Official Title: A Platform Study Evaluating the Efficacy and Safety of Investigational Therapies in Participants with Chronic Hepatitis B Infection (PREVAIL)

NCT Number: NCT05612581

Document Date: 11 October 2022, Version 3.0

PREVAIL PLATFORM CLINICAL STUDY

MASTER PROTOCOL
PROTOCOL AMENDMENT 2

Study Title	A Platform Study Evaluating the Efficacy and Safety of Investigational Therapies in Participants with Chronic Hepatitis B Infection (PREVAIL)
Brief Title	A Platform Study to Evaluate Investigational Therapies in Chronic Hepatitis B Infection
Study Number	VIR-MHB1-V200
Indication	Chronic Hepatitis B Infection
Study Phase	1b/2
Study Sponsor	Vir Biotechnology, Inc. 499 Illinois Street, Suite 500 San Francisco, CA 94158, USA
Regulatory Agency Identifying Numbers	**EudraCT**: TBD **NCT**: TBD
Protocol Date	11 October 2022, Version 3.0

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 Platform Study Evaluating the Efficacy and Safety of Investigational Therapies in Participants with Chronic Hepatitis B Infection (PREVAIL)

This Master 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 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 2 (11 OCTOBER 2022) SUMMARY OF CHANGES TABLE

Table 1: Protocol Document History

Document	Date
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 2 Summary of Changes

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis 3. Objectives and Endpoints 9.1. Statistical Hypotheses 9.4.2. Primary Endpoint(s) Analysis 9.4.2.3. Population Level Summary	Added new potential primary endpoint to evaluate the proportion of participants achieving hepatitis B virus (HBV) DNA suppression of HBV DNA (< LLOQ [lower limit of quantitation]) with hepatitis B surface antigen (HBsAg) loss (< 0.05 IU/mL) at the end of treatment.	Added for better understanding of the effect of the study interventions on both viral parameters and to better align with the FDA HBV clinical guidance (FDA 2022). The statistical analysis and hypotheses sections were updated to incorporate this change.
4.1.1. Brief Summary	In Table 3, added Protocol Population VII: HBeAg negative, HBV DNA > LLOQ, alanine aminotransferase (ALT) ≤ upper limit of normal (ULN).	This study population was added to allow evaluation of study interventions in participants that have low levels of HBV DNA but elevated ALT.
7.1. Study Stopping Rules	Added new subsection to refer to sub-protocols for specific details regarding study stopping rules.	To allow sub-protocols to describe the criteria to discontinue, modify or continue the study(ies).
7.4. Replacement of Participants	Modified to not replace any participants that have received any dose of study intervention(s).	To allow analyses using data from all participants enrolled in study that receive study intervention(s).
8.1. Screening Period	Allowed screening laboratory tests to be repeated with Sponsor medical monitor approval.	To allow repeat laboratory tests when, in the opinion of the medical monitor and investigator, there may be erroneous results.

Section # and Name	Description of Change	Brief Rationale
8.3.1. Physical Examinations	Clarified that any abnormal findings at screening will be recorded as medical history.	To distinguish medical history from adverse events.
8.3.4. Pregnancy Testing 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.
9.3. Analysis Sets	Definition of the Full Analysis Set modified to include all participants who received at least one dose of study intervention(s) irrespective of post-dose assessments.	To allow inclusion of all participants enrolled in the study and receiving at least 1 dose of study intervention(s) in the full analysis population.
9.4.2.2. Missing Data (new section title; previously Possible Intercurrent Events)	Removed possible intercurrent events. Added additional procedures for handling of missing data.	To reflect the removal of estimands from the protocol and to clarify handling of missing data.
10.2. Appendix 2: Clinical Laboratory Tests	Added proteins, red blood cells (RBCs), and urobilinogen under urinalysis lab test.	To align with urinalysis lab tests listed in the sub-protocols.
10.3.4. Definition of Adverse Event of Interest (AEI) 10.3.5. Recording and Follow-Up of AEs, SAEs, SSRs (including Pregnancies) and/or AEIs	Updated definitions and procedures for recording, evaluating, and reporting for adverse event of interest (AEI) and AE assessment of causality. The term adverse event of special interest (AESI) was changed to AEI.	To provide updated information regarding Sponsor's current safety reporting procedures.
10.7. Appendix 7: Schedule of Activities	In footnote “f”, removed specific guidance for liver scans and replaced with cross-reference to sub-protocols for additional details regarding liver scans.	To make liver scan guidance broader in the master protocol, allowing the use of different methods of liver scanning.
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 Platform Study Evaluating the Efficacy and Safety of Investigational Therapies in Participants with Chronic Hepatitis B Infection (PREVAIL)

Brief Title

A Platform Study to Evaluate Investigational Therapies in Chronic Hepatitis B Infection

Background and Rationale

Chronic HBV infection remains an important global public health problem with significant morbidity and mortality (Trepo 2014). It is estimated that approximately 300 million people are living with chronic HBV infection worldwide (Polaris Observatory Collaborators 2018). Over time, chronic HBV infection leads to serious sequelae, including cirrhosis, liver failure, hepatocellular carcinoma (HCC), and death. Almost 800,000 people worldwide are estimated to die annually due to chronic HBV infection (Stanaway 2016). 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, ALT, and liver inflammation (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 NRTI therapy can suppress HBV replication and viremia but do 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). Moreover, treatment indication is restricted to patients with certain disease characteristics such as elevated ALT in addition to having high HBV DNA (EASL 2017; Sarin 2015; Terrault 2018). This highlights an unmet need for patients with chronic HBV infection in all stages of the disease. The goal of this platform study is to evaluate safety and efficacy of investigational therapies aimed to achieve functional cure in patients at different stages of chronic HBV infection.

Primary and Secondary Objectives and Endpoints

The general primary and secondary objectives and endpoints for this platform study are outlined below. Depending on the phase of the development in the sub-protocol, the primary and secondary endpoints will vary as described. Each sub-protocol will describe specific objectives and endpoints relevant to the investigational therapy(ies) being evaluated.

Objectives	Endpoints
Primary	Depending on the development phase, the primary endpoint(s) associated analysis methods and power calculations will be from those listed below. The time point at which it will be assessed will be specified within the sub-protocol.
• To evaluate the efficacy of the investigational regimen(s)	• Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at 24 weeks after discontinuation of all treatment[a] • Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) at 24 weeks after discontinuation of all treatment[a] • Proportion of participants with HBsAg loss (< 0.05 IU/mL) at 24 weeks post-end of treatment[b] • 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[b] • Proportion of participants with HBsAg loss (< 0.05 IU/mL) at the end of treatment[b] • Mean change in serum HBsAg from baseline across timepoints in the study
Secondary	
• To evaluate the safety and tolerability of the investigational regimens • To assess the effect of the investigational regimens on serum hepatitis B surface antigen (HBsAg) • To assess the effect of the investigational regimens on anti-HBs	1. Proportion of participants with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) 2. Proportion of participants with serum HBsAg < 10 IU/mL at the end of treatment[b] 3. Proportion of participants with serum HBsAg < 10 IU/mL at 24 weeks post-end of treatment[b]

Objectives	Endpoints
	4. Serum HBsAg levels and change from baseline across timepoints in the study 5. Serum HBsAg level at nadir during the study 6. Time to achieve nadir of serum HBsAg during the study 7. Time to achieve serum HBsAg loss (< 0.05 IU/mL) 8. Proportion of participants with HBsAg loss and anti-HBs seroconversion at end of treatment and at 24 weeks post-end of treatment[b]

[a] Discontinuation of all therapies as defined in the sub-protocols (including investigational therapies and background NRTI, if applicable)
[b] End of treatment as defined in the sub-protocols

Overall Study Design

The intention of the PREVAIL Master Protocol is to provide a standard Phase 1b/2 platform study framework to evaluate the safety and efficacy of investigational candidate(s) and their combinations as potential treatments for adults with chronic HBV infection. The Master Protocol describes the overall study outline, study populations, common objectives and endpoints, common inclusion and exclusion criteria, common elements of randomization scheme, statistical methodology, general study assessments (which include efficacy and safety assessments), and the planned analyses that are common to all sub-protocols. The Master Protocol should be read in conjunction with each sub-protocol. The sub-protocols will identify specific investigational therapy(ies), the population(s) in which they will be tested, the study-specific design, and any additional information pertinent to the investigational intervention(s) included.

