Study Title: A Randomized Phase 2a, Multicenter, Open-Label, Multiple-Cohort Study Evaluating Regimens Containing Vebicorvir in Subjects with Chronic Hepatitis B Virus Infection

NCT Number: NCT04820686

Date of Document: 27 October 2021

CLINICAL STUDY PROTOCOL

PROTOCOL TITLE	A Randomized Phase 2a, Multicenter, Open-Label, Multiple-Cohort Study Evaluating Regimens Containing Vebicorvir in Subjects with Chronic Hepatitis B Virus Infection
PROTOCOL NUMBER	ABI-H0731-204
DRUG NAME	Vebicorvir (VBR; formerly ABI-H0731) AB-729
REGULATORY AGENCY IDENTIFIER NUMBER(S)	US IND 136780
SPONSOR	Assembly Biosciences, Inc. 331 Oyster Point Boulevard, 4th Floor South San Francisco, California 94080, USA (833) 509-4583
PROTOCOL VERSION – DATE	Amendment 1 – 27 October 2021
PROTOCOL HISTORY	Original – 20 November 2020

CONFIDENTIALITY STATEMENT

CLINICAL STUDY PROTOCOL SPONSOR APPROVAL FORM

Protocol Title	A Randomized Phase 2a, Multicenter, Open-Label, Multiple-Cohort Study Evaluating Regimens Containing Vebicorvir in Subjects with Chronic Hepatitis B Virus Infection
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This clinical study protocol was subject to critical review and has been approved by the appropriate protocol review personnel of the Sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational products.
- The ethical and scientific standards governing clinical research that are set out in the current International Council for Harmonisation (ICH) guideline (E6) on Good Clinical Practice (GCP), US Title 21 of the Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312, and other applicable local requirements.

The Principal Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Sponsor Signatory:

[redacted] Assembly Biosciences Approval Signature and Date	[redacted]

INVESTIGATOR STATEMENT

Protocol Title	A Randomized Phase 2a, Multicenter, Open-Label, Multiple-Cohort Study Evaluating Regimens Containing Vebicorvir in Subjects with Chronic Hepatitis B Virus Infection
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I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as described herein, in accordance with Good Clinical Practice (GCP) as set out in the current International Council for Harmonisation (ICH) guidelines (E6) and other applicable national or local requirements, 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 any amendments, and access to all information provided by Assembly Biosciences or specified designees. I will discuss the material with them to ensure that they are fully informed about Assembly Biosciences and the study.

Principal Investigator Signature:	
Print Name:	
Date:	

Please keep the original, signed copy of this Investigator signature page in your records and email a copy to your site monitor for archival in the Trial Master File (TMF).

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ABBREVIATIONS AND TERMS

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALT	Alanine aminotransferase
APRI	AST to platelet ratio index
AST	Aspartate aminotransferase
cccDNA	Covalently closed circular DNA
cHBV	Chronic hepatitis B virus infection
CMV	Cytomegalovirus
CRO	Clinical research organization
CSR	Clinical Study Report
DAIDS	Division of AIDS
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
eCRF	Electronic Case Report Form
EOT	End of treatment
EOS	End of study
ETV	Entecavir
EU	European Union
FDA	Food and Drug Administration
GalNAc	*N*-Acetylgalactosamine
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBcAb	Antibody to the HBV core protein
HBcrAg	Hepatitis B core-related antigen
HBeAb	Anti-hepatitis B e antigen antibody

Abbreviation	Definition
HBeAg	Hepatitis B e antigen
HBsAb	Anti-hepatitis B surface antigen antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LLOQ	Lower limit of quantitation
NrtI	Nucleos(t)ide/reverse transcriptase inhibitor
PBO	Placebo
PCR	Polymerase chain reaction
Peg-IFNα	Pegylated-interferon alpha
pgRNA	Pregenomic ribonucleic acid
PK	Pharmacokinetic(s)
RNA	Ribonucleic acid
RNAi	Ribonucleic acid interference
RT-qPCR	Quantitative reverse transcription PCR
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Definition
siRNA	Small interfering ribonucleic acid
SOC	Standard-of-care
SVR	Sustained virologic response
TD	Target detected
TDF	Tenofovir disoproxil fumarate
TNA	Total nucleic acids
TND	Target not detected
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
VBR	Vebicorvir
WHO	World Health Organization

