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

NCT Number: NCT05612581

Document Date: 14 December 2023, Version 1.0

PREVAIL PLATFORM CLINICAL STUDY

SUB-PROTOCOL A (STRIVE)
PROTOCOL AMENDMENT 3

This sub-protocol should be read and conducted in conjunction with the PREVAIL Master Protocol

Study Title	A Phase 2 Study Evaluating the Efficacy and Safety of VIR-3434 and/or VIR-2218 Containing Regimens in Participants with Chronic Hepatitis B Infection (STRIVE)
Brief Title	A Phase 2 Study to Evaluate VIR-3434 and/or VIR-2218 Containing Regimens for Treatment of Chronic Hepatitis B Infection
Master Study Number	VIR-MHB1-V200
Sub-Study Number	VIR-SHB1-V201
Compounds	VIR-3434 (tobevibart), VIR-2218 (elebsiran), tenofovir disoproxil fumarate (TDF) and pegylated interferon alfa-2a (PEG-IFNα)
Indication	Chronic Hepatitis B Infection
Study Phase	2
Study Sponsor	Vir Biotechnology, Inc. 1800 Owens Street, Suite 900 San Francisco, CA 94158, USA
Regulatory Agency Identifying Numbers	IND: TBD EudraCT: 2022-002014-16 (under Master Protocol) NCT: 05612581 (under Master Protocol)
Protocol Date	14 December 2023, Version 1.0

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

INVESTIGATOR SIGNATURE PAGE

VIR BIOTECHNOLOGY, INC

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STUDY ACKNOWLEDGMENT

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

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

PPD	
Printed Name	**Signature and Date**

INVESTIGATOR STATEMENT

I have read the Master Protocol, current sub-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

PROTOCOL AMENDMENT 3 (14 DECEMBER 2023) SUMMARY OF CHANGES TABLE

Table 1: Protocol Document History

Document	Date
Amendment 3	14 December 2023
Amendment 2	11 October 2022
Amendment 1	16 May 2022
Original Protocol	01 April 2022

Summaries of changes for Amendment 1 are provided in Section 10.5.

Table 2: Protocol Amendment 3 Summary of Changes

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis (Number of Participants), 4.1.1. Number of Participants, 9.2. Sample Size Determination, 9.5. Interim Analysis	Clarified that floater participants may be added at any time at Sponsor's discretion. As a result of this clarification, language in Section 9.5 (Interim Analysis) was updated for consistency	To clarify when floater participants can be added during the study
1.1. Synopsis (Intervention Groups and Duration), 4.1.3. NRTI Discontinuation	Changed one of the NRTI discontinuation criteria from participants discontinue NRTI after EOT (in addition to other criteria) if HBsAg < 100 IU/mL and ≥1 log10 IU/mL reduction from baseline HBsAg to participants discontinue NRTI after EOT (in addition to other criteria) if HBsAg < LLOQ	Based on emerging literature, requiring HBsAg levels < LLOQ to discontinue NRTI therapy is a conservative threshold to lower the risk of viral relapse after NRTI discontinuation (Pavlovic 2023).
4.1.4. NRTI Retreatment	Clarified that confirmatory test for HBV DNA > 20,000 IU/mL should occur no later than 7 calendar days after initial result is received. Also clarified that central laboratory testing is preferred, but local laboratory results will be accepted if it is not feasible to collect central laboratory results in time	To ensure re-testing is done promptly for safety management of participants who may be recommended to restart their NRTI therapy

Section # and Name	Description of Change	Brief Rationale
Section 7.2. Discontinuation of Study Intervention(s)	Added the following additional treatment discontinuation criteria: Serum ALT or aspartate aminotransferase (AST) > 3 × ULN with: • serum albumin <3.0g/dL or • ascites, hepatic encephalopathy, or liver-related symptoms (eg, severe fatigue, nausea, vomiting, right upper quadrant pain in the absence of an alternative medical explanation) Also added study intervention may be discontinued in the occurrence of a condition that in the opinion of the Investigator significantly jeopardizes the wellbeing and safety of the participant. Investigator must promptly inform the Sponsor Medical Monitor if any such condition arises.	This change was made to include additional criteria for treatment discontinuation and clarification for when the Investigator may stop study intervention. This change was previously made in Addendum France-1 of VIR-SHB1-V201 (STRIVE) Amendment 2, Version 3.0 in response to a request made by ANSM of France and is being added to VIR-SHB1-V201 (STRIVE) Amendment 3 to harmonize into a single global protocol.
8.8. Pharmacokinetic Assessments	Clarified that PK assessments are exploratory and may or may not be analyzed, and specific assays used for these assessments may be changed at the Sponsor's discretion based on emerging data	To allow for appropriate analyses of exploratory PK assessments based on emerging data
10.2. Appendix 2: Clinical Laboratory Tests, 10.7. Appendix 7: Additional Assessments in Participants That Experience ALT Elevation Meeting ECI Criteria	Added serum phosphate to the protocol-required safety laboratory tests	To align with renal monitoring guidance in the Viread® SmPC. This change was previously made in Addendum-1 and Addendum France-1 of VIR-SHB1-V201 (STRIVE) Amendment 2, Version 3.0 and is being added to VIR-SHB1-V201 (STRIVE) Amendment 3 to harmonize into a single global protocol.

Section # and Name	Description of Change	Brief Rationale
10.2. Appendix 2: Clinical Laboratory Tests	Added footnote to clarify creatinine clearance calculation for study visits where weight is not measured (creatinine clearance will be calculated using the value measured from the most recent study visit)	To provide further guidance for creatinine clearance calculation. This clarification was described in Protocol Administrative Letter 1 for VIR-SHBV1-V201 Amendment 2, Version 3.0 and is being added to VIR-SHB1-V201 (STRIVE) Amendment 3 to harmonize into a single global protocol.
Entire document	Other administrative, formatting, and other minor changes	These changes were made to clarify, ensure consistency, provide up-to-date information, or rectify typographical errors.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Study Title

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

Brief Title

A Phase 2 Study to Evaluate VIR-3434 and/or VIR-2218 Containing Regimens for Treatment of Chronic Hepatitis B Infection

Background and Rationale

Chronic hepatitis B virus (HBV) infection remains an important global public health problem with significant morbidity and mortality (Trepo 2014). Chronic HBV infection is a dynamic process characterized by the interplay of viral replication and the host immune response. Patients can be divided into different stages of the disease based on the levels of Hepatitis B e antigen (HBeAg), HBV DNA, alanine aminotransferase (ALT), and liver inflammation (EASL 2017; Sarin 2015; Terrault 2018).

Among non-cirrhotic patients with chronic HBV infection, treatment is only recommended for the subset that have high levels of viremia (HBV DNA) and elevated levels of alanine aminotransferase (ALT) (EASL 2017; Sarin 2015; Terrault 2018). Current treatment options for chronic HBV infection are limited to nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and peginterferon-alfa-2a (PEG-IFNα) (Liang 2015). Long-term therapy NRTI therapy can suppress HBV DNA but does not eliminate the cccDNA or integrated DNA. In contrast to NRTIs, PEG-IFNα can induce long-term viral control, but only in a small percentage of patients (< 10%) and after 48 weeks of therapy (Konerman 2016). Therefore, there exists an unmet need for better treatment options that can achieve functional cure.

VIR-3434 is a monoclonal antibody targeting Hepatitis B surface antigen (HBsAg) with multiple potential mechanisms of action including strong neutralizing activity and enhanced immunologic activity due to Fc domain engineering. VIR-2218 is a small interfering RNA (siRNA) that is associated with substantial reductions in HBsAg in patients with chronic HBV infection. VIR-3434, either alone, in combination with VIR-2218, or in combination with both VIR-2218 and PEG-IFNα, has the potential to achieve a functional cure of chronic HBV infection.

Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of VIR-3434 and tenofovir disoproxil fumarate (TDF) with or without VIR-2218, or VIR-2218 and PEG-IFNα	• Proportion of participants achieving suppression of HBV DNA (< LLOQ [lower limit of quantitation]) with HBsAg loss (< 0.05 IU/mL) at the end of treatment[a]
Secondary	
<u>In addition to the Master Protocol,</u> • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBsAg • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBV DNA • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBeAg and anti-HBe • To assess the immunogenicity of VIR-3434 • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on ALT levels	<u>In addition to the Master Protocol secondary endpoints 1-8,</u> 9. Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) after discontinuation of all treatment a. at 24 weeks b. at the F48 Follow-Up visit 10. Proportion of participants achieving HBsAg loss (< 0.05 IU/mL) a. at end of treatment[a] b. at 24 weeks post-end of treatment[a] 11. Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) after discontinuation of all treatment a. at 24 weeks b. at the F48 Follow-Up visit 12. For HBeAg-positive participants: proportion of participants with HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion 13. Incidence and titers of anti-drug antibodies (ADA; if applicable) to VIR-3434 14. Mean change in serum HBsAg level from baseline across timepoints in the study 15. Proportion of participants achieving HBV DNA < LLOQ across timepoints in the study 16. Proportion of participants achieving ALT ≤ ULN across timepoints in the study

[a] End of treatment as defined in SOA

Overall Study Design

This sub-protocol (STRIVE) should be read and conducted in conjunction with the PREVAIL Master Protocol. The Master Protocol provides a study framework: study outline, populations, common objectives and endpoints, common inclusion and exclusion criteria, statistical methodology, assessments and planned analyses for all sub-protocols. This sub-protocol is a Phase 2, multi-center, open-label study designed to evaluate the safety and efficacy of regimens containing VIR-3434, VIR-2218, PEG-IFNα, and an NRTI in non-cirrhotic adult participants with chronic HBV infection that have not received prior NRTI or PEG-IFNα treatment.

Brief Summary

This sub-protocol is intended to evaluate combinations of VIR-3434 and NRTI (TDF) with or without VIR-2218, and VIR-3434 and TDF in combination with both VIR-2218 and PEG-IFNα in participants with chronic HBV infection. Study populations II and III as defined in the Master Protocol (and table) will be included in this sub-protocol. Participants that have not received any prior NRTI or PEG-IFNα treatment will be eligible for enrollment into this study.

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

Number of Participants

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

Intervention Groups and Duration

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

[a] The dose of VIR-3434 will be determined before participants are enrolled in the cohort
[b] Tenofovir disoproxil fumarate dose (TDF) will be 300 mg as approved by the FDA. Supply outside the United States may be Tenofovir disoproxil (TD) 245 mg.
[c] The minimum number of doses received by participant. Participants will continue receiving additional doses of TDF until they qualify for NRTI discontinuation (Section 4.1.3).
[d] The dosing regimen will be finalized before participants are enrolled in the cohort. See Section 4.1.2.2.

The total duration in the study for participants will be up to 100 weeks in Cohorts 1a, 2a and Cohort 4a, 92-96 weeks for Cohort 3a and 104 weeks for Cohort 5a. This includes a Screening Period (up to 56 days or 8 weeks), Treatment Period (44 weeks for Cohorts 1a and 2a, 36 or 40 weeks for Cohort 3a, 44 weeks for Cohort 4a, and 48 weeks for Cohort 5a) and a Follow-Up-Period (up to 48 weeks) for all cohorts.

Participants will discontinue NRTI at F1 or at F12 Follow-Up visits based on most recent data available if they meet all of the following criteria (Section 4.1.3):

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

Participants that meet the criteria to discontinue NRTI treatment will continue per the Follow-Up Period Schedule of Activities (SOA).

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

Liver Flare Adjudication Committee (LFAC)

The Liver Flare Adjudication Committee (LFAC) will provide hepatic safety oversight by performing periodic reviews of data pertaining to participants who meet certain prespecified criteria for alanine transaminase elevations (Section 8.7.6). 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 (Section 10.1.6.1).

1.2. Study Schema

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

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

The SOAs for Cohorts 1a/2a, 3a, 4a, and 5a are provided in Table 8, Table 9, Table 10 and Table 11. Table 12 shows the SOA for the Follow-Up Period.

Figure 1: Study Schema

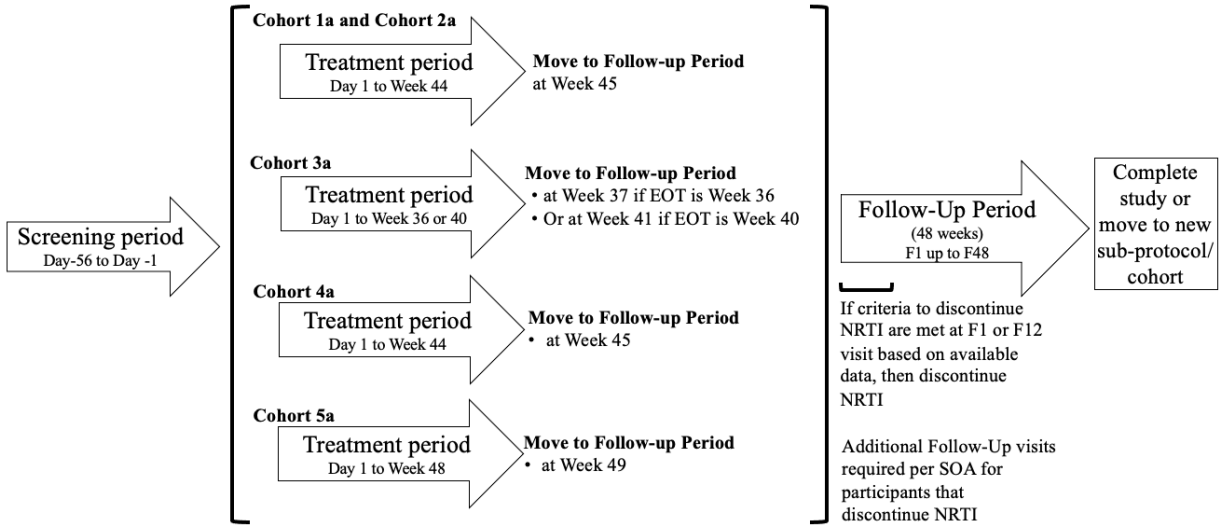
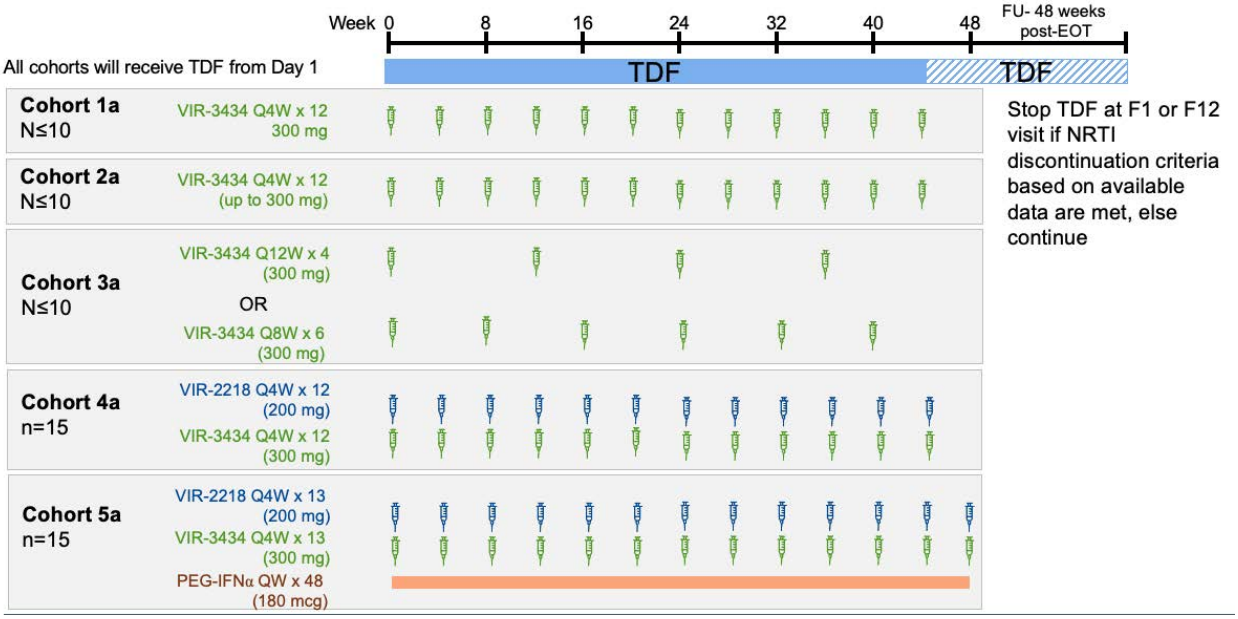


Figure 2: Dosing Scheme by Cohort



FU = Follow-Up; EOT = end of treatment; QW = every week; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; PEG-IFNα = pegylated interferon alfa-2a; TDF = Tenofovir disoproxil fumarate (or Tenofovir disoproxil where applicable); F1 = Follow Up Visit 1; F12 = Follow-Up visit 12
See Section 4.1 for more details.

1.3. Schedule of Activities

Schedules of activities are provided in Section 10.9.

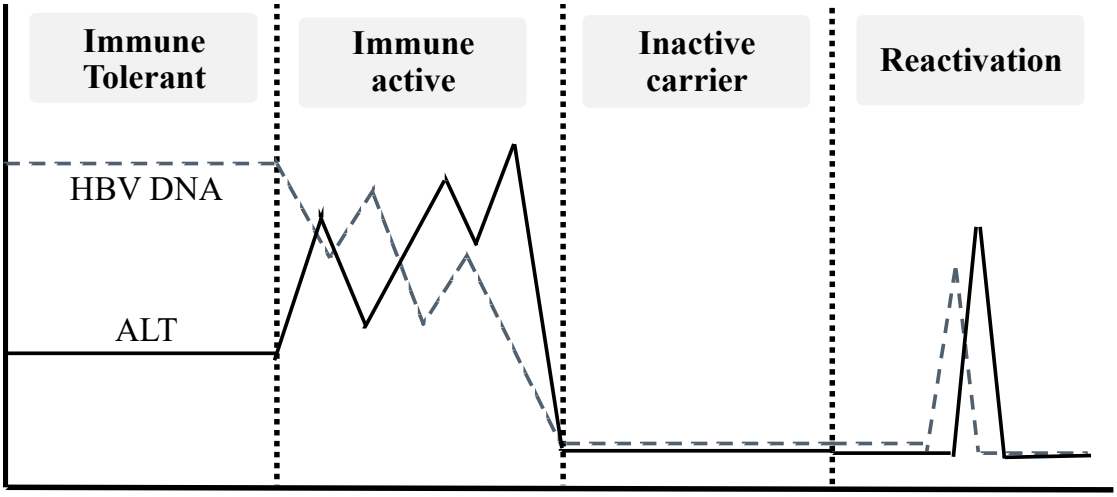
2. INTRODUCTION

This sub-protocol should be read and conducted in conjunction with the PREVAIL Master Protocol (VIR-MHB1-V200).