The safety and efficacy of investigational therapies may be evaluated simultaneously, in parallel or sequentially in cohorts as described in the specific sub-protocol. The exact duration of the study and the individual study periods will be described in the sub-protocols. Overall, the study duration will be as follows:

- Screening period – up to 56 days (8 weeks).
- Treatment period – Minimum of 8 weeks, maximum duration as defined in respective sub-protocol based on the investigational candidate(s).
- Follow-Up Period – Minimum of 24 weeks after the end of Treatment Period, maximum duration as defined in respective sub-protocol based on the investigational candidate(s).

At the end of the Follow-Up Period, the participants may either end the study or be provided with an option to enroll into another cohort within the sub-protocol, another sub-protocol, or another study, if available and all eligibility criteria are met.

Brief Summary

This platform study will evaluate the safety and efficacy of investigational therapies in one or more of the populations of adult participants with chronic HBV infection as follows:

Protocol Population	HBeAg Status	HBV DNA Level	ALT Level
I	Positive	High[a]	≤ ULN
II	Positive	High[a]	> ULN
III	Negative	> LLOQ[a]	> ULN
IV	Negative	≤ 2,000 IU/mL	≤ ULN
V	Positive	≤ LLOQ or low (on NRTI therapy) [a]	Variable[a]
VI	Negative	≤ LLOQ or low (on NRTI therapy) [a]	Variable[a]
VII	Negative	> LLOQ [a]	≤ ULN

HBeAg: Hepatitis B e Antigen; LLOQ: Lower limit of quantitation; ALT: Alanine Aminotransferase; ULN: Upper limit of normal; NRTI: Nucleos(t)ide Reverse Transcriptase Inhibitor

[a] As defined in the respective sub-protocol

Specific details of the population(s) included and investigational therapies will be included in the respective sub-protocol(s).

Number of Participants

Refer to specific sub-protocol.

Intervention Groups and Duration

Refer to specific sub-protocol.

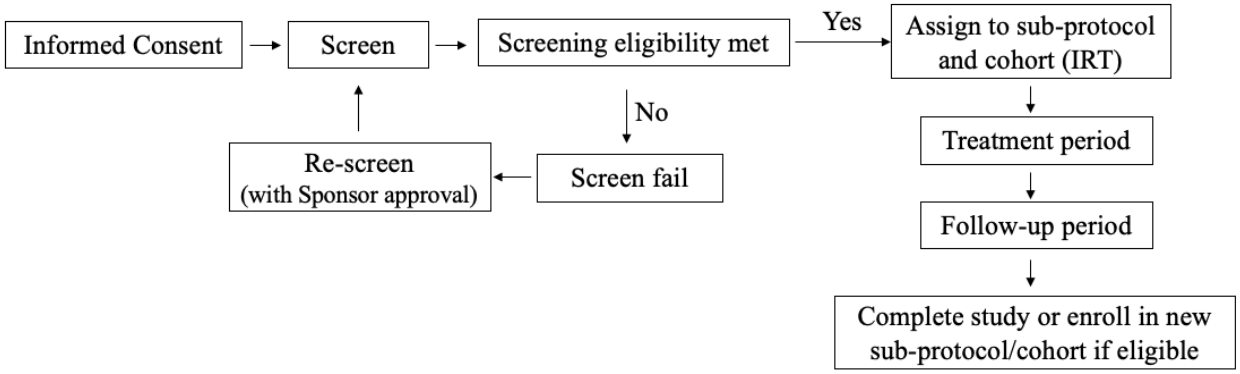
Study Committees

The committees in the sub-protocols may include but not be limited to a Liver Flare Adjudication Committee (LFAC), Safety Review Committee (SRC), and/or Independent Data Monitoring Committee (IDMC).

1.2. Study Schema

Patients will be screened for eligibility and enrolled into active sub-protocols. Eligible participants may be assigned or randomized to treatment groups as specified in the sub-protocols. Once enrolled in a sub-protocol, participants will follow the schedule of activities for the respective sub-protocol/cohort Treatment and Follow-Up Periods. After the participants complete the Follow-Up Period, they may be enrolled into another cohort, sub-protocol, or study, if eligible. If not, participants will exit the study (Figure 1).

Figure 1: Study Schema



1.3. Schedule of Activities

Schedules of activities are provided in Section 10.7.

2. INTRODUCTION

2.1. Background

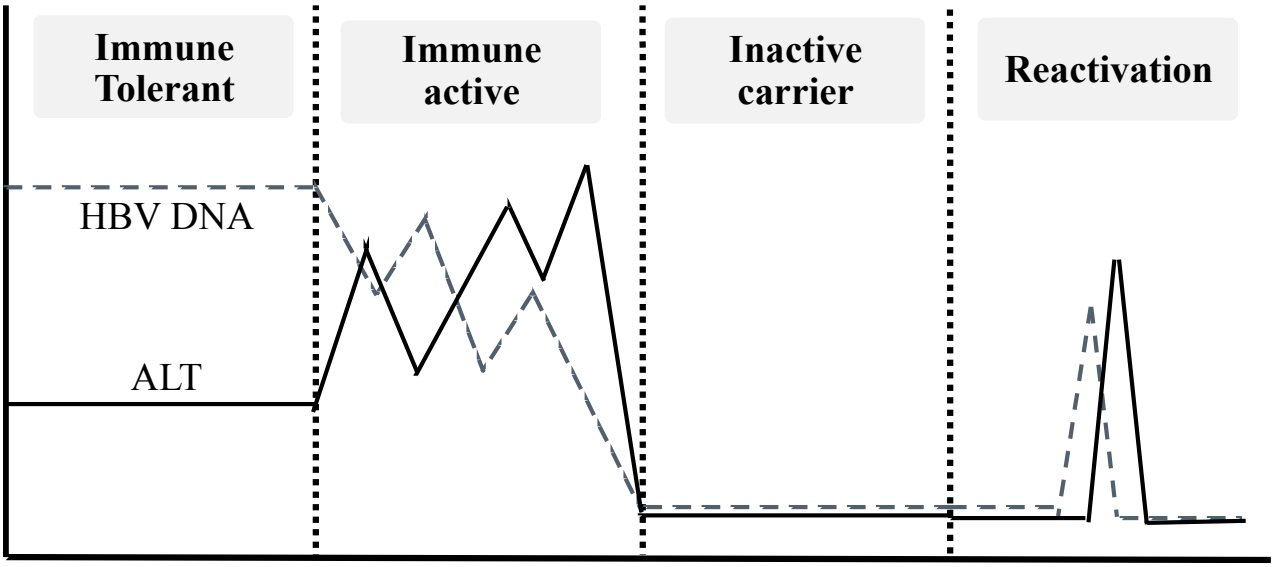
Chronic hepatitis B virus (HBV) infection remains an important global public health problem with significant morbidity and mortality (Trepo 2014). It is estimated that approximately 300 million people are living with chronic HBV infection worldwide (Polaris Observatory Collaborators 2018). Chronic HBV infection leads to serious sequelae, including cirrhosis, liver failure, hepatocellular carcinoma (HCC), and death. Almost 800,000 people worldwide are estimated to die annually due to chronic HBV infection (Stanaway 2016).

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

There are 10 major genotypes of HBV (A-J) that have been identified with 35 sub-genotypes. The prevalence of the different genotypes is usually associated with geographic locations. In North America and Africa, genotype A, B and genotype C are most commonly observed. In east Asia, genotypes B and C are most predominant, with genotype D being most common in Europe and India (Castaneda 2021; EASL 2017; Tang 2018; Terrault 2018). The response to therapy may also differ based on the genotype. For example, in comparison to genotypes B and D, genotype A has been associated with higher rates of HBeAg and Hepatitis B surface antigen (HBsAg) loss after interferon therapy.