1 SYNOPSIS

Protocol Title	A Randomized Phase 2a, Multicenter, Open-Label, Multiple-Cohort Study Evaluating Regimens Containing Vebicorvir in Subjects with Chronic Hepatitis B Virus Infection
Protocol Number	ABI-H0731-204
Test Product, Dose, and Mode of Administration	Cohort 1 300 mg vebicorvir (VBR; formerly ABI-H0731) (100 mg tablets), oral, once daily + 60 mg AB-729 (180 mg/mL solution), subcutaneous, once every 8 weeks + nucleos(t)ide/reverse transcriptase inhibitor (NrtI) tablets, oral, once daily
Reference Therapy, Dose, and Mode of Administration	Cohort 1 • 300 mg VBR (100 mg tablets) + NrtI tablets; both oral, once daily • 60 mg AB-729 (180 mg/mL solution), subcutaneous, once every 8 weeks + NrtI tablets, oral, once daily
Target Population	Male or female subjects with chronic hepatitis B virus (HBV) infection (cHBV), aged 18 to 50 years (inclusive), with no evidence of cirrhosis or end-stage liver disease. Virologically-suppressed subjects on NrtI therapy with HBeAg negative cHBV will be enrolled in Cohort 1. Additional cohorts may be added in future protocol amendments to evaluate other populations and/or treatment regimens.
Phase	2a
Number of Subjects Planned	Approximately 60 in Cohort 1 Up to 2 additional cohorts, with approximately 60 subjects per cohort, may be added in future protocol amendments, for a maximum sample size of approximately 180 subjects.
Study Sites	Approximately 25 study sites worldwide
Treatment Duration	Cohort 1: 48 Weeks
Study Duration	Cohort 1: Up to 45 days for Screening, 48 weeks of treatment, and 48 weeks of follow-up.
Rationale	Chronic hepatitis B virus infection is a major cause of liver-related morbidity and mortality affecting >250 million people worldwide. While standard-of-care (SOC) therapy with NrtIs is able to achieve adequate viral suppression in most HBeAg negative patients and three quarters of HBeAg positive patients, sustained virologic response (SVR) off treatment, and loss of hepatitis B surface antigen (HBsAg) are rare (<5%). Compared to NrtIs, finite treatment with pegylated

interferon alpha (Peg-IFNα) leads to lower rates of viral suppression, although small increases in the rate of HBsAg loss (5-10%) have been observed. However, any advantages associated with immunomodulation are offset by poor tolerability of Peg-IFNα. New therapeutic modalities are required to improve the depth of suppression and provide the potential for cure. Combination regimens utilizing agents with complementary mechanisms of action and resistance profiles may be required to support finite treatment durations.

Vebicorvir is an orally administered, potent and selective small molecule inhibitor of the HBV core protein. Through this mechanism, VBR interferes with multiple steps in the viral lifecycle including capsid disassembly and deoxyribonucleic acid (DNA) delivery to the nucleus, pregenomic ribonucleic acid (pgRNA) encapsidation, capsid assembly, and DNA recirculation, preventing de novo establishment of covalently closed circular DNA (cccDNA).

AB-729 is a subcutaneously administered novel *N*-Acetylgalactosamine (GalNAc) conjugated small interfering ribonucleic acid (siRNA), which cleaves and degrades HBV ribonucleic acid (RNA), inhibiting production of all viral proteins, including HBsAg. Suppression of HBsAg production by AB-729 may contribute to breaking immune tolerance to HBV and restoring T-cell activity directed toward HBV, thereby promoting functional cure. The addition of VBR and AB-729 to other treatments for cHBV will provide multiple complementary antiviral mechanisms, with potential collateral immunological consequences, that may act synergistically to increase cure rates. This Phase 2a study will explore the safety and antiviral activity of VBR and AB-729 in combination with other cHBV treatments (NrtIs).

Objectives

Primary Objective

The primary objective of Cohort 1 is:

- To evaluate the safety and tolerability of combination treatment with VBR, AB-729, and NrtI

Secondary Objectives

The secondary objectives of Cohort 1 are:

- To evaluate the effect of adding VBR and AB-729 to NrtI on reduction in and loss of HBsAg
- To evaluate the effect of adding VBR and AB-729 to NrtI in reducing HBV DNA levels
- To evaluate the effect of adding VBR and AB-729 to NrtI in reducing HBV RNA levels
- To evaluate the effect of adding VBR and AB-729 to NrtI in reducing other HBV antigens (ie, hepatitis B core-related antigen [HBcrAg])

- To evaluate the effect of adding VBR and AB-729 to NrtI on HBsAg seroconversion
- To evaluate the effect of adding VBR and AB-729 to NrtI on normalization of alanine aminotransferase (ALT)
- To evaluate the off-treatment durability of response to treatment with VBR and AB-729
- To evaluate the pharmacokinetics (PK) of VBR and AB-729 when coadministered with NrtI