2.1. Background

Chronic HBV infection remains an important global public health problem with significant morbidity and mortality (Trepo 2014). Chronic HBV infection is a dynamic process and depends on the relationship between viral replication and host immune responses. Patients may oscillate between different phases of the disease, and serial monitoring of biomarkers such as HBV DNA, alanine aminotransferase (ALT) and HBV antigens helps determine the natural history of the disease (Figure 3). Following infection, the HBV virus may replicate as a stealth virus without a host immune response. After years of viral replication (high HBV DNA), the immune system mounts a response against infected hepatocytes leading to elevated ALT in Hepatitis B e antigen (HBeAg)-positive patients. During this stage of the disease, patients are also characterized by moderate to severe inflammation in the liver and accelerated progression of fibrosis. Patients infected perinatally may reach this stage of chronic HBV infection following 10-30 years after infection, whereas those infected as adults or in childhood progress faster or may even skip this stage altogether. The outcomes are also variable for this population. Among patients that are HBeAg-positive, some patients become HBeAg-negative rapidly, and others take much longer with or without treatment to become HBeAg-negative and positive for anti-HBe (EASL 2017; Fattovich 2008; Terrault 2018; Wang 2021).

Figure 3: Stages of Chronic HBV Infection



Patients with elevated ALT who are HBeAg positive with HBV DNA > 20,000 IU/mL or HBeAg negative with HBV DNA > 2,000 IU/mL are eligible for treatment with nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and/or peginterferon-alfa-2a (PEG-IFNα) (Liang 2015). NRTIs can suppress HBV DNA with long-term therapy but do not eliminate cccDNA or integrated DNA. In contrast to NRTIs, PEG-IFNα can induce long-term viral control, but only in a small percentage of patients (< 10%) and after 48 weeks of therapy (Konerman 2016). Therefore, there exists an unmet need for better treatment options that can achieve functional cure.

2.2. Study Rationale

VIR-3434 is a monoclonal antibody (mAb) targeting HBsAg with multiple potential mechanisms of action, including strong neutralizing activity and enhanced immunologic activity due to Fc domain engineering. VIR-2218 is a siRNA targeting all HBV RNA transcripts that is associated with substantial reductions in HBsAg in patients with chronic HBV infection. VIR-3434 and an NRTI (TDF [tenofovir disoproxil fumarate]), in combination with VIR-2218, or in combination with both VIR-2218 and PEG-IFNα, have the potential to achieve a functional cure of chronic HBV infection.

See Section 4.2 for additional scientific rationale for the different investigational regimens in this sub-protocol.

2.3. Benefit/Risk Assessment

Detailed information about the known and potential benefits and risks of VIR-2218 and VIR-3434 may be found in the respective Investigator's Brochures (IBs).

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: VIR-2218		
Injection site reactions (ISRs)	Based on available preliminary clinical data from studies VIR-2218-1001 and VIR-2218-1006, ISRs are a recognized risk of subcutaneous (SC) administered siRNA therapies and are typically transient.	Participants are monitored for local tolerability after injection and all AEs will be collected to reflect any ISRs that may be reported. Routine safety monitoring and reporting procedures are in place to provide safety overview.
Immunogenicity: Immunogenicity is a potential risk associated with siRNA molecules. In general, the development of anti-drug antibodies (ADA) may impact safety, efficacy, or both.	Immunogenicity data from Parts B/C of the VIR-2218-1001 study indicated a low immunogenicity risk based on all confirmed subjects yielding negative titers.	While there were no apparent clinical consequences related to the presence of VIR-2218 ADA, immunogenicity will continue to be assessed in Parts D/F of study VIR-2218-1001.
Liver function test abnormalities: VIR-2218 is targeted for delivery to the liver, and transient transaminase elevations have been observed with SC administration with other GalNAc-conjugated siRNA therapeutics.	Based on available preliminary clinical data from studies VIR-2218-1001 and VIR-2218-1006, minor ALT elevations (Grade 1 or Grade 2) have been observed in participants receiving VIR-2218 monotherapy. However, none of the participants met Hy's law and the majority resolved the ALT elevations by the end of treatment.	Monitoring of liver function is recommended. In addition, ALT flares in chronic HBV patients may be a sign of restoration of HBV-targeted immunity, therefore close monitoring of liver function and HBV-viral parameters may be warranted. Low probability: Events of Clinical Interest (ECI) defined as ALT elevations ≥ 5X and > 2X baseline must be reported within 5 business days of Investigator notification. The Sponsor will monitor ECI and an independent Liver Flare Adjudication Committee (LFAC) reviews the liver safety and assesses etiology to recommend changes in study conduct.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: VIR-3434		
Probability of significant non-target mediated toxicity: Hypersensitivity reactions (including infusion related reactions [IRRs]/injection site reactions [ISRs], and anaphylaxis): Hypersensitivity reactions (including IRRs/ISRs and anaphylaxis), which may be severe or life-threatening, are a potential risk associated with the mAb class. The distinct risk of developing such conditions after dosing with VIR-3434 is unknown.	Two clinical studies with VIR-3434 are ongoing. In VIR-3434-1002, Parts A and B/C, VIR-3434 has been generally well tolerated in healthy subjects and in subjects with chronic HBV infection. ISRs occurred in 20% of subjects in Part A and 10.7% in Part B/C; all ISRs were Grade 1 or 2, considered related to VIR-3434, and resolved without sequelae. In VIR-2218-1006 (VIR-2218 + VIR-3434) most AEs were Grade 1 or 2 in severity, and most were considered not related to VIR-2218 and/or VIR-3434. No ISRs were considered related to VIR-3434.	Low probability: participants will be closely monitored to evaluate any patterns of non-target mediated toxicity. Participants are monitored for local tolerability after injection and all AEs will be collected to reflect any hypersensitivity reactions that may be reported. Routine safety monitoring and reporting procedures are in place to provide safety overview.
Immunogenicity: Immunogenicity is a potential risk associated with the mAb class. VIR-3434 is a human immunoglobulin G (IgG) mAb; therefore, the development of ADA may impact its safety, efficacy, or both.	Immunogenicity data for VIR-3434 is not available at this time. An appropriate risk-based bioanalytical strategy is being used to assess immunogenicity in the study.	Immunogenicity data will be assessed in relation to associated VIR-3434 PK and clinical safety measures.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential target-mediated risks: immune complex disease and hepatotoxicity due to the elimination of infected hepatocytes via cytotoxic T-cells induced via a vaccinal effect. As no or only low levels of HBsAg is detected on the surface of infected hepatocytes, antibody-dependent cellular cytotoxicity (ADCC)/ antibody-dependent cellular phagocytosis (ADCP)-mediated elimination of hepatocytes is possible but unlikely to occur.	In Part B/C of study VIR-3434-1002, single doses up to 300 mg were well tolerated. No clinically significant changes in laboratory parameters were observed, and no participant developed clinical or laboratory evidence of immune complex disease. These preliminary results are consistent with prior clinical experience supporting the safety of anti-HBsAg monoclonal antibodies. HBV-AB^{XTL}, a mixture of two anti-HBsAg monoclonal antibodies, was evaluated at doses up to 80 mg administered weekly for 4 doses in patients with baseline HBsAg ranging from approximately 20 to 80,000 IU/mL, and no signs of immune complex disease or hepatotoxicity were observed (Galun 2002). Additionally, several studies have evaluated the use of hepatitis B immune globulin (HBIG) in patients with chronic HBV infection and reported favorable safety and tolerability (Perrillo 2013; Reed 1973; Tsuge 2016). In the largest study, 64 patients with baseline HBsAg ranging from 0.09 to 11,214 IU/mL (mean 1,965 IU/mL) received HBIG therapy for multiple weeks, and no clinical manifestations of immune complex disease or other safety concerns were observed (Perrillo 2013).	Low probability: participants will be closely monitored to evaluate any patterns of non-target mediated toxicity

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: VIR-3434 + VIR-2218 + TDF +/- PEG-IFNα		
Hepatotoxicity	Combination of these study interventions may result in hepatotoxicity (eg, elevated ALT). Based on available preliminary clinical data from VIR-2218-1001, VIR-2218-1006 and VIR-3434-1002, VIR-2218 or VIR-3434 monotherapy in virally suppressed participants have resulted in minor ALT elevations (Grade 1 or Grade 2). Combination of VIR-2218 with PEG-IFNα resulted in up to Grade 3 elevations in ALT. However, none of the participants met Hy's law and majority have resolved the ALT elevations after the end of treatment.	Addition of NRTI (TDF) to the treatment regimen to suppress viral replication Excluding patients with significant fibrosis or cirrhosis, significant chronic liver disease (except HBV infection), history of hepatic decompensation. Routine safety monitoring and reporting procedures ECI defined as ALT elevations ≥ 5X and > 2X baseline must be reported within 5 business days of Investigator notification. Sponsor monitors ECI and an independent LFAC reviews the liver safety and assesses etiology to recommend changes in study conduct. Stopping criteria for study interventions have been provided in Section 7.1
Injection site reactions	Combination of VIR-3434 +/- VIR-2218 +/- PEG-IFNα may result in injection site reactions (ISRs) such as injection site pain, bruising, itching, rash. In the ongoing VIR-3434-1002, VIR-2218-1001 and VIR-2218-1006 studies, these interventions alone on or in combination have resulted in ISRs Grade 1 or 2 in severity that usually resolve within a few days to weeks. There is no potential cumulative risk for the combination intervention of VIR-3434 + VIR-2218.	Participants are monitored for local tolerability after injection and all AEs will be collected to reflect any ISRs that may be reported. Routine safety monitoring and reporting procedures are in place to provide safety overview.

2.3.2. Benefit Assessment

Single doses of VIR-2218 up to 900 mg in healthy volunteers and up to 6 doses of up to 200 mg administered every 4 weeks (ie, the highest dose tested) were well tolerated and exhibited safety profiles supportive of continued clinical development (VIR-2218 Investigator's Brochure) in participants with chronic HBV infection. Regardless of HBeAg status, VIR-2218 was associated with a -1.96 log10 IU/mL mean decrease in HBsAg after 6 every 4-week (Q4W) doses (Lim 2022).

VIR-3434 has the potential to further reduce HBsAg, inhibit infection of new hepatocytes via entry inhibition, eliminate infected hepatocytes, and stimulate an adaptive immune response against HBV. Lower HBsAg levels may be achieved by lead-in or concomitant administration of VIR-2218 and has the potential to augment the effects of VIR-3434 and achieve a functional cure of chronic HBV infection. Additionally, multiple-dose regimens of VIR-3434 may produce rapid and sustained reductions of HBsAg in the absence of VIR-2218 and potentially achieve functional cure of chronic HBV infection as monotherapy.

PEG-IFNα 180 µg administered weekly for 48-52 weeks results in HBsAg loss in approximately ≤ 10% of patients overall (Konerman 2016). This duration of therapy is associated with poor tolerability and safety concerns that resulted in treatment discontinuation in approximately 5% of patients in Phase 3 clinical trials for chronic HBV infection (PEGASYS® Prescribing Information). Shorter durations of PEG-IFNα therapy may ameliorate these effects while still providing antiviral and immunomodulatory activity, particularly when combined with VIR-2218 and VIR-3434.

In the ongoing VIR-2218-1001 study, multiple regimens of VIR-2218 and PEG-IFNα combination therapy are being evaluated in virally suppressed (on NRTIs) participants with chronic HBV infection. Preliminary safety and tolerability data suggest that the addition of VIR-2218 does not result in additional risks beyond those associated with PEG-IFNα alone (Yuen 2021). Additionally, substantial reductions in HBsAg were observed, but few participants achieved HBsAg loss. In this study, it is hypothesized that the addition of VIR-3434 to VIR-2218 and PEG-IFNα will lead to higher rates of HBsAg loss and functional cure.

2.3.3. Overall Benefit Risk Conclusion

This study will provide information on the safety, tolerability, and efficacy of VIR-3434 and NRTI (TDF) in combination with VIR-2218 and/or PEG-IFNα. The study is designed to test the hypothesis that regimens containing VIR-3434, TDF and/or VIR-2218, and/or PEG-IFNα may lead to a functional cure of chronic HBV infection by reducing HBsAg and stimulating a host immune response. Compared to the current standard of care, the regimens in this study offer the potential benefits of finite duration, pangenotypic activity, and the potential to achieve functional cure, which may be associated with a reduction in serious HBV-associated sequelae such as cirrhosis, liver failure, hepatocellular carcinoma, or death.

The mechanistic rationale, together with available clinical data, supports a favorable risk-benefit profile for evaluation of regimens containing VIR-3434 and TDF with or without VIR-2218, and with or without VIR-2218 and PEG-IFNα in patients with chronic HBV infection.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα	• Proportion of participants achieving suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at the end of treatment[a]
Secondary	
<u>In addition to the Master Protocol,</u> • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBsAg • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBV DNA • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBeAg and anti-HBe • To assess the immunogenicity of VIR-3434 • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on ALT levels	<u>In addition to the Master Protocol secondary endpoints 1-8,</u> 9. Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) after discontinuation of all treatment a. at 24 weeks b. at the F48 Follow-Up visit 10. Proportion of participants achieving HBsAg loss (< 0.05 IU/mL) a. at end of treatment[a] b. at 24 weeks post-end of treatment[a] 11. Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) after discontinuation of all treatment a. at 24 weeks b. at the F48 Follow-Up visit 12. For HBeAg-positive participants: proportion of participants with HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion 13. Incidence and titers of ADA (if applicable) to VIR-3434 14. Mean change in serum HBsAg level from baseline across timepoints in the study 15. Proportion of participants achieving HBV DNA (< LLOQ) across timepoints in the study 16. Proportion of participants achieving ALT ≤ ULN across timepoints in the study

Objectives	Endpoints
Exploratory	
In addition to the Master Protocol objectives, • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBeAg and anti-HBe • To evaluate proportion of participants meeting criteria for nucleos(t)ide reverse transcriptase inhibitor (NRTI) discontinuation or retreatment • To assess the effect of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα on HBV DNA • To characterize the pharmacokinetics (PK) of VIR-3434 • To characterize the PK of VIR-2218 (for cohorts with VIR-2218) • To assess the immunogenicity of VIR-2218 (for cohorts with VIR-2218) • To assess the effect of duration of treatment of VIR-3434 and TDF with or without VIR-2218, or VIR-2218 and PEG-IFNα • To assess potential virological relapse	In addition to the Master Protocol exploratory endpoints 1-6, 7. For HBeAg-positive participants: time to achieve HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion 8. Proportion of participants meeting criteria for NRTI discontinuation or retreatment in the study 9. HBV DNA levels and change from baseline across timepoints in the study 10. Nadir and maximum change of HBV DNA level from baseline in the study 11. VIR-3434 PK parameters 12. VIR-2218 PK parameters (for cohorts with VIR-2218) 13. Incidence and titers of ADA (if applicable) to VIR-2218 (for cohorts with VIR-2218) 14. Proportion of participants with virological relapse (defined as either (1) an increase of ≥ 1 $\log_{10}$ HBV DNA IU/mL above nadir for at least 2 consecutive visits OR (2) quantifiable HBV DNA of ≥ 1 $\log_{10}$ IU/mL above LLOQ for at least 2 consecutive visits after being < LLOQ)

[a] End of Treatment as defined in SOA

4. STUDY DESIGN

4.1. Overall Study Design

The STRIVE sub-protocol should be read and conducted in conjunction with the PREVAIL Master Protocol. The Master Protocol provides a study framework: study outline, populations, common objectives and endpoints, common inclusion and exclusion criteria, statistical methodology, assessments and planned analyses for all sub-protocols. STRIVE is a Phase 2, multi-center, open-label study designed to evaluate the safety and efficacy of regimens containing VIR-3434, VIR-2218, PEG-IFNα, and NRTI in non-cirrhotic adult participants with chronic HBV infection that have not received prior NRTI or PEG-IFNα treatment. The study is planned to be conducted at multiple clinical investigative sites globally.

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

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

4.1.1. Number of Participants

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

4.1.2. Intervention Groups and Duration

4.1.2.1. Intervention Groups

There are 5 cohorts planned in this sub-protocol (Table 3).

Table 3: Intervention Groups

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

[a] The dose of VIR-3434 will be determined before participants are enrolled in the cohort
[b] Tenofovir disoproxil fumarate dose (TDF) will be 300 mg as approved by the FDA. Supply outside the United States may be Tenofovir disoproxil (TD) 245 mg.
[c] The minimum number of doses received by participant. Participants will continue receiving additional doses of TDF until they qualify for NRTI discontinuation (Section 4.1.3).
[d] The dosing regimen will be finalized before participants are enrolled in the cohort. See Section 4.1.2.2.

4.1.2.2. Cohort Initiation and VIR-3434 Dosing Selection

Cohorts in this study may be enrolled in parallel. Cohorts may be opened, closed, or discontinued at the Sponsor's discretion.