Chronic HBV infection is a dynamic process based on the relationship between viral replication and the host immune response. Based on the levels of biomarkers such as HBV antigens, HBV DNA, and HBsAg, patients may oscillate between different phases of the disease (Figure 2). Serial monitoring of these biomarkers is essential in determining the stage of infection and disease and thereby the clinical management of these patients. Patients that are HBeAg positive and have high levels of serum HBV DNA (> 2,000 IU/mL) but normal alanine aminotransferase (ALT) are often referred to as “immune tolerant” and are not currently indicated for treatment. Patients that are HBeAg positive, have high HBV DNA (usually > 2,000 or > 20,000 IU/mL) and have elevated ALT levels are referred to as “immune active” and are currently indicated for treatment. Patients with high levels of HBV DNA (> 2,000 IU/mL) and elevated ALT but that are HBeAg negative are also grouped as “immune active” and are indicated for treatment. However, patients that are HBeAg negative, with normal ALT and HBV DNA < 2,000 IU/mL persistent for at least 1 year are considered “inactive carriers” or “immune inactive” and are not indicated for treatment (EASL 2017; Sarin 2015; Terrault 2018).

Figure 2: Stages of Chronic HBV Infection



HBV DNA: Hepatitis B viral DNA; ALT: Alanine Aminotransferase

Currently, there are 2 standard-of-care treatment options for patients with chronic HBV infection: nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and peginterferon-alfa-2a (PEG-IFNα) (Liang 2015). NRTIs inhibit HBV replication by interfering with polymerase/reverse transcriptase (pol/RT) activity, leading to DNA chain termination, thus preventing the production of HBV DNA containing virions. Although HBV DNA suppression can be achieved with NRTIs alone, NRTIs do not directly eliminate cccDNA or integrated DNA, and, therefore, transcription and translation of viral proteins continues. Thus, continued HBV DNA suppression requires lifelong treatment and rarely results in HBsAg loss. Consequently, expression of viral proteins on hepatocytes, secretion of subviral particles, and immune dysfunction remain largely unaffected by NRTI therapy. Additionally, while NRTI therapy reduces the incidence of HCC, it does not eliminate the increased risk of HCC due to the reservoir of cccDNA and integrated HBV forms. Patients that are on NRTIs and have sustained low to undetectable levels of HBV DNA, irrespective of HBeAg status or ALT levels are "virally-suppressed."

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). While the exact mechanism of action of PEG-IFNα treatment is unknown, interferon induces multiple innate immune mechanisms and exerts antiproliferative and antiviral effects at various points of the HBV lifecycle in vitro (PEGASYS® Prescribing Information; Rijckborst 2010). The low response rate coupled with limited tolerability and a long treatment course preclude the treatment of most patients with PEG-IFNα monotherapy (PEGASYS® Prescribing Information). The limitations of NRTI and PEG-IFNα therapy highlight the need for novel HBV therapies that are well tolerated and have a finite duration of administration.

Several investigational agents are currently under development for the treatment of chronic HBV infection. These include HBsAg targeting monoclonal antibodies, small interfering RNA, viral entry inhibitors, capsid assembly modulators, innate immune stimulators, therapeutic vaccines, checkpoint inhibitors, and nucleic acid polymers. Early clinical data suggests that a combination

of multiple therapeutic modalities may be necessary to achieve functional cure in the majority of chronic HBV patients and that lowering HBsAg is a critical component of any combination regimen (Revill 2019; Zoulim 2015).

2.2. Study Rationale

This study is intended to evaluate multiple study intervention(s) and their combinations in different populations of chronic HBV infected participants. A platform design has been chosen to implement this study. The platform design will allow for a modular approach with a Master Protocol that contains common elements shared across all sub-protocols and interventions. The sub-protocols may contain additional interventions, patient populations, or study-specific elements. A platform study design will allow for evaluation of safety and efficacy of study interventions across the sub-protocols among the different patient populations. Platform study designs are routinely used in oncology and Coronavirus disease 2019 (COVID-19) clinical trials and are also being currently utilized to evaluate interventions in chronic HBV infection (clinicaltrials.gov identifiers: NCT04225715, NCT04667104, NCT04129554, NCT04746183, NCT04518410, NCT03697304, NCT01042379).

CCI

2.3. Benefit/Risk Assessment

This platform design study is intended to evaluate different regimens of investigational therapies in participants with chronic HBV infection. Compared to the current standard of care, the regimens to be evaluated will offer the potential benefits of finite duration, pan-genotypic activity, and the potential to achieve a functional cure, which may be associated with a reduction in HBV-associated severe sequelae such as cirrhosis, liver failure, HCC, or death. Given the nature of chronic HBV infection, all the sub-protocols are designed with an emphasis on hepatic safety. These include but are not limited to specific participant selection criteria, regular monitoring of laboratory evaluations, and procedures for timely reporting and oversight of any safety-related events. The sub-protocols describe the intervention-specific benefit/risk assessments.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	Depending on the development phase, the primary endpoint(s) associated analysis methods and power calculations will be from those listed below. The time point at which it will be assessed will be specified within the sub-protocol.
• To evaluate the efficacy of the investigational regimen(s)	• Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at 24 weeks after discontinuation of all treatment[a] • Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) at 24 weeks after discontinuation of all treatment[a] • Proportion of participants with HBsAg loss (< 0.05 IU/mL) at 24 weeks post-end of treatment[b] • 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[b] • Proportion of participants with HBsAg loss (< 0.05 IU/mL) at the end of treatment[b] • Mean change in serum HBsAg from baseline across timepoints in the study
Secondary	
• To evaluate the safety and tolerability of the investigational regimens • To assess the effect of the investigational regimens on serum hepatitis B surface antigen (HBsAg) • To assess the effect of the investigational regimens on anti-HBs	1. Proportion of participants with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) 2. Proportion of participants with serum HBsAg ≤ 10 IU/mL at end of treatment[b] 3. Proportion of participants with serum HBsAg ≤ 10 IU/mL at 24 weeks post-end of treatment[b] 4. Serum HBsAg levels and change from baseline across timepoints in the study 5. Serum HBsAg level at nadir during the study

Objectives	Endpoints
	6. Time to achieve nadir of serum HBsAg during the study 7. Time to achieve serum HBsAg loss (< 0.05 IU/mL) 8. Proportion of participants with HBsAg loss with anti-HBs seroconversion at end of treatment and at 24 weeks post-end of treatment[b]
Exploratory	
• To evaluate additional viral parameters associated with HBV and/or study intervention(s) CCI	1. Additional viral parameters associated with HBV and/or study intervention(s), including but not limited to HBV RNA and Hepatitis B core-related antigen (HBcrAg) CCI
• To evaluate the emergence of viral resistance to study intervention(s) CCI	4. Emergence of viral resistance to study intervention(s) CCI

[a] Discontinuation of all therapies as defined in the sub-protocols (including investigational therapies and background NRTI, if applicable)
[b] End of treatment as defined in the sub-protocols

4. STUDY DESIGN

4.1. Overall Study Design

The intention of the PREVAIL Master Protocol is to provide a standardized platform study design to evaluate the safety and efficacy of investigational candidate(s) and their combinations as potential treatments for adults with chronic HBV infection. The Master Protocol describes the overall study outline, study populations, common objectives and endpoints, common inclusion exclusion criteria, common elements of randomization scheme, statistical methodology, general study assessments which include efficacy and safety assessments, and the planned analyses that are common to all sub-protocols. The Master Protocol should be read in conjunction with each sub-protocol. The sub-protocols will identify specific investigational therapy(ies), the population(s) in which they will be tested, the study-specific design and any additional information pertinent to the regimen(s). Additional sub-protocols may be added to this Master Protocol to evaluate novel study intervention(s) and combinations in populations defined herein.

The safety and efficacy of investigational therapies may be evaluated in parallel or sequentially in cohorts as described in the specific sub-protocol. Participants will consent to the Master Informed Consent Form (ICF) and the sub-protocol ICF prior to enrollment into a cohort. All protocol-related activities will be conducted only after the participant has signed the ICFs. After the participant has consented to participating in the study, they will be screened. Based on the screening data and the eligibility for sub-protocol(s), the participants will be enrolled into a cohort by the Interactive Response Technology (IRT). The exact duration of the study and the individual study periods will be described in the sub-protocols.

At the end of the Follow-Up Period, the participants may either end the study or be provided with an option to enroll into another cohort, sub-protocol, or study, if available. Participants who have provided informed consent will undergo evaluation for eligibility for optional enrollment into another study cohort. Data collection will be carried out per cohort or sub-protocol in which the participant is enrolled. If a participant is not eligible, data collection will stop which will conclude study participation.

4.1.1. Brief Summary

This platform study will evaluate the safety and efficacy of investigational interventions in one or more of the following populations of adult participants with chronic HBV infection as described in Table 3.