Exploratory Objectives

The exploratory objectives of Cohort 1 are:

- To evaluate the emergence of resistance to VBR and AB-729 when coadministered with NrtI
- To evaluate the effect of VBR, AB-729, and NrtI on immunological biomarkers, where applicable
- To evaluate the effect of VBR, AB-729, and NrtI on HBsAg isoforms and immune complexes, where applicable
- To evaluate the effect of AB-729 on an HBV-derived RNA interference biomarker, where applicable

Endpoints

Primary Endpoint

The primary endpoint of Cohort 1 is:

- Proportion of subjects with adverse events (AEs), premature treatment discontinuation due to AEs, and abnormal laboratory results

Secondary Endpoints

The secondary endpoints of Cohort 1 are:

- Mean change in $\log_{10}$ HBsAg from Baseline at each timepoint
- Proportion of subjects with HBsAg <LLOQ at each timepoint
- Proportion of subjects with HBV DNA target not detected (TND; <5 IU/mL) at Week 48
- Proportion of subjects with HBV RNA <LLOQ at Week 48
- Mean change in $\log_{10}$ HBV RNA from Baseline at each timepoint

- Mean change in $\log_{10}$ HBcrAg from Baseline at each timepoint
- Proportion of subjects with HBsAg seroconversion at Week 48
- Proportion of subjects with abnormal ALT at Baseline who have normal ALT (by central laboratory and American Association for the Study of Liver Diseases [AASLD] criteria) at each timepoint
- Proportion of subjects achieving Treatment Stopping Criteria at end of treatment (EOT)
- Proportion of subjects who remain off-treatment at end of study (EOS)
- Analysis of VBR and AB-729 drug concentrations. NrtI concentrations may be analyzed, as needed

Exploratory Endpoints

The exploratory endpoints of Cohort 1 are:

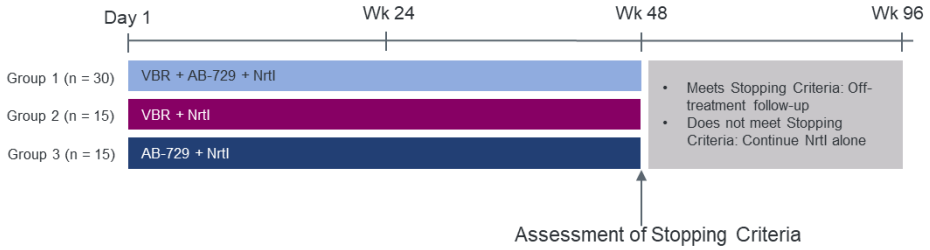
- Proportion of subjects who continued NrtI after Week 48 and subsequently met the Treatment Stopping Criteria
- The incidence of HBV variants with reduced susceptibility to VBR and AB-729
- The evaluation of immune response markers, where applicable
- The evaluation of the effect on HBsAg isoforms, where applicable
- The evaluation of the effect on HBsAg immune complexes, where applicable
- The evaluation of the effect on an HBV-derived RNA interference biomarker over time, where applicable

Study Design

This is a randomized Phase 2a, multicenter, open-label, multiple-cohort study evaluating the safety and antiviral activity of VBR and AB-729 in combination with other cHBV treatments in subjects with cHBV.

Cohort 1 is prespecified and will enroll virologically-suppressed subjects on NrtI therapy with HBeAg negative cHBV. Approximately 60 eligible subjects will be randomized 2:1:1 in 1 of 3 treatment groups as shown in the following figure. Up to 2 additional cohorts may be added in future protocol amendments to evaluate other populations and/or treatment regimens.

Study Design Schematic



Abbreviations: VBR=vebicorvir; NrtI=nucleos(t)ide /reverse transcriptase inhibitor; Wk=week

Treatment with VBR and NrtI will be administered orally, once daily; treatment with AB-729 will be administered subcutaneously, once every 8 weeks, for a total of 6 doses.

Treatment assignments will be stratified by HBsAg level (ie, HBsAg ≤1000 IU/mL vs >1000 IU/mL) during the Screening visit.

Treatment Stopping Criteria:

At Week 48, all subjects will have an assessment of Treatment Stopping Criteria. Any subjects who meet the below Treatment Stopping Criteria, will discontinue their assigned treatment including NrtI, and continue with off-treatment follow-up through Week 96, unless they meet the NrtI-restart criteria specified below. Decisions to discontinue assigned treatment and undergo off-treatment follow-up will be based on laboratory results from blood samples collected at the Week 48 visit. Subjects will remain on their assigned oral agents (ie, VBR+NrtI for Groups 1 and 2; NrtI for Group 3) until Week 48 laboratory results required for Treatment Stopping Criteria assessment are available.