Information regarding cohort initiation will be provided in communications to the study sites. Initially, Cohorts 1a, 4a and 5a will be opened for enrollment. For cohorts in which a VIR-3434 range of dose or duration is specified in the protocol in lieu of an exact dose or duration, the Sponsor will provide communication to study sites regarding the VIR-3434 dose or duration prior to initiation of the cohort based on safety, PK, and efficacy data generated in the ongoing clinical studies, VIR-2218-1006 and VIR-3434-1002 (see Section 4.3.1 for dose rationale).

The dose level for Cohort 2a and the frequency of dosing for Cohort 3a will be decided based on the efficacy and safety data obtained from Cohort 1a in the current sub-protocol and other VIR-3434 monotherapy cohort(s) in the VIR-2218-1006 study. As more data (eg, PK, efficacy, safety) are available from ongoing studies in which VIR-3434 is dosed every 4 weeks, an alternative dosing regimen (every 8 week or every 12 weeks) may be explored in Cohort 3a.

4.1.2.3. Duration

The total duration in the study for participants will be up to 100 weeks in Cohorts 1a, 2a, and Cohort 4a, 92-96 weeks for Cohort 3a, and 104 weeks for Cohort 5a. This includes a Screening Period (up to 56 days or 8 weeks), Treatment Period (44 weeks for Cohorts 1a and 2a, 36 or 40 weeks for Cohort 3a, 44 weeks for Cohort 4a, and 48 weeks for Cohort 5a) and a Follow-Up-Period (up to 48 weeks) for all cohorts.

4.1.2.3.1. Screening Period

The Screening Period for all participants will be up to 56 days (8 weeks).

4.1.2.3.2. Treatment Period

The Treatment Period will be 44 weeks for Cohorts 1a and 2a, 36 or 40 weeks for Cohort 3a, 44 weeks for Cohort 4a, and 48 weeks for Cohort 5a.

4.1.2.3.3. Follow-Up Period

Once participants complete the Treatment Period per their respective cohort, they will enter the Follow-Up Period. The maximum duration of the Follow-Up Period is 48 weeks after the last dose of the study intervention(s). Participants will discontinue the NRTI at the F1 or F12 visit in the Follow-Up Period if they meet the criteria to discontinue NRTI (Section 4.1.3) based on the data available. Additional study visits are required for participants that discontinue NRTI in the Follow-Up Period as indicated in the SOA (see Table 12). Participants that discontinue NRTI at F1 visit will be required to return to the site for additional visits at F2, F6, F10, F28, F32, F40 and F44. Participants that discontinue NRTI at F12 visit will be required to return to the site for additional visits F14, F18, F22, F28, F32, F40 and F44.

4.1.3. NRTI Discontinuation

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

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

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

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

4.1.4. NRTI Retreatment

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

- HBV DNA increase ≥ 2 $\log_{10}$ IU/mL within a 2-week period
- HBV DNA > 100,000 IU/mL at any Follow-Up Period visit (regardless of other biochemical parameters or ALT values)
- Confirmed increase of HBV DNA > 20,000 IU/mL (ie, at 2 consecutive collections, regardless of other biochemical parameters or ALT values)
  - Note: The repeat HBV DNA test should be performed as soon as possible and no later than 7 calendar days after the initial result is received. Central laboratory testing is preferred, but local laboratory results will be accepted if it is not feasible to collect central laboratory results in time.
- HBV DNA > 2,000 IU/mL concurrent with any of the following criteria at the same visit:
  - Confirmed total bilirubin > 2x ULN and ALT > ULN
  - Any sign of hepatic decompensation (including, but not limited to, confirmed increase in prothrombin time [PT] ≥ 2 or international normalized ratio [INR] ≥ 0.5 from baseline, jaundice, ascites, encephalopathy, etc.)
  - ALT > 10x ULN
  - ALT > 2x ULN persisting for ≥ 12 consecutive weeks
  - ALT > 5x ULN persisting for ≥ 4 consecutive weeks
- Confirmed HBeAg seroreversion (ie, HBeAg positive after being HBeAg negative at NRTI discontinuation)
- Any other clinically significant event(s) warranting initiation of NRTI therapy in the opinion of the investigator after discussion with Sponsor

Participants who are retreated with NRTI therapy should continue to be followed per the SOA for the Follow-Up Period (Table 12) through the Week 48 visit. Participants with HBV DNA increase ≥ 2 $\log_{10}$ IU/mL within a 2-week period should:

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

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

4.1.5. Long-Term and Follow-Up Care

Once a participant has completed the study, long-term care should be determined by the Investigator or primary treating physician based on local clinical guidelines.

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for VIR-3434 for the Treatment of Chronic HBV Infection

VIR-3434 offers a novel strategy for the treatment of chronic HBV infection by neutralizing HBV viral and subviral particles through the targeting of HBsAg and inhibition of viral entry into hepatocytes. Additionally, the Fc region of VIR-3434 is engineered to increase binding affinity to the neonatal Fc receptor (FcRn) and promote the Fc-gamma receptor (FcγR) binding profile towards the activating receptors. These modifications may prolong serum half-life, increase potency, and induce a 'vaccinal' effect (the induction of antigen-specific T cell responses).

The normal serum half-life of IgG is approximately 21 days and regulated by a balance of FcRn-mediated endocytosis and recycling versus endosomal degradation. The well characterized LS modification (M428L and N434S) (Gaudinski 2018; Ko 2014; Zalevsky 2010) was included in the Fc region of VIR-3434 to have sustained activity against HBV. The LS modification increases IgG1 binding to FcRn only at the acidic pH of the endosomal compartment thereby increasing IgG recycling back into circulation. Monoclonal antibodies containing the LS mutation have previously been studied in humans (Gaudinski 2018). For example, VRC01LS, a mAb against the CD4 binding site of the HIV-1 glycoprotein, was deemed safe and well tolerated at doses of 5 to 40 mg/kg IV and 5 mg/kg SC in healthy volunteers. No ADAs were detected out to 48 weeks. VIR-3434 is similarly anticipated to have an extended half-life in humans, resulting in a prolonged duration of exposure. In vitro data for VIR-3434 suggests that the LS mutation is not anticipated to interfere with the additional Fc modifications described below.

The Fc region of VIR-3434 was also engineered to include a modification which modulates binding to human FcγRs by enhancing binding to the activating receptors FcγRIIa and FcγRIIIa, while diminishing binding to the inhibitory receptor FcγRIIb. This Fc modification is designed to enhance ADCP of HBsAg and HBV virions and antigen presentation and, as a result, promote the induction of T cell responses ("vaccinal effect"). The impact of similar modifications on mAb efficacy have been studied in a FcγR-humanized lymphoma mouse model. In this model, anti-CD20 antibodies promoted direct killing of tumor cells via engagement of FcγRIIIa on macrophages and monocytes. In addition, anti-CD20-immune complexes induced CD8+ T cell responses via FcγRIIa-dependent presentation of tumor antigens by dendritic cells. Overall, Fc-engineering of anti-CD20 antibodies to increase FcγRIIa and FcγRIIIa binding (GASDALIE mutation) had superior therapeutic activity (DiLillo 2015). Parallel reduction of binding to the inhibitory FcγRIIb has the potential to further augment this vaccinal effect (DiLillo 2015).

Available data regarding the use of HBsAg-directed antibodies in the treatment of patients with chronic HBV infection suggest that these molecules have the potential to reduce HBsAg levels while maintaining an acceptable safety and tolerability profile. GC1102, a fully human anti-HBsAg mAb in development for chronic HBV infection and prevention of recurrent HBV following liver transplantation, effectively lowered HBsAg by 2-3 $\log_{10}$ IU/mL and was well tolerated in a Phase 1 study in patients with chronic HBV infection, with no evidence of serious sequelae such as immune complex disease (Lee 2018). HBV-AB^{XTL} (HepeX-B), a mixture of two human anti-HBsAg mAbs, was administered to 27 patients with levels of HBsAg ranging from approximately 20 to 85,000 IU/mL. HBV-AB^{XTL} was found to have a favorable safety and

tolerability profile at doses up to 80 mg administered weekly for 4 doses, and no signs of immune complex disease or hepatotoxicity were reported (Galun 2002). Similarly, no adverse events were reported in two studies of chronic HBV patients receiving high doses of HBIG to prevent re-infection following liver transplantation (Reed 1973; Tsuge 2016).

Clinical data from the oncology setting suggests that Fc engineering designed to enhance ADCC/ADCP, and antigen presentation may improve efficacy without compromising safety or tolerability (Im 2018). Margetuximab is a modified version of trastuzumab that is approved by the FDA for the treatment of HER2-positive carcinomas. Margetuximab contains modifications designed to enhance ADCC/ADCP and antigen presentation. Margetuximab was well tolerated in a first-in-human (FIH) Phase 1 study in patients with HER-2 positive carcinomas. Common toxicities were primarily ≤ Grade 2, including no evidence of cardiotoxicity (Bang 2017), which has been observed with the non-Fc modified parent mAb, trastuzumab, in late-stage clinical trials (Ponde 2016; Riccio 2016).

Taken together, these data suggest that mAbs that are Fc engineered to prolong serum half-life and optimize immune effector cell activity have the potential to improve the efficacy of therapeutic mAbs without compromising safety. VIR-3434 is predicted to decrease serum HBsAg, inhibit intrahepatic viral spread, eliminate infected hepatocytes, and stimulate HBV-specific immune responses. Therefore, VIR-3434 has the potential to achieve a functional cure of chronic HBV infection, with or without other agents such as VIR-2218, PEG-IFNα and an NRTI (TDF).

VIR-3434 is being evaluated in VIR-3434-1002 and VIR-2218-1006 studies in participants with chronic HBV. Cohorts 1a, 2a and 3a will assess the contribution of VIR-3434 to combination therapies and its potential to achieve functional cure in the absence of any other investigational agents. To assess patient responses and a potential vaccinal effect from VIR-3434, peripheral blood mononuclear cells (PBMCs) will be collected to perform evaluation of host cellular immune responses (eg, T cells) against HBV antigens. Cohorts 1a and 2a will evaluate 2 dose levels of 12 doses of VIR-3434 given every 4 weeks. Depending on the data observed in the currently ongoing VIR-3434-1002 and VIR-2218-1006 studies, Cohort 3a may be initiated to study the effect of a different dosing regimen of 4-6 doses of VIR-3434, given every 8 or 12 weeks.

4.2.2. Rationale for VIR-2218 for the Treatment of Chronic 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. Removal of viral antigens thought to be tolerogenic may result in the return of a functional immune response directed against HBV, either alone or in combination with other therapies.

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 HBV 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. In this sub-protocol, VIR-2218 will be evaluated in combination regimens containing VIR-3434 and NRTI (TDF) in the presence (Cohort 5a) and absence (Cohort 4a) of PEG-IFNα.

4.2.3. Rationale for VIR-3434 + VIR-2218 + TDF for the Treatment of Chronic HBV Infection

Emerging clinical data suggests that a combination of multiple therapeutic modalities may be necessary to achieve functional cure in the majority of chronic HBV patients (Revill 2019; Zoulim 2015). The massive secretion of HBsAg in chronic HBV infection is thought to contribute to T and B cell dysfunction and to impair the host's ability to clear or control the virus (Bertoletti 2016; Burton 2018; Maini 2016). Therefore, development of functional cure is likely to require a reduction or elimination of HBsAg in conjunction with the induction of host immunity against the infection.

When administered individually, VIR-2218 and VIR-3434 are associated with substantial reductions in HBsAg in patients with chronic HBV infection (Gane 2021; Yuen 2021). The combination of VIR-2218 and VIR-3434 is thus anticipated to result in deep, sustained reductions in HBsAg. This is supported by AAV-HBV mouse model of chronic HBV infection, in which combination treatment with VIR-2218 and VIR-3434 was associated with marked reductions in HBsAg. Additionally, lower HBsAg levels achieved by prior or concomitant treatment with VIR-2218 may augment the effect of VIR-3434.

Reduction in HBsAg may also augment the potential immunologic effects of VIR-3434. The Fc modifications of VIR-3434 are designed to enhance ADCP of HBsAg and HBV virions and antigen presentation and, as a result, promote the induction of T cell responses. Given the putative impact of HBsAg on immune function, these potential effects of VIR-3434 may be enhanced in the setting of lower HBsAg, which can be achieved with lead-in and/or concurrent treatment with VIR-2218. Longer durations of VIR-3434 dosing may also enhance these effects.

In the VIR-2218-1006 study, combination regimens of VIR-2218 (up to 3 doses of 200 mg administered every 4 weeks) and VIR-3434 (up to 12 doses of up to 75 mg administered weekly) have been evaluated in participants with chronic HBV infection who are on NRTIs. No significant safety concerns have been identified to date, and the study is ongoing.

The patient population included in this sub-protocol have a high viral burden and elevated ALT, therefore are indicated for treatment with an NRTI. NRTIs such as TDF help reduce viral replication and thereby reduce the HBV DNA levels. Therefore, they are included as part of all regimens in this sub-protocol in addition to VIR-3434.

Because the optimal timing and duration of VIR-3434 and TDF in combination with or without VIR-2218 to achieve functional cure is unknown, a response-guided approach will be evaluated in this sub-protocol. In Cohort 4a, VIR-3434 and VIR-2218 will be administered every 4 weeks starting on Day 1 along with TDF administered daily. TDF will be administered daily starting on Day 1 and end when the NRTI discontinuation criteria are met up to Week 12 in the Follow-Up Period.

4.2.4. Rationale for VIR-3434 + VIR-2218 + PEG-IFNα + TDF 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 1,000-1,500 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 2020; Li 2016; 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 regimen consisting of VIR-2218 and VIR-3434, both of which are associated with substantial reductions in HBsAg, plus PEG-IFNα could increase the rate of functional cure beyond that associated with PEG-IFNα monotherapy.

The combination of VIR-2218 and PEG-IFNα is associated with substantial reductions in HBsAg beyond those associated with either agent alone. In participants receiving VIR-2218 200 mg for 6 doses, the mean HBsAg reduction at Week 24 was 1.89 $\log_{10}$ IU/mL (Section 2.2.3). In a study of PEG-IFNα add-on therapy, the mean HBsAg reduction at Week 24 was 0.57 $\log_{10}$ IU/mL (Farag 2019). By contrast, in participants receiving both VIR-2218 and PEG-IFNα in Cohort 1f of the VIR-2218-1001 study, the mean HBsAg reduction at Week 24 was 2.55 $\log_{10}$ IU/mL (Yuen 2021). However, few events of HBsAg loss were observed. It is hypothesized that the addition of VIR-3434 may lead to greater reductions in HBsAg, higher rates of HBsAg loss, and functional cure.

In the VIR-2218-1006 study, combination regimens of VIR-2218 (up to 3 doses of 200 mg administered every 4 weeks) and VIR-3434 (up to 12 doses of up to 75 mg administered weekly) have been evaluated in participants with chronic HBV infection who are on NRTIs. No significant safety concerns have been identified to date, and the study is ongoing.

Furthermore, PEG-IFNα has important effects on the immune system which may augment the potential development of HBV-specific immunity following administration of VIR-3434. Type I interferons regulate antiviral T cells both directly and indirectly via effects on accessory cells, such as antigen presenting cells (Crouse 2015) and infiltrating or liver resident immune cells (Dill 2014). Liver resident immune cells such as Kupffer cells play an important role in priming robust HBV-specific T cell responses, as recently described (De Simone 2021). These effects may further increase the likelihood of inducing a durable T cell response (“vaccinal effect”) following VIR-3434-containing combination therapies.

Because the optimal timing and duration of VIR-3434 and TDF in combination with or without VIR-2218 and PEG-IFNα to achieve functional cure is unknown, a response-guided approach will be evaluated in this sub-protocol. In Cohort 5a, VIR-3434 and VIR-2218 will be administered every 4 weeks starting on Day 1 along with TDF administered daily and PEG-IFNα weekly till Week 48. TDF will be administered daily starting on Day 1 and may end when the NRTI discontinuation criteria are met at Week 1 or Week 12 in the Follow-Up Period.

4.3. Justification for Dose

4.3.1. VIR-3434 Dose Selection

Available PK, safety, and antiviral activity from the ongoing VIR-3434-1002 and VIR-2218-1006 studies were considered for selection of the VIR-3434 dosing regimens.

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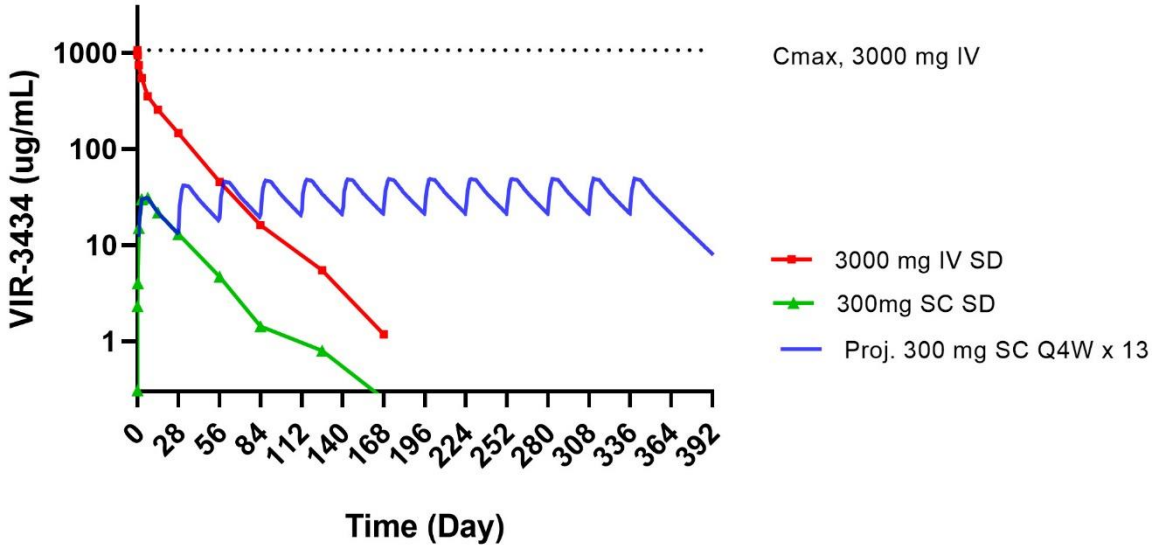
VIR-3434 has a half-life ($t_{1/2}$) of approximately 25 days, with measurable concentrations up to 24 weeks after a single SC dose of 90-900 mg in healthy volunteers (Gupta 2021). Dose-proportional increases in C_{max} and AUC_{inf} were observed across the SC dose range evaluated. A similar $t_{1/2}$ was observed following a single IV injection of 3,000 mg. Nonparametric superposition was employed to predict the concentration time profile and PK exposures following 13 SC doses of VIR-3434 300 mg administered every 4 weeks. As seen in Figure 4, the projected C_{max} of 50 µg/mL for this regimen would not exceed the observed C_{max} of a single 3,000 mg IV dose of 1,076 µg/mL. Similarly, the projected AUC_{inf} associated with this regimen (5,148 day*µg/mL) does not exceed the observed mean AUC_{inf} of the 3,000 mg IV dose (11,842 day*µg/mL). Additionally, due to target-mediated drug disposition, the PK exposure in healthy volunteers is anticipated to be an overestimate compared to participants with chronic HBV infection, as VIR-3434 is expected to be eliminated more rapidly in the presence of HBsAg.