Table 3: Populations Included in This Platform Protocol

Protocol Population	HBeAg status	HBV DNA level	ALT level
I	Positive	High[a]	≤ ULN
II	Positive	High[a]	> ULN
III	Negative	> LLOQ[a]	> ULN
IV	Negative	≤ 2,000 IU/mL	≤ ULN
V	Positive	≤ LLOQ or low (on NRTI therapy)[a]	Variable [a]
VI	Negative	≤ LLOQ or low (on NRTI therapy)[a]	Variable [a]
VII	Negative	> LLOQ[a]	≤ ULN

HBeAg: Hepatitis B e Antigen; LLOQ: Lower limit of quantitation; ALT: Alanine Aminotransferase; ULN: Upper limit of normal; NRTI: Nucleos(t)ide Reverse Transcriptase Inhibitor

[a] As defined in the respective sub-protocol

Specific details of the population(s) included and investigational therapies will be included in the respective sub-protocol(s).

4.1.2. Number of Participants

The number of participants will be specified in each sub-protocol.

In Phase 1b evaluations, each cohort will include up to approximately 10 participants.

For a single-arm Phase 2 sub-protocol, approximately 10-25 participants will be enrolled. For a Phase 2 sub-protocol with a concurrent control, approximately 75-120 total participants will be enrolled to be randomized to active and control in a 2:1 ratio.

4.1.3. Intervention Groups and Duration

Refer to specific sub-protocol.

4.1.4. Study Committees

The committees in the sub-protocols may include but not be limited to a Liver Flare Adjudication Committee (LFAC), Safety Review Committee (SRC), and/or Independent Data Monitoring Committee (IDMC).

4.2. Scientific Rationale for Study Design

Chronic HBV infection is a dynamic process based on the relationship between viral replication and the host immune response. Currently available treatment options for treatment of chronic HBV include NRTIs and/or PEG-IFNα. NRTIs provide suppression of viral replication but have low rates of functional cure, do not eliminate cccDNA or integrated DNA, and require life-long treatment. PEG-IFNα is associated with low rates (<10%) of functional cure on average and tolerability concerns. In addition, given the dynamic nature of the disease, not all patients qualify for the currently available treatment options. Therefore, there exists an unmet need for alternative treatment options with finite treatment regimens, better tolerability, and higher rates of efficacy.

This study is intended to evaluate multiple study intervention(s) and their combinations in different populations of participants with chronic HBV infection. Participants co-infected with HAV, HCV, HDV, HEV or HIV have been excluded in this study to allow better characterization of the investigational therapies in the absence of other clinically significant co-infections. A platform design has been chosen to implement this study and the advantages of utilizing a platform design are described in Section 2.2.

4.3. End of Study Definition

The end of study for this Master Protocol is defined as the date of the last scheduled visit (or scheduled contact) of the last participant in the last open sub-protocol.

5. STUDY POPULATION

Participants that fulfil the following inclusion/exclusion criteria in addition to those outlined in the sub-protocols may be included in the study.

5.1. Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for this Master Protocol. Additional clarifications and sub-protocol-specific criteria as described in respective sub-protocol(s) will be applicable:

1. Adult ≥ 18 years of age (or age of legal consent, whichever is older)
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)

   Additional characteristics of the chronic HBV infection (eg: HBeAg status, HBV DNA level, ALT level) will be required based on the patient population (Table 3) included in respective sub-protocols
3. Besides chronic infection with HBV, must be in good health, determined from medical history, and no clinically significant findings from physical examination other than those expected in persons with cirrhosis, 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 period defined in sub-protocol. Female participants must also agree to refrain from egg donation and in vitro fertilization from the time of study intervention administration through period defined in sub-protocol

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 period defined in sub-protocol: 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 period defined in sub-protocol
6. Able to understand and comply with the study requirements and able to provide written informed consent

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply. Additional exclusion criteria may be described in respective sub-protocol(s):

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), hepatitis C virus (HCV), hepatitis D virus (HDV) or hepatitis E virus (HEV). 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 IgG or HEV immunoglobulin G (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.

5.3. Lifestyle Considerations

Lifestyle considerations (eg, restrictions regarding diet, caffeine, alcohol, tobacco, etc.), if applicable, will be included in the respective sub-protocol.

5.4. Screen Failures

Screen failed participants may be re-screened after discussion with Sponsor.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

This platform study is intended to evaluate multiple study interventions alone or in combinations for the treatment of chronic HBV infection in different patient populations. Study interventions and the details of their dosage, route of administration, frequency and duration of dosing, preparation, compliance, dose modification, and any other applicable information will be defined in respective sub-protocols. Permitted and non-permitted concomitant medications will also be defined in the sub-protocol.

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

7.1. Study Stopping Rules

Refer to respective sub-protocols for specific details regarding study stopping rules.

7.2. Discontinuation of Study Intervention

Refer to respective sub-protocol for specific details. Participants that have received at least 1 dose of the study intervention(s) will not receive additional doses if any one of the criteria described are met:

1. Any clinical manifestations of hepatic decompensation
2. Grade 3 or higher study intervention-related AE of anaphylaxis, cytokine release syndrome, or immune complex disease
3. Additional criteria will be defined in sub-protocols as applicable

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, Sponsor medical monitor, and other safety review committees as applicable per sub-protocol, the participant may be considered to continue receiving study intervention.

Participants who become pregnant during the Treatment Period will not receive additional doses of study intervention. See Section 8.7.7.1 for additional details.

Participants who discontinue study intervention(s) 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 visit schedule in accordance with the Schedule of Activities (SOA) of their sub-protocol.

7.3. Participant Discontinuation/Withdrawal from the Study

If a participant discontinues from the study (eg, due to withdrawal of consent) after initiation of study intervention(s) but before the final dose of study intervention, assessments for the EOT visit should be performed.

If a participant discontinues from the study after the EOT visit, assessments for the final visit of the Follow-Up Period (EOFU) should be performed.

7.4. Replacement of Participants

Participants who receive any dose of the planned regimen will not be replaced.

7.5. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, or the vital status be determined as deceased, he/she will be considered to have withdrawn from the study. If the investigator becomes aware of an AE/SAE, the information must be recorded per Section 8.7 or Section 10.3.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in SOA (Section 10.7).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness.
- Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed by the investigator(s) to confirm that potential participants meet all eligibility criteria. The site will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF as allowable by ICH/GCP and/or CFRs may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SOA.
- Repeat or unscheduled laboratory samples may be taken for safety reasons or for technical issues with the samples.

8.1. Screening Period

Informed consent must be obtained before conducting any study procedures. Screening will be performed within 56 days (8 weeks) prior to dosing and include the assessments (such as medical history and demographics) outlined in the sub-protocol specific SOA. Screening laboratory tests may be repeated (eg, for values thought to be erroneous) with Sponsor medical monitor approval.

8.1.1. Screening Confirmation of Chronic HBV Infection

Chronic HBV infection will be determined at screening and is defined as the following:

- 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)

8.1.2. Screening Viral Serology Parameters

Screening viral serology parameters are as follows: active infection with HIV, HAV, HCV, HDV, and HEV. Participants who have positive HCV or HDV serology result must have HCV-RT PCR or HDV-RT PCR reflex testing respectively to determine eligibility. Participants with positive HAV or HEV IgM must have reflex HAV or HEV IgG, respectively.

8.1.3. Screening for Drugs of Abuse

Urine will be collected at the screening visit for drugs of abuse screening, per the SOA. The panel will include amphetamines, cocaine, methadone, and opiates.

8.2. Efficacy Assessments

Efficacy in this study will be assessed based on the changes to viral parameters as listed in endpoints. Primarily, but not limited to the following will be recorded and evaluated as the efficacy endpoints: HBsAg, HBeAg, HBV DNA, anti-HBs, and anti-HBe levels.

8.3. Safety Assessments

8.3.1. Physical Examinations

A full physical examination will be conducted to determine the overall physical health of the participant, and any abnormal findings at screening will be recorded as medical history. The physical examination may include but is not limited to general appearance, head, neck, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, extremities, skin, and screening neurological assessment

8.3.2. Vital Signs

Vital sign measurements include blood pressure, pulse rate, temperature (oral preferred), and respiratory rate. Vital signs should be measured after the participant has rested comfortably for approximately 10 minutes. When scheduled at the same timepoints, the assessments of vital signs must be performed before blood sample collections and study intervention administration(s).

