in HBsAg

were observed across all VIR-2218 dosing levels, and greater reductions were associated with higher VIR-2218 doses. At the highest dose level of 200mg, all patients achieved ≥ 1 log reduction from baseline. No notable differences in HBsAg log reductions were observed between HBeAg-negative and HBeAg-positive subjects.

The observed safety and tolerability profile of single doses of VIR-2218 in healthy volunteers and observed safety, tolerability and antiviral activity profile two doses of VIR-2218 administered every 4 weeks in subjects with chronic HBV infection are supportive of further development. Refer to Investigator's Brochure for details of clinical experience with VIR-2218.

1.2.5. Rationale for Dose Selection for Parts A – C

The recommended starting dose for VIR-2218 was determined by calculating the human equivalent doses (HEDs) of the no observed adverse effect levels (NOAELs) in the definitive animal toxicology studies and applying a safety margin to those HEDs. Body surface area (m/kg^2) conversion factors were used to calculate HEDs of animal doses.

No toxicity was observed in a rat Good Laboratory Practice (GLP) study after 3 biweekly doses of VIR-2218 at the highest dose tested, 150 mg/kg, corresponding to a HED of 24 mg/kg/dose. No toxicity was observed in a non-human primate (NHP) GLP study after 3 biweekly doses of VIR-2218 at the highest dose tested, 300 mg/kg, corresponding to a HED of 97 mg/kg/dose (Table 1). Using this methodology, the proposed starting dose of 0.8 mg/kg in humans represents the 30-fold safety margin of the HED of the NOAEL projected in rats, and the 120-fold safety margin of the HED of the NOAEL projected in NHPs.

Table 1: Proposed Starting Dose for VIR-2218

Study Species and Duration	NOAEL (mg/kg)	HED (mg/kg)	Starting Dose (mg/kg)
Cynomologous monkey 4-week study (3 biweekly doses) followed by 13-week recovery	300	97	0.8 (120-fold safety margin)
Rat 4-week study (3 biweekly doses) followed by 13-week recovery	150	24	0.8 (30-fold safety margin)

Although dosing in the GLP-toxicology studies was weight based, subjects will receive a fixed dose rather than a weight-based dose because VIR-2218, like other GalNAc-conjugated siRNAs, is taken up by the liver and minimally distributed to other organs and tissues. Therefore, weight based dosing is not anticipated to reduce the inter-individual variation in the pharmacokinetics (PK) of VIR-2218 in adults and a fixed dose has the advantage of avoiding potential dose calculation errors.

The planned and optional dose levels for Part A, were determined to support Part B/C. The planned and optional dose levels for Part B/C are based on what is estimated to result in meaningful biological activity in humans, specifically the observation that other siRNAs using the GalNAc platform have demonstrated meaningful liver target engagement at 1 to 15 mg/kg. Furthermore, a statistically significant decline in HBsAg in preclinical HBV mouse models at a dose range of 1 to 9 mg/kg was observed. See the Investigator's Brochure for additional information.

Part A: Single Ascending Dose Study in Healthy Volunteers:

Planned dose levels*:* Healthy volunteers will receive a single ascending dose. Four dose -level cohorts are planned. Doses will be increased stepwise by a factor of 2-f-old up to a maximum planned dose of 400 mg (Section 4.6 describes the criteria used for dose escalation).

Optional dose level*:* Two optional dose levels may be added. The additional dose levels will not exceed 900 mg. Doses higher than 400 mg will only be administered if 400 mg is well tolerated in subjects based on review of all available safety data collected through Week 4.

Table 2: Part A Dose Escalation Plan

Cohort	Weight-Based Dose (mg/kg)	Fixed dose[a] (mg)	Dose Escalation Factor
1a	0.8	50	-
2a	1.7	100	2.0-fold
3a	3.3	200	2.0-fold
4a	6.7	400	2.0-fold
Optional: 5a and 6a	Up to 15	Up to 900	Up to 2.25-fold

[a] Based on average adult weight of 60 kg

Part B/C: Multiple Ascending Dose Study in HBeAg-negative and HBeAg-positive Subjects with Chronic HBV Infection:

Planned dose levels*:* HBeAg -negative subjects with chronic HBV infection will be enrolled in Part B and HBeAg -positive subjects with chronic HBV infection will be enrolled in Part C. Three dose -level cohorts for HBeAg -negative subjects are planned; dose levels will be increased stepwise by a factor of 2 up to a maximum planned dose level of 200 mg and a cumulative dose of 400 mg (Section 4.6. describes the criteria used for dose escalation). To accommodate the anticipated lower prevalence of HBeAg -positive patients on NRTI therapy, only 1 dose level cohort (200 mg) is planned for HBeAg positive- subjects.

Initiation of Part B*:* Part B, Cohort 1b will be initiated after cumulative review of all available safety data, inclusive of the Week 4 laboratory and clinical data of the last available healthy volunteer subject in the 100 mg cohort (Cohort 2a).

Initiation of Part C*:* The only planned cohort in Part C, Cohort 3c, will initiate at the same time as Cohort 3b after review of all available safety data inclusive of Week 6 clinical and laboratory data from Cohort 2b, and according to the criteria outlined in Section 4.6. Subjects in Cohort 3c will receive VIR-2218 at the same dose level as subjects in Cohort 3b (200 mg administered twice at a dosing interval of 4 weeks).

Optional dose levels*:* Two optional dose level cohorts may be added for each subject population. Doses higher than 200 mg will only be administered if 200 mg is well tolerated in subjects with chronic HBV infection based on review of all available safety data collected through 8 weeks after the first dose (4 weeks after the second dose). Doses can be increased stepwise by a factor of 1.5-fold up to a maximum optional single dose of 450 mg (cumulative dose of 900 mg).

Table 3: Part B/C Dose Escalation Plan

Cohort	Weight-based dose (mg/kg)	Fixed dose[a] (mg)	Dose Escalation Factor
1b	0.8	50	-
2b	1.7	100	2.0-fold
3b and 3c	3.3	200	2.0-fold
Optional: 4b and 4c	Up to 5	Up to 300	Up to 1.5-fold
Optional: 5b and 5c	Up to 7.5	Up to 450	Up to 1.5-fold

[a] Based on average adult weight of 60 kg

1.3. VIR-2218 Alone or in Combination with PEG-IFNα

1.3.1. Rationale for VIR-2218 Given with PEG-IFNα for the Treatment of Chronic HBV Infection

In patients with chronic HBV infection, PEG-IFNα 180 µg administered weekly for 48-52 weeks generally results in HBsAg loss in approximately ≤ 10% of patients overall (Konerman 2016). However, in the subset of patients with baseline HBsAg values less than approximately 1000-1500 IU/mL, the rate of HBsAg loss following receipt of PEG-IFNα with or without an NRTI is approximately 20-40% (He 2016; Huang 2017; Lee 2018; Li 2015; Ning 2014; Takkenberg 2009). This suggests that a reduction in HBsAg during or prior to PEG-IFNα therapy may substantially increase the rate of HBsAg loss. Therefore, it is hypothesized that a combination therapy consisting of VIR-2218, which has been associated with substantial reductions in HBsAg in the current study, and PEG-IFNα could substantially increase the rate of functional cure associated with PEG-IFNα therapy.

1.3.2. Rationale for Dose Selection in Parts D - F

1.3.2.1. Rationale for VIR-2218 Dose Selection in Parts D – F

Available safety, tolerability, antiviral activity, and pharmacokinetic data from Parts A-F were considered when selecting dose levels for VIR-2218 as monotherapy or in combination with PEG-IFNα.

In Part A of the study, a single SC dose of VIR-2218 was administered to healthy volunteers over the dose range of 50 to 900 mg. In Parts B and C, 2 doses of VIR-2218 given 4 weeks apart, ranging from 20 to 200 mg were administered to participants with chronic HBV infection. In healthy volunteers, VIR-2218 was absorbed after SC injection with median T_{max} of 4-7 hours and was not measurable in plasma beyond 48 hours for any subject (Gupta 2021). Available PK data from HBV subjects were similar to healthy adults. No accumulation of VIR-2218 in plasma was evident following a second dose of VIR-2218 administered 4 weeks apart in participants with chronic HBV infection.

The VIR-2218 dose level of 200 mg was selected based on results from Parts B and C of the study. In participants with chronic HBV infection, 2 doses of VIR-2218 administered 4 weeks

apart was associated with dose-dependent reductions in HBsAg across a dose range of 20-200 mg (Gane 2021). The largest reductions in HBsAg were observed in the 200 mg cohort.

The VIR-2218 regimens selected for this study are supported by the safety profile of VIR-2218 (Section 1.2.4). VIR-2218 regimens up to 6 doses administered every 4 weeks are well tolerated and associated with deep, sustained reductions in HBsAg in patients with chronic HBV infection. The duration of VIR-2218 treatment in each cohort was selected to ensure suppression of HBsAg by VIR-2218 for the entire duration of concomitant treatment with or without PEG-IFNα. Regimens of varying durations up to 13 doses will be evaluated to assess the impact of more sustained HBsAg suppression on the outcome of functional cure.

Cohort 3f will provide the first experience with a 13-dose regimen of VIR-2218 200 mg administered every 4 weeks. Given the lack of accumulation of VIR-2218 in plasma after multiple doses and the absence of safety concerns in prior evaluations of VIR-2218 when given as 6 monthly doses, the risk of additional doses of VIR-2218 is anticipated to be low. Furthermore, subjects will be monitored closely throughout the treatment period and for at least 48 weeks following the last dose of VIR-2218 for any potential adverse events or laboratory abnormalities.

1.3.2.2. Rationale for PEG-IFNα Dose Selection in Parts D - F

PEG-IFNα will be administered at a dose of 180 µg given weekly, the FDA-approved dose level and frequency for the treatment of chronic HBV infection. The total duration of PEG-IFNα in this study will be shorter or equal to the approved monotherapy treatment duration of 48 weeks. The FDA-approved duration of 48 weeks has been associated with better rates of functional cure compared to shorter durations (Liaw 2011). However, PEG-IFNα is associated with poor tolerability and other safety concerns (see PEGASYS® Prescribing Information for details). While shorter, 24-week, treatment durations have been shown to improve the safety and tolerability of PEG-IFNα (Lim 2019), the necessary treatment duration to achieve functional cure in the setting of a combination therapy with VIR-2218 is unknown. This study will evaluate the safety and efficacy of various durations of PEG-IFNα up to 48 weeks, to determine the optimal treatment regimen for a PEG-IFNα and VIR-2218 combination. Furthermore, data from clinical studies of PEG-IFNα in chronic HBV infection suggest that early on-treatment HBsAg declines are predictive of long-term HBsAg loss after 48 weeks of therapy (Ning 2014; Rijckborst 2010; Wang 2016; Yang 2016). Therefore, to ensure patients do not receive unnecessary doses of PEG-IFNα, only subjects that achieve ≥ 1-log reduction in HBsAg from predose Day 1 baseline will be eligible to receive therapy with PEG-IFNα beyond 24 weeks (as part of Cohorts 2f and 3f).

As the optimal timing of administration of the two agents in combination is not known, regimens in which VIR-2218 and PEG-IFNα are initiated together, or regimens in which VIR-2218 therapy is dosed for 12 weeks prior to initiation of PEG-IFNα, will be explored. The 12-week VIR-2218 lead-in is based on the observation that the nadir of HBsAg after VIR-2218 administration was generally observed at Week 12, with most patients achieving HBsAg levels < 1000 IU/mL at this time. This finding suggests that HBsAg levels may be reduced sufficiently by Week 12 to enhance the rate of HBsAg loss in response to PEG-IFNα. In Cohort 3f, if subjects do not achieve undetectable HBsAg and anti-HBs ≥ 10 mIU/mL for 2 consecutive visits then they will receive the complete regimen of 13 doses of VIR-2218 and 44 doses of PEG-IFNα. The regimen has been designed such that subjects receive 2 additional doses of VIR-2218 (at Week 44 and Week 48) beyond the last dose of PEG-IFNα at Week 43. This design is to

ensure that continued VIR-2218 dosing after cessation of the PEG-IFNα treatment will maximize the chances of sustaining HBsAg decline and attaining HBsAg < LLOQ post-treatment.

1.4. Overall Risk/Benefit Assessment

1.4.1. Risk/Benefit Assessment in Parts A - C

Parts A - C of the study will provide information on the safety, PK, and antiviral activity of VIR-2218, an siRNA therapeutic targeting HBV, which has the potential to functionally cure chronic HBV infection alone or in combination with other treatment modalities.

The potential benefits of VIR-2218 over the current standard of care for the treatment of chronic HBV infection are:

- A pangenotypic therapy for HBV infection that is well-tolerated and administered via SC injection for a finite duration of time
- A reduction in serum HBsAg, which may break immune tolerance against HBV and lead to a functional cure

The safety profile of VIR-2218 has not yet been established. As VIR-2218 is taken up by the liver, ALT and other liver function tests will be monitored during this study. To further mitigate risk, a "sentinel" dose design will be used in Part A as follows.

- Two subjects will be randomized 1:1 to VIR-2218 or placebo and dosed concurrently
- These subjects will be monitored for 24 hours and if the investigator has no safety concerns, the other subjects in the same cohort are dosed. The remaining 6 subjects will be randomized 5:1 to VIR-2218 or placebo.

During the conduct of the study, the Sponsor will perform ongoing safety reviews and the SRC will meet to review safety data.

In summary, there is no approved therapy that reduces serum HBsAg in a significant percentage of patients. If serum HBsAg can be effectively reduced with a pangenotypic regimen, the anticipated safety profile would offer a favorable risk-benefit determinant in patients with chronic HBV infection.

1.4.2. Risk/Benefit Assessment in Parts D – F

Parts D-F will provide information on the safety, tolerability, antiviral activity and efficacy of 6 doses of VIR-2218 alone and 3, 6 and up to 13 doses of VIR-2218 in combination with PEG-IFNα.

This portion of the study is designed to test the hypothesis that the reduction in tolerogenic HBV antigen (eg, HBsAg) production afforded by VIR-2218 treatment during or prior to PEG-IFNα therapy may both substantially decrease the duration of PEG-IFNα therapy required to achieve HBsAg loss/functional cure as well as increase the proportion of patients achieving this goal. Published data suggest that 12- and 24-week regimens of PEG-IFNα may result in substantial improvements in safety and tolerability compared to a 48-week regimen while potentially maintaining adequate antiviral activity (Fried 2002; Hadziyannis 2004; Lawitz 2013). In this study, we will evaluate the efficacy, safety and tolerability of PEG-IFNα regimens up to 48 weeks in combination with VIR-2218 to determine the optimal treatment duration.

Data from Parts A- C of this ongoing study suggest that single doses of VIR-2218 up to 900 mg in healthy subjects and two doses of up to 200 mg administered every 4 weeks (ie, the highest dose tested) in subjects with chronic HBV infection were well tolerated and exhibited safety profiles supportive of continued clinical development. PK simulations predict that liver exposures associated with the VIR-2218 dose levels in this study will not exceed the projected liver exposure of the highest dose at which the safety and tolerability of VIR-2218 has been demonstrated ie, 900 mg single dose (see Section 1.3.2.1 for additional details). Therefore, the safety profile of VIR-2218 supports exploration of the proposed VIR-2218 treatment regimens. Based on the known mechanisms of action and the safety profile of each agent, transaminitis is the primary event of interest with VIR-2218 and PEG-IFNα. Potential hepatic events will be closely monitored and evaluated as described in Sections 4.5, 4.8, 8.1, 8.5 and Appendix 17.

In both HBeAg-negative and HBeAg-positive subjects with chronic HBV infection, dose levels of VIR-2218 up to two 200 mg doses administered every four weeks were associated with substantial reductions in HBsAg but did not lead to HBsAg clearance or HBsAb seroconversion. In addition, intersubject variability was observed in terms of both the kinetics and magnitude of the antiviral response. Given the reported association between baseline HBsAg level and response to PEG-IFNα therapy (Section 1.3.1), the proposed VIR-2218 dosing regimens were designed to provide a greater magnitude and duration of HBsAg suppression than those studied in Parts B and C in order to maximize the probability of a favorable response. The range of doses chosen will help to define dose-response relationships for both safety and efficacy to support later stage studies.

Taken together, the safety, tolerability, and antiviral activity data from Parts A-C in the current study, in conjunction with VIR-2218 PK simulations and PEG-IFNα clinical data, support a positive risk/benefit profile for VIR-2218 monotherapy and VIR-2218/PEG-IFNα combination therapy in patients with chronic HBV infection in Parts D-F.

2. OBJECTIVES

2.1. Part A Objectives

The primary objective is:

- To evaluate the safety and tolerability of a single dose of VIR-2218 in healthy adult subjects

The secondary objective is:

- To characterize the PK of VIR-2218 in healthy adult subjects

2.2. Part B/C Objectives

The primary objective is:

- To evaluate the safety and tolerability of multiple doses of VIR-2218 in non-cirrhotic subjects with HBeAg-negative (Part B) and HBeAg-positive (Part C) chronic HBV infection on NRTI therapy

The secondary objectives are:

- To characterize the PK of VIR-2218 in non-cirrhotic subjects with chronic HBV infection on NRTI therapy
- To assess the antiviral activity of VIR-2218 in non-cirrhotic subjects with chronic HBV infection on NRTI therapy

CCI [redacted]

2.3. Part D - F Objectives

The primary objective is:

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

The secondary objective is:

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

CCI [redacted]

CCI [redacted]

3. ENDPOINTS

3.1. Part A Endpoints

The primary endpoints are:

- Incidence of AEs
- Clinical assessments including but not limited to laboratory test results

The secondary endpoints are:

- PK parameters of VIR-2218 and possible metabolites (may include, but not limited to plasma: maximum concentration, time to reach maximum concentration, area under the concentration versus time curve [to last measurable timepoint and to infinity], percent of area extrapolated, apparent terminal elimination half-life, clearance, and volume of distribution; urine: fraction eliminated in the urine and renal clearance)

3.2. Part B/C Endpoints

The primary endpoints are:

- Incidence of AEs
- Clinical assessments including but not limited to laboratory test results

The secondary endpoints are:

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

CCI [redacted]

3.3. Part D - F Endpoints

Primary Endpoints

- Incidence of AEs
- Clinical assessments including but not limited to laboratory test results

Secondary Endpoints

- Mean maximum reduction of serum HBsAg at any timepoint
- Proportion of subjects with serum HBsAg loss (undetectable HBsAg) at any timepoint
- Proportion of subjects with sustained serum HBsAg loss (undetectable HBsAg) for greater than 6 months
- Proportion of subjects with anti-HBs seroconversion at any timepoint
- For HBeAg-positive patients: proportion of subjects with HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion at any timepoint

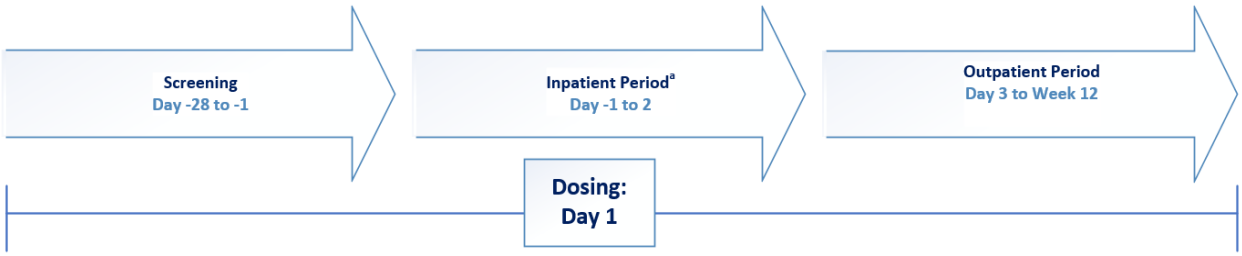
CCI [redacted]

4. STUDY DESIGN

4.1. Part A – C Treatment Plan and Regimen

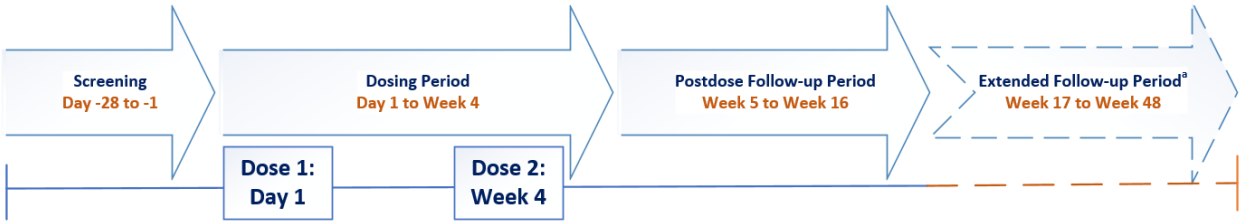
This is a randomized, double-blind, placebo-controlled study of VIR-2218 administered subcutaneously to healthy adult subjects and non-cirrhotic adult subjects with chronic HBV infection who are on NRTI therapy. The study is designed to evaluate the safety, tolerability, PK, and antiviral activity of VIR-2218. Part A is planned to be conducted at 1 clinical investigative site; Parts B and C are planned to be conducted at multiple clinical investigative sites in the Asia Pacific region. The study designs for Part A SAD and Part B/C MAD are presented in Figure 1 and Figure 2, respectively, and the cohort dosing schedule is provided in Appendix 18.

Figure 1: SAD Study Design for Part A



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

Figure 2: MAD Study Design for Part B/C



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

4.1.1. Part A Single Ascending Dose Phase in Healthy Adult Subjects

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

Subject screening will occur no more than 4 weeks prior to the Day 1 visit. Eligible subjects will be confined to the clinical investigative site on Day −1 to determine continued eligibility and for predose assessments. Subjects in each cohort will be randomized to receive VIR-2218 or placebo within 48 hours prior to study drug administration. Subjects will receive a single dose of study

drug on Day 1 (VIR-2218 or placebo). Subjects will be discharged from the clinical investigative site after all assessments are completed on Day 2.