Figure 4: VIR-3434 Observed and Projected Mean Concentration Profile in Healthy Volunteers in the Absence of HBsAg



Mean concentration of VIR-3434 observed over time in healthy volunteers in VIR-3434-1002 administered single dose of VIR-3434 either 300 mg SC (green solid line) or 3,000 mg IV (red solid line). The projected mean concentration profile of VIR-3434 following 13 doses of 300 mg SC administered every 4 weeks in the absence of HBsAg and assuming a 25-day half-life is depicted in blue.

Data from VIR-3434-1002 demonstrated that single doses of up to 300 mg VIR-3434 were generally well tolerated with no safety concerns in participants with chronic HBV infection. The majority of AEs were Grade 1 or 2. There were no study discontinuations due to AEs. In the ongoing VIR-2218-1006 study, combination regimens of VIR-3434 are being evaluated in participants with chronic HBV infection who are on NRTIs. No significant safety concerns have been identified to date for VIR-3434 up to 12 doses of up to 75 mg administered weekly. The cumulative exposure following 13 SC doses of VIR-3434 every 4 weeks at 300 mg is not anticipated to exceed the maximum exposure associated with a single dose of 3,000 mg administered IV in healthy volunteers.

Based on preliminary antiviral data in the ongoing study VIR-3434-1002, VIR-3434 is associated with HBsAg reductions > 1 $\log_{10}$ IU/mL in the majority of study participants following a single SC dose of 6 to 300 mg in a dose dependent manner (Agarwal 2021; Agarwal 2022). The 300 mg dose level was associated with the largest and most durable HBsAg reductions, with mean reductions from baseline of >2 $\log_{10}$ at Week 4 and > 1.5 $\log_{10}$ at Week 8. Repeat administration of VIR-3434 may enhance the reduction of HBsAg, increase the likelihood of eliciting the potential immunomodulatory effects of its Fc domain modifications, and prolong the duration of viral entry inhibition.

CCI

In summary, the observed PK, HBsAg kinetics, and absence of safety signals in the ongoing single dose and multiple dose studies, along with the potential for multiple doses of VIR-3434 to further lower HBsAg, support the dose level, frequency, and duration of VIR-3434 regimens selected for this sub-protocol.

4.3.2. VIR-2218 Dose Selection

Available safety, tolerability, antiviral activity, and pharmacokinetic data from Parts A-F of study VIR-2218-1001 were considered when selecting dose regimens for VIR-2218.

In Part A of the VIR-2218-1001 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 of the study, 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 a median T_{max} of 4-7 hours and was not measurable in plasma beyond 48 hours for any participant (Gupta 2021). Available PK data from HBV participants 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.

In the current sub-study, regimens containing varying durations up to 13 doses of 200 mg VIR-2218 administered every 4 weeks will be evaluated to assess the impact of more sustained HBsAg suppression on the outcome of functional cure. The duration of VIR-2218 administration in each cohort was selected to ensure suppression of HBsAg by VIR-2218 for the entire duration of concomitant administration with VIR-3434 with or without PEG-IFNα.

The VIR-2218 dose level of 200 mg was selected based on results from Parts B and C of the VIR-2218-1001 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; Lim 2022). 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 in the ongoing VIR-2218-1001 (Yuen 2021) and VIR-2218-1006 studies. In VIR-2218-1001 Cohorts 1d, 2d, 1f, and 2f, up to 6 doses of 200 mg VIR-2218 administered every 4 weeks either as monotherapy or in combination with PEG-IFNα was well tolerated and associated with deep, sustained reductions in HBsAg in patients with chronic HBV infection. In both the VIR-2218-1001 and VIR-2218-1006 studies, regimens of up to 13 doses of VIR-2218 200 mg administered every 4 weeks in combination with PEG-IFNα and/or VIR-3434 are being evaluated.

CCI

In summary, PK, safety, and antiviral activity support the VIR-2218 regimens selected for this study.

4.3.3. PEG-IFNα Dose Selection

PEG-IFNα will be administered via subcutaneous injection at a dose of 180 µg given weekly, the FDA-approved dose level and frequency for the treatment of chronic HBV infection. This study will evaluate the safety and efficacy of a 48-week regimen of PEG-IFNα in combination with VIR-3434 and VIR-2218 in Cohort 5a.

Based on the emerging data from the VIR-2218-1001 study, the combination of VIR-2218 and PEG-IFNα provides substantially greater declines in HBsAg (~0.5 $\log_{10}$ IU/mL greater reduction at Week 24) compared to VIR-2218 monotherapy (Yuen 2021). [redacted]
CCI [redacted] All participants who have achieved HBsAg loss during the VIR-2218-1001 study, to date, have received the combination including PEG-IFNα, while no patients receiving VIR-2218 monotherapy have achieved HBsAg loss. Preliminary results from this study are consistent with findings from clinical studies in which HBV-targeting siRNA monotherapy has not been associated with HBsAg loss or functional cure (Yuen 2021).

CCI [redacted]

4.3.4. TDF Dose Selection

TDF will be administered at a dose of 300 mg (or TD at 245 mg) daily, the FDA-approved dose level and frequency for the treatment of chronic HBV infection. The optimal duration of TDF treatment is unknown and not reported in the prescribing information (VIREAD® Prescribing Information). TDF will be administered daily starting on Day 1 and end when the NRTI discontinuation criteria are met in the Follow-Up Period (Section 4.1.3). If participants qualify for NRTI discontinuation, they will stop TDF and continue in the Follow-Up Period. Additional monitoring visits are required in the Follow-Up Period for participants that qualify to discontinue NRTI.

4.4. End of Study Definition

The end of study for this sub-protocol is defined as the date of the last observation of the last participant.

5. STUDY POPULATION

Participants that fulfil the following inclusion and exclusion criteria at screening are eligible for participation in this sub-protocol. Participants may be re-screened after consultation with the Sponsor. [redacted]
CCI
[redacted] To achieve these characteristics, screening and/or enrollment may be restricted by the Interactive Response Technology (IRT) at any time.

5.1. Inclusion Criteria

Inclusion criteria per Master Protocol, details provided for Sub-protocol A in bold

1. Age ≥ 18 (or age of legal consent, whichever is older) **to < 66 years**
2. Chronic HBV infection defined as a positive serum HBsAg, HBV DNA, or HBeAg on 2 occasions at least 6 months apart based on previous or current laboratory documentation (any combination of these tests performed 6 months apart is acceptable)

   In addition, as defined in Table 3 of the Master Protocol for populations II and III, the participants must be/have:
   a. HBeAg positive or negative
   b. HBV DNA > 2,000 IU/mL
   c. ALT > ULN and ≤ 5x ULN
3. Besides chronic infection with HBV, must be in good health, determined from medical history, and no clinically significant findings from physical examination, vital signs, and laboratory values
4. Female participants must have a negative pregnancy test or confirmation of postmenopausal status. Post-menopausal status is defined as 12 months with no menses without an alternative medical cause (see Section 10.6 for additional details). Women of child-bearing potential (WOCBP) must have a negative blood 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 (Section 10.6) 14 days before study intervention administration through **48 weeks after the last dose of VIR-3434, VIR-2218, or PEG-IFNα**. Female participants must also agree to refrain from egg donation and in vitro fertilization from the time of study intervention administration through **48 weeks after the last dose of VIR-3434, VIR-2218, or PEG-IFNα.**

5. Male participants with female partners of child-bearing potential must agree to meet 1 of the following contraception requirements from the time of study intervention administration through **48 weeks after the last dose of VIR-3434, VIR-2218, or PEG-IFNα**: documentation of vasectomy or azoospermia, or male condom use plus partner use of 1 of the contraceptive options listed for contraception for WOCBP (Section 10.6). Male participants must also agree to not donate sperm from the time of first study intervention administration through **48 weeks after the last dose of VIR-3434, VIR-2218, or PEG-IFNα.**
6. Able to understand and comply with the study requirements and able to provide written informed consent

Additional Inclusion Criteria for Sub-Protocol A

7. HBsAg > 10 IU/mL
8. Body Mass Index (BMI) ≥ 18 kg/m^2 to ≤ 35 kg/m^2

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Exclusion Criteria per Master Protocol

1. History of clinically significant liver disease from non-HBV etiology
2. History or current evidence of hepatic decompensation, including ascites, hepatic encephalopathy, and/or esophageal or gastric varices
3. History or current suspicion 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); participants under evaluation for malignancy are not eligible.
4. History of bone marrow or solid organ transplant
5. Known active infection other than chronic HBV infection or any clinically significant acute condition such as fever (> 38° C) or acute respiratory or GI illness within 7 days prior to Day 1
6. Co-infection with human immunodeficiency virus (HIV), hepatitis A virus (HAV) IgM, hepatitis C virus (HCV), hepatitis D virus (HDV) or hepatitis E virus (HEV) IgM. Participants who are HCV antibody or HDV antibody positive, but have a documented negative HCV RNA or HDV RNA, respectively, are eligible. Participants with positive HAV immunoglobulin M (IgM) or HEV IgM but asymptomatic and with a positive HAV immunoglobulin G (IgG) or HEV IgG are eligible.
7. 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). Note: cannabis use is permitted

8. Received an investigational agent within 90 days or 5 half-lives (if known), whichever is longer, before study intervention administration or are active in the follow-up phase of another clinical study involving interventional treatment. Participants 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.
9. Any clinically significant medical or psychiatric condition that may interfere with study intervention, assessment, or compliance with the protocol or otherwise makes the participant unsuitable for participation in the study, as determined by the investigator.

Additional Exclusion Criteria for Sub-Protocol A

10. Significant fibrosis or cirrhosis as defined by having either a FibroScan (or sponsor-approved equivalent) result of > 8.5 kPa at screening or a liver biopsy within 1 year with METAVIR F3 fibrosis or F4 cirrhosis.
11. History of immune complex disease
12. History of an autoimmune disorder
13. History of HBV-related extrahepatic disease, including but not limited to HBV-related rash, arthritis, or glomerulonephritis
14. History of allergic reactions, hypersensitivity, or intolerance to monoclonal antibodies, antibody fragments, or any excipients of VIR-3434
15. Prior NRTI or PEG-IFNα therapy
16. Use of any of the following systemic medications within 14 days before study intervention administration and throughout the study:
    a. Paracetamol (acetaminophen) ≥ 3 g/day
    b. Isoniazid
    c. Systemic steroids (prednisone equivalent of > 10 mg/day) or other immunosuppressive agents (Note: corticosteroid administration for the treatment of immune-mediated AEs is allowed.)
    d. Cohort 5a only: Theophylline
    e. Cohort 5a only: Methadone
17. Receipt of an oligonucleotide (eg, siRNA, antisense oligonucleotide) with activity against HBV within 48 weeks before study intervention administration
18. Receipt of VIR-3434 within 24 weeks prior to Day 1
19. Participant has the following laboratory parameters at screening by laboratory testing:
    a. Direct bilirubin or INR > 1.5 ULN
    b. Total bilirubin > 1.5 times ULN
    c. Platelets < 150,000 cells/μL
    d. Cohort 5a only: Serum amylase or lipase ≥ 3 times the ULN
    e. Cohort 5a only: thyroid stimulating hormone (TSH) and free T4 above the ULN or below the LLN
    f. Cohort 5a only: absolute neutrophil count (ANC) < 1,500 cells/mm^3

20. Creatinine clearance (CLcr) < 30 mL/min as calculated by the Cockcroft-Gault formula at screening
21. Cohort 5a only: Known hypersensitivity or contraindication to an interferon product
22. Cohort 5a only: Current or prior history of psychosis, bipolar disorder, schizophrenia, moderate-severe depression, suicide ideation, attempt, or gesture, or high risk for suicide
23. Cohort 5a only: Current or prior history of clinically significant retinal disease
24. Cohort 5a only: Current or prior history of chronic uncontrolled hypoglycemia, or uncontrolled hyperglycemia/diabetes (defined as HbA1c ≥ 8%) at screening
25. Cohort 5a only: Current or prior history of colitis
26. Clinically significant abnormalities on 12-lead ECG at screening (as determined by the investigator)

5.3. Lifestyle Considerations

Lifestyle considerations are not applicable to this sub-protocol.

5.3.1. Meals and Dietary Restrictions

There are no dietary restrictions in this sub-protocol.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants that regularly consume more than 10 units of alcohol per week (1 unit = 1 glass of wine [125 mL] = 1 measure of spirits [30 mL] = one-half pint of beer [284 mL]), or more than 2 units of alcohol per day are excluded from this sub-protocol. There are no limitations on the use of caffeine and tobacco in this sub-protocol.

5.3.3. Activity

There are no limitations on physical activity in this sub-protocol.

5.4. Screen Failures

Participants that screen fail will not be eligible to enroll in the sub-protocol. Participants may be re-screened after discussion with the Sponsor.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Table 4: Study Intervention (s) Administered

Intervention Label	**VIR-3434**	**VIR-2218**	**PEG-IFNα**	**TDF /TD**
Intervention Name	VIR-3434	VIR-2218	Peginterferon alfa-2a	Tenofovir disoproxil fumarate/ Tenofovir disoproxil
Type	Biologic	Oligonucleotide	Biologic	Drug
Dose Formulation	Lyophilized powder in vial	Liquid in vial	Pre-filled syringe	Tablet
Unit Dose Strength(s)	300 mg/vial	200 mg/mL at 0.5 mL	180 mcg/syringe	300 mg tablet (TDF) 245 mg tablet (TD)
Dosage Level(s)	Up to 300 mg Q4W-Q12W	200 mg Q4W	180 mcg QW	300 mg QD (TDF) or 245 mg QD (TD) based on supply source
Route of Administration	SC	SC	SC	Oral
Use	Experimental	Experimental	Experimental	Background
IMP and NIMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	Sponsor	Sponsor	Sponsor	Sponsor
Packaging and Labeling	Single-use vial labeled as required by country requirement.	Single-use vial labeled as required by country requirement.	Pre-filled syringe labeled as required per country requirement.	Bottle labeled as required per country requirement.
Current or trade name(s)	VIR-3434	VIR-2218	Pegasys®	Viread®

Table 5: Study Arm(s)

Cohort Title	**Cohort 1a/2a**	**Cohort 3a**	**Cohort 4a**	**Cohort 5a**
Cohort Type	Experimental	Experimental	Experimental	Experimental
Cohort Description	Participants will receive VIR-3434 up to 300 mg Q4W from Day 1 to Week 44 along with 300 mg TDF (or 245 mg TD) QD starting on Day 1 until they qualify to discontinue NRTI or end of Follow-Up Period, whichever is later	Participants will receive VIR-3434 300 mg Q8W or Q12W from Day 1 to Week 44 along with 300 mg TDF (or 245 mg TD) QD starting on Day 1 until they qualify to discontinue NRTI or end of Follow-Up Period, whichever is later	Participants will receive VIR-3434 300 mg and VIR-2218 200 mg Q4W from Day 1 to Week 44 along with 300 mg TDF (or 245 mg TD) QD starting on Day 1 until they qualify to discontinue NRTI or end of Follow-Up Period, whichever is later	Participants will receive VIR-3434 300 mg and VIR-2218 200 mg Q4W from Day 1 to Week 48, PEG-IFNα 180 mcg QW from Day 1 to Week 48 along with 300 mg TDF (or 245 mg TD) QD starting on Day 1 until they qualify to discontinue NRTI or end of Follow-Up Period, whichever is later
Associated Intervention Labels	VIR-3434, TDF/TD	VIR-3434, TDF/TD	VIR-3434, VIR-2218, TDF/TD	VIR-3434, VIR-2218, PEG-IFNα, TDF/TD

6.2. Preparation, Handling, Storage, and Accountability

Detailed instructions for all study interventions will be provided in the Pharmacy Manual.

6.3. Randomization and Blinding

This is an open-label study. Participants will be enrolled to one of the open cohorts in the sub-protocol.

6.4. Study Intervention Compliance

Participants are expected to comply with the dosing schedule of the investigational therapies. TDF and PEG-IFNα may be taken home by the participant to be administered daily and weekly respectively per this sub-protocol. Participants will be asked to keep a treatment diary noting the day and date they take their study intervention and any adverse events. They will be asked to bring their treatment diary to each study visit along with all used and unused study intervention containers. The investigator is responsible for assessing participant compliance.