Treatment Stopping Criteria are:

- ALT < 2 × ULN, *and*
- HBV DNA < LLOQ, *and*
- HBsAg < 100 IU/mL

Subjects who do not meet the Treatment Stopping Criteria with Week 48 laboratory results will continue treatment with NrtI alone and will remain in follow-up through Week 96.

NrtI-Restart Criteria:

Subjects who meet the Treatment Stopping Criteria at the Week 48 assessment but subsequently meet **ANY** of the below NrtI-Restart Criteria, will restart treatment with NrtI and remain in follow-up through Week 96.

NrtI-Restart Criteria are:

- Alanine aminotransferase (ALT) > 10 × upper limit of normal (ULN), confirmed by repeat

- ALT > Baseline and > ULN, confirmed by repeat, *and*
  - Direct bilirubin > 2.0 × ULN, confirmed by repeat, *or*
  - International Normalized Ratio > 1.5, confirmed by repeat
- ALT ≥ 2 – 5 × ULN AND HBV DNA > 2000 IU/mL for 12 weeks
- ALT elevations ≥ 5 – 10 × ULN AND HBV DNA > 2000 IU/mL for 4 weeks
- Any clinical decompensation, regardless of HBV DNA level
- Investigator discretion

Study Population

Key Inclusion Criteria for Cohort 1

Subjects must meet all the following key inclusion criteria in order to be eligible for Cohort 1 of the study:

1. Willing and able to provide Informed Consent
2. Male or female between the ages 18 and 50 years (inclusive) at Screening
3. Body mass index (BMI) 18 to 36 kg/m^2 and a minimum body weight of 45 kg (inclusive) at Screening
4. Female subjects of child-bearing potential (Appendix 2) must be non-pregnant and have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Day 1 predose
5. cHBV defined as HBV infection documented for ≥6 months prior to Screening
6. Must be HBeAg negative at least 3 months prior to the Screening Visit (historical documentation) AND at the Screening Visit to be eligible for Cohort 1
7. Virologically suppressed on NrtI therapy with nonquantifiable HBV DNA for at least 6 months prior to and including Screening
8. On a stable NrtI regimen of entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide for >12 months
9. HBsAg ≥100 IU/mL at Screening
10. Lack of bridging fibrosis or cirrhosis as documented by the following:
    - Fasting FibroScan® ≤8 kPa within 3 months prior to Screening (including the Screening visit) or other Sponsor-approved hepatic

imaging method within 6 months of Screening (eg, Meta-analysis of Histological Data in Viral Hepatitis [METAVIR] F0-F2 or equivalent)

OR

- Liver biopsy results (eg, METAVIR F0-F2 or equivalent) within 1 year prior to Screening

  If results from liver biopsy and FibroScan® are available, then the diagnostic method reporting the most advanced liver disease will be used to determine eligibility for the study

11. Agreement to comply with protocol-specified contraceptive requirements (Appendix 2)

12. In good general health, except for cHBV, in the opinion of the Investigator

13. Able to take oral medication, be willing to receive subcutaneous injections of AB-729, and in the opinion of the Investigator, be willing to adhere to study treatment and procedures

Key Exclusion Criteria for Cohort 1

Subjects who meet any of the following key exclusion criteria will not be eligible for the study:

1. Co-infection with human immunodeficiency virus, hepatitis C virus, hepatitis D virus, acute hepatitis A virus or acute hepatitis E virus

2. Females who are lactating or wish to become pregnant during the course of the study

3. History of liver transplant or evidence of advanced liver disease, cirrhosis, or hepatic decompensation (including jaundice, ascites, portal hypertension, gastrointestinal bleeding esophageal varices, hepatic encephalopathy) at any time prior to, or at the time of Screening

4. History of persistent alcohol abuse (alcohol consumption exceeding 2 standard drinks per day on average [1 standard drink=14 grams of alcohol]) or illicit drug abuse within 3 years prior to Screening

5. Clinically significant diseases or conditions, such as cardiac disease, including poorly-controlled or unstable hypertension; pulmonary disease; chronic or recurrent renal or urinary tract disease; liver disease other than cHBV; endocrine disorder; autoimmune disorder; poorly controlled diabetes mellitus; neuromuscular, musculoskeletal, or mucocutaneous conditions requiring frequent treatment, seizure disorders requiring treatment; ongoing infection or other medical conditions requiring frequent medical management or pharmacologic or surgical treatment that, in the

opinion of the Investigator or the Sponsor, makes the subject unsuitable for study participation