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

Based on review of the accumulated, available data in Part A, the SRC may recommend dosing of 2 optional cohorts. In addition to the optional cohorts, up to 8 "floater" subjects for Part A may be added to any cohort, as determined and approved by the SRC (see Section 4.6.2 and Appendix 18 for further information).

Fasting is not required for any study procedure/assessment.

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

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

Subjects enrolled in Part B/C of the study will remain outpatient. Subject screening will occur no more than 4 weeks prior to the Day 1 visit. Eligible subjects will undergo further assessments on Day 1 to qualify for study drug administration on Day 1. To exclude the presence of cirrhosis, screening will include a mandatory noninvasive assessment of liver fibrosis such as a FibroScan evaluation, unless the subject has results from a FibroScan evaluation performed within 6 months prior to screening or a liver biopsy performed within 1 year prior to screening that confirms the absence of Metavir F3 fibrosis or F4 cirrhosis.

Subjects in each cohort will be randomized 3:1 to receive VIR-2218 or placebo within 48 hours prior to study drug administration on Day 1. Subjects will return to the clinical investigative site at Week 4 to receive a second dose of the same study drug administered on Day 1. The decision to administer a second dose will be made based on Week 3 laboratory values in accordance with dose suspension/stopping criteria in Section 4.8.

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

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

Based on review of the accumulated, available data in Parts A, B, and C, the SRC may recommend dosing of optional cohorts following the same stratification. In addition to the

Fasting is not required for any study procedure/assessment. The assessments performed at each visit are described in Appendix 3.

4.2. Part D - F Treatment Plan and Regimen

This is an open-label study of VIR-2218 administered alone or in combination with PEG-IFNα in non-cirrhotic adult subjects 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.

The study designs for Part D – F are presented in Figure 3, Figure 4, Figure 5, Figure 6, Figure 7 and Figure 8. The cohort schedule is provided in Appendix 18.

Figure 3: Design for Cohort 1d/1e

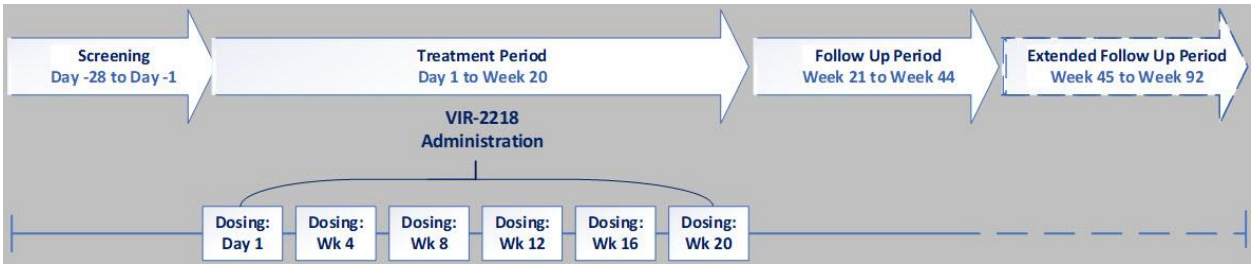


Figure 4: Design for Cohort 2d/2e

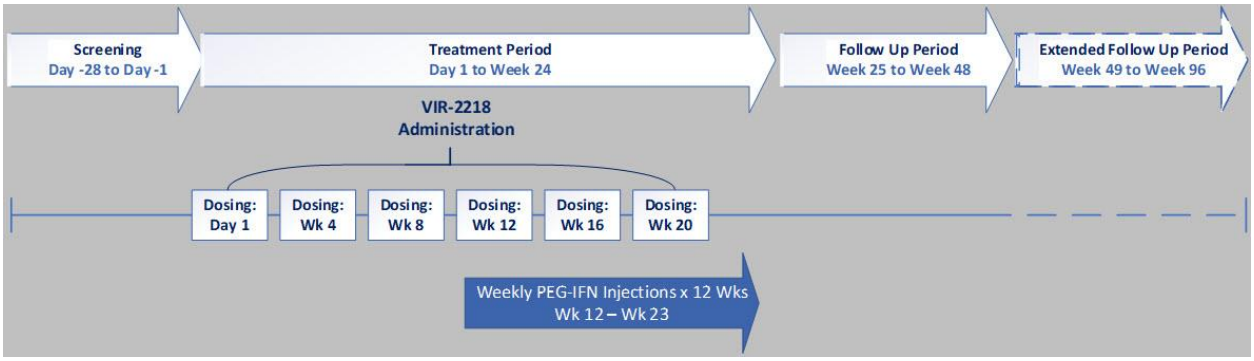


Figure 5: Design for Cohort 3d/3e

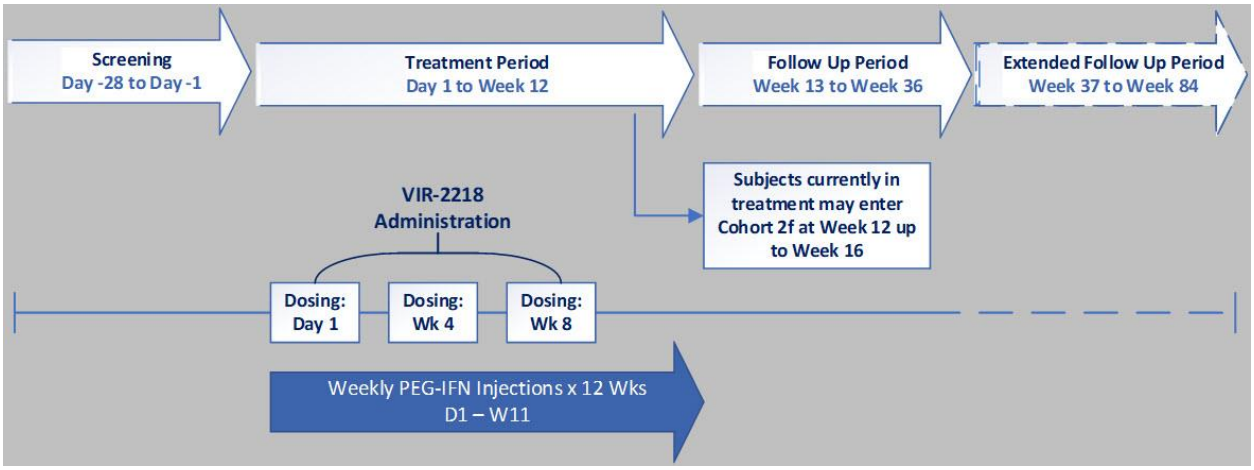


Figure 6: Design for Cohort 1f

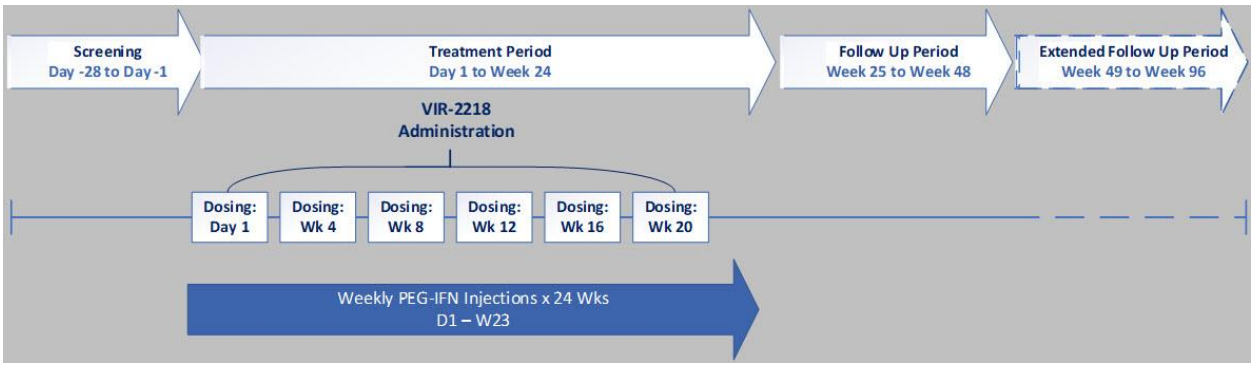


Figure 7: Design for Cohort 2f

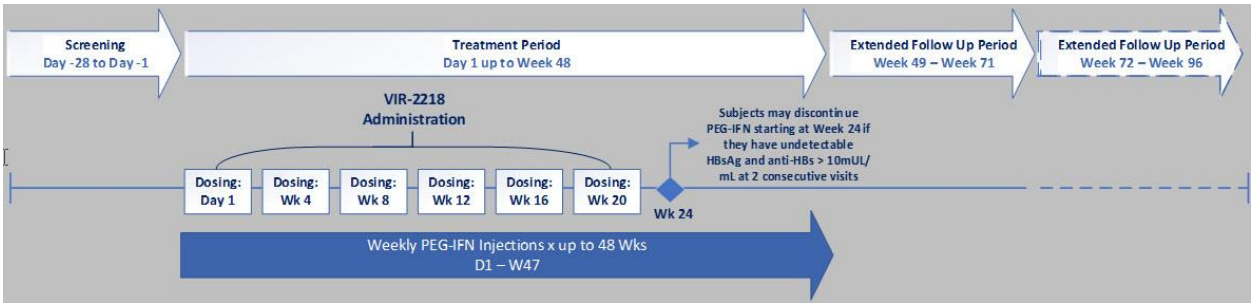
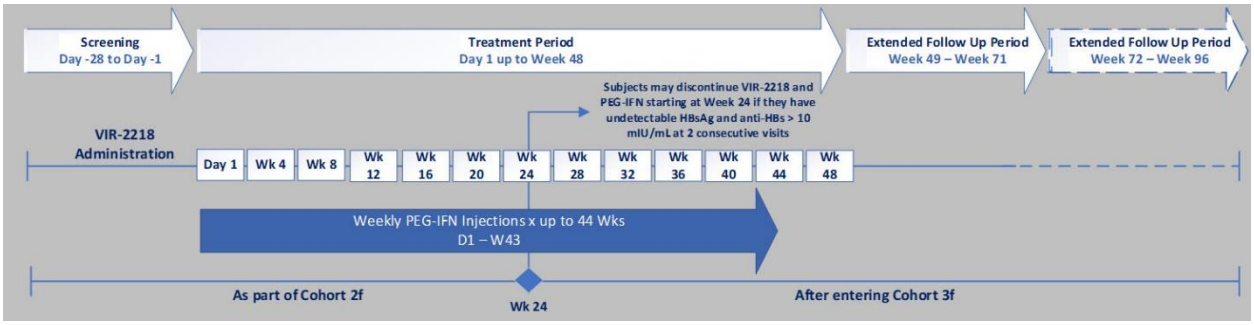


Figure 8: Design for Cohort 3f



4.2.1. Parts D – F Phase 2 Open-label Study of VIR-2218 Alone or in Combination with PEG-IFNα

Non-cirrhotic adult subjects with chronic HBV infection on NRTI therapy for ≥ 2 months will be enrolled in Parts D - F. Parts D – F will enroll both HBeAg-negative and HBeAg-positive subjects with a target of 5 HBeAg-positive subjects enrolled per cohort. The target for each cohort will be to enroll approximately 10% of subjects with screening HBsAg level >10,000 IU/mL. In Part D subjects will be enrolled to 1 of 3 planned active-treatment cohorts. In optional Part E subjects may be enrolled to 1 of 3 possible active-treatment cohorts. In optional Part F, subjects may be enrolled into Cohort 1f, Cohort 2f or Cohort 3f. Each cohort will receive multiple doses of VIR-2218 alone or in combination with PEG-IFNα in variable regimens. Cohorts 1d/e, 2d/e and 3d/e will enroll up to 15 subjects each, and Cohorts 1f and 2f will enroll up to 30 subjects each. Cohort 3f will include subjects that qualify to enter from Cohort 2f at their Week 24 visit.

Subjects enrolled in Parts D - F of the study will remain outpatient. Subject screening will occur no more than 4 weeks prior to the Day 1 visit. Prior to study drug administration on Day 1, subject eligibility will be confirmed. To exclude the presence of cirrhosis, screening will include a mandatory noninvasive assessment of liver fibrosis such as a FibroScan evaluation, unless the subject has results from a FibroScan evaluation performed within 6 months prior to screening or a liver biopsy performed within 1 year prior to screening that confirms the absence of Metavir F3 fibrosis or F4 cirrhosis.

Subjects will be enrolled into a cohort in Parts D - F within 48 hours prior to study drug administration on Day 1. Day 1 predose laboratory values are not required to be reviewed prior to dosing. Subjects currently in the Cohort 3d that have not completed the Week 12 visit may enter Cohort 2f at their Week 12 visit. At Week 12, subjects 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 subjects have completed their Week 12 visit, they may move to Cohort 2f up to their Week 16 visit and continue per Cohort 2f schedule. Subjects that enter Cohort 2f after their Week 12 visit and 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.

Subjects enrolled in Cohorts 3d, 3e, 1f, and 2f will return to the clinical investigative site on Week 1 and Week 2 to receive a dose of PEG-IFNα and training for self-administration of subsequent PEG-IFNα injections. Subjects assigned to Cohorts 2d and 2e will return to the clinical investigative site at Week 12, Week 13, and Week 14 to receive a dose of PEG-IFNα and training for self-administration of subsequent PEG-IFNα injections. Beginning at Week 3 for subjects in Cohorts 3d, 3e 1f, and 2f, and Week 15 for subjects in Cohorts 2d and 2e, subjects who are trained may choose to administer PEG-IFNα injections at home. Subjects who do not wish to self-administer injections may return weekly to the clinical investigative site to have PEG-IFNα injections administered until the study drug administration period ends. Subjects that enter Cohort 3f from Cohort 2f may continue to administer PEG-IFNα at home or in clinic, as planned in Cohort 2f. The decision to administer subsequent doses of PEG-IFNα should be made based on the laboratory values from the most recent prior visit in accordance with dose modification, suspension, and stopping criteria in Section 4.8. All Part D - F subjects will return to the clinical investigative site every 4 weeks beginning at Week 4 to receive subsequent doses of VIR-2218, until the final dose of VIR-2218 is given. The decision to administer subsequent doses of VIR-2218 should be made based on laboratory values from the most recent prior visit in accordance with dose suspension/stopping criteria in Section 4.8.

Subjects 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 subjects with HBsAg decline ≥ 1-log 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.

It is recommended that subjects who meet certain criteria discontinue from NRTI therapy, as outlined in Section 4.7.1. Subjects 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. These subjects will follow the Schedule of Assessments for subjects who

have discontinued from NRTI therapy (Appendix 16). Subjects 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.

Fasting is not required for any study procedure/assessment. The procedures/assessments performed at each visit are described in Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10, Appendix 11, Appendix 12, Appendix 13, Appendix 14, and Appendix 16.

4.3. Discontinuations

Subjects that discontinue study treatment prematurely (eg, due to meeting a stopping rule) should undergo assessments for the last treatment period visit for their assigned cohort at the time of discontinuation and remain on the study for all follow-up or extended follow up assessments in accordance with the SoA.

If a subject discontinues from study participation (eg, due to withdrawal of consent), assessments for the Early Termination visit should be performed. Under certain circumstances, subjects who discontinue from the study (as described in Section 4.4) may be replaced.

4.4. Replacement of Subjects

In Parts A – C, replacement subjects may be enrolled to ensure that the minimum data requirements for SRC dose escalation decisions and study progression are met, as described in Section 4.6. Subjects who do not receive the full planned dose, do not receive a second dose (for Part B/C), discontinue due to an AE that does not meet study progression/escalation and dose suspension/stopping rules (Section 4.8), or who withdraw from the study, may be replaced with confirmation by the SRC. Subjects who are discontinued from treatment for reasons other than experiencing an AE may be replaced following discussion between the Sponsor and investigator.

In Parts D – F, subjects may be replaced at Sponsor discretion, following discussion between the Sponsor and investigator.

The replacement subject will be assigned a unique study identification number and will receive the same treatment assignment and dose level as the subject who is being replaced, and in the same blinded fashion.

4.5. Safety Review Committee and Liver Flare Adjudication Committee

4.5.1. Safety Review Committee

In Parts A – C, an SRC will perform ongoing reviews of safety, tolerability, and available study data collected throughout the study with the primary purpose of protecting the safety of subjects participating in this clinical study. The SRC will be governed by an SRC Charter that will be finalized prior to screening the first subject.

The SRC will undertake safety data review prior to initiation of dosing a new cohort in Parts A, B, and C of the study in accordance with the SRC Charter. Ad hoc SRC meetings may take place as needed, eg, for a significant safety event such as a subject or cohort stopping criterion being reached (Section 4.8). In Parts D - F of the study, the SRC may meet ad hoc, and/or in the event an unexpected safety concern is identified.

Decisions to suspend dosing or discontinue individual subjects from study drug will be made according to predetermined stopping rules (Section 4.8). Additionally, the SRC may recommend

discontinuation of the study to the Sponsor. The SRC membership composition is described in detail in the SRC Charter.

4.5.2. Liver Flare Adjudication Committee

In order to fully characterize transaminase elevations, the Liver Flare Adjudication Committee (LFAC) may perform periodic reviews of data pertaining to patients in Parts D - F who meet certain prespecified criteria. Additionally, the Sponsor may request LFAC evaluation of specific patient data at any time. The LFAC will be governed by an LFAC Charter that will be finalized prior to screening the first subject for Parts D - F. The LFAC membership composition, laboratory criteria to trigger patient case evaluation by the LFAC, and data review requirements are described in detail in the LFAC Charter.

4.6. Part A – C Study Drug Dosing, Study Progression, and Dose Escalation

Progression rules are based on the absence of prespecified safety signals. Standard toxicity grading according to the current Common Terminology Criteria for Adverse Events (CTCAE) Version 5 will be used to grade AEs. The decision to enroll an optional cohort or expand an existing cohort will be made by the SRC based on available safety, tolerability, and antiviral activity data, if further data are considered necessary to better understand dose response and/or safety and tolerability.

Subjects in Parts, A, B and C will receive VIR-2218 or placebo via SC injection according to the schedules provided in Appendix 2 and Appendix 3 for Part A and Part B/C, respectively.

4.6.1. Part A Study Drug Dosing, Study Progression, and Dose Escalation in Planned Cohorts

The starting dose for the first cohort in Part A is 50 mg, as described in Section 1.2.5. The SRC will review available laboratory and clinical safety data, including Week 4 data from the last available subject enrolled in the cohort to proceed to the next planned cohort in Part A. There are 4 planned cohorts in Part A: 50 mg, 100 mg, 200 mg, and 400 mg (Table 4).

4.6.2. Part A Optional Cohorts and Floater Subjects

Based on SRC review of accumulated safety and tolerability data, 2 optional cohorts may be enrolled and dosed according to the same eligibility criteria and corresponding randomization scheme to better define safety and tolerability. The maximum optional dose in Part A will not exceed the defined maximum administered single dose of 900 mg (see Appendix 18 for additional information).

In addition to the optional cohorts, up to 8 “floater” subjects in total for Part A may be added to expand any of 6 possible cohorts (planned or optional), as determined and approved by the SRC. Each expansion must include a minimum of 4 “floater” subjects, randomized 3:1 to VIR-2218 or placebo, furthermore only half of the total “floater” subjects (4 subjects in Part A) may enroll in the highest optional dose cohort.

4.6.3. Part B Study Drug Dosing, Study Progression, and Dose Escalation in Planned Cohorts

Overview*:* There are 3 planned cohorts in Part B: 50 mg, 100 mg, and 200 mg. Part B is limited to subjects with chronic HBV infection who are HBeAg -negative. Each cohort will receive a dose on Day 1, and a second dose at Week 4, such that the cumulative dose received for the planned cohorts in Part B will be 100 mg, 200 mg, and 400 mg (Table 4).

Initiation of Part B*:* 2 dose levels in Part A (1a: 50 mg and 2a: 100 mg) must be completed and cumulative safety data, inclusive of the clinical and laboratory data from Week 4 from the last subject dosed in Cohort 2a (100 mg), must be reviewed by the SRC to begin dosing Part B (1b: 50 mg).

Escalation within Part B: Escalation to a higher dose-level cohort will only occur after the SRC has reviewed clinical and laboratory data including data from the Week 6 visit of the last available subject in the ongoing cohort, and the subject has completed their Week 8 visit. The SRC may review cumulative data from subjects in Parts A, B, and C at the time of meeting. The SRC will ensure that no subject in a cohort from Part B will receive a particular dose level prior to review of Week 4 data from subjects in Part A who have received at least the same cumulative dose level.

PK data will not be used for dose escalation decisions because VIR-2218 is expected to be rapidly cleared from the blood by receptor mediated uptake into the liver. Therefore, concentrations of VIR-2218 in the blood are not expected to be reflective of liver concentrations.

4.6.4. Part C Study Drug Dosing, Study Progression, and Dose Escalation in Planned Cohorts

Overview*:* There is 1 planned cohort in Part C: 200 mg (Cohort 3c). Escalations to higher dose levels may only occur in the optional cohorts (Section 4.6.5). Part C is limited to subjects with chronic HBV infection who are HBeAg -positive. This cohort will receive a dose on Day 1, and a second dose at Week 4, such that the cumulative dose received will be 400 mg (Table 4).

Initiation of Part C*:* The planned Cohort 3c will initiate at the same time as Cohort 3b (200 mg, given as 2 doses, 4 weeks apart), after the SRC has reviewed clinical and laboratory data including from the Week 6 visit of the last available subject in Cohort 2b. Initiation of Cohort 3c will not occur until the last available subject in Cohort 2b has completed their Week 8 visit.