6.5. Dose Modification

6.5.1. Dose Modifications for PEG-IFNα

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® approved local product label. Alternative dose modification strategies based on local treatment guidelines or institutional standards of care are allowed following approval from the Sponsor Medical Monitor. Participants enrolled in Cohort 5a who discontinue PEG-IFNα treatment due to PEG-IFNα-related adverse reactions may continue treatment with VIR-3434, TDF, and VIR-2218 (unless the stopping rules outlined in Section 7.1 are met). These participants will follow the schedule of assessments as provided for their cohort with the exception of PEG-IFNα administration.

6.5.2. Dose Modifications for TDF

It is recommended that TDF dose modifications be performed in accordance with the VIREAD® approved local product label.

6.6. Concomitant Therapy

6.6.1. Concomitant Therapy Not Permitted During the Study

Use of NRTIs before Day 1 is prohibited. While on the study, participants will receive TDF per this sub-protocol. No other NRTIs are permitted during this study.

Use of any of the following systemic medications is prohibited within 14 days before study intervention administration and throughout the study:

- Systemic steroids (prednisone equivalent of > 10 mg/day) or other immunosuppressive agents (Note: corticosteroid administration for the treatment of immune-mediated AEs is allowed.)
- Paracetamol (acetaminophen) ≥ 3 g/day
- Isoniazid
- Cohort 5a only: theophylline
- Cohort 5a only: methadone

Additionally, 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 participant. Medications that are potentially hepatotoxic or associated with drug-induced liver injury include, but are not limited to, the following (Björnsson 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

7. DISCONTINUATION OF STUDY, STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Study Stopping Rules

If either of the following criteria as met, dosing will be paused, and an ad hoc medical monitoring meeting will be convened with the study investigator, or their representative and/or LFAC (if related to an ECI):

- 3 or more participants experience Grade 3 or higher study intervention-related AEs in the same System Organ Class (SOC)
- 2 or more participants experience Grade 4 or higher study intervention-related AEs in the same SOC

Following an assessment of all available safety data, the committee will vote to discontinue, modify (including discontinuation of one or more cohorts), or continue the study.

7.2. Discontinuation of Study Intervention(s)

Participants that have received at least 1 dose of VIR-3434, VIR-2218 or PEG-IFNα will not receive additional doses of either study intervention if any the following criteria are met:

- Any clinical manifestations of hepatic decompensation
- Grade 3 or higher study intervention-related AE of anaphylaxis, cytokine release syndrome, or immune complex disease
- Serum ALT > 10 × ULN
- Serum ALT or aspartate aminotransferase (AST) > 3 × ULN with any of the following laboratory results or clinical symptoms:
  - total bilirubin > 2 × ULN or
  - INR > 1.5 × ULN (erroneously elevated INR due to incorrect blood volume collection should be ruled out) or
  - serum albumin < 3.0g/dL or
  - ascites, hepatic encephalopathy, or liver-related symptoms (eg, severe fatigue, nausea, vomiting, right upper quadrant pain in the absence of an alternative medical explanation)

The investigator should notify the medical monitor immediately in the event that any of the above criteria are met. Upon documented agreement with the investigator and the Sponsor Medical Monitor, the participant may be considered to continue receiving study intervention.

Study intervention may be discontinued in the occurrence of a condition that in the opinion of the Investigator significantly jeopardizes the wellbeing and safety of the participant. Investigator must promptly inform the Sponsor Medical Monitor if any such condition arises.

Female participants who become pregnant during the Treatment Period will not receive additional doses of study intervention. See Master Protocol for additional details.

Participants receiving PEG-IFNα may discontinue treatment if they meet the criteria outlined in the PEGASYS® approved local product label and in Section 6.5.1.

Participants who discontinue all study interventions (excluding NRTI) prematurely (eg, due to meeting a stopping rule) will undergo assessments for the EOT visit at the time of discontinuation. These participants will continue to the Follow-Up Period SOA.

7.3. Participant Discontinuation/Withdrawal from the Study

Refer to Master Protocol.

7.4. Replacement of Participants

Refer to Master Protocol.

7.5. Lost to Follow-up

Refer to Master Protocol.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in SOA (Section 10.9). Refer to Master Protocol for additional details

8.1. Screening Period

Refer to Master Protocol.

8.2. Efficacy Assessments

Refer to Master Protocol.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SOA.

8.3.1. Physical Examinations

Refer to Master Protocol. In addition to the Master Protocol:

- At screening, body weight and height will be measured, and BMI will be calculated.
- Body weight will also be measured at study visits as indicated in the SOA.
- A dilated fundoscopic retinal examination must be performed during screening for all participants in this sub-protocol. The participant may be referred to a specialist for performance of the retinal exam.

8.3.2. Vital Signs

Refer to Master Protocol.

8.3.3. Clinical Safety Laboratory Tests

Clinical laboratory tests that will be performed in this study are presented in Section 10.2. In the event of an unexplained clinically relevant (in the opinion of the investigator) abnormal laboratory test occurring after study intervention administration, the test may 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.

8.3.4. Pregnancy Testing

Please refer to Master Protocol.

8.3.5. Local Tolerability

If a local reaction around the injection site occurs, photographs may be obtained. Participants should be instructed to monitor for local and systemic ISRs, including signs and symptoms of anaphylaxis and instructed to seek emergency medical care, if needed. Oral analgesics may be used to manage mild to moderate local pain or tenderness. More extensive or severe symptoms (eg, suspected anaphylaxis, cytokine release syndrome, or immune complex disease) should be evaluated by the study investigator and treated as deemed appropriate by the investigator and per local standards of care. See Section 10.8 for additional details.

8.4. Assessment of Viral Parameters, Antiviral Activity, and Resistance Surveillance

In addition to the Master Protocol, assessments of antiviral activity performed after screening will include: HBsAg (quantitative), antiHBs (quantitative), HBeAg (qualitative or quantitative as specified in the SOA), anti-HBe, and HBV DNA.

Assessments of exploratory viral markers or other viral analyses may also be performed after screening; refer to Master Protocol.

Resistance surveillance to monitor for the potential development of resistance to NRTI (TDF), VIR-3434, or VIR-2218 will be conducted for all participants who receive study intervention. HBV genome sequencing will be attempted in participants with HBV DNA rebound as defined by HBV DNA ≥ 500 IU/mL. As it will not be known at the time of visit if a participant has virologic rebound, samples for resistance surveillance will be collected at all study visits noted in the SOA. Samples collected for resistance surveillance may be used to perform additional viral analyses, including but not limited to viral sequencing.

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

8.5. CCI

CCI Time points for assessments are provided in the SOA for each applicable cohort.

8.6. Exploratory Assessments

8.6.1. Exploratory Analysis Samples

Refer to Master Protocol.

8.6.2. CCI

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

8.6.2.1. CCI

Refer to Master Protocol.

8.6.2.2. CCI

Refer to Master Protocol.

8.6.2.3. CCI

Refer to Master Protocol.

8.6.3. CCI

CCI

PEG-IFNα. Samples will be collected at certain time points per the SOA for a given cohort. Details regarding sample processing, shipping, and storage are provided in the Laboratory Manual and Vir Immunology Sample Manual (if applicable).

CCI

Based on emerging safety and efficacy data, the Sponsor may restrict enrollment to certain sites or cohorts.

8.7. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

Refer to Master Protocol.

8.7.1. Time Period and Frequency for Collecting AE and SAE Information

Refer to Master Protocol.

8.7.2. Follow-up of AEs and SAEs

Refer to Master Protocol.

8.7.3. Regulatory Reporting Requirements for SAEs

Refer to Master Protocol.

8.7.4. Adverse Events of Interest

Not applicable

8.7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or SAEs

Refer to Master Protocol.

8.7.6. Laboratory Event of Clinical Interest

Laboratory events of clinical interest (ECI) for this study are defined as instances of ALT > 5x ULN and > 2x baseline.

An ECI is considered resolved when ALT returns to ≤ Day 1 baseline value. All ECIs must be reported to the Sponsor Medical Monitor within 5 business days of the investigator becoming aware of the ECI. In addition, the assessments outlined in Section 10.7 of current sub-protocol should be performed as soon as possible and no later than two weeks after the initial ALT value meeting criteria for a laboratory ECI.

8.7.7. Special Situation Reports

Refer to Master Protocol.

8.7.7.1. Pregnancy

Refer to Master Protocol.

8.8. Pharmacokinetic Assessments

Blood samples will be collected to assess concentrations of VIR-3434 and VIR-2218 (for cohorts receiving VIR-2218). Timepoints for the collection of samples for VIR-3434 and VIR-2218 PK analysis are provided in the SOA. Concentrations of VIR-3434 and VIR-2218 PK will be quantified using a validated bioanalytical assay. These assessments are exploratory and may or may not be analyzed. Specific assays used for these assessments may be changed at the Sponsor's discretion based on emerging data. Details regarding the processing, shipping, and analysis of the samples are provided in the Laboratory Manual.

8.8.1. Optional Sub-Study: VIR-3434 PK

Participants with baseline HBsAg > 3,000 IU/mL may consent to the optional VIR-3434 PK sub-study to allow better characterization of VIR-3434 PK. Participants in this sub-study will have up to two additional study visits during the treatment period to collect VIR-3434 PK samples.

- PK sub-study visit 1 will occur 5 to 7 days following either the 3rd, 4th, or 5th dose of VIR-3434.
- PK sub-study visit 2 (optional) will occur 5 to 7 days following either the 7th, 8th, or 9th dose of VIR-3434.

Detailed schedule of sample collection for the optional VIR-3434 PK sub-study is provided in Section 10.10. In addition to samples for PK, samples for HBsAg, HBV DNA and liver function tests will also be collected at the same visits. Participants enrolled in Cohort 3a are excluded from the optional VIR-3434 PK sub-study. All other study-specific PK assessments are specified in the SOAs for the respective cohorts and will remain unchanged. Details regarding sample processing, shipping, and storage are provided in the Laboratory Manual.

8.9. Immunogenicity Assessments

Blood samples will be collected for analysis of immunogenic responses to determine presence/absence and titers of ADA as applicable, according to the timepoints defined in the SOA. Samples may also be characterized for neutralizing potential of anti-VIR-3434 antibody (NAb), as appropriate. Details regarding the processing, shipping, and analysis of the samples are provided in the Laboratory Manual.

8.10. Electrocardiogram

12-lead safety ECGs will be recorded and reviewed on-site by the investigator. ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All ECGs should be measured in the supine position after the participant has rested comfortably for approximately 10 minutes. ECG should be measured before blood sample collection and administration of study intervention(s), where applicable.

8.11. Liver Elastography (eg, FibroScan)

To exclude the presence of cirrhosis, participants will have a liver elastography (eg, FibroScan or other sponsor-approved method) evaluation. This is not required to be performed if the participant has had a liver elastography 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.

9. STATISTICAL CONSIDERATIONS

This section provides a summary of the planned statistical analyses. Details of the statistical analyses will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to the first interim analysis and database lock.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the SAP and/or the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.1. Statistical Hypotheses

The null hypothesis is that the response rate, defined as the proportion of participants achieving suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at EOT, is ≤ 2%, which is the assumed rate of HBsAg loss in NRTI-suppressed patients. The alternative hypothesis is that the response rate is greater than 2%.

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

9.2. Sample Size Determination

A sample size of 10 or 15 in each cohort will provide > 70% statistical power for each cohort to reject the null hypothesis, if the true proportion of participants that achieve HBsAg loss is 25%, using a 1-sided exact binomial test with a significance level of 2.5%.

Up to 60 participants will be enrolled in this sub-protocol initially. Additionally, up to 30 floater participants may be added to the cohorts at any time at Sponsor's discretion. As described in Section 9.5, this addition may be based on the data from interim analysis. No more than 90 participants will be enrolled.

9.3. Analysis Sets

In addition to the master protocol, the following analysis sets will apply to this sub-protocol:

Analysis Sets	Description
PK Analysis Set	The PK Analysis Set includes all participants in the Full Analysis Set who had at least one measurable post-dose concentration. The PK Analysis Set will be used for all PK analyses.
Immunogenicity Analysis Set	The Immunogenicity Analysis Set includes all participants in the Full Analysis Set who had at least 1 post-dose measurement of immunogenicity, including screening, titer, or neutralizing characterization, as applicable. The Immunogenicity Analysis Set will be used for analyses of the immunogenicity endpoints. Details of immunogenicity analyses will be provided in the SAP.

9.4. Statistical Analyses

9.4.1. General Considerations

Refer to the Master Protocol.

TEAE definition for this sub-protocol: An AE that is reported with an onset date on or after the start of study intervention(s) until end of Follow-Up Period.

Prior to the final analysis, interim analyses will be conducted, and the analyses may be submitted for publication or to regulatory agencies to seek guidance for the overall clinical development program.

9.4.2. Primary Endpoint Analysis

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

9.4.2.1. Target Population

All eligible participants with chronic HBV infection, as defined in the Full Analysis Set.

9.4.2.2. Population Level Summary

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

9.4.3. Secondary Endpoint(s) Analysis

Refer to the Master Protocol for the safety data analysis.

The key secondary efficacy endpoints (see Section 3 in this sub-protocol and the Master protocol) including the effect of the study intervention on HBsAg, anti-HBs, HBeAg, and HBV DNA in the Full Analysis Set will be summarized.

9.4.4. Exploratory Endpoint(s) Analysis

CCI

Missing data due to withdrawal or all other events will not be imputed.

9.4.5. Missing Data

Values for missing safety laboratory data will not be imputed. However, a missing baseline result (defined as predose Day 1) will be replaced with a screening result, if available.

If no pre-treatment laboratory value is available, the baseline value will be assumed to be normal (ie, no grade [Grade 0]) for the summary of graded laboratory abnormalities. If safety laboratory results for a participant are missing for any reason at a time point, the participant will be excluded from the calculation of summary statistics for that time point.

9.4.6. Other Safety Analyses

Refer to the Master Protocol for other safety data analyses.

9.5. Interim Analysis

CCI

CCI

[redacted]

9.6. Pharmacokinetics Analyses

VIR-2218 and VIR-3434 concentration data from all sparse samples may be pooled with data from other 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 a separate analysis plan.

9.7. Immunogenicity Analyses

For all study parts, immunogenicity data will be listed and summarized using descriptive statistics, including incidence, 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 SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

Refer to Master Protocol.

10.1.2. Financial Disclosure

Refer to Master Protocol.

10.1.3. Informed Consent Process

Refer to Master Protocol.

10.1.4. Data Protection

Refer to Master Protocol.

10.1.5. Confidentiality

Refer to Master Protocol.

10.1.6. Committees Structure

10.1.6.1. Liver Flare Adjudication Committee (LFAC)

The Liver Flare Adjudication Committee will provide hepatic safety oversight by performing periodic reviews of data pertaining to participants who meet certain prespecified criteria for transaminase elevations (Section 8.7.6). 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 participant. 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.

10.1.7. Dissemination of Clinical Study Data

Refer to Master Protocol.

10.1.8. Data Quality Assurance

Refer to Master Protocol.

10.1.9. Source Documents

Refer to Master Protocol.

10.1.10. Electronic Case Report Forms (eCRF)

Refer to Master Protocol

10.1.11. Study and Site Start and Closure

Refer to Master Protocol.

10.1.12. Publication Policy

Refer to Master Protocol.

10.2. Appendix 2: Clinical Laboratory Tests

Table 6: Protocol-Required Safety Laboratory Tests

Chemistry	**Hematology**
Albumin Blood urea nitrogen (BUN) Calcium Bicarbonate Chloride Creatine kinase[a] Creatinine Creatinine clearance (calculated)[b] Gammaglutamyltransferase (GGT) Glucose (non-fasting) Lactate dehydrogenase (LDH) Phosphate Potassium Sodium Liver Function Tests: Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct) Complement (C3, C4, CH50)[c]	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit White blood cell (WBC) count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils RBC indices: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), %reticulocytes
Coagulation Parameters	**Pregnancy Testing**
International normalized ratio (INR) Prothrombin time (PT)	Highly sensitive (serum/plasma or urine) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
Urinalysis	**Additional Screening Tests**
Bilirubin Glucose Ketones Leukocytes Microscopy (if blood or protein is abnormal) Nitrite pH Proteins RBCs Specific gravity Urobilinogen Visual inspection for appearance and color	Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) **Serology:** Hepatitis A[d], B, C[e], D[f] and E[d] Human immunodeficiency virus I and II Lipase Amylase Follicle stimulating hormone (FSH) [g] Hemoglobin A1c (HbA1c) Thyroid stimulating hormone (TSH) [h] Free T4[h] HBV genotyping

[a] Only required if ALT and/or AST is elevated > 2x the predose Day 1 baseline value

[b] Please note the following clarification for the creatinine clearance calculation: for study visits where weight is not measured, creatinine clearance will be calculated using the value measured from the most recent study visit

[c] As indicated in the Schedule of Activities (Section 10.9)
[d] Participants with positive HAV IgM or HEV IgM but asymptomatic and with a positive HAV IgG or HEV IgG are eligible.
[e] Participants with positive HCV screening serology may have HCV RT-PCR performed to determine eligibility.
[f] Participants with positive HDV screening serology may have HDV RNA performed to determine eligibility.
[g] Required for confirmation of menopause only as applicable
[h] Required at Screening. For Cohort 5a, TSH and free T4 are also required on Day 1, Week 12, Week 24, Week 36, Week 48, F16 and F48.