8.3.3. Clinical Safety Laboratory Tests

Clinical laboratory tests (such as serum chemistry, hematology, urinalysis, etc.) that will be performed are presented in Section 10.2. The respective sub-protocols will list additional assessments required depending on the study population and study interventions being evaluated. Screening laboratory tests may be repeated once (eg, for values thought to be erroneous) with Sponsor approval.

8.3.4. Pregnancy Testing

A pregnancy test or confirmation of post-menopausal status must be confirmed for all female participants. Post-menopausal status is defined as no menses for 12 months 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. Pregnancy tests will be performed for WOCBP only. Pregnancy testing will be performed per the SOA and any time pregnancy is suspected. A WOCBP who is known to be pregnant or who does not have a negative pregnancy test at screening is not eligible for study participation. A blood pregnancy test will be performed at screening and urine pregnancy tests will be performed at subsequent visits. During the study, the results of these pregnancy tests must be known prior to study intervention administration. A WOCBP determined to be pregnant while on study will be followed until the pregnancy outcome is known, as described in Section 8.7.7.1.

8.3.5. Other Safety Assessments

Other safety assessments relevant to the study intervention will be described in the respective sub-protocol.

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

Assessment of screening viral parameters will include: HBsAg (quantitative), anti-HBs (qualitative), HBeAg (qualitative), anti-HBe (qualitative), and HBV DNA (quantitative).

Any additional viral parameters, anti-viral activity, and resistance surveillance, if applicable, will be described in the sub-protocol.

8.5. CCI

Patient Reported Outcomes (PROs) may be collected, see sub-protocol SOA for detail.

CCI

8.6. Exploratory Assessments

Exploratory assessments will be conducted as part of this study. Additional exploratory assessments will be described in respective sub-protocols.

8.6.1. Exploratory Analysis Samples

Exploratory samples may include but are not limited to the following:

CCI

- Virologic biomarkers, including but not limited to HBV RNA and HBcrAg. This may also include viral sequencing.

CCI

Details will be described in the respective sub-protocol and/or sub-protocol specific laboratory manual. Samples already collected for other tests from the same study visit may be used to run additional exploratory tests that are included in this sub-protocol. If a participant is negative for a given virologic biomarker, additional samples may not be tested.

8.6.2. CCI

Details regarding the processing, shipping, and analysis of these samples are provided in the Laboratory Manual. Refer to respective sub-protocol for details as appropriate.

8.6.2.1. CCI

CCI

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

8.6.2.2. CCI

CCI

8.6.2.3. CCI

CCI

CCI a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

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

The definitions of AEs, SAEs, and other safety events are provided in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

After signing of the ICF, but prior to initiation of study intervention, AEs/SAEs related to protocol-mandated procedures should 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.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent, and are not considered related to protocol mandated procedures, will be recorded as medical history/current medical conditions, not as AEs.

All SAEs, regardless of causal relationship, will be collected from signing of ICF until the end of study.

All SAEs must be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours from the investigator or designee awareness of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.7.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, pregnancy, and special situation reports (SSRs) (as defined in Section 10.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.5). Further information on follow-up procedures is provided in Section 10.3.

8.7.3. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential to meet legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation. The investigator will record the SAE information on the appropriate form and submit it to Sponsor or designee within 24 hours of awareness of the event.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review the

information, document the review, file the safety report along with the relevant study documents, and will notify the IRB/IEC, if appropriate, according to local requirements.

Assessment of expectedness for SAEs will be determined by the Sponsor using the reference safety information (RSI) as specified in the Investigator's Brochure (IB). Assessment of expectedness for marketed products will be determined by the Sponsor using the product label.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.7.4. Adverse Events of Interest

Refer to respective sub-protocol.

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

Laboratory abnormalities without an associated AE (signs or symptoms) and/or which do not require medical intervention, are not themselves recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study intervention interruption, modification, or discontinuation must be recorded as an AE or as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Section 10.3. If the laboratory abnormality is part of a clinical syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 or later, as specified in the respective sub-protocol (presented in Section 10.3).

Additional laboratory abnormalities and other abnormal assessment considerations, if applicable, will be included in the respective sub-protocol.

8.7.6. Laboratory Events of Clinical Interest

Laboratory Events of Clinical Interest (ECIs) will be defined in the sub-protocols, as applicable. An ECI is a laboratory value of scientific and medical interest specific to understanding of an investigational product and may require additional follow-up testing, close monitoring, and rapid communication by the investigator to the Sponsor. The rapid reporting of ECIs allows ongoing surveillance of these events to characterize and understand them in association with the use of an investigational product. The signs, symptoms, and/or clinical sequelae resulting from an ECI will be reported as AE or SAE if they fulfill the definition of an AE or SAE. The LFAC may oversee and monitor the status of the liver-related ECIs as defined in sub-protocols.

8.7.7. Special Situation Reports

All special situation reports (SSR) will be collected from the start of intervention until the end of follow-up period and include all reports of medication error, abuse, misuse, overdose, pregnancy, drug interactions, exposure via breastfeeding, unexpected benefit, occupational exposure,

transmission of infectious agents via the product, counterfeit or falsified medicine, and product complaints (definitions presented in Section 10.3).

The investigator will record the special situation information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the situation. These reports must consist of situations that involve study intervention and/or protocol required concomitant medications but do not apply to non-required concomitant medications.

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

All clinical sequelae in relation to these special situation reports (from required and non-required medication) will also be reported as AEs or SAEs. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8.7.7.1. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the end of study.

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the female participant or female partner of male participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination of a pregnancy for any reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner (after obtaining the necessary signed informed consent from the female partner) will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.7.3. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, if he/she learns of any SAE and considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

The study participant and/or pregnant female partner, as applicable, should receive any necessary counseling regarding the risk of continuing the pregnancy and the possible effects on the fetus.

8.7.8. Other Safety Reporting

Other sub-protocol-specific safety reporting requirements eg: cardiovascular events, disease-related events and/or disease related outcomes not qualifying as AEs or SAEs will be specified in the respective sub-protocol, as applicable.

8.8. Other Assessments

Other safety, efficacy, and exploratory assessments such as immunogenicity and pharmacokinetic assessments may be included as defined in respective sub-protocols

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Phase 1b sub-protocols will be exploratory, and no formal hypothesis testing will be conducted.

In Phase 2 sub-protocols, if we evaluate response rate, defined as the proportion of participants achieving HBV DNA suppression (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at end of treatment or at 24 weeks after discontinuation of all treatment, or HBsAg loss at end of treatment or 24 weeks post-end of treatment, or HBV DNA suppression 24 weeks after discontinuation of all treatment, as the primary endpoint(s), the null hypothesis is that response rate is the same as in NRTI-suppressed patients. It is assumed the response rate is ≤ 2% in NRTI-suppressed patients. The null hypotheses are described in Table 4 for a single arm study and Table 5 for a randomized controlled study with concurrent controls. The alternative hypothesis will be described in the sub-protocol.

9.1.1. Multiplicity Adjustment

The study is exploratory in nature. No multiplicity adjustment will be made.

9.2. Sample Size Determination

In a phase 1b sub-protocol, the sample size is not based on any statistical hypothesis testing. For the purposes of safety evaluation, each cohort will include up to approximately 10 participants.

For a single-arm Phase 2 sub-protocol, approximately 10-25 participants will be enrolled. For a Phase 2 sub-protocol with a concurrent control, approximately 75-120 total participants will be enrolled to be randomized to active and control in a 2:1 ratio.

Since the primary endpoints of HBsAg loss rate at EOT or 24 weeks post-EOT are good predictors for achieving the sustained HBV DNA at 24 weeks after discontinuation of all treatments, sample size calculation for the initial assessment of an investigational regimen is based on HBsAg loss rate as described below (FDA 2018; Terrault 2018).

- An investigational regimen will initially be evaluated in an open label single arm study, without a concurrent control arm. If the true HBsAg loss rate ranges from 25% to 40%, at least 10 participants will be required to provide > 70% statistical power to detect a 23% difference in HBsAg loss rate, using a 1-sided exact binomial test with a significance level of 0.025 (Table 4).
- An investigational regimen may also be evaluated in a randomized placebo-controlled study. Assuming a 2:1 active-to-placebo randomization ratio, at least 75 participants will be required to provide > 70% statistical power to detect a 23% difference in HBsAg loss rate, using a 1-sided Fisher's exact test with a significance level of 0.025 (Table 5).