4.6.5. Part B/C Optional Cohorts and Floater Subjects

Based on SRC review of accumulated safety and tolerability data, up to 2 optional dose level cohorts may be enrolled and dosed in each study part according to the randomization scheme to better define dose response and/or safety and tolerability. Enrollment of the Part B/C optional cohorts will be according to the same Part B/C eligibility criteria as the planned cohorts.

The optional cohorts may be dosed at lower, intermediate, and/or higher dose levels than the dose levels explored in the planned Part B or C cohorts. The maximum cumulative dose level in any cohort in Part B or C will not exceed the highest single dose found to be well tolerated in Part A. For example, if a single dose of 900 mg in Part A is determined by the SRC to have an acceptable safety profile, dose levels of 450 mg (cumulative dose of 900 mg) or lower dose levels can be explored in Part B/C. The maximum administered cumulative dose in any cohort will not exceed 900 mg (Table 4).

Dose escalation in the optional Part B/C cohorts will occur according to the same criteria as dose escalation within Part B (Section 4.6.3)

In addition to the optional cohorts, up to 16 "floater" subjects in total for Part B/C may be added to expand any Part B or C cohort (planned or optional), as determined and approved by the SRC. This "floater" pool is shared between Part B/C and the allocation of floater subjects does not need to be distributed evenly across parts. Subjects will be added in increments of 4 and randomized 3:1 to VIR-2218 or placebo, furthermore only half of the total "floater" subjects (8 total subjects in Part B/C) may enroll in the highest optional dose cohort.

4.7. Part D and Optional Part E/F Cohorts and Study Drug Dosing

Overview: There are 3 planned cohorts in Part D, 3 possible cohorts in optional Part E, and 2 possible cohorts in optional Part F.

- Subjects in Part D cohorts will receive multiple doses of VIR-2218 at a dose level of 200 mg.
- Subjects in Part E cohorts will receive multiple doses of VIR-2218 at a dose level of 50 mg.
- Subjects in Part F cohorts will receive multiple doses of VIR-2218 at a dose level up to 200 mg.

All cohorts within a part will receive the same dose level of VIR-2218. Cohorts 2d/e, 3d/e, 1f, 2f and 3f will also receive weekly injections of PEG-IFNα. Optional Parts E and F may be enrolled any time at Sponsor discretion, based on emerging data.

Initiation of Parts D - F*:* Part D will be commenced at a fixed dose-level of 200 mg. Optional Part E may be commenced at a fixed-dose level of 50 mg. Cohorts 1d – 3d will be initiated at the same time. Optional Parts E and F may be initiated at any point, based on emerging data; each cohort within Parts E and F are considered optional, and one or multiple cohorts within these parts may be initiated. Part F may be initiated at a dose level up to 200 mg (the dose level explored in Part D of the study) at Sponsor discretion, based on emerging data. The dose levels for Parts D - F were selected based on review of study data inclusive of safety, tolerability, pharmacokinetic, and antiviral activity (Part B/C), in Parts A – C of the study.

Cohort 1d/optional Cohort 1e: In Cohort 1d and 1e, subjects will receive 6 doses of VIR-2218 at a frequency of every 4 weeks. Each subject will receive a dose of VIR-2218 on Day 1, Week 4, and Week 8, Week 12, Week 16, and Week 20.

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

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

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

Optional Cohort 2f: In Cohort 2f, subjects will receive up to 6 doses of VIR-2218 at a frequency of every 4 weeks. Each subject will receive a dose of VIR-2218 on Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20. Additionally, subjects 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 subjects will receive a minimum of 24 doses of PEG-IFNα. Subjects with ≤ 1 log IU/mL reduction from predose Day 1 baseline in HBsAg at the Week 20 visit will discontinue PEG-IFNα after 24 weeks. All other subjects will continue PEG-IFNα up to Week 47 (ie, the 48th dose of PEG-IFNα) or, until HBsAg is undetectable AND anti-HBs is ≥ 10 mIU/mL for 2 consecutive visits. Subjects will receive no more than 48 doses of PEG-IFNα.

Subjects 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, subjects 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 subjects have already completed their Week 12 visit, they may move to Cohort 2f up to their Week 16 visit. Subjects 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 subjects enter Cohort 2f, they will follow the schedule for Cohort 2f.

Subjects from Cohort 2f that have ≥ 1 $\log_{10}$ 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.

Optional Cohort 3f: In optional Cohort 3f, starting at Week 24, subjects will continue VIR-2218 dosing every 4 weeks until Week 48 (ie, the 13th dose of VIR-2218) and PEG-IFNα weekly up to Week 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.

4.7.1. NRTI Discontinuation

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

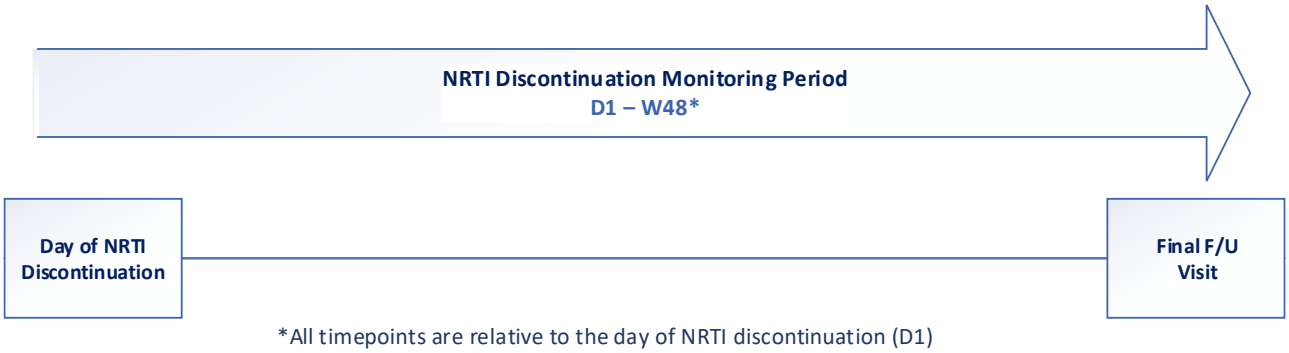
- are HBeAg-negative (defined as undetectable quantitative HBeAg)
- have ALT < 2 x ULN
- have suppression of HBV DNA (defined as < LLOQ)

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 the Treatment 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 subject eligibility for NRTI discontinuation. Subjects 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 subjects will follow the Schedule of Assessments for subjects who have discontinued from NRTI therapy (Appendix 16). Subjects 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.

Figure 9: NRTI Discontinuation Monitoring Period



4.7.2. NRTI Retreatment

It is recommended that the investigator should consider retreatment with NRTI therapy during the NRTI Discontinuation Monitoring Period if subjects 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

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

4.8. Stopping Rules

The following stopping rules are based on potential safety signals. Standard toxicity grading according to the CTCAE Version 5.0 (Table 7) will be used to grade AEs. When a Cohort Stopping Rule is met, no further study drug will be administered at the dose level and further dose escalation/progression will be suspended. An ad hoc SRC meeting will be held, and only following SRC approval, may dosing be resumed at the same or a higher dose level; if required, additional approval from the concerned regulatory authority and the independent ethics committee (IEC)/institutional review board (IRB), in accordance with applicable requirements, will be obtained. De-escalation to a lower dose will be allowed at Sponsor discretion.

4.8.1. Cohort Stopping Rules in Parts A - C

In Parts A – C, if any of the criteria described below are met as determined by the Sponsor, cohort dosing will be suspended or stopped:

- Part A only: If a sentinel subject experiences a study drug-related Grade 3 or higher AE
- If 1 or more subjects experience a Grade 3 study drug-related rash
- If 2 or more subjects experience the same study drug-related Grade 3 or higher AE
- If 1 or more subjects experience a study drug-related serious adverse event (SAE)
- If 1 or more subjects experiences a Grade 4 AE of rash, regardless of assessed causality

4.8.2. Individual Subject Stopping Rules in Part B and C

Individual subjects in Part B - C who have received one dose of study drug will not receive additional doses of study drug if any the following criteria are met:

- Serum ALT > 10 × ULN
- Serum ALT > 5 × ULN, with no change in HBsAg, defined as a < 50% decrease from the baseline predose value
- Serum ALT or AST > 3 × ULN with a concomitant total bilirubin > 2 × ULN
- Any clinical manifestations of hepatic decompensation

The investigator should notify the Sponsor medical monitor immediately, in the event that any of the above criteria are met.

4.8.3. Individual Subject Stopping Rules in Parts D - F

Individual subjects in Parts D – F who have received one or more doses of VIR-2218 and/or PEG-IFNα will not receive additional doses of either study drug if any the following criteria are met:

- Serum ALT > 10 × ULN
- Serum ALT > 5 × ULN, with no change in HBsAg, defined as a < 50% decrease from the baseline predose value
- Serum ALT or AST > 3 × ULN with a concomitant total bilirubin > 2 × ULN or INR > 1.5 (erroneously elevated INR due to incorrect blood volume collection should be ruled out)
- Any clinical manifestations of hepatic decompensation

The investigator should notify the Sponsor medical monitor immediately, in the event that any of the above criteria are met. An ad hoc SRC meeting will be convened if any Individual Subject Stopping rule is met. Only following formal approval from the SRC, and upon agreement with the investigator and the Sponsor Medical Monitor, can the subject be considered to continue receiving study treatment.

4.8.4. Dose Modifications for PEG-IFNα in Parts D - F

Dose modifications of PEG-IFNα in response to PEG-IFNα-related adverse reactions are permitted at the discretion of the investigator. It is recommended that PEG-IFNα dose modifications be performed in accordance with the PEGASYS® Prescribing Information. Alternative dose modification strategies based on local treatment guidelines or institutional standards of care are allowed following approval from the Sponsor Medical Monitor. Subjects enrolled in Parts D - F who discontinue PEG-IFNα treatment due to PEG-IFNα-related adverse reactions may continue treatment with VIR-2218. These subjects will follow the schedule of assessments as provided for their cohort with the exception of PEG-IFNα administration. If the subject previously elected to have PEG-IFNα injections administered at the clinical investigative site (instead of at-home self-administration), they are not required to return for these visits.

5. SUBJECT POPULATION

5.1. Number of Subjects and Subject Selection

A total of up to 254 subjects are planned to complete this study, comprising up to 56 healthy adult subjects in Part A, up to 48 non-cirrhotic adult subjects with chronic HBV infection on NRTI therapy in Part B/C, and up to 150 non-cirrhotic adult subjects with chronic HBV infection on NRTI therapy in Parts D – F.

- **Part A Planned/Optional Dose Cohorts:** Up to 48 healthy subjects
    - **Part A "Floater" Subjects**: Up to 8 "floater" subjects may be added
- **Part B Planned/Optional Dose Cohorts:** Up to 20 non-cirrhotic adult subjects with chronic HBV infection that are HBeAg-negative on NRTI therapy
- **Part C Planned/Optional Dose Cohorts:** Up to 12 non-cirrhotic adult subjects with chronic HBV infection that are HBeAg-positive on NRTI therapy
    - **Part B/C "Floater" Subjects:** Up to 16 "floater" subjects may be added
- **Part D - F Planned/Optional Cohorts:** Up to 150 non-cirrhotic adult subjects with chronic HBV infection that are HBeAg-positive or HBeAg-negative on NRTI therapy

5.2. Part A Inclusion Criteria

Each subject must meet all the following inclusion criteria at screening to be eligible for enrollment in the study:

1. Age 18 (or age of legal consent, whichever is older) to 55 years
2. 12-lead electrocardiogram (ECG) within normal limits; or, with no clinically significant abnormalities at screening, as determined by the clinical investigator.
3. Female subjects must have a negative pregnancy test or confirmation of post-menopausal status. Post-menopausal status is defined as age > 50 years with no menses for at least 2 years. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test at screening and a negative urine pregnancy test on Day -1, cannot be breast feeding, and must be willing to use highly effective methods of contraception 14 days before study drug administration through 12 weeks after study drug administration. Refer to Section 6.7 for more information on highly effective methods of contraception.
4. Male subjects with female partners of child-bearing potential must agree to meet 1 of the following contraception requirements from the time of study drug administration until the last follow-up visit: vasectomy with documentation of azoospermia, or male condom use plus partner use of 1 of the contraceptive options listed for contraception for WOCBP. Male subjects must also agree to not donate sperm for the 12 weeks following study drug administration. Refer to Section 6.7 for more information on highly effective methods of contraception.
5. Agrees not to donate blood during the duration of the study
6. Willing to comply with the study requirements and able to provide written informed consent

7. Body mass index (BMI) ≥ 18.0 kg/m2 and ≤ 32 kg/m2
8. Agree to not increase physical activity for 4 weeks after study drug administration

5.3. Part A Exclusion Criteria

Each subject must not meet any of the following exclusion criteria to be eligible for enrollment in the study:

1. Any clinically significant chronic medical condition that, in the opinion of the investigator, makes the volunteer unsuitable for participation in the study
2. Any clinically significant acute condition such as fever (> 38ºC) or acute respiratory illness within 7 days of study drug administration
3. Receipt of a vaccine 14 days prior to Day 1
4. Previous or current psychiatric condition that precludes compliance with the protocol. Specifically excluded are persons with psychoses, ongoing risk for suicide, or history of suicide attempt or gesture within the past 5 years
5. Systolic blood pressure > 140 mmHg and a diastolic blood pressure of > 90 mmHg after approximately 10 minutes resting at screening
6. Subject has the following laboratory parameters at screening:
    a. ALT, AST, creatinine or total bilirubin above the upper limit of normal (ULN)
    b. hemoglobin (Hgb), absolute neutrophil count (ANC), platelets, or albumin below the lower limit of normal (LLN)
    c. white blood cells (WBC), potassium (K), or sodium (Na) above the ULN or below the LLN

    Study laboratory tests may be repeated once (eg, for values thought to be erroneous) with Sponsor medical monitor approval.
7. Received an investigational agent within 90 days before study drug administration or are active in the follow-up phase of another clinical study involving interventional treatment. Subjects must also agree not to take part in any other study at any time during their participation in this study, inclusive of the follow-up period.
8. Laboratory evidence of active infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or HBV
9. Consume more than 7 units of alcohol per week (unit: 1 glass of wine [125 mL] = 1 measure of spirits [30 mL] = one half pint of beer [284 mL]). Alcohol is limited to no more than 1 unit per day for the duration of the study
10. History or clinical evidence of alcohol or drug abuse, within the 12 months before screening or a positive drug screen for amphetamines, cocaine, methadone, or opiates at screening unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator.
11. Known hypersensitivity or contraindication to an siRNA or GalNAc
12. History of intolerance to SC injection

13. Any conditions which, in the opinion of the investigator, would make the subject unsuitable for enrollment or could interfere with the subject's participation in or completion of the study
14. Donated more than 500 mL of blood within 90 days before study drug administration
15. Creatinine clearance (CL_{cr}) < 90 mL/min as calculated by the Cockcroft-Gault formula at screening
16. Used prescription drugs within 14 days before study drug administration except for a stable dose of: medication to treat hypertension, inhaler or nebulizer to treat asthma, hormone replacement therapy, antihistamines, and contraceptive therapy (refer to Section 6.5.1 for more information). Hypertension must be well controlled on 1 medication (two active components in one medication is permitted) for > 6 months. Asthma must be well controlled, requiring, on average, use of a rescue bronchodilator no more than twice per week.
17. Use of over-the-counter (OTC) medication or herbal remedy within 14 days before study drug (≤ 2g/day of paracetamol (acetaminophen), ≤ 3g/day of aspirin or < 1.2 g/day of ibuprofen is permitted) and throughout the study.

5.4. Part B/C Inclusion Criteria

Each subject must meet all the following inclusion criteria at screening to be eligible for enrollment in the study:

1. Age 18 (or age of legal consent, whichever is older) to 65 years at the time of screening
2. 12-lead ECG within normal limits; or, with no clinically significant abnormalities at screening, as determined by the clinical investigator
3. Female subjects must have a negative pregnancy test or confirmation of post-menopausal status. Post-menopausal status is defined as age > 50 years with no menses for at least 2 years at the time of screening. WOCBP must have a negative serum pregnancy test (using central laboratory) at screening and a negative urine pregnancy test on Day 1, cannot be breast feeding, and must be willing to use highly effective methods of contraception 14 days before study drug administration through 12 weeks after last study drug administration. Refer to Section 6.7 for more information on highly effective methods of contraception.
4. Male subjects with female partners of child-bearing potential must agree to meet 1 of the following contraception requirements from the time of study drug administration until the last follow-up visit: vasectomy with documentation of azoospermia, or male condom use plus partner use of 1 of the contraceptive options listed for contraception for WOCBP. Male subjects must also agree not to donate sperm for the 12 weeks following last study drug administration. Refer to Section 6.7 for more information on highly effective methods of contraception.
5. Agrees to not donate blood during the duration of the study
6. Willing to comply with the study requirements and able to provide written informed consent

7. BMI ≥ 18.0 kg/m^2 and ≤ 32 kg/m^2
8. Chronic HBV infection as defined by a positive serum HBsAg for ≥ 6 months
9. On NRTI therapy for at least 6 months without an interruption of 7 or more consecutive days
10. HBsAg > 150 IU/mL (by central laboratory)
11. HBV DNA < 90 IU/mL (by central laboratory)
12. Serum ALT and AST ≤ 2 × ULN (by central laboratory)
13. Agrees not to increase physical activity for 4 weeks after each study drug administration

5.5. Part B/C Exclusion Criteria

1. Any clinically significant chronic medical condition other than chronic HBV infection that, in the opinion of the investigator makes the volunteer unsuitable for participation in the study
2. Any clinically significant acute condition such as fever (> 38ºC) or acute respiratory illness within 7 days of study drug administration
3. Significant fibrosis or cirrhosis as defined by having either a FibroScan result of > 8.5kPa at screening or a liver biopsy within 1 year with Metavir F3 fibrosis or F4 cirrhosis. Refer to Section 7.2.9 for more information.
4. Receipt of a vaccine 14 days prior to Day 1
5. Previous or current psychiatric condition that precludes compliance with the protocol. Specifically excluded are persons with psychoses, ongoing risk for suicide, or history of suicide attempt or gesture within the past 5 years
6. Systolic blood pressure > 140 mmHg and a diastolic blood pressure of > 90 mmHg after approximately 10 minutes resting at screening
7. Subject has the following laboratory parameters at screening by central laboratory:
    a. creatinine, total bilirubin, INR or prothrombin time above the ULN
    b. hemoglobin, ANC, platelets, or albumin below the LLN
    c. WBC, potassium, or sodium above the ULN or below the LLN
    d. serum ALT or AST > 2 × ULN

    Study laboratory tests may be repeated once (eg, for values thought to be erroneous) with Sponsor approval.
8. Received an investigational agent within 90 days before study drug administration or are active in the follow-up phase of another clinical study involving interventional treatment. Subjects must also agree not to take part in any other study at any time during their participation in this study, inclusive of the follow-up period.

9. Used prescription drugs within 14 days before study drug administration except for a stable dose of: medication to treat hypertension, inhaler or nebulizer to treat asthma, hormone replacement therapy, antihistamines, and contraceptive therapy (refer to Section 6.5.1 for more information). Hypertension must be well controlled on no more than 2 medications **or** 1 medication with two active components for > 6 months. Asthma must be well controlled, requiring, on average, use of a rescue bronchodilator no more than twice per week.
10. Use of over-the-counter (OTC) medication or herbal remedy within 14 days before study drug and throughout the study, with the following exceptions of permitted OTC medications: Paracetamol (acetaminophen) ≤ 2g/day, aspirin ≤ 3g/day or ibuprofen < 1.2 g/day.
11. Active infection with HIV, HCV or hepatitis Delta virus as determined by the central laboratory
12. Consume more than 7 units of alcohol per week (unit: 1 glass of wine [125 mL] = 1 measure of spirits [30 mL] = one half pint of beer [284 mL]). Alcohol is limited to no more than 1 unit per day for the duration of the study
13. History or clinical evidence of alcohol or drug abuse, within the 12 months before screening or a positive drug screen for amphetamines, cocaine, methadone or opiates at screening unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator. Screening results must be reviewed by the investigator to confirm eligibility prior to dosing.
14. Known hypersensitivity or contraindication to an siRNA or GalNAc
15. History of intolerance to SC injection
16. Any conditions which, in the opinion of the investigator, would make the subject unsuitable for enrollment or could interfere with the subject's participation in or completion of the study
17. Donated more than 500 mL of blood within 90 days before study drug administration
18. CL_{cr} < 60 mL/min as calculated by the Cockcroft-Gault formula at screening
19. History of chronic liver disease from any cause other than chronic HBV infection
20. History of hepatic decompensation, including ascites, hepatic encephalopathy and/or esophageal or gastric varices

5.6. Parts D - F Inclusion Criteria

1. Male or female between the ages of 18 (or age of legal consent, whichever is higher) to < 66 years at the time of screening
2. Body Mass Index (BMI) ≥ 18 kg/m^2 and ≤ 32 kg/m^2
3. Chronic HBV infection defined as a positive serum HBsAg test for ≥ 6 months prior to screening
4. On NRTI therapy for at least 2 months at the time of screening without an interruption of 7 or more consecutive days

5. HBV DNA < 90 IU/mL measured at screening
6. HBsAg > 50 IU/mL measured at screening
7. Male subjects with female partners of child-bearing potential must agree to meet 1 of the following contraception requirements from the time of study drug administration until the end of follow-up or extended follow-up period, whichever is later: documentation of successful vasectomy or azoospermia, or consistent male condom use plus partner use of 1 of the contraceptive options listed for contraception for WOCBP. Additionally, male subjects with pregnant partners must use a condom from the time of study drug administration until the end of follow-up or extended follow-up period, whichever is later. All male subjects must also agree not to donate sperm until the end of follow-up period or extended follow-up period, whichever is later.