10.3. Appendix 3: AEs, SAEs, SSRs and AEIs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Refer to Master Protocol.

10.4. Appendix 4: List of Abbreviations and Definitions of Terms

ADA	anti-drug antibodies
ADCC/ADCP	antibody-dependent cellular cytotoxicity/ antibody-dependent cellular phagocytosis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	events of clinical interest
EOT	end of treatment
FcγR	Fc-gamma receptor
FcRn	Fc receptor
FSH	follicle stimulating hormone
GGT	gammaglutamyltransferase
HBIG	hepatitis B immune globulin
CCI	
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IRR	infusion related reaction
IRT	Interactive Response Technology
ISR	injection site reaction
IV	intravenous

LDH	lactate dehydrogenase
LFAC	Liver Flare Adjudication Committee
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
NAb	neutralizing antibodies
NRTI	nucleos(t)ide reverse transcriptase inhibitors
NSAID	non-steroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cells
PEG-IFNα	peginterferon-alfa-2a
PK	pharmacokinetics
PT	prothrombin time
QD	once a day
QW	every week
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
RBC	red blood cell
SAP	Statistical Analysis Plan
SC	subcutaneous
siRNA	small interfering ribonucleic acid
SRC	Safety Review Committee
SOA	Schedule of Activities
TD	tenofovir disoproxil
TDF	tenofovir disoproxil fumarate
TND	target not detected
TSH	thyroid stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WOCBP	women of child-bearing potential

10.5. Appendix 5: Summary of Changes for Previous Protocol Amendment

Protocol Amendment 2 (11 October 2022) Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis 3. Objectives and Endpoints 9.1. Statistical Hypotheses 9.4.2. Primary Endpoint Analysis 9.4.2.2 Population Level Summary	Modified primary endpoint to include achieving hepatitis B virus (HBV) DNA suppression (<lower limit of quantitation [LLOQ]) in addition to Hepatitis B surface antigen (HBsAg) loss (< 0.05 IU/mL) at the end of treatment. Added proportion of participants achieving HBsAg loss (< 0.05 IU/mL) at the end of treatment to the secondary endpoints.	The prior primary endpoint to evaluate proportion of participants achieving HBsAg loss (<0.05 IU/mL) at the end of treatment was moved to be secondary endpoint and the primary endpoint was modified to include HBV DNA suppression (<LLOQ) and HBsAg loss (<0.05 IU/mL) at the end of treatment for better understanding of the effect of the study interventions on both viral parameters and better align with the FDA HBV clinical guidance (FDA 2022).
1.1. Synopsis 1.2. Study Schema 4.1.2.1. Intervention Groups 4.1.2.3. Duration 4.1.2.3.2. Treatment Period 4.2.4. Rationale for VIR-3434 + VIR-2218 + PEG-IFNα + TDF for the Treatment of Chronic HBV Infection 6.1. Study Arm 9.4.1. General Considerations 10.9. Appendix 9: Schedule of Activities	Removed option for Cohorts 4a and 5a participants to discontinue study intervention (except nucleos(t)ide reverse transcriptase inhibitors [NRTI]) after Week 20 if they are Hepatitis B e antigen (HBeAg) negative, have undetectable HBsAg and HBV DNA < LLOQ at 2 consecutive visits. As a result of this change, dosing of study intervention and duration of treatment was updated for Cohorts 4a and 5a. In addition, in Section 3 (Objectives and Endpoints), the exploratory endpoint assessing the proportion of participants with HBsAg loss maintained 24 weeks post-end of treatment (EOT) of Week 20 (for Cohorts 4a and 5a only) was removed.	Removal of the option to discontinue treatment early would allow for all participants within the cohort to receive the same duration of treatment and thereby allow consistency in analyses evaluating of the regimen.
2.3.1. Risk Assessment	Updated immunogenicity risks for VIR-2218 and VIR-3434. Additional edits were made to terminology and definitions to align with the most recent VIR-2218 and VIR-3434 Investigator's Brochures (IBs).	To provide updated risk assessment information for VIR-2218 and VIR-3434 per the most recent IBs.

Section # and Name	Description of Change	Brief Rationale
4.1.2.3.3. Follow-Up Period 4.3.4 TDF Dose Selection 10.9. Appendix 9: Schedule of Activities	Added additional visits in the Follow-up Period at Weeks 28, 32, 40, and 44 for participants who discontinue NRTI.	Additional safety monitoring visits were included for participants that discontinue NRTI to ensure close monitoring of participants off all treatment.
4.1.4. NRTI Retreatment	Added the following to the NRTI retreatment criteria for participants in the Follow-Up Period: HBV DNA > 100,000 IU/mL at any Follow-Up Period visit (regardless of other biochemical parameters or alanine aminotransferase (ALT) values) Confirmed increase of HBV DNA > 20,000 IU/mL (ie, at 2 consecutive collections, regardless of other biochemical parameters or ALT values) Confirmed HBeAg seroreversion (ie, HBeAg positive after being HBeAg negative at NRTI discontinuation)	Additional criteria were added to ensure prompt identification of participants that may be at a risk for safety complications. Recommendations for retreatment with NRTI and additional safety monitoring for these participants are outlined in Section 4.1.4.
4.1.5. Long-Term and Follow-Up Care	Added guidance that long-term care should be determined by the Investigator or primary treating physician based on local clinical guidelines once a participant has completed the study.	Added to provide clarity on long-term care for participants after the end of study.
5.2. Exclusion Criteria 8.11. Liver Elastography (new section) 10.9. Appendix 9: Schedule of Activities	Clarified that, in addition to FibroScan, liver elastography can be assessed with other sponsor-approved methods.	Some study sites may not have access to FibroScan to measure liver elastography. Sponsor may approve alternate methods to determine fibrosis in these cases.
5.2 Exclusion Criteria	To Exclusion Criterion (EC) #19 added the following laboratory parameters: • Total bilirubin > 1.5 times ULN • Platelets < 150,000 cells/µL (and removed previous platelet exclusionary threshold of < 90,000 cells/mm^3 for Cohort 5a)	Added total bilirubin and platelet count limits in exclusion criteria for clarity.

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria 8.10. Electrocardiogram 10.9. Appendix 9: Schedule of Activities	Added EC #26: Clinically significant abnormalities on 12-lead electrocardiogram (ECG) at screening (as determined by the investigator). In addition to at screening, added 12-lead safety ECGs assessments at Day 8 of the Treatment Period and Follow-up Period.	Screening and post-dose safety ECG assessments have been added to assess cardiac safety.
7.1. Study Stopping Rules	Added study stopping rules.	Criteria were added to trigger an ad hoc medical monitoring meeting in which a recommendation to discontinue, modify, or continue the study will be made.
8.3.1. Physical Examinations 10.9. Appendix 9: Schedule of Activities	In addition to at screening, body weight measurements were also added at study visits as indicated in the Schedule of Activities.	Body weight is required to calculate creatinine clearance.
8.8.1. Optional Sub-Study: VIR-3434 PK 10.10. Appendix 10: Schedule of Sample Collection for Optional VIR-3434 PK Sub-study	Added optional VIR-3434 pharmacokinetic (PK) sub-study.	To enable characterization of VIR-3434 PK in subjects with high levels of HBsAg at baseline.
9.3. Analysis Sets	Modified PK Analysis Set to include all participants in the Full Analysis Set (previously All Enrolled Set) who had at least one measurable postdose concentration. Modified Immunogenicity Analysis Set to include all participants in the Full Analysis Set (previously Safety Analysis Set) who had at least one postdose measurement of immunogenicity.	To align with the updated definition of the Full Analysis Set in the master protocol. The Full Analysis Set includes all participants who received at least one dose of study intervention(s) irrespective of post-dose assessments.
9.6. Pharmacokinetic Analyses	Clarified that VIR-2218 and VIR-3434 concentration data from all sparse PK samples may be pooled with data from future studies and may be used for estimation of population PK parameters	To provide updated PK analyses plan

Section # and Name	Description of Change	Brief Rationale
10.6. Appendix 6: Contraceptive and Barrier Guidance	Clarified that an elevated follicle stimulating hormone (FSH) in the post-menopausal range should be used to confirm a post-menopausal state in women not using hormonal contraception or hormone replacement therapy.	To correct FSH criteria used to confirm a post-menopausal state.
Entire document	Other administrative, formatting, and other minor changes	These changes were made to clarify, ensure consistency, provide up-to-date information, or rectify typographical errors.

Protocol Amendment 1 (16 May 2022) Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Study Title	Modified study title to "A Phase 2 Study Evaluating the Efficacy and Safety of VIR-3434 and/or VIR-2218 Containing Regimens in Participants with Chronic Hepatitis B Infection (STRIVE)"	Study title was modified to be concise
1.1 Synopsis 3. Objectives, endpoints and estimands 9.4.2 Primary Endpoint Analysis	Moved one co-primary endpoint (Proportion of participants with HBsAg loss at 24 weeks post-end of treatment) to be a secondary endpoint, making "Proportion of participants with HBsAg loss (< 0.05 IU/mL) at the end of treatment" the only primary endpoint	This modification was made to focus the primary endpoint of the study to evaluate the proportion of participants that achieve HBsAg loss on-treatment. The sustained HBsAg loss and any additional off-treatment HBsAg loss will be evaluated as secondary endpoints in this study.
1.1 Synopsis 3. Objectives, endpoints and estimands	Added secondary endpoints #10 and 11 and modified #16 *# 10 Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) after discontinuation of all treatment* *at 24 weeks* *at the F48 Follow-Up visit*	Endpoints 10, and 11 were added/modified to conform with the FDA HBV clinical guidance (FDA 2022). Endpoint 16 was added for better understanding of the change in HBsAg levels through the study. (FDA 2022)

	#11 Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) after discontinuation of all treatment *at 24 weeks* *at the F48 Follow-Up visit* *#16 Mean change in serum HBsAg level from baseline across timepoints in the study*	
1.1 Synopsis 3. Objectives, endpoints and estimands	Moved these secondary endpoints and the respective objectives to exploratory endpoints • *For HBeAg-positive participants: time to achieve HBeAg loss (undetectable HBeAg) and/or anti-HBe seroconversion* • Proportion of participants meeting criteria for NRTI discontinuation or retreatment in the study • *HBV DNA levels and change from baseline across timepoints in the study* • *Nadir and maximum change of HBV DNA levels from baseline in the study*	These endpoints will provide additional understanding of the timing of HBeAg loss and seroconversion for HBeAg positive patients, the changes in the HBV DNA and participants that do qualify for NRTI discontinuation or retreatment. Therefore, they were better suited as exploratory endpoints
1.1 Synopsis 3. Objectives, endpoints and estimands	Added exploratory objective and corresponding endpoint #11 *Proportion of participants with virological relapse (defined either as (1) an increase of ≥ 1 log10 HBV DNA IU/mL above nadir for at least 2 consecutive visits OR (2) quantifiable HBV DNA of ≥ 1 log10 IU/mL above LLOQ for at least 2 consecutive visits after being < LLOQ)*	This endpoint was added to conform to the FDA HBV clinical guidance to evaluate any virological relapse. This will distinguish virological relapse from transient increases in HBV DNA that are possible after discontinuing NRTI (FDA 2022)
1.1 Synopsis 3. Objectives, endpoints and estimands	Other minor clarifications to primary and secondary endpoints: Defining HBsAg loss as < 0.05 IU/mL Modifying TND or undetectable HBV DNA across different secondary endpoints as < LLOQ	These changes were made to provide clarifications to the level of viral marker referenced. The HBV DNA level was modified from being TND (target not detected) to < LLOQ to conform to the FDA HBV clinical guidance (FDA 2022)

4.1.2.3.2 Treatment Period	Criteria to stop study interventions at W20 for Cohorts 4a and 5a were modified to include HBV DNA < LLOQ in addition to undetectable HBeAg and HBsAg	This criterion was added to ensure that participants that stop study interventions have achieved HBV DNA suppression and thereby increasing the probability of long-term sustained suppression off-treatment.
4.1.3 NRTI discontinuation	NRTI discontinuation criterion for HBsAg level was modified from < 10 IU/mL to < 100 IU/mL with ≥ 1 $\log_{10}$ IU/mL reduction from baseline	There is limited correlation between the sustained suppression of HBV DNA and HBsAg loss (< 0.05 IU/mL). The modified criteria will allow inclusion of participants that have achieved HBV DNA suppression with ≥ 1 $\log_{10}$ decline in HBsAg from baseline and an absolute HBsAg level lower than 100 IU/mL to be evaluated for sustained suppression of HBV DNA. Furthermore, we expect a proportion of these participants could achieve HBsAg loss during the Follow-Up Period after discontinuation of all treatments
4.1.3 NRTI discontinuation	Timing of NRTI discontinuation was clarified to be either at F1 visit based on data available or at F12 visit based on data available	These timings were clarified to ensure that participants have adequate monitoring based on visits per the Follow-Up Period SOA
4.1.4 NRTI retreatment	Added criteria to consider restarting NRTI if participants have HBV DNA ≥ 2 $\log_{10}$ IU/mL within a 2-week period or any other clinically significant event(s) warranting initiation of NRTI therapy in the opinion of the investigator. In addition, additional monitoring requirements for participants that discontinue NRTI and experience an increase in HBV DNA plus weekly monitoring of participants that experience HBV DNA ≥ 2 $\log_{10}$ IU/mL within a 2-week period has been added	Added to ensure participant safety in case of a virological relapse after discontinuation of all study treatments.
5.2 Exclusion criteria	Added sub-criterion *#27, d. Cohort 5a only: Platelets < 90,000 cells/mm^3, absolute neutrophil count (ANC) < 1,500 cells/mm^3*	Added to comply with Pegasys® Prescribing Information

9.3 Analysis Sets	Clarified that the PK and immunogenicity analysis sets will include all participants from the Safety Analysis Set who received at least one dose of study drug and had at least one measurable post-dose concentration or at least one post-dose immunogenicity measurement respectively.	Modified to provide clarity
Table 12 Schedule of Activities: Follow-Up Period for all cohorts	Addition of Follow-Up visits for participants that discontinue NRTI: If discontinuing at F1 visit then additional visits at F2, F6 and F10 If discontinuing NRTI at F12 visit then additional visits include F14, F18 and F22	These visits were added to ensure additional periodic monitoring of participants after discontinuation of all treatments including NRTI
Entire document	Other administrative, formatting, and other minor changes	These changes were made to clarify, ensure consistency, or rectify typographical errors.

10.6. Appendix 6: Contraceptive and Barrier Guidance

WOCBP may be included in this study and include any female participant who has experienced menarche and who is not post-menopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).

WOCBP must be willing to use highly effective methods of contraception from 14 days before the first dose of study intervention to 48 weeks after the final dose of VIR-3434, VIR-2218, PEG-IFNα. After the end of study, use of TDF in WOCBP should be determined per the VIREAD® approved local product label.

Highly effective methods of birth control are defined as those that 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 or VIR-3434 will impact the effectiveness of hormonal contraceptive methods; therefore, it is recommended to use an additional form of contraception (ie, barrier method) for 48 weeks after the last administration of VIR-3434, VIR-2218, or PEG-IFNα. After the end of study, use of TDF in WOCBP should be determined per the VIREAD® approved local product label.
- Placement of an intrauterine device
- Placement of an intrauterine hormone-releasing system
- Surgical sterilization of male partner (with the appropriate documentation of vasectomy or the absence of sperm in the ejaculate; for female participants on the study, the vasectomized male partner should be the sole partner for that participant)
- True sexual abstinence from heterosexual contact, when in line with the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent participants must agree to use 1 of the above-mentioned contraceptive methods for 48 weeks after study intervention administration if they start heterosexual relationships during the study.
- Barrier method in combination with hormonal contraceptive, as described above

Post-menopausal status is defined as 12 months with no menses without an alternative medical cause. An elevated follicle stimulating hormone (FSH) level in the post-menopausal range should be used to confirm a post-menopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Female participants must also agree to refrain from egg donation and in vitro fertilization from the time of study intervention administration through 48 weeks after the last dose of VIR-3434, VIR-2218, or PEG-IFNα. After the end of study, use of TDF in WOCBP should be determined per the VIREAD® approved local product label.

Male participants with female partners of child-bearing potential must agree to meet 1 of the following contraception requirements from the time of study intervention administration until 48 weeks after the last administration of VIR-3434, VIR-2218, or PEG-IFNα. After the end of study, use of TDF in males with female partners of child-bearing potential should be determined per the VIREAD® approved local product label.

- Documentation of azoospermia or vasectomy
- Male condom plus partner use of 1 of the contraceptive options listed above for contraception for WOCBP (hormonal contraceptive, intrauterine device)

Male participants must also agree not to donate sperm from the first dose of study intervention through 48 weeks after the last dose of VIR-3434, VIR-2218, or PEG-IFNα. After the end of study, use of TDF in males donating sperm should be determined per the VIREAD® approved local product label.

10.7. Appendix 7: Additional Assessments in Participants That Experience ALT Elevation Meeting ECI Criteria

Additional assessments will be performed in participants who experience ALT elevations meeting ECI criteria as outlined in Section 8.7.6. Following the occurrence of elevated ALT meeting ECI criteria per central laboratory, the assessments in Table 7 will be performed as soon as possible and no later than 2 weeks after the initial ALT value meeting criteria for a laboratory ECI.

The full panel of assessments should only be performed once per ECI occurrence. An ECI occurrence is considered resolved when ALT returns to ≤ Day 1 baseline value. Individual assessments may be repeated per investigator discretion, as needed.

Participants who meet ECI criteria will continue to receive study intervention unless criteria for study intervention discontinuation are met. Criteria for individual participation discontinuation from further dosing are described in Section 7.1.