Table 4: Power and Sample Size Calculation for Single Arm Efficacy Evaluation

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

Table 5: Power and Sample Size Calculation for Efficacy Evaluation with Concurrent Controls

Null Hypothesis: Response rate in the study intervention arm is not greater than that in the concurrent control. **Assumptions:** (1) Randomization ratio of 2:1 to active and control arms; (2) ≤ 2% of the controls will achieve HBsAg loss; (3) Use Fisher's exact test with 1-sided significance level of 0.025.		
Sample Size (Active: Control)	Power to detect 23% difference in response rate, if the true response rate is 25%	Power to detect 38% difference in response rate, if the true response rate is 40%
50:25	71.2%	98.5%
60:30	83.6%	> 99%
70:35	91.2%	> 99%

The larger sample size may be considered to assess efficacies in participant subgroups according to their baseline disease characteristics, eg, HBsAg levels, HBeAg status, HBV DNA levels, HBV genotypes, or based on other factors such as site or country.

Refer to the sub-protocols for additional information regarding sample size determination, including considerations for cohort expansion will be based on interim analysis of response rate for the primary endpoint.

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Analysis Sets	**Description**
All Screened Set	The All Screened Set includes all participants who signed the informed consent form. The listing of Eligibility Criteria will be based on All Screened Set.
All Enrolled Set	The All Enrolled Set includes all participants in the All Screened Set who were assigned to study intervention. Summaries for disposition, demographics and baseline characteristics will be reported based on the All Enrolled Set.
Full Analysis Set (FAS)	The FAS includes all participants in the All Enrolled Set who received at least one dose of study intervention(s). This is the primary analysis set for efficacy and antiviral analyses.
Safety Analysis Set	Safety Analysis Set includes all participants who received any amount of study intervention. All safety analyses will be based on the Safety Analysis Set.

9.4. Statistical Analyses

9.4.1. General Considerations

All disposition, demographics and baseline characteristics will be reported based on the All Enrolled Set. All safety analyses will be on the Safety Analysis Set. All efficacy and antiviral activity analyses will be based on the FAS.

The Statistical Analysis Plan (SAP) will be finalized prior to Database Lock (DBL) and will include technical details and description of the statistical analyses including sensitivity analyses that will be performed.

Unless otherwise stated, the following rules will apply:

- Summaries and displays will be presented by treatment cohort.
- Categorical endpoints will be summarized by number and percentage of participants who meet the endpoint by treatment cohort.
- Continuous endpoints will be summarized using conventional descriptive statistics (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, and maximum) by treatment cohort.
- TEAE definition: An AE that is reported with an onset date on or after the start of study intervention(s) until the duration specified in the subprotocol after the last dose of study intervention(s).
- Missing value will not be imputed

Only scheduled visits will be presented in summaries. Unscheduled visits will be listed but will not be summarized.

9.4.2. Primary Endpoint(s) Analysis

The primary efficacy objective evaluation in a sub-protocol will be performed using the FAS. Depending on the development phase, each sub-protocol will specify the primary endpoint(s) from the list below.

- Proportion of participants achieving suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at EOT
- Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) at 24 weeks after discontinuation of all treatment
- Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at 24 weeks after discontinuation of all treatment
- Proportion of participants with HBsAg loss (< 0.05 IU/mL) at EOT
- Proportion of participants with HBsAg loss (< 0.05 IU/mL) at 24 weeks post-EOT
- Mean change in serum HBsAg from baseline across timepoints in the study

9.4.2.1. Population

All eligible participants with chronic HBV infection, as defined in the FAS.

9.4.2.2. Missing Data

Every effort will be made to reduce missing data. Missing data for the HBV DNA will be assumed to be < LLOQ if HBV DNA measures were < LLOQ at both the prior and subsequent visits. Missing data for HBsAg loss will be assumed to be < 0.05 IU/mL if HBsAg measures were < 0.05 IU/mL at both the prior and subsequent visits. Other than the imputation specified above, no other imputation will be done. For all efficacy response variables, the missing equals failure (MEF) approach will be used for the primary analysis. As a sensitivity analysis, the primary endpoints may be evaluated in participants with a minimum level of incompliance with the investigational regimen, defined in the SAP, and without important major protocol deviations that could substantially affect the outcome of the treatment. When applicable and sample size permits, the primary endpoints may also be evaluated in participants meeting specified threshold criteria (eg: NRTI discontinuation criteria).

Further details will be specified in the SAP of the sub-protocol.

9.4.2.3. Population Level Summary

Proportion of participants who achieved suppression of HBV DNA [< LLOQ] with HBsAg loss (< 0.05 IU/mL) at EOT and the corresponding two-sided 95% confidence interval will be calculated for each cohort.

Proportion of participants who achieved sustained suppression of HBV DNA [< LLOQ] at 24 weeks after discontinuation of all treatment and the corresponding two-sided 95% confidence interval will be calculated for each cohort.

Proportion of participants who achieved sustained suppression of HBV DNA [< LLOQ] with HBsAg loss (< 0.05 IU/mL) 24 weeks after discontinuation of all treatment and the corresponding two-sided 95% confidence interval will be calculated for each cohort.

Proportion of participants who achieved HBsAg loss (< 0.05 IU/mL) at EOT and the corresponding two-sided 95% confidence interval will be calculated for each cohort.

Proportion of participants who achieved HBsAg loss (< 0.05 IU/mL) at 24 weeks post-EOT and the corresponding two-sided 95% confidence interval will be calculated for each cohort.

The maximum reduction of serum HBsAg from baseline will be summarized using the conventional descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for each cohort.

9.4.3. Secondary Endpoint(s) Analysis

The number and percentage of participants with adverse events will be summarized by severity, seriousness, relationship to the study drug, MedDRA system organ class, and preferred term based on the Safety Analysis Set.

The key secondary efficacy endpoints including the effect of the study intervention on HBsAg, anti-HBs, HBeAg, and HBV DNA in the FAS will be summarized.

9.4.4. Exploratory Endpoint(s) Analysis

Refer to sub-protocol for details.

9.4.5. Missing Data

Handling of missing data will be described in the sub-protocols and SAP as applicable.

9.4.6. Other Safety Analyses

Additional safety will be evaluated by assessment of clinical laboratory tests, physical examinations, and vital signs measurements at various time points during the study and by the documentation of AEs, when applicable.

All safety data collected on or after administration of study intervention(s) up to the last scheduled visit, unless specified otherwise, will be summarized by treatment cohort.

9.5. Interim Analysis

Interim analysis may be performed. The timing and adaption rule of the interim analysis will be defined in the respective sub-protocols for each experimental regimen.

9.6. Other Analyses

Other analyses that may be conducted for a sub-protocol include but are not limited pharmacokinetics, genetics, biomarkers, etc. These will be defined in the respective sub-protocols as applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the Master Protocol and applicable sub-protocols with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The Master Protocol, sub-protocols, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators, sub-investigators, and applicable site staff will provide the Sponsor or designee with sufficient, accurate financial information as requested to allow the Sponsor/designee to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators, sub-investigators, and applicable site staff are responsible for providing information on financial interests during the course of the study and for 1 year after site closure.

10.1.3. Informed Consent Process

The participant's signed and dated informed consent (either signed by participant or their legally authorized representative [LAR]) must be obtained before conducting any study procedures.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will be anonymized except for the identifier; participant names or any information which would make the participant identifiable will not be transferred.
- All participants must provide informed consent to the use and disclosure of their information obtained during the study. This includes informing the participant how their personal study-related data will be used by the Sponsor and the level of disclosure.
- The participant must also be informed and consent to the possible examination of their medical records by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Confidentiality

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

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

10.1.6. Committees Structure

The committees in the sub-protocols may include but not be limited to a LFAC, SRC and/or IDMC.

10.1.6.1. Liver Flare Adjudication Committee (LFAC)

The LFAC is an independent committee that will provide hepatic safety oversight by performing periodic reviews of hepatic safety data as well as adjudicate ECI. Laboratory ECI will be pre-defined in each of the respective sub-protocols. The LFAC membership composition and data review requirements are described in detail in the LFAC Charter.