   Female subjects must not be pregnant or nursing. All females must have a negative pregnancy test or confirmation of post-menopausal status (> 50 years with no menses for at least 2 years at the time of screening) or surgically sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy). WOCBP must have a negative serum pregnancy test (using central laboratory) at screening and a negative urine pregnancy test on Day 1 and must be willing to use highly effective methods of contraception 14 days before study drug administration through the follow-up period or extended follow-up period, whichever is later.

   Refer to Section 6.7 for more information on contraception requirements.
8. Agrees to not significantly increase physical activity from the time of screening through 4 weeks after final administration of study drug
9. Willing and able to comply with the study requirements and to provide written informed consent

5.7. Parts D - F Exclusion Criteria

1. Significant fibrosis or presence of cirrhosis defined as having either a FibroScan result of > 8.5 kPa at screening or a liver biopsy within 1 year prior to screening with Metavir F3 or F4.
2. Current or prior history of clinically significant liver disease from any cause other than chronic HBV infection
3. Current or prior history of hepatic decompensation, including ascites, hepatic encephalopathy, and/or known esophageal or gastric varices
4. History of hypersensitivity or contraindication to an siRNA, oligonucleotide, GalNAc, or any component of VIR-2218
5. History of allergy to greater than 2 drug classes
6. Cohorts 2d/3d/2e/3e/1f/2f/3f only: Known hypersensitivity or contraindication to an interferon product
7. Any prior receipt of an interferon product
8. Current or prior history of psychosis, bipolar disorder, schizophrenia, moderate-severe depression, suicide ideation, attempt, or gesture, or high risk for suicide

9. Known active infection other than chronic HBV infection or any clinically significant acute condition such as fever (> 38° C) or acute respiratory illness within 7 days prior to Day 1
10. Myocardial infarction (based on ECG and/or clinical history), moderate-severe congestive heart failure (New York Heart Association Class III or IV), or history of angina or arrhythmia within one year prior to screening
11. Current or prior history of severe chronic obstructive pulmonary disorder (defined as history of FEV1 < 50% predicted value)
12. Cohorts 2d/3d/2e/3e/1f/2f/3f only: Current or prior history of clinically significant retinal disease
13. Cohorts 2d/3d/2e/3e/1f/2f/3f only: Current or prior history of an autoimmune disorder
14. Cohorts 2d/3d/2e/3e/1f/2f/3f only: Current or prior history of chronic uncontrolled hypoglycemia, or uncontrolled hyperglycemia/diabetes (defined as HbA1c ≥ 8%) at screening
15. Cohorts 2d/3d/2e/3e/1f/2f/3f only: Current or prior history of colitis
16. History of malignancy diagnosed or treated within 5 years (localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ is allowed if appropriately treated prior to screening); subjects under evaluation for malignancy are not eligible.
17. History of hematopoietic stem cell or solid organ transplant
18. Receipt of any systemic antineoplastic or immunomodulatory treatment (including supraphysiologic doses of steroids [prednisone equivalent > 10 mg/day], and radiation) within 6 months prior to the first dose of study drug or the expectation that such treatment will be needed at any time during the study
19. Infection with HIV, hepatitis delta virus (HDV), or HCV per central laboratory results at screening
20. CLcr < 30 mL/min (CLcr <60 mL/min for sites located in Republic of South Korea only) as calculated by the Cockcroft-Gault formula at screening

21. Any of the following laboratory parameters at screening:
    a. Serum ALT and/or AST > 2 times the ULN
    b. Direct bilirubin, INR, or prothrombin time above the ULN
    c. Hemoglobin < 10 g/dL
    d. ANC < 1500 cells/mm^3
    e. Platelets < 90,000 cells/mm^3
    f. Albumin below the LLN
    g. Potassium or sodium above the ULN or below the LLN
    h. Cohorts 2d/3d/2e/3e/1f/2f/3f only: Serum lipase ≥ 2 times the ULN
    i. Cohorts 2d/3d/2e/3e/1f/2f/3f only: TSH and free T4 above the ULN or below the LLN

    Note: Study laboratory tests may be repeated once (eg, for values thought to be erroneous) with Sponsor Medical Monitor approval.
22. Regular consumption of more than 7 units of alcohol per week (unit: 1 glass of wine [125 mL] = 1 measure of spirits [30 mL] = one-half pint of beer [284 mL]), or more than 1 unit of alcohol per day for the duration of the study
23. History or clinical evidence of alcohol or drug abuse within the 12 months before screening or a positive drug screen at screening unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator. History of cannabis use is permitted.
24. Use of any prohibited concomitant medications within 28 days prior to Day 1 (Refer to Section 6.5.2 for prohibited concomitant medications)
25. Received an investigational agent within 90 days before study drug administration or are active in the follow-up phase of another clinical study involving interventional treatment. Subjects must also agree not to take part in any other interventional study at any time during their participation in this study, inclusive of the follow-up period.
26. Receipt of an oligonucleotide (eg, siRNA, antisense oligonucleotide) with activity against HBV within 48 weeks before study drug administration.
27. History of intolerance to SC injection
28. Loss or donation of more than 500 mL of blood within 90 days before study drug administration
29. Any clinically significant medical or psychiatric condition that may interfere with study treatment, assessment, or compliance with the protocol or otherwise makes the subject unsuitable for participation in the study as determined by the investigator.

6. INVESTIGATIONAL MEDICINAL PRODUCTS

6.1. Randomization, Blinding, and Treatment Codes

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

6.1.1. Procedures for Breaking of Treatment Codes for Parts A - C

In Parts A – C, blinding of study treatment will be managed by the clinical investigative site's pharmacy in accordance with the Pharmacy Manual. In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment for that subject. IWRS should be used as the primary method of breaking the blind. If IWRS cannot be accessed, the investigator should contact the Sponsor medical monitor to break the blind. Treatment assignment should remain blinded unless that knowledge is necessary to guide subject emergency medical care. The investigator is requested to contact the Sponsor medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator in Parts A, B, and C, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

The Sponsor or designee may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) as required by regulators.

6.2. Description and Handling of VIR-2218 and Placebo

6.2.1. Formulation

VIR-2218 is a clear, colorless to pale yellow solution, which will be supplied by the Sponsor as a sterile solution for subcutaneous injection at a free acid concentration of 200 mg/mL. Placebo is a sterile, preservative-free normal saline 0.9% solution for SC injection, which will be supplied by the clinical investigative site or the Sponsor where required.

6.2.2. Packaging and Labeling

VIR-2218 (solution for SC injection) is packaged in 2-mL glass vials with a fill volume of no less than 0.7 mL to allow for complete withdrawal of 0.5 mL of drug product at the pharmacy. The container closure system consists of a Type I glass vial, a Teflon-faced 13-mm stopper, and a flip-off aluminum seal.

6.2.3. Storage and Handling

Study drug may be dispensed only by the investigator, by a staff member specifically authorized by the investigator, or by pharmacy staff, as appropriate.

Each clinical investigative site will be responsible for assembly and labeling of injection syringe(s) according to procedures detailed in the Pharmacy Manual. The pharmacy staff will prepare the study drug using an aseptic technique. The amount (in mg) of study drug to be administered will be determined based on the assigned dose level for the cohort for healthy subjects and subjects with chronic HBV infection. All syringes will be covered in Parts A, B, and

C to ensure the study blind is maintained since the IP solution may have a slight yellow coloring and the placebo (sterile normal saline) is clear. No syringe-masking is required for Parts D – F. Additional details regarding the procedure for preparing study drug, the volume to be loaded into each syringe, and how the syringes are to be 'blinded' are provided in the Pharmacy Manual.

No special procedures for the safe handling of VIR-2218 are required. Study drug will be stored upright in the carton and refrigerated at 2 to 8°C in the storage area of the clinical investigative site pharmacy, in a secure, temperature-controlled, locked environment with restricted access. Any deviation from the recommended storage conditions should be reported to the Sponsor and use of the study drug halted until authorization for its continued use has been provided by the Sponsor or designee. Refer to the Pharmacy Manual for additional storage details.

6.2.4. Dosage and Administration of VIR-2218 and Placebo

Dose and dose cohorts for this study are described in Sections 4.1, and 4.2. Study drug dose and administration are summarized by dose cohort in Table 4. On dosing days, the pharmacist or designee will withdraw the required amount of study drug into 1 or more syringes containing up to 1.5 mL/per syringe. A qualified clinical investigative site staff member under the supervision of the investigator or designee will administer study drug to subjects via SC injection. The injection site(s) will be marked and mapped for later observation and should be documented. If a local reaction around the injection site occurs, photographs may be obtained. Refer to the Pharmacy Manual for detailed study drug preparation and administration instructions.

Table 4: VIR-2218 Dose and Administration

Study Part	Cohort	Visit Dose Level (mg)	Visit Dose Volume (mL)	Cumulative Dose (mg)	Injections Per Dose Administration	Injections Total	Cumulative Dose Volume (mL)[a]
Part A	1a	50	0.25	50	1	1	0.25
	2a	100	0.50	100	1	1	0.50
	3a	200	1.0	200	1	1	1.0
	4a	400	2.0	400	2	2	2.0
	Optional 5a	≤ 900	≤ 4.5	≤ 900	3	3	≤ 4.5
	Optional 6a	≤ 900	≤ 4.5	≤ 900	3	3	≤ 4.5
Part B	1b	50	0.25	100	1	2	0.50
	2b	100	0.50	200	1	2	1.0
	3b	200	1.0	400	1	2	2.0
	Optional 4b	≤ 300	≤ 1.5	≤ 600	1	2	≤ 3
	Optional 5b	≤ 450	≤ 2.25	≤ 900	2	4	≤ 4.5
Part C	3c	200	1.0	400	1	2	2.0
	Optional 4c	≤ 300	≤ 1.5	≤ 600	1	2	≤ 3
	Optional 5c	≤ 450	≤ 2.25	≤ 900	2	4	≤ 4.5
Part D	1d	200	1.0	1200	1	6	6.0
	2d	200	1.0	1200	1	6	6.0
	3d	200	1.0	600	1	3	3.0
Part E	Optional 1e	50	0.25	300	1	6	1.5
	Optional 2e	50	0.25	300	1	6	1.5
	Optional 3e	50	0.25	150	1	3	0.75
Part F	Optional 1f	≤ 200	≤ 1.0	≤ 1200	1	6	≤ 6.0
	Optional 2f	≤ 200	≤ 1.0	≤ 1200	1	6	≤ 6.0
	Optional 3f	≤ 200	≤ 1.0	≤ 2600	1	≤13	≤ 13.0

[a] Injection volume per visit per site will not exceed 1.5 mL

6.3. Description and Handling of PEG-IFNα

PEG-IFNα is an alpha interferon product with broad immunomodulatory and direct antiviral effects against HBV that is approved for the treatment of adults with HBeAg-positive and HBeAg-negative chronic HBV infection. In Cohorts 2d/e, 3d/e, 1f, and 2f subjects will receive 180 µg PEG-IFNα administered weekly by SC injection for 12 weeks (Cohorts 2d/e, Cohorts 3d/e), 24 weeks (Cohort 1f), up to 48 weeks (Cohort 2f) or up to 44 weeks (Cohort 3f).

Dose modifications or discontinuation of PEG-IFNα are permitted at the discretion of the investigator, according to the recommendations found in the PEGASYS® Prescribing Information. See Section 4.8.4 for additional details.

PEGASYS is a sterile, preservative-free, colorless to slightly yellowish solution administered subcutaneously. Store in the refrigerator at 2°C to 8°C (36°F to 46°F). Do not leave PEGASYS out of the refrigerator for more than 24 hours. Do not freeze or shake. Protect from light.

PEG-IFNα will be supplied by the Sponsor.

6.4. Study Drug Accountability

The investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including but not limited to, date of receipt, quantity, and temperature. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each subject in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all Sponsor-supplied study drugs.

Further instructions about drug accountability and disposal are detailed in the Pharmacy Manual.

6.5. Concomitant Therapy

6.5.1. Permitted Concomitant Medications

- For Part A and B/C, the following medications/treatments are permitted:
  - NRTI Therapy (Part B/C only; see Section 6.6)
  - Hormone replacement therapy
  - Oral, injectable, subdermal, intravaginal, or implantable contraceptives, as well as intrauterine device, and intrauterine hormone-releasing system are permitted for contraception
  - Prescription drugs necessary to treat hypertension. Hypertension must be well controlled (on a stable dose of no more than 2 medications **or** 1 medication with two active components for > 6 months)
  - Paracetamol (≤ 2g/day), aspirin (≤ 3g/day), or ibuprofen (< 1.2 g/day)
  - Antihistamines
  - Prescription inhaler or nebulizer to treat asthma (inhaled bronchodilator or inhaled steroid). Asthma must be well controlled, defined as historical use of a rescue bronchodilator on average no more than twice per week.
- For Parts D – F, the following medications/treatments are permitted:
  - NRTI Therapy (See Section 6.6)
  - Hormone replacement therapy
  - Oral, injectable, subdermal, intravaginal, or implantable contraceptives, as well as intrauterine device, and intrauterine hormone-releasing system are permitted for contraception
  - Paracetamol (≤ 2g/day), aspirin (≤ 3g/day), or ibuprofen (< 1.2 g/day)
  - Antihistamines

- Prescription inhaler or nebulizer to treat asthma (inhaled bronchodilator or inhaled steroid). Asthma must be well controlled, defined as historical use of a rescue bronchodilator on average no more than twice per week.
- A stable dose and regimen of any medication(s) (prescription or OTC) that the subject is taking regularly (i.e. medications for chronic conditions such as hypertension, high cholesterol, or depression must be unchanged in dose or type for at least 6 months), is permitted, except those listed in Section 6.5.2.

Investigators may initiate new prescription and non-prescription concomitant medications or treatments deemed necessary to provide adequate care for AEs or other new onset medical conditions, except those listed in Section 6.5.2.

6.5.2. Prohibited Concomitant Medications

- For Part A, B, and C the following medications/treatments are prohibited:
  - Any OTC medications or herbal remedy within 14 days before of study drug administration except for those specified in Section 6.5.1
  - Any prescription medications within 14 days before study drug administration except for those specified in Section 6.5.1 and NRTI therapy for Part B/C subjects
- For Parts D – F, the following medications/treatments are prohibited:
  - Steroids (prednisone equivalent of > 10 mg/day) or other immunosuppressive agents
  - Paracetamol (acetaminophen) ≥ 2 g/day
  - Isoniazid
  - Methadone (Cohorts 2d/3d/2e/3e/1f/2f/3f only)
  - Theophylline (Cohorts 2d/3d/2e/3e/1f/2f/3f only)

Additionally, given the safety profile of multiple doses of VIR-2218 has not been well characterized and the use of VIR-2218 in combination with interferon has not previously been assessed, the administration of any potentially hepatotoxic medications during the study should be considered only if no therapeutic alternative can be identified and after a careful consideration of the potential risks and benefits for the subject. Medications that are potentially hepatotoxic or associated with drug-induced liver injury include, but are not limited to, the following (Bjornsson 2016):

- Aspirin > 3 g/day or ibuprofen ≥ 1.2 g/day
- Tricyclic antidepressants
- Valproate
- Phenytoin
- Amiodarone
- Anabolic steroids
- Allopurinol

- Amoxicillin-clavulanate
- Minocycline
- Nitrofurantoin
- Sulfamethoxazole/trimethoprim
- Erythromycin
- Rifampin
- Azole antifungals
- Herbal or natural remedies

6.6. NRTI Therapy

Examples of allowed NRTI therapy for subjects in Parts B – F include, but are not limited to, the following:

- Tenofovir (at recommended dose for the given formulation)
- Entecavir
- Lamivudine
- Adefovir/adefovir dipivoxil

6.7. Contraceptive Requirements

WOCBP may be included in this study, defined as any female subject who has experienced menarche and who is not post-menopausal or surgically sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy).

WOCBP must be willing to use highly effective methods of contraception 14 days before dose, throughout study participation, and for the follow-up period or extended follow-up period, whichever is later. Highly effective methods of birth control result in a low failure rate (ie, less than 1% per year). Birth control methods which are considered highly effective include:

- Established use of combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal methods of contraception associated with inhibition of ovulation **OR** established use of progestogen-only oral, injectable, or implantable hormonal methods of contraception associated with inhibition of ovulation. It is not currently known whether VIR-2218 will impact the effectiveness of hormonal contraceptive methods; therefore, it is recommended to use an additional form of contraception (ie, barrier method) throughout the study and for the follow-up period or extended follow-up period, whichever is later.
- Placement of an intrauterine device
- Placement of an intrauterine hormone-releasing system
- Surgical sterilization of male partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female subjects on the study, the vasectomized male partner should be the sole partner for that subject)

- True sexual abstinence from heterosexual contact, when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use 1 of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for the follow-up period or extended follow-up period, whichever is later.
- Barrier method in combination with hormonal contraceptive, as described above

Post-menopausal status is defined as no menses for 2 years in subjects > 50 years of age.

Male subjects with female partners of child-bearing potential must agree to meet 1 of the following contraception requirements from the time of study treatment administration until the last follow-up visit or extended follow-up period, whichever is later. If the subject discontinues prior to the last follow up visit, the subject must agree to follow the contraceptive requirements for the follow-up period or extended follow-up period, whichever is later.

- Documentation of successful vasectomy or azoospermia
- Male condom plus partner use of 1 of the contraceptive options listed above for contraception for WOCBP (hormonal contraceptive, intrauterine device)
- Male subjects must also agree not to donate sperm for the follow-up period or extended follow-up period, whichever is later

Additionally, male subjects with pregnant partners must use a condom from the time of study drug administration until the end of follow-up or extended follow-up period, whichever is later.

7. STUDY PROCEDURES

7.1. Procedures and Specifications

The Schedule of Study Assessments is provided in Appendix 2 for Part A, Appendix 3 for Part B/C, and Appendix 6, Appendix 7, Appendix 9, Appendix 11, Appendix 13, and Appendix 16 for Parts D - F. Unscheduled visits are permitted at the discretion of the investigator as needed for safety assessment.

7.1.1. Medical History

A complete medical history, including details regarding illnesses and allergies, date(s) of onset, and whether condition(s) is currently ongoing, medication history, including prior HBV treatment history (Part B - F) and HBV genotype history (if available; Part B - F), will be collected on all subjects during screening and should be updated prior to dosing.

7.1.2. Assessment of Antiviral Activity and Development of Resistance

During Parts B - F, assessments of antiviral activity will include:

- HBsAg
- HBeAg
- HBcrAg
- anti-HBs
- anti-HBe
- HBV DNA
- HBV RNA
- HBV genome may be sequenced and analyzed for mutations that can confer resistance to VIR-2218 and NRTIs in subjects with HBV DNA above the limit of the sequencing assay
- Part D - F: Samples collected for resistance surveillance may be used to perform viral analyses related to antiviral efficacy or resistance (e.g. viral sequencing or viral genotyping)

Details regarding the processing, shipping, and analysis of samples are provided in the Laboratory Manual.

7.1.3. Screening Viral Serology Parameters

Screening viral serology parameters are as follows:

- Part A: Active infection with HIV infection, HCV infection, and HBV infection.
- Part B/C: Active infection with HIV infection, HCV infection, chronic HBV infection and hepatitis Delta virus infection. Chronic HBV infection is defined as serum HBsAg positive for > 6 months. In cases of occult HBV, chronic HBV infection is defined as serum HBV DNA positive for > 6 months.
- Parts D - F: 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.

7.1.4. Pharmacokinetic Assessments

Blood and urine samples will be collected to assess concentrations of VIR-2218 and metabolites, as applicable. Detailed schedules of timepoints for the collection of samples for VIR-2218 PK analysis for Part A of the study are provided in Appendix 4. Timepoints for the collection of samples for VIR-2218 PK analysis for Part B/C of the study are provided in Appendix 5. Timepoints for the collection of samples for VIR-2218 PK for Parts D – F are indicated in the SoA (see Appendix 6, Appendix 7, Appendix 9, Appendix 11, and Appendix 13).

Subjects in Part D Cohort 1d and Part E Cohort 1e may also be asked to participate in an optional pooled urine PK sub-study to further assess concentrations of VIR-2218 and metabolites in the urine.

Details regarding the processing, shipping, and analysis of the samples are provided in the Laboratory Manual.

CCI [redacted]

7.2. Safety Assessments

The assessment of safety during the study will consist of the surveillance and recording of AEs including SAEs, recording of prior and concomitant medications, physical examination findings, alcohol assessment, ECG (Parts A – C only), and laboratory tests. All AEs related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards.

7.2.1. Prior and Concomitant Medications

Medications (including prescription medications, over the counter medications, natural remedies, herbal remedies, vitamins, and supplements) taken by the subject from 30 days prior to the screening visit and up to the last study visit will be recorded.

7.2.2. Physical Examination

A full physical examination will include general appearance, head, neck, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, extremities, skin, and screening neurological assessments. For Parts D-F, a dilated fundoscopic retinal examination must be performed during Screening. The subject may be referred to a specialist for performance of the retinal exam.

A symptom-directed physical examination will be performed according to investigator discretion.

7.2.3. Alcohol Assessment

Alcohol intake during the study will be recorded.

7.2.4. Height and Weight

Height and body weight will be measured. Body mass index will be calculated from height and weight.

7.2.5. Vital Signs

Vital sign measurements include blood pressure, pulse rate, temperature (oral preferred), and respiratory rate. Vital signs should be measured after the subject has rested comfortably for approximately 10 minutes. When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed first, before the physical examinations, blood sample collections, and urine collections.

7.2.6. Electrocardiogram

Safety ECGs: 12-lead safety ECGs will be recorded and reviewed on-site by the investigator as outlined in Appendix 2 and Appendix 3. Specified collection timepoints for each visit are provided in Appendix 4 and Appendix 5. In Parts D – F, 12-lead safety ECGs are only required to be performed at Screening.