Table 7: Assessments in Participants That Experience ALT Elevation Meeting ECI Criteria

Chemistry	**Hematology**
Albumin Blood urea nitrogen (BUN) Calcium Bicarbonate Chloride Calcium Creatine kinase Creatinine Creatinine clearance (calculated) Gammaglutamyltransferase (GGT) Glucose Lactate dehydrogenase (LDH) Phosphate Potassium Sodium Uric acid Lipase Liver Function Tests: Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct)	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit White blood cell (WBC) count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils RBC indices: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), %reticulocytes
Coagulation Parameters	**Exploratory testing**
International normalized ratio (INR) Prothrombin time (PT)	CCI CCI CCI CCI CCI

Extended Hepatic Panel	**Imaging**
Quantitative HBsAg HBV DNA Quantitative HBeAg HAV antibody IGM HCV antibody HCV RNA PCR (qualitative and quantitative) HDV antibody or RNA HEV antibody IgM Epstein-Barr Virus antibodies (IgM and IgG) Cytomegalovirus antibodies (IgM and IgG) Varicella Zoster Virus antibodies IgG HSV-I and II IgG IgG Phosphatidylethanol Aldolase Anti-nuclear antibodies Anti-Smooth muscle antibodies Anti-LKM1 antibody Anti-mitochondrial antibodies Anti-SLA antibodies Ferritin Ceruloplasmin IgM Urinary ethylglucuronide Acetaminophen	Abdominal ultrasound, including doppler flow if available (CT or MRI is 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 Exposure to other potentially hepatotoxic agents including any work-related exposures (eg, solvents, pesticides, etc.) Alcohol consumption and drugs of abuse Travel History Exercise History	

10.8. Appendix 8: Anaphylaxis, Cytokine Release Syndrome, And Immune Complex Disease Supportive Measures

The following equipment or agents may be needed in the event of a suspected anaphylactic reaction or cytokine release syndrome:

- ECG monitor
- Blood pressure monitor
- Oxygen saturation monitor
- Thermometer
- Tourniquet
- Oxygen
- Mechanical ventilator
- Renal replacement therapy
- IV infusion solutions, tubing, catheters, and tape
- Fresh-frozen plasma and/or cryoprecipitate
- Epinephrine
- Antihistamines, such as diphenhydramine
- Corticosteroids, such as hydrocortisone, prednisolone, and methylprednisolone

The following are procedures that may be followed in the event of a suspected anaphylactic reaction or cytokine release syndrome:

- Maintain an adequate airway
- Stop study intervention injection (if reaction occurs during injection)
- Call for additional medical assistance
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study intervention (if reaction occurs during injection). Do not obstruct arterial flow in the limb.
- Ensure appropriate monitoring is in place, such as continuous ECG and pulse oximetry monitoring
- Administer epinephrine, antihistamines, corticosteroids or other medications/products as necessary based on the status of the participant and as directed by the physician
- Draw local laboratory samples as appropriate, possibly including evaluation of cytokines
- The following equipment or agents may be needed in the event of suspected immune complex disease
- Thermometer
- Analgesic and antipyretic agents, such as non-steroidal anti-inflammatory drugs (NSAIDs)

- Antihistamines, such as diphenhydramine
- Corticosteroids, such as prednisone and methylprednisolone
- In extreme cases, equipment for plasmapheresis may be needed

The following are procedures that may be followed in the event of suspected immune complex disease:

- Though unlikely to occur acutely, stop study intervention injection (if reaction occurs during injection)
- Ensure temperature is appropriately monitored
- Monitor for most common manifestations, including rheumatic (arthralgias) and dermatologic (pruritic rash) findings
- Administer NSAIDs, antihistamines, corticosteroids, or other medications/products as necessary based on the status of the participant and as directed by the physician
- Draw local laboratory samples as appropriate, possibly including complete blood count, erythrocyte sedimentation rate, C-reactive protein, urinalysis, serum chemistry, and evaluation of complement
- In extreme cases, plasmapheresis may be employed

10.9. Appendix 9: Schedule of Activities

Assessments in **bold** are in addition to those listed in the PREVAIL Master protocol.

Table 8: Schedule of Activities: Cohort 1a/2a (PBMC- Qualified Sites Only)

Study Stage	**Screen-ing**	**Treatment Period**[a]												
Visit Week		**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44/ EOT**[b]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**D29±2**	**D57±2**	**D85±2**	**D113±2**	**D141±2**	**D169±2**	**D197±2**	**D225±2**	**D253±2**	**D281±2**	**D309±2**
Study Procedures														
Informed consent	X													
Inclusion/exclusion criteria	X	X[c]												
Demography	X													
Physical examination [d]	X													X
Body weight	X													
Medical history	X													
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event review/record[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver elastography (eg, Fibroscan) [g]	X													
12-lead safety ECG[h]	X		X											
ECI surveillance [i]		X	X	X	X	X	X	X	X	X	X	X	X	X
VIR-3434 local tolerability [j]		X												

Study Stage	**Screen-ing**	**Treatment Period**[a]												
Visit Week		**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44/ EOT**[b]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**D29±2**	**D57±2**	**D85±2**	**D113±2**	**D141±2**	**D169±2**	**D197±2**	**D225±2**	**D253±2**	**D281±2**	**D309±2**
Drug Administration														
VIR-3434 administration[k]		X		X	X	X	X	X	X	X	X	X	X	X
TDF administration (QD)[l]		X												
CCI														
CCI														
CCI														
Treatment Diary		X												
Laboratory Assessments[n]														
Pregnancy test[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Screening viral serology[p]	X													
Liver function tests[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation parameters [q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[qr]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine for drugs of abuse [s]	X													
HBsAg quantitative	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-HBs qualitative	X													
Anti-HBs quantitative		X		X	X	X	X	X	X	X	X	X	X	X
HBeAg qualitative	X													

Study Stage	**Screen-ing**	**Treatment Period**[a]											
Visit Week		**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44/ EOT**[b]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**D29±2**	**D57±2**	**D85±2**	**D113±2**	**D141±2**	**D169±2**	**D197±2**	**D225±2**	**D253±2**	**D281±2**	**D309±2**
HBeAg quantitative		X		X	X	X	X	X	X	X	X	X	X	X
Anti-HBe qualitative	X													
HBV DNA quantification	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV genotyping		X												
Complement testing[r]		X	X	X	X	X	X	X	X	X	X	X	X	X
VIR-3434 PK[t]		X	X	X	X	X	X	X		X		X		X
VIR-3434 immunogenicity[u]		X		X	X	X	X	X	X	X	X	X	X	X
Exploratory Assessments														
CCI														
CCI														
CCI														
CCI														
CCI														
CCI														
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Study Stage	Screen-ing	Treatment Period[a]											
Visit Week		W1		W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44/ EOT[b]
Visit Day ± Visit Window	D -56 to -1	D1	D8±2	D29±2	D57±2	D85±2	D113±2	D141±2	D169±2	D197±2	D225±2	D253±2	D281±2	D309±2
CCI [redacted]														

D = day; EOT = end of treatment; W = week

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

[b] If a participant discontinues treatment or withdraws prematurely from the study prior to the Week 44 visit, EOT assessments should be performed.

[c] Prior to study intervention administration on Day 1, participant eligibility will be confirmed.

[d] See Section 8.3.1 for assessments to be performed during a full physical examination. A dilated fundoscopic retinal examination must be performed during Screening. The participant may be referred to a specialist for performance of the retinal exam.

[e] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the participant has rested comfortably for approximately 10 minutes.

[f] After signing of the informed consent form (ICF), but prior to initiation of study intervention, AEs/SAEs related to protocol-mandated procedures will be reported. Following initiation of study intervention, all AEs/SAEs, regardless of cause or relationship, will be recorded for the entire duration of the study. Further details can be found in Section 8.7.

[g] Does not need to be performed if the participant has had a liver elastography (eg, FibroScan or other sponsor-approved method) 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.

[h] 12-lead safety ECG will be recorded and should be measured in the supine position after the participant has rested comfortably for approximately 10 minutes. Further details can be found in Section 8.10.

[i] Participants will be monitored for ECI, and additional assessments may be performed if indicated. Section 8.7.6 and Section 10.7 for more information.

[j] On Day 1, local tolerability should be assessed approximately 1 hour after VIR-3434 administration. At the discretion of the investigator, unscheduled visits are permitted as needed for follow-up of any unresolved local tolerability symptoms. Local tolerability symptoms occurring at other visits should be reported as AEs.

[k] VIR-3434 will be administered via SC injection every 4 weeks. Participants will be monitored for at least 1 hour after VIR-3434 administration.

[l] TDF will be administered orally every day until the criteria in Section 4.1.3 are met.

CCI [redacted]

[n] Screening laboratory tests may be repeated (eg, for values thought to be erroneous) with Sponsor approval.

[o] WOCBP are required to have pregnancy tests. A blood pregnancy test will be performed at screening, and a urine pregnancy test will be performed at subsequent visits. Negative pregnancy test must be confirmed prior to study intervention administration.

[p] See Section 8.4 for viral serology parameters.

[q] Clinical laboratory and urinalysis parameters are described in Section 10.2.

[r] Additional samples for urinalysis and complement testing will be collected at any time if fever, rash, or arthralgia are observed in a participant without alternative explanation per the assessment of the investigator, or if immune complex disease is suspected by the investigator based on other signs or symptoms

consistent with immune complex disease. Other signs and symptoms consistent with immune complex disease include, but are not limited to, decreased complement, hematuria, proteinuria, and/or decreased renal function. Urinalysis parameters are described in Section 10.2.

[s] Drugs of abuse included in the panel are described in Section 10.2.

[t] At all visits during the Treatment Period where PK collection is required, samples will be collected predose only. On Day 8, no VIR-3434 will be dosed, therefore PK sample can be collected anytime during visit. VIR-3434 PK sample collection includes samples for free and total PK assays, as applicable. Predose samples will be collected within 1 hour prior to dose. Further details can be found in Section 8.8.

[u] Includes samples for ADA and neutralizing antibodies (NAb), as applicable for VIR-3434. Samples will be collected prior to dosing and at each indicated timepoint thereafter. Additional samples for immunogenicity analysis may be collected if a persistent drug related immunologic event is suspected.

[v] See Section 8.4 for more information.

CCI

CCI

Table 9: Schedule of Activities: Cohort 3a (PBMC- Qualified Sites Only)

Study Stage	**Screen-ing**	**Treatment Period**[a]											
Visit Week		**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36/ EOT**[bc]	**W40/ EOT**[bc]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**D29±2**	**D57±2**	**D85±2**	**D113±2**	**D141±2**	**D169±2**	**D197±2**	**D225±2**	**D253±2**	**D281±2**
Study Procedures													
Informed consent	X												
Inclusion/exclusion criteria	X	X[d]											
Demography	X												
Physical examination [e]	X											X[f]	X[g]
Body weight	X												
Medical history	X												
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event review/record[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver elastography (eg, Fibroscan)[j]	X												
12-lead safety ECG[k]	X		X										
ECI surveillance [l]		X	X	X	X	X	X	X	X	X	X	X	X
VIR-3434 local tolerability [m]		X											

Study Stage	**Screen-ing**	**Treatment Period**[a]											
Visit Week		**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36/ EOT**[bc]	**W40/ EOT**[bc]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**D29±2**	**D57±2**	**D85±2**	**D113±2**	**D141±2**	**D169±2**	**D197±2**	**D225±2**	**D253±2**	**D281±2**
Drug administration													
VIR-3434 administration (Q8W) [n]		X			X		X		X		X		X
VIR-3434 administration (Q12W) [n]		X				X			X			X	
TDF administration (QD)[o]		X											
CCI													
CCI													
CCI													
Treatment Diary		X											
Laboratory Assessments[q]													
Pregnancy test[r]	X	X	X	X	X	X	X	X	X	X	X	X	X
Screening viral serology[s]	X												
Liver function tests [t]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry [t]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology [t]	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation parameters [t]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis [tu]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine for drugs of abuse [v]	X												
HBsAg quantitative	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-HBs qualitative	X												

Study Stage	**Screen-ing**	**Treatment Period**[a]										
Visit Week		**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36/ EOT**[bc]	**W40/ EOT**[bc]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**D29±2**	**D57±2**	**D85±2**	**D113±2**	**D141±2**	**D169±2**	**D197±2**	**D225±2**	**D253±2**	**D281±2**
Anti-HBs quantitative		X		X	X	X	X	X	X	X	X	X	X
HBeAg qualitative	X												
HBeAg quantitative		X		X	X	X	X	X	X	X	X	X	X
Anti-HBe qualitative	X												
HBV DNA quantification	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV genotyping		X											
Complement testing[u]		X	X	X	X	X	X	X	X	X	X	X	X
VIR-3434 PK[w]		X	X	X	X	X	X	X	X	X	X	X	X
VIR-3434 immunogenicity[x]		X		X	X	X	X	X	X	X	X	X	X
Exploratory Assessments													
CCI													
CCI													
CCI													
CCI													
CCI													
CCI													
CCI													
CCI													
CCI													

Study Stage	Screen-ing	Treatment Period[a]										
Visit Week		W1		W4	W8	W12	W16	W20	W24	W28	W32	W36/ EOT[bc]	W40/ EOT[bc]
Visit Day ± Visit Window	D -56 to -1	D1	D8±2	D29±2	D57±2	D85±2	D113±2	D141±2	D169±2	D197±2	D225±2	D253±2	D281±2
CCI													
CCI													
CCI													

D = day; EOT = end of treatment; W = week

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

CCI

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

[c] If a participant discontinues treatment or withdraws prematurely from the study prior to the Week 36 (Q12W) or Week 40 (Q8W) visit, EOT assessments should be performed.

[d] Prior to study intervention administration on Day 1, participant eligibility will be confirmed.

[e] See Section 8.3.1 for assessments to be performed during a full physical examination. A dilated fundoscopic retinal examination must be performed during Screening. The participant may be referred to a specialist for performance of the retinal exam.

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

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

[h] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the participant has rested comfortably for approximately 10 minutes.

[i] After signing of the informed consent form (ICF), but prior to initiation of study intervention, AEs/SAEs related to protocol-mandated procedures will be reported. Following initiation of study intervention, all AEs/SAEs, regardless of cause or relationship, will be recorded for the entire duration of the study. Further details can be found in Section 8.7

[j] Does not need to be performed if the participant has had a liver elastography (eg, FibroScan or other sponsor-approved method) 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.

[k] 12-lead safety ECG will be recorded and should be measured in the supine position after the participant has rested comfortably for approximately 10 minutes. Further details can be found in Section 8.10.

[l] Participants will be monitored for ECI, and additional assessments may be performed if indicated. See Section 8.7.6 and Section 10.7 for more information.

[m] On Day 1, local tolerability should be assessed approximately 1 hour after VIR-3434 administration. At the discretion of the investigator, unscheduled visits are permitted as needed for follow-up of any unresolved local tolerability symptoms. Local tolerability symptoms occurring at other visits should be reported as AEs.

[n] VIR-3434 will be administered via SC injection either every 8 weeks or every 12 weeks. Participants will be monitored for at least 1 hour after VIR-3434 administration.

[o] TDF will be administered orally every day until the criteria in Section 4.1.3 are met

CCI

[q] Screening laboratory tests may be repeated (eg, for values thought to be erroneous) with Sponsor approval.

[r] WOCBP are required to have pregnancy tests. A blood pregnancy test will be performed at screening, and a urine pregnancy test will be performed at subsequent visits. Negative pregnancy test must be confirmed prior to study intervention administration.

[s] See Section 8.4 for viral serology parameters.

[t] Clinical laboratory and urinalysis parameters are described in Section 10.2.

[u] Additional samples for urinalysis and complement testing will be collected at any time if fever, rash, or arthralgia are observed in a participant without alternative explanation per the assessment of the investigator, or if immune complex disease is suspected by the investigator based on other signs or symptoms consistent with immune complex disease. Other signs and symptoms consistent with immune complex disease include, but are not limited to, decreased complement, hematuria, proteinuria, and/or decreased renal function. Urinalysis parameters are described in Section 10.2.

[v] Drugs of abuse included in the panel are described in Section 10.2.

[w] At all visits during the Treatment Period where PK collection is required, samples will be collected predose only. On Day 8, PK sample will be collected anytime during visit. VIR-3434 PK sample collection includes samples for free and total PK assays, as applicable. Predose samples will be collected within 1 hour prior to dose. Further details can be found in Section 8.8

[x] Includes samples for ADA and neutralizing antibodies (NAb), as applicable for VIR-3434. Samples will be collected prior to dosing and at each indicated timepoint thereafter. Additional samples for immunogenicity analysis may be collected if a persistent drug related immunologic event is suspected.

[y] See Section 8.4 for more information.

CCI

Table 10: Schedule of Activities: Cohort 4a

Study Stage	**Screen-ing**	**Treatment Period**[a]													
Visit Week		**W1**			**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44/ EOT**[b]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D2**	**D8 ±2**	**D29 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±2**	**D225 ±2**	**D253 ±2**	**D281 ±2**	**D309 ±2**
Study Procedures															
Informed consent	X														
Inclusion/exclusion criteria	X	X[c]													
Demography	X														
Physical examination [d]	X														X
Body weight	X														
Medical history	X														
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event review/record[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver elastography (eg, Fibroscan)[g]	X														
12-lead safety ECG[h]	X			X											
ECI surveillance[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
VIR-3434 local tolerability[j]		X													
Drug Administration															
VIR-3434 and VIR-2218 administration[k]		X			X	X	X	X	X	X	X	X	X	X	X
TDF administration (QD)[l]		X													

Study Stage	**Screen-ing**	**Treatment Period**[a]													
Visit Week		**W1**			**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44/ EOT**[b]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D2**	**D8 ±2**	**D29 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±2**	**D225 ±2**	**D253 ±2**	**D281 ±2**	**D309 ±2**
CCI															
CCI															
CCI															
Treatment Diary		X													
Laboratory Assessments[n]															
Pregnancy test[o]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Screening viral serology[p]	X														
Liver function tests[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry [q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology [q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation parameters [q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis [qr]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Urine for drugs of abuse [s]	X														
HBsAg quantitative	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-HBs qualitative	X														
Anti-HBs quantitative		X	X		X	X	X	X	X	X	X	X	X	X	X
HBeAg qualitative	X														
HBeAg quantitative		X	X		X	X	X	X	X	X	X	X	X	X	X
Anti-HBe qualitative	X														
HBV DNA quantification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Stage	**Screen-ing**	**Treatment Period**[a]													
Visit Week		**W1**			**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44/ EOT**[b]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D2**	**D8 ±2**	**D29 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±2**	**D225 ±2**	**D253 ±2**	**D281 ±2**	**D309 ±2**
HBV genotyping		X													
Complement testing[r]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
VIR-3434 PK predose[t]		X			X	X	X	X	X		X		X		X
VIR-3434 PK postdose			X[u]	X[v]											
VIR-2218 PK predose[w]		X							X						X
VIR-2218 PK postdose		X[x]	X[y]						X[x]						X[x]
VIR-3434 immunogenicity[z]		X			X	X	X	X	X	X	X	X	X	X	X
VIR-2218 immunogenicity[aa]		X			X	X		X		X		X		X	
Exploratory Assessments															
CCI															
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Study Stage	Screen-ing	Treatment Period[a]												
Visit Week		W1			W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44/ EOT[b]
Visit Day ± Visit Window	D -56 to -1	D1	D2	D8 ±2	D29 ±2	D57 ±2	D85 ±2	D113 ±2	D141 ±2	D169 ±2	D197 ±2	D225 ±2	D253 ±2	D281 ±2	D309 ±2
CCI															
CCI															

D = day; EOT = end of treatment; W = week

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

[aa] Includes samples for ADA of VIR-2218. Samples will be collected prior to dosing at each indicated timepoint. Additional samples for immunogenicity analysis may be collected if a persistent drug related immunologic event is suspected.