10.1.7. Dissemination of Clinical Study Data

- A clinical study report for each sub-protocol will be written and may be provided to the appropriate regulatory authorities.
- This clinical study may be registered, and its results posted on public registries in compliance with local and/or regional regulations.

10.1.8. Data Quality Assurance

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial process and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the clinical investigative site to perform audits or inspections, including source data verification. The investigator should contact the Sponsor, or its designee, immediately if contacted by a regulatory agency about an inspection.

10.1.9. Source Documents

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

10.1.10. Electronic Case Report Forms (eCRF)

- Data collected during the study (except clinical laboratory results, PK analysis, study disease testing results, immunogenicity) will be recorded in each participant's eCRF provided by the Sponsor or designee.
- The study site(s) will use an Electronic Data Capture (EDC) system that is compliant with relevant Food and Drug Administration (FDA) regulatory requirements per 21 CFR Part 11.
- Data queries and data correction on the eCRF will be handled through the same system.
- All transactions within the EDC system are fully documented within an electronic audit trail.

- Data reported on the eCRF must be transcribed from a source document with consistency and accuracy.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm the accuracy of data entered into the eCRF. Each set of completed eCRFs must be reviewed after being source verified by the monitor and electronically signed and dated by the investigator.
- Validated and secure electronic access will be granted to qualified Sponsor staff to review the participants' electronic records to verify that the information in the records matches the information entered in the EDC system. If required, in the event of audit, auditor(s) may be granted access to electronic records.
    - In cases where validated and secure electronic access to the participant's electronic records is not available, unredacted source documents (including ICF, Regulatory Documents and Source data) will be uploaded into a regulatory and data privacy-compliant cloud environment, generating certified copies of source documents (as per ICH/GCP guidelines) to be verified by the study monitor against the information entered in the EDC. As per ICH/GCP guidelines, the principal investigator and site staff users remain in control of the source documents, only site personnel can upload or invalidate source data, while only Clinical Research Associates (or auditors, as required) assigned to a given site can view the source documents remotely.

10.1.11. Study and Site Start and Closure

First Act of Recruitment

The first act of recruitment is the first participant enrolled and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site and/or terminate one or more individual cohorts, sub-protocols or the overall study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. If the investigator terminates or suspends a trial without the prior agreement of the Sponsor, the investigator should inform the institution (where applicable) of the suspension or termination at the investigative site. The investigator / institution should promptly inform the IRB/EC and the Sponsor of the termination/ suspension with a detailed, written explanation of the reason for the suspension or termination of the trial.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.12. Publication Policy

- Site-specific results of this study may be published or presented at scientific meetings subject to the terms and requirements of the clinical trial agreement

10.2. Appendix 2: Clinical Laboratory Tests

Table 6: Protocol-Required Safety Laboratory Tests

Additional tests will be listed in respective sub-protocol

Chemistry	**Hematology**
Albumin Blood urea nitrogen Calcium Bicarbonate Chloride Creatine kinase[a] Creatinine Creatinine clearance (calculated) Gammaglutamyltransferase (GGT) Glucose (non-fasting) Lactate dehydrogenase (LDH) Potassium Sodium Liver Function Tests: Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct) Complement (C3, C4, CH50)[b]	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[c], B, C[d], D[e] and E[c] Human immunodeficiency virus I and II Lipase Amylase Follicle stimulating hormone (FSH)[f]

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

[b] As indicated in the sub-protocols Schedule of Activities

[c] Participants with positive HAV IgM or HEV IgM but asymptomatic and with a positive HAV IgG or HEV IgG are eligible.

[d] Participants with positive HCV screening serology may have HCV RT-PCR performed to determine eligibility.

[e] Participants with positive HDV screening serology may have HDV RNA performed to determine eligibility.

[f] Required for confirmation of menopause only as applicable

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, vital signs measurements) that require medical or surgical intervention or lead to study intervention interruption, modification, discontinuation, or are considered clinically significant in the medical and scientific judgment of the investigator • Exacerbation of a chronic or intermittent pre-existing condition (recorded as medical history) including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected study intervention interaction, including drug/drug, drug/food, drug/device and drug/alcohol interactions. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy, transfusion, tooth extraction): the condition that leads to the procedure is the AE • Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, hospitalization for elective surgery) • Overdose of study intervention without clinical sequelae • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the screening visit that do not worsen

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:
1. Results in death
2. Is life threatening • The term "life threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent or significant disability/incapacity

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:
• The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other medically important events • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. – Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse, suspected transmission of any infectious agent via an authorized medicinal product.

10.3.3. Definitions of Special Situations (SSR)

Situations Defined as Special Situations (SSR)
• Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, participant, or consumer. • Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a participant. • Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information. • An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the pharmacist cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the additional dose(s) were administered to the participant.

Situations Defined as Special Situations (SSR)
• Occupational exposure is defined as exposure to a study intervention as a result of one's professional or nonprofessional occupation. • Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction. • Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial. • Transmission of infectious agents is defined as any suspected transmission of an infected agent through Sponsor's study intervention. • Counterfeit or falsified medicine: Any study intervention with a false representation of (a) its identity, (b) its source, or (c) its history. • Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product. The signs, symptoms, and/or clinical sequelae resulting from a special situation will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

10.3.4. Definition of Adverse Event of Interest (AEI)

AEI Definition
• An AEI is a noteworthy event for the particular product or class of products that the Sponsor may wish to monitor carefully. It could be serious or non-serious (eg, hair loss, loss of taste, impotence). • Such events will be described in the sub-protocol, if applicable, and instructions provided for investigators as to how and when they should be reported to the Sponsor.

10.3.5. Recording and Follow-Up of AEs, SAEs, SSRs (including Pregnancies) and/or AEIs

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information into the section of the participant's AE eCRF and the event description section of the SAE form. • All AEs/SAEs should be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the required forms.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For fatal or life-threatening events, copies of hospital case reports, discharge summaries, autopsy reports, and other documents should be submitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the AE/SAE must be recorded onto the concomitant medication section of the participant's eCRF and the event description section of the SAE form.

SSR (including Pregnancy) and/or AEI Recording

- When an SSR (including Pregnancy)/AEI occurs, it is the responsibility of the investigator to review all documentation and record the relevant information on the corresponding report form.
- If the SSR/AEI is associated with an AE/SAE, the information will also be recorded as per AE/SAE recording procedures.

Assessment of Severity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study according to the standard toxicity grading in the CTCAE v5.0 (or later, if specified in the respective sub-protocol). Definitions of severity per CTCAE (v5.0) are presented in Table 7.
  - For each event, the highest grade attained should be reported.

Table 7: CTCAE (v5.0) Definitions of Severity

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

ADL=activities of daily living
Source: NCI 2017

Assessment of Causality
• The investigator is obligated to assess the relationship between each study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship (Yes or No). • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. • An answer of Yes should be entered when, in the investigator's opinion, there is a reasonable possibility that the AE is associated with study intervention. Otherwise, relationship to study intervention should be categorized as No. • The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

Assessment of Causality
• There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs, SAEs, SSRs (including Pregnancies) and/or AEIs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE, SAE or AEI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated data to Sponsor within 24 hours of receipt of the information.