Cardiodynamic ECG evaluation (Part A only): (12-lead ECGs extracted from continuous Holter recordings): Up to 10 replicate ECGs may be extracted by the central ECG core laboratory at timepoints provided in Appendix 4 and Appendix 5. Subjects will be resting supine for at least 10 minutes prior to and 5 minutes after each nominal time point. 12-lead ECGs will be extracted

from the 5-minute time window following the nominal time point. When scheduled at the same time points, the assessments of vital signs and 12-lead ECGs should be performed first, before the physical examinations, blood sample collections, and urine collections.

In Part A, the 12-lead Holter monitor and ECG equipment will be supplied and supported by the central ECG core laboratory. All cardiodynamic ECG data will be collected using a Global Instrumentation M12R ECG continuous 12-lead digital recorder. The continuous 12-lead digital ECG data will be stored onto SD memory cards. ECGs to be used in the analyses may be selected by pre-determined time points as defined in Appendix 4 and Appendix 5, and cardiodynamic ECGs will be stored and may be read by the central ECG core laboratory.

The following principles will be followed in the central ECG core laboratory:

- ECG analysts are blinded to the subject, visit, and treatment allocation
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader
- The primary analysis lead is lead II. If lead II is not analyzable, then primary lead of analysis will be changed to another lead for the entire subject data set.

The following is a brief description of ECG analysis methods utilized by the central ECG core laboratory.

TQT Plus ECG Extraction Technique

Ten 14-second digital 12-lead ECG tracings may be extracted from the continuous Holter monitor recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by the central ECG core laboratory. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (eg, the HR and QT changes from beat-to-beat in the range of < 10%). At each protocol-specified timepoint, 10 ECG replicates may be extracted from a 5 minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position).

Expert-Precision QT Analysis

Expert-precision QT analysis may be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely).
- RR values exceeding or below certain thresholds (biologically unlikely).
- Rapid changes in QT, QTc or RR from beat to beat.

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" are performed using COMPAS software. All low-confidence beats are reviewed manually and adjudicated using pass-fail criteria. The final QC assessment is performed by a cardiologist. The beats found acceptable by manual review are included in the analysis. The median QT, QTc, and RR value from each extracted replicate is calculated, and then the mean of all available medians from a nominal timepoint is used as the subject's reportable value at that timepoint.

T-wave morphology categories are presented in Table 5. Categorical T-wave morphology analysis and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) is electronically marked.

In addition to the T-wave categorical analysis, the presence of abnormal U-waves is noted.

Table 5: Wave Morphology Categories (Assessed Manually)

Category	Description
Normal T-wave	Any T-wave not meeting any criterion below
Flat T-waves	T amplitude < 1 mm (either positive or negative) including flat isoelectric line
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive and negative/positive and polyphasic T-waves included)
Normal T-wave (-)	T amplitude that is negative, without biphasic T-wave or notches
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave

7.2.7. Pregnancy Testing

A pregnancy test or confirmation of post-menopausal status must be confirmed for all female subjects. Post-menopausal status is defined as age > 50 years with no menses for at least 2 years at the time of screening. Pregnancy tests will be performed for WOCBP only. Pregnancy testing will be performed per the schedule of assessments and any time pregnancy is suspected. A WOCBP who is known to be pregnant or who does not have a negative pregnancy test at screening is not eligible for study participation. A serum pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. During the study, the results of these pregnancy tests must be known prior to study drug administration. A WOCBP determined to be pregnant while on study will be followed until the pregnancy outcome is known, as described in Section 8.6.2.

7.2.8. Clinical Laboratory Assessments

Clinical laboratory tests that will be performed in this study are presented in Table 6. In the event of an unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the investigator until it has returned to the normal range or stabilized, and/or a diagnosis is made to adequately explain the abnormality.

Table 6: Clinical Laboratory Tests

Hematology	
• Complete blood count with differential	
Chemistry	
• Albumin	• Creatinine clearance
• Blood urea nitrogen (BUN)	• Gamma glutamyl transferase (GGT)
• Calcium	• Glucose
• Carbon dioxide/bicarbonate	• Lactate dehydrogenase (LDH)
• Chloride	• Potassium
• Creatine kinase[a]	• Sodium
• Creatinine	• Uric acid
• Lipase[b]	
Liver Function Tests	
• Alkaline phosphatase (ALP)	• Aspartate aminotransferase (AST)
• Alanine aminotransferase (ALT)	• Bilirubin (total and direct)
Coagulation Parameters	
• International normalized ratio (INR) time	• Prothrombin
Urinalysis	
• Bilirubin	• Proteins
• Glucose	• Red blood cells (RBCs)
• Ketones	• Screen for drugs of abuse
• Leukocytes	• Specific gravity
• Microscopy (if clinically indicated)	• Urobilinogen
• Nitrite	• Visual inspection for appearance and color
• pH	
Pregnancy Testing (WOCBP only)	
• Beta-human chorionic gonadotropin	• Urine pregnancy test
Serology	
• Hepatitis B, C, and Delta	• Human immunodeficiency virus I and II
Other Laboratory Assessments (Parts D-F only)[c]	
• TSH	• Free T4
• Hemoglobin A1c (HbA1c)	

[a] Only required if ALT and/or AST is elevated 2 × higher than predose Day 1 baseline value

[b] Required at Screening for Parts D-F only

[c] Required at Screening for all cohorts in Parts D-F. For Cohorts 2d/2e/1f, TSH and free T4 are also required on Day 1, Week 12, Week 24, and Week 48. For Cohorts 3d/3e, TSH and free T4 are also required on Day 1, Week 12, and Week 36. For Cohort 2f and 3f, TSH and free T4 are also required on Day 1, Week 12, Week 24, Week 48, and Week 72.

7.2.9. FibroScan

To exclude the presence of cirrhosis, subjects in Parts B – F will have a FibroScan evaluation, unless the subject has results from a FibroScan evaluation performed within 6 months prior to screening or liver biopsy performed within 1 year prior to screening that confirm the absence of Metavir F3 fibrosis or F4 cirrhosis. If a subject has had both procedures in the specified timeframes, the most recent result should be used to determine eligibility.

8. ADVERSE EVENTS MANAGEMENT

8.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

8.1.1. Adverse Events

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Pre-existing conditions (recorded as medical history), which change in nature or severity should also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose of study drug without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF (Case Report Form).
- Unless associated with signs or symptoms, laboratory abnormalities (eg, low platelets) should not be recorded as AEs, as these abnormalities will be captured as laboratory abnormalities
- Procedures should not be recorded as AEs; however, the condition that led to the procedure may be an AE

8.1.2. Serious Adverse Events

An SAE is any event that results in the following:

- Death
- Life-threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.
- Inpatient hospitalization or prolongation of existing hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria. In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.
- Persistent or significant disability/incapacity: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions
- Congenital anomaly/birth defect in the offspring of a subject who received the study drug

Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse

8.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Per Section 8.1.1, laboratory abnormalities without an associated AE (signs or symptoms) and/or which do not require medical intervention, are not themselves recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 8.1.1 and 8.1.2. If the laboratory abnormality is part of a

clinical syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

8.1.4. Clinical Laboratory Abnormalities as Events of Clinical Interest

A clinical laboratory event of clinical interest (ECI) is a laboratory value of scientific and medical interest specific to understanding of the investigational product and may require additional follow-up testing, close monitoring, and rapid communication by the investigator to the sponsor. The rapid reporting of ECIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product. Certain ALT abnormalities will be considered laboratory ECIs. A laboratory ECI may or may not meet criteria for an AE (see Section 8.1.3). See Section 8.5 for the definition and reporting of laboratory ECIs related to ALT abnormalities.

8.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

8.2.1. Assessment of Causality for Study Drugs and Procedures

Causality (Yes or No) should be determined by the investigator or qualified sub-investigator. An answer of Yes, should be entered when, in their opinion, there is either (a) a *reasonable* possibility that the AE is associated with study drug **or** (b) no reasonable alternative explanation can be identified. Otherwise, causality to study drug should be categorized as No. A mere possibility of a causal relationship is not grounds for a Yes categorization.

For Parts D – F Cohorts 2d, 2e, 3d, 3e, 1f, 2f and 3f causality should be determined by investigator or qualified sub-investigator for relationship to VIR-2218 or PEG-IFNα. The investigator or qualified sub- investigator should provide their best assessment of causality based upon their expertise. Action taken with VIR-2218 and/or PEG-IFNα should also be recorded.

8.2.2. Assessment of Severity

Standard toxicity grading according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used to grade AEs and laboratory abnormalities. Definitions of severity per CTCAE (v5.0) are presented in Table 7.

Table 7: CTCAE (V5.0) Definitions of Severity

Severity	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only;intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL. Instrumental ADL refer to preparing meals, shoppingfor groceries or clothes, using the telephone, managing money, etc.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalizationor prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using thetoilet, taking medications, and not bedridden.
Grade 4	Life-threatening consequences: urgent intervention indicated.
Grade 5	Death related to AE.

ADL=activities of daily living
Source: NCI 2017

8.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Vir

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported:

- AEs related to protocol-mandated procedures
- All SAEs

Adverse Events

For Part A – C: Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 12 weeks after last administration of study drug.

For Parts D – F: Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 24 weeks after the last visit in the Treatment Period. AEs related to study procedures in the Extended Follow Up Period and NRTI Discontinuation Monitoring Period should be captured.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required follow-up period, must be reported as instructed. This also includes any SAEs resulting from protocol-mandated procedures performed after informed consent is signed. All SAEs should be followed up until resolution or until stable, if possible.

Investigators are not obligated to actively seek SAEs after the protocol -defined follow–up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to Vir.

- For fatal or life-threatening events, copies of hospital case reports, discharge summaries, autopsy reports, and other documents should be submitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.
- Email or fax the SAE form within 24 hours of the investigator's knowledge of the event. Contact information is as follows:

PPD

8.4. Vir Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US Food and Drug Administration Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, the Sponsor may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or SUSARs. In accordance with the EU Clinical Trials Directive (2001/20/EC), the Sponsor or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by the Sponsor using reference safety information specified in the VIR-2218 Investigator's Brochure and the Prescribing Information for PEG-IFNα (PEGASYS® Prescribing Information).

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

8.5. Laboratory Events of Clinical Interest

8.5.1. Definition of Laboratory Events of Clinical Interest

Laboratory events of clinical interest (ECI) for this study are the following:

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

Laboratory ECI is considered resolved when the ALT levels return to ≤ Day 1 baseline or ≤ ULN, whichever is higher.

8.5.2. Instructions for Reporting Laboratory Events of Clinical Interest

All laboratory ECIs must be reported to PRA (now ICON) Pharmacovigilance within 24 hours of the investigator becoming aware of the ECI. Contact information is as follows:

PRA (now ICON) Pharmacovigilance

E-mail : MHGSafety@prahs.com

Fax : +44 1792 525 720

In addition to reporting the event to PRA (now ICON) Pharmacovigilance, the assessments outlined in Appendix 17 should be performed as soon as possible and no later than two weeks after the initial ALT value meeting criteria for a laboratory ECI.

The laboratory ECI will also be evaluated by the investigator per Sections 8.1.1 and 8.1.3 to determine if the event meets criteria for an AE. The protocol-specified requirement for additional assessment of ECIs does not in and of itself qualify laboratory ECIs as AEs. If AE criteria are met, all clinical sequelae in relation to these laboratory ECIs will be reported as AEs or SAEs, if applicable. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8.6. Special Situations Reports

8.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the

subject has taken the excess dose(s). Overdose cannot be established when the pharmacist cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the additional dose(s) were administered to the subject.

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

8.6.2. Instructions for Reporting Special Situations

Pregnancy Reporting

If a female subject becomes pregnant after the first study drug administration through the follow-up period or extended follow-up period, whichever is later, the investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. The subject should receive any necessary counseling regarding the risk of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the investigator until completion. The investigator should collect follow-up information on the mother and infant and will notify the Sponsor within 24 hours of obtaining updated information regarding the pregnancy. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death or congenital anomaly, then the investigator should follow the procedures for reporting an SAE as outlined in Section 8.3. Every effort will be done to follow the infant for up to 1 year after birth.

If the partner of a male subject becomes pregnant after the subject's first study drug administration through the follow-up period or extended follow-up period, whichever is later, the subject will be instructed to report this to the investigator. The partner may be asked to provide consent to be followed until the outcome of the pregnancy is known and for up to 1 year after birth (where permitted). The investigator must report the pregnancy to the Sponsor or designee within 24 hours of being notified of the pregnancy. The subject and the partner should receive any necessary counseling regarding the risk of continuing the pregnancy and the possible effects on the fetus. After obtaining consent, the investigator must report available follow-up information on the course and outcome of the pregnancy within 24 hours of learning of the information.

Reporting Other Special Situations

All other special situations must be reported to PRA (now ICON) Pharmacovigilance within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or protocol-required concomitant medications, but do not apply to non-required concomitant medications. Contact information is as follows:

PRA (now ICON) Pharmacovigilance

E-mail : MHGSafety@prahs.com

Fax : +44 1792 525 720

Special situations involving non-required concomitant medications do not need to be reported; however, for special situations that result in AEs due to a non-required concomitant medication, the AE should be reported.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

9. STATISTICAL CONSIDERATIONS

9.1. Objectives

The objectives are listed in Section 2.

9.2. Endpoints

The endpoints are listed in Section 3.

9.3. Analysis Conventions

Descriptive statistics will be presented for continuous variables, and frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of nonmissing values in a dose group.

9.3.1. Analysis Sets

Safety

The primary analysis set for safety analyses will be the Safety Analysis Set, which includes all subjects who received at least 1 dose of study drug.

Pharmacokinetic

The primary analysis set for PK analyses will be the PK Analysis Set, which includes all subjects in the Safety Analysis Set who have at least 1 nonmissing concentration data to provide interpretable results for the specific parameters of interest for the analyte under evaluation.

Antiviral Activity

The primary analysis set for antiviral activity analyses will be the Antiviral Analysis Set, which includes all subjects in the Safety Analysis Set who have at least 1 nonmissing data to provide interpretable results for the specific antiviral activity parameters of interest.

9.3.2. Data Handling Conventions

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).

9.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive statistics including sample size, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous variables and numbers and of subjects for categorical variables.

9.5. Safety Analysis

All safety analyses will be performed using the Safety Analysis Set. Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, ECGs, vital signs measurements at various timepoints during the study, and by the documentation of AEs.

For Parts A – C, all safety data collected up to 12 weeks after the last study drug administration will be summarized by cohort for each VIR-2218 dose and placebo.

For Parts D – F, all safety data collected up to 24 weeks after the last visit in the Treatment Period will be summarized by cohort for each VIR-2218 dose and PEG-IFNα dose.

9.5.1. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lowest-Level Term (LLT) will be attached to the clinical database.

Treatment-Emergent Adverse Events (TEAEs) are defined as any AEs with an onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug.

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided by cohort. TEAEs will also be summarized by relationship to study drug and severity.

9.5.2. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by cohort and study visit along with corresponding change from baseline.

Graded laboratory abnormalities will be defined using CTCAE Version 5.0 grading scale.

The incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline (predose Day 1; if predose values are missing, screening values will be used) at any post-baseline timepoint up to 30 days after permanent discontinuation of study drug will be summarized by cohort. If the relevant baseline laboratory data are missing, then any abnormality of at least Grade 1 will be considered as treatment-emergent.

If applicable, the incidence of ECIs and relevant information will be summarized by cohort.

If applicable, assessments of the LFAC will be summarized by cohort.

9.5.3. Other Safety Evaluations

Individual data for physical examination findings, prior and concomitant medications and medical history will be provided. Twelve-lead ECGs and vital signs measurements will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistics as appropriate.

9.6. Pharmacokinetic/Pharmacodynamic Analysis

PK parameters of VIR-2218 and possible metabolites will be computed using standard noncompartmental methods as applicable. Parameters may include, but not be limited to, plasma: maximum concentration, time to reach maximum concentration, area under the concentration

versus time curve (to the last measurable timepoint and to infinity), percent of area extrapolated, apparent terminal elimination half-life, clearance, and volume of distribution; urine: fraction eliminated in the urine and renal clearance, and will be listed and summarized using descriptive statistics. Other parameters may be calculated, if deemed necessary. Concentration data from all sparse and intensive plasma PK samples may be pooled with data from future studies and may be used for estimation of population PK parameters.

PK/pharmacodynamic analyses will be conducted to explore exposure-response relationships between PK parameters and selected antiviral variables. These analyses may include graphical plots, tabular summaries, and various linear and/or nonlinear analyses. Details of the analysis will be provided in the Statistical Analysis Plan.

9.7. Immunogenicity Analysis

For Parts D – F, immunogenicity data will be listed and summarized using descriptive statistics, including rates, titers, and neutralization data, as applicable.

Correlations between immunogenicity data and safety, efficacy, and PK data will be explored. These analyses may include graphical plots, tabular summaries, and various linear and/or nonlinear analyses. Details of immunogenicity analyses will be provided in the Statistical Analysis Plan.

9.8. Antiviral Activity Analysis

For Parts B – F selected data relating to the antiviral activity of VIR-2218, alone or in combination with PEG-IFNα, such as HBsAg, HBeAg, HBcrAg, anti-HBs, anti-HBe, HBV RNA, and HBV DNA levels, will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by analysis groups and study visit along with corresponding change from baseline. Summaries (number and proportion of subjects) of HBsAg loss, anti-HBs seroconversion, HBeAg loss, and anti-HBe seroconversion will be provided by cohort and study visit.

Additionally, for Parts D – F, number and proportion of subjects reaching HBsAg loss, meeting protocol defined NRTI discontinuation criteria as well as number and proportion of subjects achieving functional cure (Section 3.3), will be summarized and compared across the different regimens of VIR-2218 alone or in combination with PEG-IFNα. Details will be described in SAP.

9.9. Statistical Hypothesis

Analyses for Parts A-E are descriptive only. No hypothesis tests will be performed.

In Parts F, the null hypothesis is that the HBsAg loss rate, the efficacy secondary endpoint, in each cohort is not different from the 8% HBsAg loss rate for patients assessed 24 weeks after completing 48 weeks of PEG-IFNα therapy (Wong 1993; Konerman 2016). The alternative hypothesis is that each cohort will achieve HBsAg loss rate of at least 30% by the end of the extended follow-up. This study is exploratory in nature. No multiplicity adjustment will be made.

9.10. Sample Size

In total, up to 232 subjects are planned to complete the study, including completed enrollment of 82 subjects in Parts A-C and planned enrollment of 150 subjects in Parts D-F.

For Parts A-E, no formal sample size calculation was conducted.

For Parts A-C, up to 104 subjects (up to 56 healthy subjects and up to 48 subjects with chronic HBV infection) were planned to complete the study. The 104 subjects include "floater" subjects (up to 8 healthy subjects and up to 16 subjects with chronic HBV infection) that may be added as part of expansion of an existing cohort or cohorts based on SRC recommendations if further data are necessary. The first subject was screened on 02 November 2018. The enrollment has been complete with 50 healthy subjects and 32 subjects with chronic HBV infection.

For Parts D-E, the sample size is up to 15 subjects per cohort in Cohorts 1d/e, 2d/e and 3d/e (up to 90 subjects in total).

For Part F, up to 30 subjects in Cohorts 1f and up to 30 subjects between Cohorts 2f and 3f (up to 60 subjects in total) are planned to complete the study, including subjects rolled over from Cohort 3d into Cohort 2f and subjects rolled over from Cohort 2f into Cohort 3f.

The maximum sample size of 30 subjects 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.

9.11. Statistical Analysis

The statistical analysis plan (SAP) for Parts A-C has been finalized.

Separate SAP for Parts D-F will be finalized prior to Database Lock (DBL) and it will include technical and detailed description of the statistical analyses. For Parts D – F, summary tables will present results by analysis grouping, which will be defined in SAP. Prior to the final analysis, interim analyses may be conducted, and the analyses may be submitted for publication or to regulatory agencies to seek guidance for the overall clinical development program.

10. RESPONSIBILITIES

10.1. Investigator and Sponsor Responsibilities

10.1.1. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.2. Informed Consent

The investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that participation is completely voluntary and that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The investigator must maintain the original, signed Informed Consent Form (ICF). A copy of the signed ICF must be given to the subject.

10.1.3. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials and date of birth (where local regulations allow) and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from the Sponsor, including but not limited to the Investigator's Brochure, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the clinical investigative site to any third party or otherwise into the public domain.

In compliance with local and/or regional regulations, this clinical study may be registered and study results may be posted on public registries, such as ClinicalTrials.gov.

10.1.4. Study Files and Retention of Records

All documentation relating to the study should be retained for the period of time required by applicable local law. If it becomes necessary for the Sponsor or designee, applicable IRB/IEC, or applicable regulatory authorities to review or audit any documentation relating to the study, the investigator must permit direct access to all source documents/data. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the Sponsor's expense.

10.1.5. Financial Disclosure

Investigators and sub-investigators will provide the sponsor or designee with sufficient, accurate financial information as requested to allow the sponsor/designee to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

10.1.6. Electronic Case Report Forms (eCRF)

Data collected during the study (except clinical laboratory results, PK analysis, study disease testing results, immunogenicity) will be recorded in each subject's eCRF provided by the Sponsor or designee. The study site(s) will use an EDC system that is compliant with relevant Food and Drug administration (FDA) regulatory requirements per 21 CFR Part 11. Data queries and data correction on the eCRF will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Data reported on the CRF must be transcribed from a source document with consistency and accuracy. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm the accuracy of data entered into the eCRF. Each set of completed eCRFs must be reviewed after being source verified by the monitor and electronically signed and dated by the investigator.