[b] If a participant discontinues treatment or withdraws prematurely from the study prior to the Week 44 visit, EOT assessments should be performed.

[bb] See Section 8.4 for more information.

[c] Prior to study intervention administration on Day 1, participant eligibility will be confirmed.

CCI

[d] See Section 8.3.1 for assessments to be performed during a full physical examination. A dilated fundoscopic retinal examination must be performed during Screening. The participant may be referred to a specialist for performance of the retinal exam.

CCI

[e] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the participant has rested comfortably for approximately 10 minutes.

[f] After signing of the informed consent form (ICF), but prior to initiation of study intervention, AEs/SAEs related to protocol-mandated procedures will be reported. Following initiation of study intervention, all AEs/SAEs, regardless of cause or relationship, will be recorded for the entire duration of the study. Further details can be found in Section 8.7

[g] Does not need to be performed if the participant has had a liver elastography (eg, FibroScan or other sponsor-approved method) 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.

[h] 12-lead safety ECG will be recorded and should be measured in the supine position after the participant has rested comfortably for approximately 10 minutes. Further details can be found in Section 8.10.

[i] Participants will be monitored for ECI, and additional assessments may be performed if indicated. See Section 8.7.6 and Section 10.7 for more information.

[j] On Day 1, local tolerability should be assessed approximately 1 hour after VIR-3434 administration. At the discretion of the investigator, unscheduled visits are permitted as needed for follow-up of any unresolved local tolerability symptoms. Local tolerability symptoms occurring at other visits should be reported as AEs.

[k] VIR-3434 and VIR-2218 will be administered via SC injection every 4 weeks. Participants will be monitored for at least 1 hour after VIR-3434 administration.
[l] TDF will be administered orally every day until the criteria in Section 4.1.3 are met.
CCI
[n] Screening laboratory tests may be repeated (eg, for values thought to be erroneous) with Sponsor approval.
[o] WOCBP are required to have pregnancy tests. A blood pregnancy test will be performed at screening, and a urine pregnancy test will be performed at subsequent visits. Negative pregnancy test must be confirmed prior to study intervention administration.
[p] See Section 8.4 for viral serology parameters.
[q] Clinical laboratory and urinalysis parameters are described in Section 10.2.
[r] Additional samples for urinalysis and complement testing will be collected at any time if fever, rash, or arthralgia are observed in a participant without alternative explanation per the assessment of the investigator, or if immune complex disease is suspected by the investigator based on other signs or symptoms consistent with immune complex disease. Other signs and symptoms consistent with immune complex disease include, but are not limited to, decreased complement, hematuria, proteinuria, and/or decreased renal function. Urinalysis parameters are described in Section 10.2.
[s] Drugs of abuse included in the panel are described in Section 10.2.
[t] VIR-3434 PK sample collection includes samples for free and total PK assays, as applicable. Predose samples will be collected within 1 hour prior to dose. Further details can be found in Section 8.8.
[u] Day 2 VIR-3434 PK postdose sample will be collected between 22 to 28 hours post D1 dose.
[v] VIR-3434 PK postdose sample can be collected at any time during the D8 visit.
[w] VIR-2218 PK predose samples will be collected within 1 hour prior to dose. Further details can be found in Section 8.8.
[x] Day 1, Week 20, and Week 44 VIR-2218 PK postdose samples will be collected between 2 to 6 hours postdose.
[y] Day 2 VIR-2218 PK samples will be collected between 22 to 28 hours post D1 dose.
[z] Includes samples for ADA and neutralizing antibodies (NAb), as applicable for VIR-3434. Samples will be collected prior to dosing at each indicated timepoint. Additional samples for immunogenicity analysis may be collected if a persistent drug related immunologic event is suspected.

Table 11: Schedule of Activities: Cohort 5a

Study Stage	**Screen-ing**		**Treatment Period[a]**													
Visit Week			**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48/ EOT[b]**
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D2**	**D8 ±2**	**D29 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±2**	**D225 ±2**	**D253 ±2**	**D281 ±2**	**D309 ±2**	**D337 ±2**
Study Procedures																
Informed consent	X															
Inclusion/exclusion criteria	X	X[c]														
Demography	X															
Physical examination [d]	X															X
Body weight	X															
Medical history	X															
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event review/record[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver elastography (eg Fibroscan)[g]	X															
12-lead safety ECG[h]	X			X												
ECI surveillance[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VIR-3434 local tolerability [j]		X														

Study Stage	**Screen-ing**		**Treatment Period[a]**													
Visit Week			**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48/ EOT[b]**
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D2**	**D8 ±2**	**D29 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±2**	**D225 ±2**	**D253 ±2**	**D281 ±2**	**D309 ±2**	**D337 ±2**
Drug Administration																
VIR-3434 and VIR-2218 administration[k]		X			X	X	X	X	X	X	X	X	X	X	X	X
PEG-IFNα administration (QW)[l]		X		X						X						
TDF administration (QD)[m]		X														
CCI																
CCI																
CCI																
Treatment Diary		X														
Laboratory Assessments[o]																
Pregnancy test [p]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Screening viral serology [q]	X															
Liver function tests [r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry [r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology [r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation parameters [r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[rs]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine for drugs of abuse [t]	X															
HBsAg quantitative	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-HBs qualitative	X															

Study Stage	**Screen-ing**		**Treatment Period**[a]												
Visit Week			**W1**		**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48/ EOT**[b]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D2**	**D8 ±2**	**D29 ±2**	**D57 ±2**	**D85 ±2**	**D113 ±2**	**D141 ±2**	**D169 ±2**	**D197 ±2**	**D225 ±2**	**D253 ±2**	**D281 ±2**	**D309 ±2**	**D337 ±2**
Anti-HBs quantitative		X	X		X	X	X	X	X	X	X	X	X	X	X	X
HBeAg qualitative	X															
HBeAg quantitative		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Anti-HBe qualitative	X															
HBV DNA quantification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV genotyping		X														
Complement testing [s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VIR-3434 PK predose [u]		X			X	X	X	X	X		X		X			X
VIR-3434 PK postdose			X[v]	X[w]												
VIR-2218 PK predose[x]		X							X							X
VIR-2218 PK postdose		X[y]	X[z]						X[y]							X[y]
VIR-3434 immunogenicity [aa]		X			X	X	X	X	X	X	X	X	X	X	X	X
VIR-2218 immunogenicity [bb]		X			X	X		X		X		X		X		X
Exploratory Assessments																
CCI																
CCI																
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CCI																
CCI																
CCI																

Study Stage	Screen-ing		Treatment Period[a]												
Visit Week			W1		W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/ EOT[b]
Visit Day ± Visit Window	D -56 to -1	D1	D2	D8 ±2	D29 ±2	D57 ±2	D85 ±2	D113 ±2	D141 ±2	D169 ±2	D197 ±2	D225 ±2	D253 ±2	D281 ±2	D309 ±2	D337 ±2
CCI																
CCI																
CCI																
CCI																
CCI																

D = day; EOT = end of treatment; W = week

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

[aa] Includes samples for ADA and neutralizing antibodies (NAb), as applicable for VIR-3434. Samples will be collected prior to dosing and at each indicated timepoint thereafter. Additional samples for immunogenicity analysis may be collected if a persistent drug related immunologic event is suspected.

[b] If a participant discontinues treatment or withdraws prematurely from the study prior to the Week 48 visit, EOT assessments should be performed.

[bb] Includes samples for ADA of VIR-2218. Samples will be collected prior to dosing at each indicated timepoint thereafter. Additional samples for immunogenicity analysis may be collected if a persistent drug related immunologic event is suspected.

[c] Prior to study intervention administration on Day 1, participant eligibility will be confirmed.

[cc] See Section 8.4 for more information.

[d] See Section 8.3.1 for assessments to be performed during a full physical examination. A dilated fundoscopic retinal examination must be performed during Screening. The participant may be referred to a specialist for performance of the retinal exam.

CCI

[e] Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) should be measured after the participant has rested comfortably for approximately 10 minutes.

CCI

[f] After signing of the informed consent form (ICF), but prior to initiation of study intervention, AEs/SAEs related to protocol-mandated procedures will be reported. Following initiation of study intervention, all AEs/SAEs, regardless of cause or relationship, will be recorded for the entire duration of the study. Further details can be found in Section 8.7.

[g] Does not need to be performed if the participant has had a liver elastography (eg, FibroScan or other sponsor-approved method) 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.

[h] 12-lead safety ECG will be recorded and should be measured in the supine position after the participant has rested comfortably for approximately 10 minutes. Further details can be found in Section 8.10.

[i] Participants will be monitored for ECI, and additional assessments may be performed if indicated. See Section 8.7.6 and Section 10.7 for more information.

[j] On Day 1, local tolerability should be assessed approximately 1 hour after VIR-3434 administration. At the discretion of the investigator, unscheduled visits are permitted as needed for follow-up of any unresolved local tolerability symptoms. Local tolerability symptoms occurring at other visits should be reported as AEs.

[k] VIR-3434 and VIR-2218 will be administered via SC injection every 4 weeks. Participants will be monitored for at least 1 hour after VIR-3434 administration.

[l] PEG-IFNα will be administered via SC injection every week.

[m] TDF will be administered orally every day until the criteria in Section 4.1.3 are met.

CCI

[o] Screening laboratory tests may be repeated (eg, for values thought to be erroneous) with Sponsor approval.

[p] WOCBP are required to have pregnancy tests. A blood pregnancy test will be performed at screening, and a urine pregnancy test will be performed at subsequent visits. Negative pregnancy test must be confirmed prior to study intervention administration.

[q] See Section 8.4 for viral serology parameters.

[r] Clinical laboratory and urinalysis parameters are described in Section 10.2.

[s] Additional samples for urinalysis and complement testing will be collected at any time if fever, rash, or arthralgia are observed in a participant without alternative explanation per the assessment of the investigator, or if immune complex disease is suspected by the investigator based on other signs or symptoms consistent with immune complex disease. Other signs and symptoms consistent with immune complex disease include, but are not limited to, decreased complement, hematuria, proteinuria, and/or decreased renal function. Urinalysis parameters are described in Section 10.2.

[t] Drugs of abuse included in the panel are described in Section 10.2.

[u] VIR-3434 PK sample collection includes samples for free and total PK assays, as applicable. Predose samples will be collected within 1 hour prior to dose. Further details can be found in Section 8.8.

[v] Day 2 VIR-3434 PK postdose sample will be collected between 22 to 28 hours post D1 dose.

[w] VIR-3434 PK postdose sample can be collected at any time during the D8 visit.

[x] VIR-2218 PK predose samples will be collected within 1 hour prior to dose. Further details can be found in Section 8.8.

[y] Day 1, Week 20, and Week 48 VIR-2218 PK post-dose samples will be collected between 2 to 6 hours postdose.

[z] Day 2 VIR-2218 PK samples will be collected between 22 to 28 hours post D1 dose.

Table 12: Schedule of Activities: Follow-Up Period for all Cohorts

Study Stage	**Follow-Up Period**																		
Follow up Visit	**F1**	**F2[a]**	**F4**	**F6[a]**	**F8**	**F10[a]**	**F12**	**F14[b]**	**F16**	**F18[b]**	**F20**	**F22[b]**	**F24**	**F28[c]**	**F32[c]**	**F36**	**F40[c]**	**F44[c]**	**F48/ EOFU**
Visit Day ± Visit Window	**D8 ±2**	**D15 ±2**	**D29 ±7**	**D43 ±7**	**D57 ±7**	**D71 ±7**	**D85 ±7**	**D99 ±7**	**D113 ±7**	**D127 ±7**	**D141 ±7**	**D155 ±7**	**D169 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D281 ±7**	**D309 ±7**	**D337 ±7**
Study Procedures																			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X		X		X		X		X		X		X			X			X
Adverse event review/record[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead safety ECG[e]	X																		
ECI surveillance[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug administration																			
TDF administration[g]	X																		
CCI																			
CCI																			
CCI																			
Treatment Diary	X																		
Laboratory Assessments																			
Pregnancy test[i]	X		X		X		X												X
Liver function tests[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Stage	**Follow-Up Period**																		
Follow up Visit	**F1**	**F2[a]**	**F4**	**F6[a]**	**F8**	**F10[a]**	**F12**	**F14[b]**	**F16**	**F18[b]**	**F20**	**F22[b]**	**F24**	**F28[c]**	**F32[c]**	**F36**	**F40[c]**	**F44[c]**	**F48/ EOFU**
Visit Day ± Visit Window	**D8 ±2**	**D15 ±2**	**D29 ±7**	**D43 ±7**	**D57 ±7**	**D71 ±7**	**D85 ±7**	**D99 ±7**	**D113 ±7**	**D127 ±7**	**D141 ±7**	**D155 ±7**	**D169 ±7**	**D197 ±7**	**D225 ±7**	**D253 ±7**	**D281 ±7**	**D309 ±7**	**D337 ±7**
Coagulation parameters[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[kj]	X		X		X		X												
HBsAg quantitative	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-HBs quantitative	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBeAg quantitative	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-HBe qualitative	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA quantification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complement testing[k]	X		X																
VIR-3434 PK[l]	X		X		X		X		X		X		X			X			X
VIR-3434 immunogenicity[m]	X		X		X				X		X					X			X
VIR-2218 immunogenicity[n]	X		X		X				X		X					X			X
Exploratory Assessments																			
CCI																			
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Study Stage	Follow-Up Period																		
Follow up Visit	F1	F2[a]	F4	F6[a]	F8	F10[a]	F12	F14[b]	F16	F18[b]	F20	F22[b]	F24	F28[c]	F32[c]	F36	F40[c]	F44[c]	F48/ EOFU
Visit Day ± Visit Window	D8 ±2	D15 ±2	D29 ±7	D43 ±7	D57 ±7	D71 ±7	D85 ±7	D99 ±7	D113 ±7	D127 ±7	D141 ±7	D155 ±7	D169 ±7	D197 ±7	D225 ±7	D253 ±7	D281 ±7	D309 ±7	D337 ±7
CCI																			
CCI																			
CCI																			
CCI																			

D = day; E = End of Follow-Up; F= Follow-Up visit week

[a] Visits are only required in participants who discontinue NRTI at F1 Follow-Up visit.

[b] Visits are only required in participants who discontinue NRTI at F12 Follow-Up visit.

[c] Visits are only required in participants who discontinue NRTI.

[d] In the Follow-Up Period, all AEs/SAEs, regardless of cause or relationship, will be recorded for the entire duration of the study. Further details can be found in Section 8.7.

[e] 12-lead safety ECG will be recorded and should be measured in the supine position after the participant has rested comfortably for approximately 10 minutes. Further details can be found in Section 8.10.

[f] Participants will be monitored for ECI, and additional assessments may be performed if indicated. See Section 8.7.6 and Section 10.7 for more information.

[g] TDF will be administered orally every day unless the criteria in Section 4.1.3 are met.

CCI

[i] WOCBP are required to have pregnancy tests. A urine pregnancy test will be performed.

[j] Clinical laboratory and urinalysis parameters are described in Section 10.2.

[k] Additional samples for urinalysis and complement testing will be collected at any time if fever, rash, or arthralgia are observed in a participant without alternative explanation per the assessment of the investigator, or if immune complex disease is suspected by the investigator based on other signs or symptoms consistent with immune complex disease. Other signs and symptoms consistent with immune complex disease include, but are not limited to, decreased complement, hematuria, proteinuria, and/or decreased renal function. Urinalysis parameters are described in Section 10.2.

[l] VIR-3434 PK sample collection includes samples for free and total PK assays, as applicable. Further details can be found in Section 8.8.

[m] Includes samples for ADA and neutralizing antibodies (NAb), as applicable for VIR-3434. Additional samples for immunogenicity analysis may be collected if a persistent drug related immunologic event is suspected.

[n] (Cohorts 4a and 5a). Includes samples for ADA of VIR-2218. Additional samples for immunogenicity analysis may be collected if a persistent drug related immunologic event is suspected.

CCI

CCI

CCI

10.10. Appendix 10: Schedule of Sample Collection for Optional VIR-3434 PK Sub-study

Collection Visit	**PK sub-study visit 1** any **one** of the three visits is needed[a]			**PK sub-study visit 2 (optional)** any **one** of the three visits is needed[a]		
Study Visit	**W9**	**W13**	**W17**	**W25**	**W29**	**W33**
Visit Day ± Visit Window	**D64 -2**	**D92 -2**	**D120 -2**	**D176 -2**	**D204 -2**	**D232 -2**
Laboratory Assessments						
VIR-3434 PK[b]	X			X		
Liver function tests	X			X		
HBsAg quantitative	X			X		
HBV DNA quantification	X			X		

Participants enrolled in Cohort 3a are excluded from the optional VIR-3434 PK sub-study.
[a] VIR-3434 PK sample will be collected any time during the visit. VIR-3434 PK sample collection includes samples for free and total PK assays, as applicable.
[b] See Sections 8.8 and 8.8.1 for more details.

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