10.3.6. Reporting of SAEs, SSRs (including Pregnancies) and/or AEIs

Safety (SAE, SSR, Pregnancy and/or AEI) Reporting to Sponsor

- Email or Facsimile transmission of the paper data collection tool is the primary method to transmit this information to Sponsor within 24 hours.
- The investigator is responsible for assessing SAEs and AEIs for causality and severity, and for final review and confirmation of accuracy of event information and assessments on the reporting forms.
- Sponsor's designee for receipt of all reports is UBC Pharmacovigilance.
- Contacts for safety reporting is as follows:

CCI [redacted]

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

ADL	activities of daily living
AE	adverse events
AEI	adverse events of interest
ALT	alanine aminotransferase
CIOMS	Council for International Organizations of Medical Sciences
CCI	
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
ECI	event of clinical interest
eCRF	electronic case report form
EDC	Electronic Data Capture
EOFU	End of Follow-Up
EOT	End of Treatment
FAS	full analysis set
CCI	
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBcAg	HBV core antigen
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBx	hepatitis B x antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
CCI	
CCI	
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IRB	institutional review board
IDMC	Independent Data Monitoring Committee
IRT	Interactive Response Technology
LAR	legally authorized representative
LFAC	Liver Flare Adjudication Committee
LLOQ	Lower Limit of Quantitation
MEF	missing equals failure
NRTI	nucleos(t)ide reverse transcriptase inhibitor
PEG-IFNα	peginterferon-alfa-2a
pol/RT	polymerase/reverse transcriptase
PreS1/PreS2/HBsAg	large, medium, and small surface envelope glycoproteins
CCI	
Q1	1st quartile
Q3	3rd quartile
rcDNA	relaxed-circular DNA
RNA	ribonucleic acid
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOA	schedule of activities
SRC	Safety Review Committee
SSR	special situation reports
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WOCBP	women of child-bearing potential

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10.5. Appendix 5: Summaries of Changes for Previous Protocol Amendments

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

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3. Objectives, endpoints and estimands 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.4.2 Primary Endpoint Analysis	Additional potential primary endpoints added *Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) at 24 weeks after discontinuation of all treatment* *Proportion of participants achieving sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/mL) at 24 weeks after discontinuation of all treatment* Clarified existing primary endpoint's viral marker levels. Relevant changes were made to the primary estimands, primary endpoint analysis sections, sample size determination	Two additional optional primary endpoints were added to conform with the FDA HBV guidance (FDA 2022)
1.1 Synopsis Table 3 Populations Included in This Platform Protocol	Modified the protocol populations I and IV to include participants that are at the limits indicated below: ALT < ULN modified to ALT ≤ ULN and/or HBV DNA < 2,000 IU/mL modified to HBV DNA ≤ 2,000 IU/mL	These modifications were made to include participants that may have the limit values and to align with major clinical practice guidelines (AASLD and EASL)
4.2 Scientific Rationale for Study Design	Added rationale for not including co-infected participants (HAV, HCV, HDV, HEV or HIV) in the study	To allow better characterization of the investigational therapies in the absence of other clinically significant co-infections

Table 9 Schedule of Activities: Follow-Up Period	Removed exploratory assessments from additional Follow-Up visits SOA	Additional Follow-Up visits that added to sub-protocols may not require collection of these exploratory assessments. If required, the sub-protocols will specify the exploratory assessments needed. This will ensure reduction of participant burden in terms of sample collection unless necessary for analyses.
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 through period described in sub-protocol. 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 study interventions will impact the effectiveness of hormonal contraceptive methods; therefore, it is recommended to use an additional form of contraception (i.e., barrier method) for period defined in sub-protocol.
- 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 period defined in sub-protocol 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 FSH level in the post-menopausal range should be used to confirm a post-menopausal state in women not using hormonal contraception or 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 period defined in sub-protocol.

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 period defined in sub-protocol.

- 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 period defined in sub-protocol.

10.7. Appendix 7: Schedule of Activities

Sub-protocols will define the timing of the visits and any additional assessments in the Treatment Period.

Table 8: Schedule of Activities: Screening and Treatment Periods

Study Stage	**Screening**	**Treatment Period**[a]			
Visit Week			**W1**	**On-Treatment Visit Week (Week Defined in Sub-Protocol)**	**EOT**[b]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**On-Treatment Visit Day (Day Defined in Sub-Protocol)**	
Study Procedures					
Informed consent	X				
Inclusion/exclusion criteria	X	X[c]			
Demography	X				
Physical examination	X				X
Medical history	X				
Vital signs[d]	X	X	X	X	X
Adverse event review/record[e]	X	X	X	X	X
Prior and concomitant medication	X	X	X	X	X
Liver scan (eg, Fibroscan)[f]	X				
Drug Administration[g]	**As defined in sub-protocol**				
Laboratory Assessments[h]					
Pregnancy test[i]	X	X	X	X	X
Screening viral serology[j]	X				
Liver function tests[k]	X	X	X	X	X
Serum chemistry[k]	X	X	X	X	X

Study Stage	**Screening**	**Treatment Period**[a]			
Visit Week			**W1**	**On-Treatment Visit Week (Week Defined in Sub-Protocol)**	**EOT**[b]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**On-Treatment Visit Day (Day Defined in Sub-Protocol)**	
Hematology [k]	X	X	X	X	X
Coagulation parameters [k]	X	X	X	X	X
Urinalysis [k]	X	X	X	X	X
Urine for drugs of abuse [l]	X				
HBsAg quantitative	X	X	X	X	X
Anti-HBs qualitative	X				
Anti-HBs quantitative		X		X	X
HBeAg qualitative	X				
HBeAg quantitative		X		X	X
Anti-HBe qualitative	X				
HBV DNA quantification	X	X	X	X	X
Exploratory Assessments					
CCI					
CCI					
Resistance surveillance[m]		X		X	X
CCI					
CCI					
CCI					
CCI					
CCI					

Study Stage	**Screening**	**Treatment Period**[a]			
Visit Week			**W1**	**On-Treatment Visit Week (Week Defined in Sub-Protocol)**	**EOT**[b]
Visit Day ± Visit Window	**D -56 to -1**	**D1**	**D8±2**	**On-Treatment Visit Day (Day Defined in Sub-Protocol)**	
Stabilized whole blood for immune cell assays		X	X	X	X

D = day; W = week; EOT= End of Treatment

[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 last visit in the Treatment Period, EOT assessments should be performed.

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

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

[e] After signing of the 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.

[f] As described in respective sub-protocols.

[g] Will be defined in sub-protocol as applicable.

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

[i] 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.

[j] See Section 8.4 for viral serology parameters.

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

[l] Drugs of abuse included in the panel are described in Section 8.1.3.

[m] See Section 8.4 and Section 8.1.2 for more information.

[n] As this assessment is exploratory, the collection and specific assays used may be changed or removed at the Sponsor's discretion based on emerging data. Further details can be found in Section 8.6.

Table 9: Schedule of Activities: Follow-Up Period

Sub-protocols will define any additional visits or additional assessments in the Follow-Up Period.

Study Stage	**Follow-Up Period[a]**								
Follow-Up Week	**F1**	**F4**	**F8**	**F12**	**F16**	**F20**	**F24**	**Fx[b] (additional F visits)**	**EOFU[c]**
Visit Day ± Visit Window	**D7±2**	**D29±7**	**D57±7**	**D85±7**	**D113±7**	**D141±7**	**D169±7**	**Dx**	**Dx**
Study Procedures									
Vital signs	X	X	X	X	X	X	X	X	X
Adverse event review/record	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
CCI									
CCI									
CCI									
Laboratory Assessments									
Pregnancy testing[e]	X	X	X	X					X
Liver function tests[f]	X	X	X	X	X	X	X	X	X
Serum chemistry[f]	X	X	X	X	X	X	X	X	X
Hematology[f]	X	X	X	X	X	X	X	X	X
Coagulation parameters[f]	X	X	X	X	X	X	X	X	X
Urinalysis[f]	X	X	X	X					
HBsAg quantitative	X	X	X	X	X	X	X	X	X
Anti-HBs quantitative	X	X	X	X	X	X	X	X	X
HBeAg quantitative	X	X	X	X	X	X	X	X	X
Anti-HBe qualitative	X	X	X	X	X	X	X	X	X

Study Stage	**Follow-Up Period**[a]								
Follow-Up Week	**F1**	**F4**	**F8**	**F12**	**F16**	**F20**	**F24**	**Fx**[b] **(additional F visits)**	**EOFU**[c]
Visit Day ± Visit Window	**D7±2**	**D29±7**	**D57±7**	**D85±7**	**D113±7**	**D141±7**	**D169±7**	**Dx**	**Dx**
HBV DNA quantitation	X	X	X	X	X	X	X	X	X
Exploratory Assessments									
CCI									
CCI									
CCI									
CCI									
CCI									
CCI									

D = day; F= Follow-Up visit week; EOFU= End of Follow-Up; WPAI:GH= Work Productivity and Activity Impairment Questionnaire: General Health (v2.0)

[a] Certain assessments may be performed remotely. The start of the Follow-Up Period relative to the end of the Treatment Period will be defined in the respective sub-protocol.

[b] Additional follow up visits as provided in sub-protocol.

[c] The assessments will be done at the last visit in the follow up period, if F24 is the last FU visit then EOFU assessments supersede those listed in F24.

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[e] Urine pregnancy test for WOCBP only.

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

11. REFERENCES

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