10.1.7. Good Clinical Practice

This study will be conducted in accordance with the protocol, all applicable regulatory requirements, and the guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study subjects are protected consistent with the principles that have their origin in the Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

10.1.8. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. Refer to the Pharmacy Manual for further information.

10.1.9. Quality Control and Assurance

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial process and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reports according to the protocol, GCP guidelines of ICH, an any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the clinical investigative site to perform audits or

inspections, including source data verification. The investigator should contact the Sponsor, or its designee, immediately if contact by a regulatory agency about an inspection.

10.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.1.11. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

10.1.12. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies).

The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from the Sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- the results of the study in their entirety have been publicly disclosed by or with the consent of the Sponsor in an abstract, manuscript, or presentation form; or
- the study has been completed at all clinical investigative sites for at least 2 years

No such communication, presentation, or publication will include the Sponsor's confidential information (Section 10.1.3).

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with the Sponsor's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days to obtain patent protection if deemed necessary.

10.2. Study Monitoring

In accordance with ICH GCP guidelines, the study monitor must have access to the investigator's source documentation to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

10.2.1. Study Discontinuation

The Sponsor reserves the right to terminate the overall study or one or more individual parts of the study at any time. The investigator reserves the right to discontinue the study at their institution at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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APPENDIX 1. INVESTIGATOR SIGNATURE PAGE

VIR BIOTECHNOLOGY, INC

499 ILLINOIS STREET SUITE 500

SAN FRANCISCO, CA 94158

STUDY ACKNOWLEDGMENT

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

VIR-2218-1001, Protocol Amendment 8, 02 December 2021

This protocol has been approved by Vir Biotechnology, Inc. The following signature documents this approval.

PPD [redacted]	*{See Appended Electronic Signature Page}*
Prin Na	**Signature and Date**

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Vir Biotechnology, Inc. I will discuss this material with them to ensure they are fully informed about the drugs and the study.

Principal Investigator Printed Name	**Signature**
	Date

APPENDIX 2. PART A SCHEDULE OF STUDY ASSESSMENTS FOR SAD COHORTS IN HEALTHY ADULT SUBJECTS

Part A											
Study Stage	**Screening**	**Inpatient[a]**			**Outpatient (Post-dose Follow-up Period)**						
Study Visit Week						**W1**	**W2**	**W3**	**W4**	**W8**	**W12**
Study Visit Day±Visit Window	**D −28 to −2**	**D −1**	**D1[b]**	**D2**	**D3**	**D8±2**	**D15±2**	**D22±2**	**D29±2**	**D57±7**	**D85±7/ET**
Informed consent	X										
Demography	X										
Medical history[c]	X										
Inclusion/exclusion criteria	X	X[d]									
Full physical examination[e]	X										X
Symptom-directed physical examination		X	X	X		X	X	X	X	X	
Alcohol assessment[f]		X				X	X	X	X	X	X
Body weight	X										
Height and BMI	X										
Vital signs[g]	X	X	X	X		X	X	X	X	X	X
Safety ECGs[h]	X		X	X		X					
Cardiodynamic ECG evaluation[i]			X	X							
Pregnancy test[j]	X	X							X	X	X
Screening viral serology[k]	X										

Part A											
Study Stage		**Inpatient[a]**			**Outpatient (Post-dose Follow-up Period)**						
	Screening										
Study Visit Week						**W1**	**W2**	**W3**	**W4**	**W8**	**W12**
Study Visit Day±Visit Window	**D −28 to −2**	**D −1**	**D1[b]**	**D2**	**D3**	**D8±2**	**D15±2**	**D22±2**	**D29±2**	**D57±7**	**D85±7/ET**
Laboratory assessments[l]	X		X	X	X	X	X	X	X	X	X
Urinalysis[l]	X		X	X							
Urine for drugs of abuse[m]	X	X									
Randomization			X								
Study drug administration[n]			X								
Blood samples for PK analysis[o]			X	X	X	X					
Urine samples for PK analysis[o]			X		X	X					
Pooled urine[o]			X	X							
Review/record AEs[p]	X										
Concomitant medications	X										

AE = adverse event; BMI = body mass index; ECG = electrocardiogram; ET = End of Treatment; PK = pharmacokinetic; SAD = single ascending dose
All AEs related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards.
Note: When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed first, before the physical examinations, blood sample collections, and urine collections.

[a] Subjects will be admitted to the clinical investigative site on Day −1 and discharged following the completion of the Day 2 assessments. If a subject discontinues prematurely, ET assessments should be performed.
[b] Assessments performed predose unless otherwise specified.
[c] Complete medical history will be taken at screening and any changes should be updated prior to dosing.
[d] Evaluation of inclusion criteria related to urine pregnancy testing and urine drug screen.
[e] See Section 7.2.2 for assessments to be performed during a full physical examination.
[f] Subjects' alcohol intake will be recorded while on study.

[g] Vital signs (blood pressure, pulse rate, respiratory rate and temperature) should be measured after the subject has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours predose and 4 hours post-dose. On all other visit days, vital signs are only required to be recorded once during the visit.

[h] 12-lead safety ECGs will be recorded on the timepoints listed in Appendix 5 and should be measured in the supine position after the subject has rested comfortably for 10 minutes.

[i] Replicate 12-lead ECGs will be extracted at the central ECG laboratory at timepoints shown in Appendix 5. Subjects must be resting supine for at least 10 minutes prior to and 5 minutes after each nominal timepoint.

[j] WOCBP are required to have pregnancy tests. A blood pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. Negative pregnancy test must be confirmed prior to study drug administration.

[k] See Section 7.1.3 for viral serology parameters.

[l] Clinical laboratory and urinalysis parameters are described in Section 7.2.8.

[m] Drugs of abuse included in the screen are described in the inclusion/exclusion criteria. Screening results for drugs of abuse must be reviewed prior to dosing.

[n] Study drug will be administered via SC injection as described in Section 6.2.4.

[o] Blood and urine samples for PK analysis will be collected at the timepoints listed in Appendix 5.

APPENDIX 3. PART B/C SCHEDULE OF STUDY ASSESSMENTS FOR MAD COHORTS IN SUBJECTS WITH CHRONIC HBV INFECTION

Part B/C																
Study Stage	**Screening**	**Treatment Period**						**Post-dose Follow-up Period[b]**						**Extended Follow-up Period[c]**		
Study Visit Week				**W1**	**W2**	**W3**	**W4[a]**	**W5**	**W6**	**W7**	**W8**	**W12**	**W16**	**W20**	**W24**	
Study Visit Day ±Visit Window	**D −28 to −1**	**D1[a]**	**D2**	**D8 ±2**	**D15 ±2**	**D22 ±2**	**D29[a] ±2**	**D36 ±2**	**D43 ±2**	**D50 ±2**	**D57 ±2**	**D85 ±7**	**D113 ±7/ET**	**D141 ±7**	**D169 ±7**	**Q28D ±7**
Informed consent	X															
Demography	X															
Medical history including HBV genotype[d]	X															
Inclusion/exclusion criteria	X	X[e]														
Full physical examination[f]	X						X						X			
Symptom-directed physical examination		X	X	X	X	X		X	X	X	X	X				
Alcohol intake assessment[g]		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X															
Height and BMI	X															
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Safety ECG[i]	X	X	X				X									
Pregnancy test[j]	X	X					X				X	X	X			

Part B/C																
Study Stage	**Screening**	**Treatment Period**						**Post-dose Follow-up Period[b]**						**Extended Follow-up Period[c]**		
Study Visit Week				**W1**	**W2**	**W3**	**W4[a]**	**W5**	**W6**	**W7**	**W8**	**W12**	**W16**	**W20**	**W24**	
Study Visit Day ±Visit Window	**D −28 to −1**	**D1[a]**	**D2**	**D8 ±2**	**D15 ±2**	**D22 ±2**	**D29[a] ±2**	**D36 ±2**	**D43 ±2**	**D50 ±2**	**D57 ±2**	**D85 ±7**	**D113 ±7/ET**	**D141 ±7**	**D169 ±7**	**Q28D ±7**
FibroScan[k]	X															
Screening viral serology[l]	X															
Laboratory assessments[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]	X[n]	X[n]
Urinalysis[m]	X	X														
Urine for drugs of abuse[o]	X															
Randomization		X														
Study drug administration[p]		X					X									
Blood samples for PK analysis[q]		X	X	X			X[r]	X								
Blood sample for HBsAg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for anti-HBs	X										X		X		X	X[s]
Blood sample for HBeAg qualitative	X															
Blood sample for HBeAg quantitative for Part C only[t]		X					X				X	X	X		X	X[s]
Blood sample for anti-HBe for Part C only	X										X		X		X	X[s]

Part B/C																
Study Stage	**Screening**	**Treatment Period**						**Post-dose Follow-up Period[b]**						**Extended Follow-up Period[c]**		
Study Visit Week				**W1**	**W2**	**W3**	**W4[a]**	**W5**	**W6**	**W7**	**W8**	**W12**	**W16**	**W20**	**W24**	
Study Visit Day ±Visit Window	**D −28 to −1**	**D1[a]**	**D2**	**D8 ±2**	**D15 ±2**	**D22 ±2**	**D29[a] ±2**	**D36 ±2**	**D43 ±2**	**D50 ±2**	**D57 ±2**	**D85 ±7**	**D113 ±7/ET**	**D141 ±7**	**D169 ±7**	**Q28D ±7**
Blood sample for HBV DNA quantitation[u]	X	X					X				X	X	X	X	X	X[s]
Blood sample for HBV RNA quantitation and HBcrAg quantitative		X					X				X		X		X	X[s]
CCI [redacted]																
HBV genome sequencing[w]		X														
Review/Record AEs[x]	X															
Concomitant Medications	X															
NRTI medication adherence	X															

AE = adverse event; ECG = electrocardiogram; ET=end of treatment; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PK = pharmacokinetics; MAD = multiple ascending dose

Note: When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed first, before the physical examinations, blood sample collections, and urine collections.

[a] Assessments performed predose unless otherwise specified.

[b] If a subject withdraws prematurely from the study prior to their Week 16 visit, ET assessments should be performed.

[c] Additional HBsAg monitoring is required for subjects with HBsAg levels with a > 10% decrease from the Day 1 predose level at the Week 16 visit. Visits will occur every 4 weeks starting at Week 20 up to Week 48 or until the HBsAg level returns to ≥ 90% of the Day 1 predose level. For example, if Day 1 predose HBsAg is 560 IU/mL and Week 16 HBsAg is 490 IU/mL, the subject will be followed until HBsAg levels returns to ≥ 504 IU/mL. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

[d] A complete medical history will be taken at screening including HBV genotype if available. Any changes should be updated prior to dosing.

[e] Evaluation of inclusion criteria related to urine pregnancy testing and urine drug screen.
[f] See Section 7.2.2 for assessments to be performed during a full physical examination.
[g] Subjects' alcohol intake will be recorded while on study.
[h] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured in the supine position after the subject has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours predose and 4 hours post-dose. On all other visit days, vital signs are only required to be recorded once during the visit.
[i] 12-lead safety ECGs will be recorded on the timepoints listed in Appendix 5 and should be measured in the supine position after the subject has rested comfortably for 10 minutes.
[j] WOCBP are required to have pregnancy tests. A serum pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. Negative pregnancy test must be confirmed prior to study drug administration.
[k] Does not need to be performed if the subject has had a FibroScan in the 6 months prior to screening or liver biopsy in the year prior to screening that confirmed the absence of Metavir F3 fibrosis or F4 cirrhosis.
[l] See Section 7.1.3 for viral serology parameters.
[m] Clinical laboratory and urinalysis parameters are described in Section 7.2.8.
[n] Liver function tests only.
[o] Drugs of abuse included in the screen are described in the inclusion/exclusion criteria. Screening results for drugs of abuse must be reviewed prior to dosing.
[p] Study drug will be administered via SC injection as described in Section 6.2.4.
[q] Blood samples for PK analysis will be collected at the timepoints listed in Appendix 5.
[r] As a part of the Week 4 visit, subjects will return to the study center 24-hours after their initial post dose Week 4 PK sample is drawn to have a 24-hour post dose PK sample drawn.
[s] Testing should occur again only at Week 36 and Week 48.
[t] For subjects in Part C, if HBeAg has become undetectable for 2 consecutive assessments, no further quantitative testing is needed.
[u] If a subject experiences ALT flare (as defined by ALT > 2x ULN) additional HBV DNA quantitation sample(s) may be collected

[redacted] CCI

[w] HBV genome sequencing will only be performed if a subject experiences HBV DNA breakthrough. See Section 7.1.2 for more information.
[x] All AEs related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards.

APPENDIX 4. PART A PHARMACOKINETIC ASSESSMENT TIMEPOINTS

Study Day/Week	Protocol Time	PK Blood	Urine PK	Pooled Urine	Cardiodynamic Extracted ECGs	Safety ECGs
Screening						X
Day 1	Predose	X[a]	X[a]		X[b]	X
	Dose			X 0-4 hours		
	30 min	X			X	
	1 hour	X			X	X
	2 hours	X			X	
	4 hours	X		X 4-8 hours	X	X
	6 hours	X			X	
	8 hours	X		X 8-12 hours	X	X
	10 hours	X			X	
	12 hours	X		X 12-24 hours	X	
Day 2	24 hours	X			X	X
Day 3	48 hours	X	X			
Week 1		X	X			X

[a] At ≤ 15 minutes prior to dosing
[b] At 3 timepoints (-45, -30 and -15 minutes) prior to dosing

APPENDIX 5. PART B/C PHARMACOKINETIC ASSESSMENT TIMEPOINTS

Study Day/Week	Protocol Time	PK Blood	Safety ECGs
Screening			X
Day 1	Predose	X[a]	X
	Dose		
	1 hour	X	
	2 hours	X	
	4 hours	X	X
	8 hours	X	X
Day 2	24 hours	X	X
Week 1		X	
Week 4	Predose	X[a]	X
	Dose		
	1 hour	X	
	2 hours	X	
	4 hours	X	X
	8 hours	X	
	24 hours	X	
Week 5		X	

[a] At ≤ 15 minutes prior to dosing

APPENDIX 6. COHORT 1D/OPTIONAL COHORT 1E SCHEDULE OF STUDY ASSESSMENTS (VIR-2218 ALONE)

Study Stage	**Screening**	**Treatment Period[a]**											**Follow-up Period**						**Extended Follow-up Period[b]**					
Study Visit Week			**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44/ ET[c]**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**
Study Visit Day ±Visit Window	**D−28 to −1**	**D1**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2**	**D71 ±2**	**D85 ±2**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D281 ±7**	**D309 ±7**	**D365 ±7**	**D421 ±7**	**D477 ±7**	**D533 ±7**	**D589 ±7**	**D645 ±7**
Informed consent	X																							
Demography	X																							
Medical history including HBV genotype[d]	X																							
Inclusion/exclusion criteria	X	X[e]																						
Full physical examination[f]	X																	X						
Symptom-directed physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Body weight	X																							
Height	X																							
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Safety ECG	X																							
Pregnancy test[h]	X	X		X		X		X		X		X	X	X	X									

Study Stage	Screening	Treatment Period[a]											Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W24	W28	W32	W36	W40	W44/ ET[c]	W52	W60	W68	W76	W84	W92
Study Visit Day ±Visit Window	D−28 to −1	D1	D15 ±2	D29 ±2	D43 ±2	D57 ±2	D71 ±2	D85 ±2	D99 ±2	D113 ±2	D127 ±2	D141 ±2	D169 ±2	D197 ±7	D225 ±7	D253 ±7	D281 ±7	D309 ±7	D365 ±7	D421 ±7	D477 ±7	D533 ±7	D589 ±7	D645 ±7
FibroScan[i]	X																							
Screening viral serology[j]	X																							
Laboratory assessments[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Urinalysis[k]	X																							
Urine for drugs of abuse[m]	X																							
Study drug administration[n]		X		X		X		X		X		X												
Blood sample for quantitative HBsAg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for anti-HBs qualitative and quantitative	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for HBeAg quantitative		X		X		X		X		X		X			X			X	X	X	X	X	X	X
Blood sample for HBeAg qualitative	X																							

Study Stage	Screening	Treatment Period[a]											Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W24	W28	W32	W36	W40	W44/ ET[c]	W52	W60	W68	W76	W84	W92
Study Visit Day ±Visit Window	D−28 to −1	D1	D15 ±2	D29 ±2	D43 ±2	D57 ±2	D71 ±2	D85 ±2	D99 ±2	D113 ±2	D127 ±2	D141 ±2	D169 ±2	D197 ±7	D225 ±7	D253 ±7	D281 ±7	D309 ±7	D365 ±7	D421 ±7	D477 ±7	D533 ±7	D589 ±7	D645 ±7
Blood sample for anti-HBe	X			X		X		X		X		X			X			X	X	X	X	X	X	X
Blood sample for HBV DNA quantitation	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X
CCI		CCI																						
CCI		CCI																						
Resistance surveillance[q]		X		X		X		X		X		X	X	X	X	X	X	X			X	X	X	X
CCI		CCI																						
Pooled urine for PK[s]			X	X								X												
CCI		CCI																						

Study Stage	Screening	Treatment Period[a]												Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W24	W28	W32	W36	W40	W44/ ET[c]	W52	W60	W68	W76	W84	W92
Study Visit Day ±Visit Window	D−28 to −1	D1	D15 ±2	D29 ±2	D43 ±2	D57 ±2	D71 ±2	D85 ±2	D99 ±2	D113 ±2	D127 ±2	D141 ±2	D169 ±2	D197 ±7	D225 ±7	D253 ±7	D281 ±7	D309 ±7	D365 ±7	D421 ±7	D477 ±7	D533 ±7	D589 ±7	D645 ±7
Alcohol intake assessment	X																							
Exercise assessment	X																							
Review/Record AEs[u]		X																						
Prior and Concomitant Medications	X																							
NRTI medication adherence[v]		X																						
ECI surveillance[w]		X																						

AE = adverse event; ECG = electrocardiogram; ECI = event(s) of clinical interest; ET=early termination; HBeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PK = pharmacokinetics.
Note: When scheduled at the same timepoints, the assessments of vital signs must be performed before blood sample collections.
[a] On Days in which study drug is administered, assessments performed predose unless otherwise specified.
[b] Additional HBsAg monitoring is required for subjects with HBsAg decline ≥ 1-log relative to the Day 1 predose level or HBsAg <1000 IU/mL at the final required follow-up visit. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.
[c] Section 4.3 for assessments to be performed if a subject discontinues treatment or withdraws prematurely from the study.
[d] A complete medical history will be taken at screening including HBV genotype if available. Any changes should be updated prior to dosing.
[e] Review of subject eligibility including but not limited to any changes to medical history or current medications. The investigator must confirm that no exclusion criteria were met up to Day 1. Day 1 predose laboratory values do not need to be reviewed for eligibility purposes.
[f] See Section 7.2.2 for assessments to be performed during a full physical examination. A dilated fundoscopic retinal examination must be performed during Screening. The subject may be referred to a specialist for performance of the retinal exam.

[g] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the subject has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours predose and at 3 hours (+/- 1 hour) post-dose. On all other visit days, vital signs are only required to be recorded once during the visit. When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed first, before the physical examinations, blood sample collections, and urine collections.

[h] WOCBP are required to have pregnancy tests. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter. When pregnancy testing and study drug administration occur at the same visit, a negative urine pregnancy test must be confirmed prior to study drug administration. If urine pregnancy test is positive, confirm immediately with serum pregnancy test.

[i] Does not need to be performed if the subject has had a FibroScan in the 6 months prior to screening or liver biopsy in the year prior to screening that confirmed the absence of Metavir F3 fibrosis or F4 cirrhosis.

[j] See Section 7.1.3 for viral serology parameters.

[k] Clinical laboratory and urinalysis parameters are described in Section 7.2.8. HbA1c and lipase testing will only be performed at screening. Thyroid panel will only be performed at screening.

[l] Limited to liver function tests and coagulation parameters.

[m] Drugs of abuse included in the screen are described in the inclusion/exclusion criteria.

[n] VIR-2218 will be administered via SC injection as described in Section 6.2.4. Starting on Day 1, VIR-2218 will be administered every 4 weeks for 6 doses.

CCI [redacted]

CCI [redacted]

[q] HBV sequence analysis may be performed if a subject experiences viral breakthrough (including but not limited to HBV DNA breakthrough) or is otherwise indicated. See Section 7.1.2 for more information.

CCI [redacted]

[s] Subjects who participate in the optional sub-study will begin pooled urine collection for the 24 hours prior to the scheduled study visit in order to return samples on W2, W4, and W20. Pooled urine collection is not required for any other study visit. (ex. for the W2 visit, subjects will begin collecting urine on D14, and provide their sample to the site staff upon arrival at the site for the W2 visit).

CCI [redacted]

[u] All AEs related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards. All AEs must be collected from Day 1 through the last visit of the follow-up period. For subjects who continue into the extended follow-up period, AEs related to study procedures should be captured.

[v] NRTI therapy will be continued until the criteria described in Section 4.7.1 are met, and will be discontinued at investigator discretion.

[w] Subjects will be monitored for ECI, and additional assessments may be performed if indicated. See Section 8.5 and Appendix 17 for more information.

APPENDIX 7. COHORT 2D/OPTIONAL COHORT 2E SCHEDULE OF STUDY ASSESSMENTS (VIR-2218 + PEG-IFNα)

Study Stage	Screen-ing	Treatment Period[a]														Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			W2	W4	W6	W8	W10	W12	W13	W14	W15	W16	W18	W20	W24	W28	W32	W36	W40	W44	W48/ ET[c]	W56	W64	W72	W80	W88	W96
Study Visit Day ±Visit Window	D −28 to −1	D1	D15 ±2	D29 ±2	D43 ±2	D57 ±2	D71 ±2	D85 ±2	D92 ±2	D99 ±2	D106 ±2	D113 ±2	D127 ±2	D141 ±2	D169 ±2	D197 ±7	D225 ±7	D253 ±7	D281 ±7	D309 ±7	D337 ±7	D393 ±7	D449 ±7	D505 ±7	D561 ±7	D617 ±7	D673 ±7
Informed consent	X																										
Demography	X																										
Medical history including HBV genotype[d]	X																										
Inclusion/exclusion criteria	X	X[e]																									
Full physical examination[f]	X																				X						
Symptom-directed physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Body weight	X																										
Height	X																										
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Safety ECG	X																										
Pregnancy test[h]	X	X		X		X		X				X		X	X	X	X	X									
FibroScan[i]	X																										

Study Stage	Screen-ing	Treatment Period[a]														Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			W2	W4	W6	W8	W10	W12	W13	W14	W15	W16	W18	W20	W24	W28	W32	W36	W40	W44	W48/ ET[c]	W56	W64	W72	W80	W88	W96
Study Visit Day ±Visit Window	D −28 to −1	D1	D15 ±2	D29 ±2	D43 ±2	D57 ±2	D71 ±2	D85 ±2	D92 ±2	D99 ±2	D106 ±2	D113 ±2	D127 ±2	D141 ±2	D169 ±2	D197 ±7	D225 ±7	D253 ±7	D281 ±7	D309 ±7	D337 ±7	D393 ±7	D449 ±7	D505 ±7	D561 ±7	D617 ±7	D673 ±7
Screening viral serology[j]	X																										
Laboratory assessments[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Urinalysis[k]	X																										
Urine for drugs of abuse[m]	X																										
Study drug administration[n]		X																									
Blood sample for quantitative HBsAg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for anti-HBs qualitative and quantitative	X	X		X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for HBeAg quantitative		X		X		X		X				X		X			X		X		X	X	X	X	X	X	X
Blood sample for HBeAg qualitative	X																										
Blood sample for anti-HBe	X			X		X		X				X		X			X		X		X	X	X	X	X	X	X
Blood sample for HBV DNA quantitation	X	X		X		X		X				X		X		X	X	X	X	X	X	X	X	X	X	X	X

Study Stage	Screen-ing	Treatment Period[a]														Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			W2	W4	W6	W8	W10	W12	W13	W14	W15	W16	W18	W20	W24	W28	W32	W36	W40	W44	W48/ ET[c]	W56	W64	W72	W80	W88	W96
Study Visit Day ±Visit Window	D −28 to −1	D1	D15 ±2	D29 ±2	D43 ±2	D57 ±2	D71 ±2	D85 ±2	D92 ±2	D99 ±2	D106 ±2	D113 ±2	D127 ±2	D141 ±2	D169 ±2	D197 ±7	D225 ±7	D253 ±7	D281 ±7	D309 ±7	D337 ±7	D393 ±7	D449 ±7	D505 ±7	D561 ±7	D617 ±7	D673 ±7
CCI		CCI																									
CCI		CCI																									
Resistance surveillance[q]		X		X		X		X				X		X		X	X	X	X	X	X			X	X	X	X
CCI		CCI																									
CCI		CCI																									
Alcohol intake assessment															X												
Exercise assessment															X												
Review/Record AEs[t]															X												
Prior and Concomitant Medications															X												

Study Stage	Screen-ing	Treatment Period[a]														Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			W2	W4	W6	W8	W10	W12	W13	W14	W15	W16	W18	W20	W24	W28	W32	W36	W40	W44	W48/ ET[c]	W56	W64	W72	W80	W88	W96
Study Visit Day ±Visit Window	D −28 to −1	D1	D15 ±2	D29 ±2	D43 ±2	D57 ±2	D71 ±2	D85 ±2	D92 ±2	D99 ±2	D106 ±2	D113 ±2	D127 ±2	D141 ±2	D169 ±2	D197 ±7	D225 ±7	D253 ±7	D281 ±7	D309 ±7	D337 ±7	D393 ±7	D449 ±7	D505 ±7	D561 ±7	D617 ±7	D673 ±7
NRTI medication adherence[u]		X																								
ECI surveillance[v]		X																								

AE = adverse event; ECG = electrocardiogram; ECI = event(s) of clinical interest; ET=early termination; HBeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor.

Note: When scheduled at the same timepoints, the assessments of vital signs must be performed before blood sample collections.

[a] On Days in which study drug is administered, assessments performed predose unless otherwise specified.

[b] Additional HBsAg monitoring is required for subjects with HBsAg decline ≥ 1-log relative to the Day 1 predose level or HBsAg <1000 IU/mL at the final required follow-up visit. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

[c] Section 4.3 for assessments to be performed if a subject discontinues treatment or withdraws prematurely from the study.

[d] A complete medical history will be taken at screening including HBV genotype if available. Any changes should be updated prior to dosing.

[e] Review of subject eligibility including but not limited to any changes to medical history or current medications. The investigator must confirm that no exclusion criteria were met up to Day 1. Day 1 predose laboratory values do not need to be reviewed for eligibility purposes.

[f] See Section 7.2.2 for assessments to be performed during a full physical examination. A dilated fundoscopic retinal examination must be performed during Screening. The subject may be referred to a specialist for performance of the retinal exam.

[g] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the subject has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours predose and at 3 hours (+/- 1 hour) post-dose. On all other visit days, vital signs are only required to be recorded once during the visit. When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed first, before the physical examinations, blood sample collections, and urine collections.

[h] WOCBP are required to have pregnancy tests. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed thereafter. When pregnancy testing and study drug administration occur at the same visit, a negative urine pregnancy test must be confirmed prior to study drug administration. If urine pregnancy test is positive, confirm immediately with serum pregnancy test.

[i] Does not need to be performed if the subject has had a FibroScan in the 6 months prior to screening or liver biopsy in the year prior to screening that confirmed the absence of Metavir F3 fibrosis or F4 cirrhosis.

[j] See Section 7.1.3 for viral serology parameters.

[k] Clinical laboratory and urinalysis parameters are described in Section 7.2.8. HbA1c and lipase testing will only be performed at screening. Thyroid panel will only be performed at screening, Day 1, Week 12, Week 24, and Week 48.

[l] Limited to liver function tests and coagulation parameters.

[m] Drugs of abuse included in the screen are described in the inclusion/exclusion criteria.

[n] Study drugs will be administered via SC injection as described in Section 6.2.4. Starting on Day 1, VIR-2218 will be administered every 4 weeks for 6 doses. PEG-IFNα will be administered once weekly for 12 doses (starting at Week 12 and through Week 23). See Appendix 8 for full schedule of Cohort 2d/optional Cohort 2e study drug administration.

CCI [redacted]

CCI [redacted]

[q] HBV sequence analysis may be performed if a subject experiences viral breakthrough (including but not limited to HBV DNA breakthrough) or is otherwise indicated. See Section 7.1.2 for more information.

CCI [redacted]

CCI [redacted]

[t] All AEs related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards. All AEs must be collected from Day 1 through the last visit of the follow-up period. For subjects who continue into the extended follow-up period, AEs related to study procedures should be captured.

[u] NRTI therapy will be continued until the criteria described in Section 4.7.1 are met and will be discontinued at investigator discretion.

[v] Subjects will be monitored for ECI, and additional assessments may be performed if indicated. See Section 8.5 and Appendix 17 for more information.

APPENDIX 8. COHORT 2D/OPTIONAL COHORT 2E STUDY DRUG ADMINISTRATION SCHEDULE

	D1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11
VIR-2218	X				X				X			
PEG-IFNα[a, b]												

	W12	W13	W14	W15	W16	W17	W18	W19	W20	W21	W22	W23
VIR-2218	X				X				X			
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

[a] Subjects are required to return to clinic for W12, W13, and W14 PEG-IFNα administrations/to receive self-administration training. If the subject has been trained for self-administration, all other scheduled PEG-IFNα administrations may be self-administered. Subjects may return to clinic for PEG-IFNα administration after the week W14 visit if unable or unwilling to self-administer injections.

[b] Subjects who discontinue from PEG-IFNα treatment due to PEG-IFNα-related adverse reactions may continue to receive treatment with VIR-2218. These subjects should follow the schedule of study visits per the schedule of assessments in Appendix 7.

APPENDIX 9. COHORT 3D/OPTIONAL COHORT 3E SCHEDULE OF STUDY ASSESSMENTS (VIR-2218 + PEG-IFNα)

Study Stage	**Screening**	**Treatment Period[a]**							**Follow-up Period**						**Extended Follow-up Period[b]**					
Study Visit Week			**W1**	**W2**	**W4**	**W6**	**W8**	**W12[w]**	**W16[w]**	**W20**	**W24**	**W28**	**W32**	**W36/ ET[c]**	**W44**	**W52**	**W60**	**W68**	**W76**	**W84**
Study Visit Day ±Visit Window	**D −28 to −1**	**D1**	**D8 ±2**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±7**	**D141 ±7**	**D169 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D309 ±7**	**D365 ±7**	**D421 ±7**	**D477 ±7**	**D533 ±7**	**D589 ±7**
Informed consent	X																			
Demography	X																			
Medical history including HBV genotype[d]	X																			
Inclusion/ exclusion criteria	X	X[e]																		
Full physical examination[f]	X													X						
Symptom-directed physical examination		X	X	X	X	X	X	X	X	X	X	X	X							
Body weight	X																			
Height	X																			
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Safety ECG	X																			

Study Stage	**Screening**	**Treatment Period[a]**							**Follow-up Period**						**Extended Follow-up Period[b]**					
Study Visit Week			**W1**	**W2**	**W4**	**W6**	**W8**	**W12[w]**	**W16[w]**	**W20**	**W24**	**W28**	**W32**	**W36/ ET[c]**	**W44**	**W52**	**W60**	**W68**	**W76**	**W84**
Study Visit Day ±Visit Window	**D −28 to −1**	**D1**	**D8 ±2**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±7**	**D141 ±7**	**D169 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D309 ±7**	**D365 ±7**	**D421 ±7**	**D477 ±7**	**D533 ±7**	**D589 ±7**
Pregnancy test[h]	X	X			X		X	X	X	X	X									
FibroScan[i]	X																			
Screening viral serology[j]	X																			
Laboratory assessments[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Urinalysis[k]	X																			
Urine for drugs of abuse[m]	X																			
Study drug administration[n]		X																		
Blood sample for quantitative HBsAg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for anti-HBs qualitative and quantitative	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for HBeAg quantitative		X			X		X			X		X		X	X	X	X	X	X	X

Study Stage	Screening	Treatment Period[a]							Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			**W1**	**W2**	**W4**	**W6**	**W8**	**W12[w]**	**W16[w]**	**W20**	**W24**	**W28**	**W32**	**W36/ ET[c]**	**W44**	**W52**	**W60**	**W68**	**W76**	**W84**
Study Visit Day ±Visit Window	**D −28 to −1**	**D1**	**D8 ±2**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±7**	**D141 ±7**	**D169 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D309 ±7**	**D365 ±7**	**D421 ±7**	**D477 ±7**	**D533 ±7**	**D589 ±7**
Blood sample for HBeAg qualitative	X																			
Blood sample for anti-HBe	X				X		X			X		X		X	X	X	X	X	X	X
Blood sample for HBV DNA quantitation	X	X			X		X		X	X	X	X	X	X	X	X	X	X	X	X
CCI		CCI																		
CCI		CCI																		
Resistance surveillance[q]		X			X		X		X	X	X	X	X	X			X	X	X	X
CCI		CCI																		

Study Stage	Screening	Treatment Period[a]							Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			**W1**	**W2**	**W4**	**W6**	**W8**	**W12[w]**	**W16[w]**	**W20**	**W24**	**W28**	**W32**	**W36/ ET[c]**	**W44**	**W52**	**W60**	**W68**	**W76**	**W84**
Study Visit Day ±Visit Window	**D −28 to −1**	**D1**	**D8 ±2**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±7**	**D141 ±7**	**D169 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D309 ±7**	**D365 ±7**	**D421 ±7**	**D477 ±7**	**D533 ±7**	**D589 ±7**
CCI		CCI																		
Alcohol intake assessment	X																			
Exercise assessment	X																			
Review/Record AEs[t]		X																		
Prior and Concomitant Medications	X																			
NRTI medication adherence[u]		X																		
ECI surveillance[v]		X																		

AE = adverse event; ECG = electrocardiogram; ECI = event(s) of clinical interest; ET=early termination; HBeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor.
Note: When scheduled at the same timepoints, the assessments of vital signs must be performed before blood sample collections.
[a] On Days in which study drug is administered, assessments performed predose unless otherwise specified.
[b] Additional HBsAg monitoring is required for subjects with HBsAg decline ≥ 1-log relative to the Day 1 predose level or HBsAg <1000 IU/mL at the final required follow-up visit. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.
[c] Section 4.3 for assessments to be performed if a subject discontinues treatment or withdraws prematurely from the study.

[d] A complete medical history will be taken at screening including HBV genotype if available. Any changes should be updated prior to dosing.
[e] Review of subject eligibility including but not limited to any changes to medical history or current medications. The investigator must confirm that no exclusion criteria were met up to Day 1. Day 1 predose laboratory values do not need to be reviewed for eligibility purposes.
[f] See Section 7.2.2 for assessments to be performed during a full physical examination. A dilated fundoscopic retinal examination must be performed during Screening. The subject may be referred to a specialist for performance of the retinal exam.
[g] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the subject has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours predose and at 3 hours (+/- 1 hour) post-dose. On all other visit days, vital signs are only required to be recorded once during the visit. When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed first, before the physical examinations, blood sample collections, and urine collections.
[h] WOCBP are required to have pregnancy tests. A serum pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. When pregnancy testing and study drug administration occur at the same visit, a negative urine pregnancy test must be confirmed prior to study drug administration. If urine pregnancy test is positive, confirm immediately with serum pregnancy test.
[i] Does not need to be performed if the subject has had a FibroScan in the 6 months prior to screening or liver biopsy in the year prior to screening that confirmed the absence of Metavir F3 fibrosis or F4 cirrhosis.
[j] See Section 7.1.3 for viral serology parameters.
[k] Clinical laboratory and urinalysis parameters are described in Section 7.2.8. HbA1c and lipase testing will only be performed at screening. Thyroid panel will only be performed at screening, Day 1, Week 12, and Week 36.
[l] Limited to liver function tests and coagulation parameters.
[m] Drugs of abuse included in the screen are described in the inclusion/exclusion criteria.
[n] Study drugs will be administered via SC injection as described in Section 6.2.4. VIR-2218 will be administered on Day 1, Week 4, and Week 8. PEG-IFNα will be administered once weekly for 12 doses (starting on Day 1 and through Week 11). See Appendix 10 for full schedule of Cohort 3d/optional Cohort 3e study drug administration.
[CCI]
[CCI]
[q] HBV sequence analysis may be performed if a subject experiences viral breakthrough (including but not limited to HBV DNA breakthrough) or is otherwise indicated. See Section 7.1.2 for more information.
[CCI]
[CCI]
[t] All AEs related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards. All Aes must be collected from Day 1 through the last visit of the follow-up period. For subjects who continue into the extended follow-up period, Aes related to study procedures should be captured.
[u] NRTI therapy will be continued until the criteria described in Section 4.7.1 are met and will be discontinued at investigator discretion.
[v] Subjects will be monitored for ECI, and additional assessments may be performed if indicated. See Section 8.5 and Appendix 17 for more information.
[w] Subjects currently in treatment will move to Cohort 2f starting at Week 12 and up to Week 16 at the corresponding Cohort 2f timepoint per Section 4.7

APPENDIX 10. COHORT 3D/OPTIONAL COHORT 3E STUDY DRUG ADMINISTRATION SCHEDULE

	D1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11
VIR-2218	X				X				X			
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

[a] Subjects are required to return to clinic for D1, W1, and W2 PEG-IFNα administrations/to receive self-administration training. If the subject has been trained for self-administration, all other scheduled PEG-IFNα administrations may be self-administered. Subjects may return to clinic for PEG-IFNα administration after the week W2 visit if unable or unwilling to self-administer injections.

[b] Subjects who discontinue from PEG-IFNα treatment due to PEG-IFNα-related adverse reactions may continue to receive treatment with VIR-2218. These subjects should follow the schedule of study visits per the schedule of assessments in Appendix 9.

APPENDIX 11. OPTIONAL PART F COHORT 1F SCHEDULE OF STUDY ASSESSMENTS (VIR-2218 + PEG-IFNα)

Study Stage	Screen-ing	Treatment Period[a]													Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48/ ET[c]**	**W56**	**W64**	**W72**	**W80**	**W88**	**W96**
Study Visit Day ±Visit Window	**D −28 to −1**	**D1**	**D8 ±2**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2**	**D71 ±2**	**D85 ±2**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D281 ±7**	**D309 ±7**	**D337 ±7**	**D393 ±7**	**D449 ±7**	**D505 ±7**	**D561 ±7**	**D617 ±7**	**D673 ±7**
Informed consent	X																									
Demography	X																									
Medical history including HBV genotype[d]	X																									
Inclusion/ exclusion criteria	X	X[e]																								
Full physical examination[f]	X																			X						
Symptom-directed physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Body weight	X																									
Height	X																									
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Safety ECG	X																									
Pregnancy test[h]	X	X			X		X		X		X		X	X	X	X	X									
FibroScan[i]	X																									

Study Stage	Screen-ing	Treatment Period[a]													Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48/ ET[c]**	**W56**	**W64**	**W72**	**W80**	**W88**	**W96**
Study Visit Day ±Visit Window	**D −28 to −1**	**D1**	**D8 ±2**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2**	**D71 ±2**	**D85 ±2**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D281 ±7**	**D309 ±7**	**D337 ±7**	**D393 ±7**	**D449 ±7**	**D505 ±7**	**D561 ±7**	**D617 ±7**	**D673 ±7**
Screening viral serology[j]	X																									
Laboratory assessments[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Urinalysis[k]	X																									
Urine for drugs of abuse[m]	X																									
Study drug administration[n]		X																								
Blood sample for quantitative HBsAg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for anti-HBs qualitative and quantitative	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for HbeAg quantitative		X			X		X		X		X		X			X		X		X	X	X	X	X	X	X
Blood sample for HbeAg qualitative	X																									
Blood sample for anti-Hbe	X				X		X		X		X		X			X		X		X	X	X	X	X	X	X
Blood sample for HBV DNA quantitation	X	X			X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X

Study Stage	Screen-ing	Treatment Period[a]													Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48/ ET[c]**	**W56**	**W64**	**W72**	**W80**	**W88**	**W96**
Study Visit Day ±Visit Window	**D −28 to −1**	**D1**	**D8 ±2**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2**	**D71 ±2**	**D85 ±2**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D281 ±7**	**D309 ±7**	**D337 ±7**	**D393 ±7**	**D449 ±7**	**D505 ±7**	**D561 ±7**	**D617 ±7**	**D673 ±7**
CCI		CCI																								
CCI		CCI																								
Resistance surveillance[q]		X			X		X		X		X		X		X	X	X	X	X	X			X	X	X	X
CCI		CCI																								
CCI		CCI																								
Alcohol intake assessment		X																								
Exercise assessment		X																								
Review/ Record Aes[t]		X																								
Prior and Concomitant Medications		X																								

Study Stage	Screen-ing	Treatment Period[a]													Follow-up Period						Extended Follow-up Period[b]					
Study Visit Week			**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48/ ET[c]**	**W56**	**W64**	**W72**	**W80**	**W88**	**W96**
Study Visit Day ±Visit Window	**D −28 to −1**	**D1**	**D8 ±2**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2**	**D71 ±2**	**D85 ±2**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D281 ±7**	**D309 ±7**	**D337 ±7**	**D393 ±7**	**D449 ±7**	**D505 ±7**	**D561 ±7**	**D617 ±7**	**D673 ±7**
NRTI medication adherence[u]		X																								
ECI surveillance[v]		X																								

AE = adverse event; ECG = electrocardiogram; ECI = event(s) of clinical interest; ET=early termination; HbeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor.

Note: When scheduled at the same timepoints, the assessments of vital signs must be performed before blood sample collections.

[a] On Days in which study drug is administered, assessments performed predose unless otherwise specified.

[b] Additional HBsAg monitoring is required for subjects with HBsAg decline ≥ 1-log relative to the Day 1 predose level or HBsAg <1000 IU/mL at the final required follow-up visit. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.

[c] Section 4.3 for assessments to be performed if a subject discontinues treatment or withdraws prematurely from the study.

[d] A complete medical history will be taken at screening including HBV genotype if available. Any changes should be updated prior to dosing.

[e] Review of subject eligibility including but not limited to any changes to medical history or current medications. The investigator must confirm that no exclusion criteria were met up to Day 1. Day 1 predose laboratory values do not need to be reviewed for eligibility purposes.

[f] See Section 7.2.2 for assessments to be performed during a full physical examination. A dilated fundoscopic retinal examination must be performed during Screening. The subject may be referred to a specialist for performance of the retinal exam.

[g] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the subject has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours predose and at 3 hours (+/- 1 hour) post-dose. On all other visit days, vital signs are only required to be recorded once during the visit. When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed first, before the physical examinations, blood sample collections, and urine collections.

[h] WOCBP are required to have pregnancy tests. A serum pregnancy test will be performed at screening and urine pregnancy tests will be performed thereafter. When pregnancy testing and study drug administration occur at the same visit, a negative urine pregnancy test must be confirmed prior to study drug administration. If urine pregnancy test is positive, confirm immediately with serum pregnancy test.

[i] Does not need to be performed if the subject has had a FibroScan in the 6 months prior to screening or liver biopsy in the year prior to screening that confirmed the absence of Metavir F3 fibrosis or F4 cirrhosis.

[j] See Section 7.1.3 for viral serology parameters.

[k] Clinical laboratory and urinalysis parameters are described in Section 7.2.8. HbA1c and lipase testing will only be performed at screening. Thyroid panel will only be performed at screening, Day 1, Week 12, Week 24, and Week 48.

[l] Limited to liver function tests and coagulation parameters.

[m] Drugs of abuse included in the screen are described in the inclusion/exclusion criteria.

[n] Study drugs will be administered via SC injection as described in Section 6.2.4 . Starting on Day 1, VIR-2218 will be administered every 4 weeks for 6 doses. PEG-IFNα will be administered once weekly for 24 doses (starting on Day 1 and through Week 23). See Appendix 12 for full schedule of Cohort 1f study drug administration.

CCI [redacted]

[q] HBV sequence analysis may be performed if a subject experiences viral breakthrough (including but not limited to HBV DNA breakthrough) or is otherwise indicated. See Section 7.1.2 for more information.

CCI [redacted]

[t] All AEs related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards. All AEs must be collected from Day 1 through the last visit of the follow-up period. For subjects who continue into the extended follow-up period, AEs related to study procedures should be captured.

[u] NRTI therapy will be continued until the criteria described in Section 4.7.1 are met and will be discontinued at investigator discretion.

[v] Subjects will be monitored for ECI, and additional assessments may be performed if indicated. See Section 8.5 and Appendix 17 for more information.

APPENDIX 12. OPTIONAL PART F COHORT 1F STUDY DRUG ADMINISTRATION SCHEDULE

	D1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11
VIR-2218	X				X				X			
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

	W12	W13	W14	W15	W16	W17	W18	W19	W20	W21	W22	W23
VIR-2218	X				X				X			
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

[a] Subjects are required to return to clinic for D1, W1, and W2 PEG-IFNα administrations/to receive self-administration training. If the subject has been trained for self-administration, all other scheduled PEG-IFNα administrations may be self-administered. Subjects may return to clinic for PEG-IFNα administration after the week W2 visit if unable or unwilling to self-administer injections.

[b] Subjects who discontinue from PEG-IFNα treatment due to PEG-IFNα-related adverse reactions may continue to receive treatment with VIR-2218. These subjects should follow the schedule of study visits per the schedule of assessments in Appendix 11.

APPENDIX 13. OPTIONAL PART F COHORT 2F/COHORT 3F SCHEDULE OF STUDY ASSESSMENTS (VIR-2218 + PEG-IFNα)

Study Stage	Screen-ing	Treatment Period[a]																			Extended Follow-up Period[b]					
Study Visit Week			W1	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W24	W28	W32	W36	W40	W44	W48 / ET[c]	W56	W64	W72	W80	W88	W96
Study Visit Day ±Visit Window	D −28 to −1	D1	D8 ±2	D15 ±2	D29 ±2	D43 ±2	D57 ±2	D71 ±2	D85 ±2	D99 ±2	D113 ±2	D127 ±2	D141 ±2	D169 ±2	D197 ±2	D225 ±2	D253 ±2	D281 ±2	D309 ±2	D337 ±2	D393 ±7	D449 ±7	D505 ±7	D561 ±7	D617 ±7	D673 ±7
Informed consent	X																									
Demography	X																									
Medical history including HBV genotype[d]	X																									
Inclusion/ exclusion criteria	X	X[e]																								
Full physical examination[f]	X																			X						
Symptom-directed physical examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Body weight	X																									
Height	X																									
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Safety ECG	X																									
Pregnancy test[h]	X	X			X		X		X		X		X	X	X	X	X	X	X	X	X	X				
FibroScan[i]	X																									
Screening viral serology[j]	X																									
Laboratory assessments[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Urinalysis[k]	X																									

Study Stage	Screen-ing	Treatment Period[a]																		Extended Follow-up Period[b]					
Study Visit Week			W1	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W24	W28	W32	W36	W40	W44	W48 / ET[c]	W56	W64	W72	W80	W88	W96
Study Visit Day ±Visit Window	D −28 to −1	D1	D8 ±2	D15 ±2	D29 ±2	D43 ±2	D57 ±2	D71 ±2	D85 ±2	D99 ±2	D113 ±2	D127 ±2	D141 ±2	D169 ±2	D197 ±2	D225 ±2	D253 ±2	D281 ±2	D309 ±2	D337 ±2	D393 ±7	D449 ±7	D505 ±7	D561 ±7	D617 ±7	D673 ±7
Urine for drugs of abuse[m]	X																									
Study drug administration[n]		X																								
Blood sample for quantitative HBsAg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for anti-HBs qualitative and quantitative	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for HBeAg quantitative		X			X		X		X		X		X			X		X		X	X	X	X	X	X	X
Blood sample for HBeAg qualitative	X																									
Blood sample for anti-HBe	X				X		X		X		X		X			X		X		X	X	X	X	X	X	X
Blood sample for HBV DNA quantitation	X	X			X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X
CCI		CCI																								
CCI		CCI																								
Resistance surveillance[q]		X			X		X		X		X		X		X	X	X	X	X	X			X	X	X	X

Study Stage	Screen-ing	Treatment Period[a]																		Extended Follow-up Period[b]					
Study Visit Week			**W1**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48 / ET[c]**	**W56**	**W64**	**W72**	**W80**	**W88**	**W96**
Study Visit Day ±Visit Window	**D −28 to −1**	**D1**	**D8 ±2**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2**	**D71 ±2**	**D85 ±2**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±2**	**D225 ±2**	**D253 ±2**	**D281 ±2**	**D309 ±2**	**D337 ±2**	**D393 ±7**	**D449 ±7**	**D505 ±7**	**D561 ±7**	**D617 ±7**	**D673 ±7**
CCI		CCI																							
CCI		CCI																							
Alcohol intake assessment	X																								
Exercise assessment	X																								
Review/ Record AEs[t]		X																							
Prior and Concomitant Medications	X																								
NRTI medication adherence[u]		X																							
ECI surveillance[v]		X																							

AE = adverse event; ECG = electrocardiogram; ECI = event(s) of clinical interest; ET=early termination; HBeAg = hepatitis e-antigen; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor.
Note: When scheduled at the same timepoints, the assessments of vital signs must be performed before blood sample collections.

a. On Days in which study drug is administered, assessments performed predose unless otherwise specified.
b. Additional HBsAg monitoring is required for subjects with HBsAg decline ≥ 1-log relative to the Day 1 predose level or HBsAg <1000 IU/mL at the Week 72 visit. Additional HBsAg monitoring may be discontinued at the Sponsor's discretion based on emerging data.
c. See Section 4.3 for assessments to be performed if a subject discontinues treatment or withdraws prematurely from the study.
d. A complete medical history will be taken at screening including HBV genotype if available. Any changes should be updated prior to dosing.

e. Review of subject eligibility including but not limited to any changes to medical history or current medications. The investigator must confirm that no exclusion criteria were met up to Day 1. Day 1 predose laboratory values do not need to be reviewed for eligibility purposes.
f. See Section 7.2.2 for assessments to be performed during a full physical examination. A dilated fundoscopic retinal examination must be performed during Screening. The subject may be referred to a specialist for performance of the retinal exam.
g. Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the subject has rested comfortably for approximately 10 minutes. On Day 1, vital signs should be measured within 2 hours predose and at 3 hours (+/- 1 hour) post-dose. On all other visit days, vital signs are only required to be recorded once during the visit. When scheduled at the same timepoints, the assessments of vital signs and 12-lead ECGs must be performed first, before the physical examinations, blood sample collections, and urine collections.
h. WOCBP are required to have pregnancy tests. A serum pregnancy test will be performed at screening and urine pregnancy tests will be performed throughout the Follow Up period. When pregnancy testing and study drug administration occur at the same visit, a negative urine pregnancy test must be confirmed prior to study drug administration. If urine pregnancy test is positive, confirm immediately with serum pregnancy test.
i. Does not need to be performed if the subject has had a FibroScan in the 6 months prior to screening or liver biopsy in the year prior to screening that confirmed the absence of Metavir F3 fibrosis or F4 cirrhosis.
j. See Section 7.1.3 for viral serology parameters.
k. Clinical laboratory and urinalysis parameters are described in Section 7.2.8. Thyroid panel will only be performed at screening, Day 1, Week 12, Week 24, and Week 48 and Week 72.
l. Limited to liver function tests and coagulation parameters.
m. Drugs of abuse included in the screen are described in the inclusion/exclusion criteria.
n. Study drugs will be administered via SC injection as described in Section 6.2.4. Starting on Day 1, VIR-2218 will be administered every 4 weeks for 6 doses. PEG-IFNα will be administered once weekly for up to 48 doses (starting on Day 1 and through Week 47). After Week 23, subjects may discontinue PEG-IFNα if they meet criteria outlined in Section 4.7. Even if a subject discontinues PEG-IFNα dosing per Section 4.7 prior to the Week 48 visit, they will continue to follow the Schedule of Assessments. See Appendix 14 for full schedule of Cohort 2f study drug administration
CCI [redacted]
CCI [redacted]
q. HBV sequence analysis may be performed if a subject experiences viral breakthrough (including but not limited to HBV DNA breakthrough) or is otherwise indicated. See Section 7.1.2 for more information.
CCI [redacted]
m [redacted]
CCI [redacted]
t. All AEs related to screening activities must be collected from the time of consent onwards; any other events occurring during the screening period should be reported as medical history. All SAEs must be collected from the time of consent onwards. All AEs must be collected from Day 1 through the last visit of the follow-up period. For subjects who continue into the extended follow-up period, AEs related to study procedures should be captured.
u. NRTI therapy will be continued until the criteria described in Section 4.7.1 are met and will be discontinued at investigator discretion.
v. Subjects will be monitored for ECI, and additional assessments may be performed if indicated. See Section 8.5 and Appendix 17 for more information.

APPENDIX 14. OPTIONAL PART F COHORT 2F STUDY DRUG ADMINISTRATION SCHEDULE

	D1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11
VIR-2218	X				X				X			
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

	W12	W13	W14	W15	W16	W17	W18	W19	W20	W21	W22	W23
VIR-2218	X				X				X			
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

	W24[c]	W25	W26	W27	W28	W29	W30	W31	W32	W33	W34	W35
VIR-2218												
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

	W36	W37	W38	W39	W40	W41	W42	W43	W44	W45	W46	W47
VIR-2218												
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

[a.] Subjects are required to return to clinic for D1, W1, and W2 PEG-IFNα administrations/to receive self-administration training. If the subject has been trained for self-administration, all other scheduled PEG-IFNα administrations may be self-administered. Subjects may return to clinic for PEG-IFNα administration after the week W2 visit if unable or unwilling to self-administer injections.

[b.] Subjects who discontinue from PEG-IFNα treatment due to PEG-IFNα-related adverse reactions may continue to receive treatment with VIR-2218. These subjects should follow the schedule of study visits per the schedule of assessments in Appendix 13.

[c.] Subjects may discontinue the weekly PEG-IFNα doses starting at Week 24 as per criteria outlined in Section 4.7.

APPENDIX 15. OPTIONAL PART F COHORT 3F STUDY DRUG ADMINISTRATION SCHEDULE

	D1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11
VIR-2218	X				X				X			
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

	W12	W13	W14	W15	W16	W17	W18	W19	W20	W21	W22	W23
VIR-2218	X				X				X			
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

	W24[c]	W25	W26	W27	W28	W29	W30	W31	W32	W33	W34	W35
VIR-2218	X				X				X			
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X	X	X	X	X

	W36	W37	W38	W39	W40	W41	W42	W43	W44	W45	W46	W47
VIR-2218	X				X				X			
PEG-IFNα[a, b]	X	X	X	X	X	X	X	X				

	W48
VIR-2218	X
PEG-IFNα[a, b]	-

a. Subjects are required to return to clinic for D1, W1, and W2 PEG-IFNα administrations/to receive self-administration training. If the subject has been trained for self-administration, all other scheduled PEG-IFNα administrations may be self-administered. Subjects may return to clinic for PEG-IFNα administration after the week W2 visit if unable or unwilling to self-administer injections.

b. Subjects who discontinue from PEG-IFNα treatment due to PEG-IFNα-related adverse reactions may continue to receive treatment with VIR-2218. These subjects should follow the schedule of study visits per the schedule of assessments in Appendix 13.

c. Subjects may discontinue the VIR-2218 and weekly PEG-IFNα doses starting at Week 24 as per criteria outlined in Section 4.7.

APPENDIX 16. SCHEDULE OF ASSESSMENTS FOR NRTI DISCONTINUATION MONITORING PERIOD

Study Stage	**NRTI Discontinuation Monitoring Period[b, c]**									
Timepoint[a]		**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**
Visit Timepoint ±Visit Window	**D1**	**D15 ±2**	**D29 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±2**	**D141 ±7**	**D169 ±7**	**D253 ±7**	**D337 ±7**
Laboratory Assessments[d]	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical exam	X	X	X	X	X	X	X	X	X	X
Blood sample for quantitative HBsAg	X	X	X	X	X	X	X	X	X	X
Blood sample for anti-HBs qualitative and quantitative	X	X	X	X	X	X	X	X	X	X
Blood sample for HBV DNA quantitation	X	X	X	X	X	X	X	X	X	X
Blood sample for HBeAg qualitative	X	X	X	X	X	X	X	X	X	X
Blood sample for anti-HBe	X	X	X	X	X	X	X	X	X	X
CCI [redacted]	CCI [redacted]									
CCI [redacted]	CCI [redacted]									
Resistance surveillance[g]	X									
Prior and Concomitant Medications	X									

Study Stage	NRTI Discontinuation Monitoring Period[b, c]									
Timepoint[a]		**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**
Visit Timepoint ±Visit Window	**D1**	**D15 ±2**	**D29 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±2**	**D141 ±7**	**D169 ±7**	**D253 ±7**	**D337 ±7**
Exercise Assessment	X									
NRTI retreatment surveillance[h]	X									
Review/Record AEs	X									
ECI surveillance[i]	X									
Alcohol intake assessment	X									

[a] All timepoints are relative to the day of NRTI discontinuation (D1) which is the first day subjects do not take their NRTI therapy
[b] All subjects who discontinue NRTI therapy will be followed through 48 weeks, even if NRTI retreatment occurs
[c] NRTI retreatment guidelines are provided in Section 4.7.2
[d] Limited to liver function tests and coagulation parameters
CCI [redacted]
CCI [redacted]
[g] HBV sequence analysis may be performed if a subject experiences viral breakthrough (including but not limited to HBV DNA breakthrough) or is otherwise indicated. See Section 7.1.2 for more information.
[h] Investigator should monitor subject for NRTI retreatment criteria. See Section 4.7.2 for more information.
[i] Subjects will be monitored for ECI, and additional assessments may be performed if indicated. See Section 8.5 and Appendix 17 for more information.

APPENDIX 17. ADDITIONAL ASSESSMENTS IN PATIENTS WHO EXPERIENCE ALT ELEVATION MEETING ECI CRITERIA

Additional assessments will be performed in patients enrolled in Parts D-F who experience ALT elevations meeting ECI criteria as outlined in Section 8.5. Following the occurrence of elevated ALT meeting ECI criteria per central laboratory, the assessments in Table 8 will be performed one time, as soon as possible, and no later than 2 weeks after the initial ALT value meeting criteria for a laboratory ECI.

Criteria for individual patient discontinuation from further dosing and PEG-IFNα dose modification or discontinuation are described in Section 4.8.3 and 4.8.4, respectively.

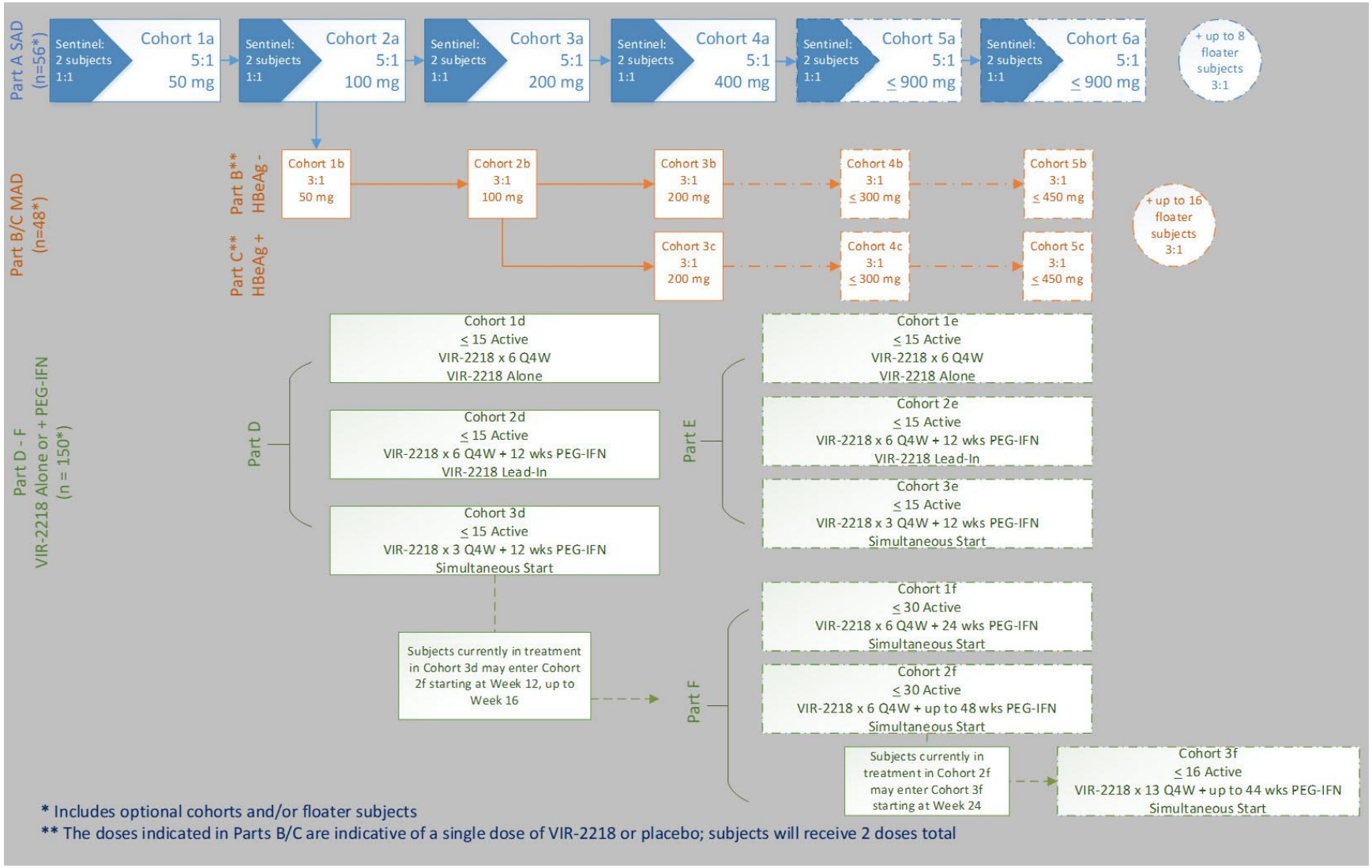
Table 8: Assessments in Patients Who Experience ALT Elevation Meeting ECI Criteria

Hematology	
• Complete blood count with differential	
Chemistry	
• Albumin	• Creatinine clearance
• Blood urea nitrogen (BUN)	• Gamma glutamyl transferase (GGT)
• Calcium	• Glucose
• Carbon dioxide/bicarbonate	• Lactate dehydrogenase (LDH)
• Chloride	• Potassium
• Creatine kinase	• Sodium
• Creatinine	• Uric acid
• Lipase	
Liver Function Tests	
• Alkaline phosphatase (ALP)	• Aspartate aminotransferase (AST)
• Alanine aminotransferase (ALT)	• Bilirubin (total and direct)
Coagulation Parameters	
• International normalized ratio (INR) time	• Prothrombin
Extended Hepatic Panel	
• Quantitative HBsAg, quantitative HBV DNA	
• Qualitative and quantitative HBeAg	• Aldolase
• HAV antibody IgM	• Anti-nuclear antibodies
• HCV antibody	• Anti-smooth muscle antibodies
• HCV RNA PCR – qualitative and quantitative	• Anti-LKM1 antibody

Hematology	
• HDV antibody or RNA	• Anti-mitochondrial antibodies
• HEV antibody IgM	• Anti-SLA antibodies
• Epstein-Barr Virus antibodies, IgM and IgG	• Ferritin
• Cytomegalovirus antibodies, IgM and IgG	• Ceruloplasmin
• IgG	• IgM
• Phosphatidylethanol	• Urinary ethylglucuronide
Imaging	
• Abdominal ultrasound; including Doppler flow (if available); CT or MRI acceptable in place of ultrasound if clinically indicated	
Focused Medical History	
• Use of any potentially hepatotoxic concomitant medications, including over the counter medications and herbal remedies	• Alcohol consumption and drugs of abuse
• Exposure to other potentially hepatotoxic agents including any work-related exposures (eg. solvents, pesticides, etc.)	• Exercise history

Abbreviations: CT=computed tomography; HAV=hepatitis A virus; HBsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HEV=hepatitis E virus; IgG=immunoglobulin G antibody; IgM=immunoglobulin M antibody; LKM1=liver/kidney microsome-1 antibody; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PT=prothrombin time; RNA=ribonucleic acid; SLA=soluble liver antigen.
Note: The full panel of assessments should only be performed once; individual assessments may be repeated per investigator discretion, as needed.

APPENDIX 18. COHORT DOSING SCHEDULE



APPENDIX 19. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION FOR HEART FAILURE

Stage	Description
I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of heart failure.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of heart failure.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of heart failure.
IV	Unable to carry on any physical activity without symptoms of heart failure, or symptoms of heart failure at rest.

Adapted from: Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70(6):776-803.

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Approval Task	PPD [redacted]

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