6. History of hepatocellular carcinoma (HCC)

7. History of malignancy other than HCC unless the subject's malignancy has been in complete remission off chemotherapy and without additional medical or surgical interventions during the 3 years before Screening

8. History or presence at Screening of electrocardiogram abnormalities deemed clinically significant, in the opinion of the Investigator

9. History of hypersensitivity or idiosyncratic reaction to any components or excipients of the investigational drugs

10. History of any significant food or drug-related allergic reactions such as anaphylaxis or Stevens-Johnson syndrome

11. The following are exclusionary laboratory results at Screening:

    a. Platelet count <100,000/mm^3

    b. Albumin <3 g/dL

    c. Direct bilirubin >1.2× upper limit of normal (ULN)

    d. ALT ≥5× ULN

    e. Serum alpha fetoprotein (AFP) ≥100 ng/mL. If AFP at Screening is >ULN but <100 ng/mL, the subject is eligible if hepatic imaging prior to initiation of study drug reveals no lesions indicative of possible HCC

    f. International Normalized Ratio (INR) >1.5× ULN

    g. Estimated creatinine clearance <50 mL/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight at Screening

    h. Any other laboratory abnormality deemed clinically significant by the Investigator

12. Current or prior use of prohibited concomitant medications from 28 days prior to Day 1 (Section 6.3.1)

13. Current or prior treatment for cHBV with:

    - Lamivudine, telbivudine or adefovir (any duration)

	• HBV core inhibitor (any duration) • siRNA or other oligonucleotide therapeutic (any duration) • Interferon in the 6 months prior to Screening • Any investigational agent for cHBV in the 6 months prior to Screening 14. Participation in another clinical study of a drug or device whereby the last investigational drug/device administration is within 60 days or 5 half-lives prior to the first study drug administration, whichever is longer
Statistical Methods	This is a proof-of-concept study. The sample size is similar to that previously utilized for this type of study and is not based upon statistical considerations. All safety, PK, and antiviral activity endpoints will be summarized using descriptive statistics by treatment groups. Continuous endpoints will be summarized using the mean, standard deviation, median, minimum, and maximum. Categorical endpoints will be described using the number and percent of subjects who meet the endpoint criterion. Due to sample size limitations, no formal statistical inference is planned.

2 INTRODUCTION

2.1 Chronic Hepatitis B Virus Infection

Worldwide >250 million people are chronically infected with the hepatitis B virus (HBV), and chronic hepatitis B virus infection (cHBV) is a major cause of severe liver morbidity and liver-related mortality (WHO 2019). An estimated 600,000 to 1 million people die each year due to cirrhosis and hepatocellular carcinoma (HCC), the end-stage complications of cHBV (Colvin 2010, El-Serag 2012, EASL 2017, Terrault 2018, WHO 2019). The global prevalence of chronic HBV infection shows wide geographic variation, with a prevalence of more than 8% of people in highly endemic regions (eg, East Asia and equatorial Africa), 2% to 7% of people in moderately endemic regions (eg, the Middle East and the Indian subcontinent), and less than 2% in locales of low endemicity (eg, North America and Europe) (Schweitzer 2015). Despite broad implementation of HBV vaccination programs, new cases of HBV infection are still common. The World Health Organization (WHO) estimates that there are greater than 4 million acute HBV infections worldwide each year (WHO 2019).

The clinical stages of cHBV represent different risks for ongoing liver injury depending on the degree of HBV replication and individuals' concurrent immune responses (Yim 2006, Hoofnagle 2007, Lok 2009, Sorrell 2009, Pungpapong 2013, Gish 2015, EASL 2017). The standard virologic and serologic markers for HBV infection include HBV deoxyribonucleic acid (DNA), hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antigen antibody (HBsAb), hepatitis B e antigen (HBeAg), anti-hepatitis B e antigen antibody (HBeAb), and in almost all patients, antibody to the HBV core protein (HBcAb). More recently, HBV pregenomic ribonucleic acid (pgRNA) and HBV core-related antigen (HBcrAg) have also been used as markers of infection. In particular, HBV pgRNA is recognized as a direct measure of covalently closed circular DNA (cccDNA) transcriptional activity, and the number of infected cells (Fanning 2019). Historically, treatment goals include prevention of HBV-related liver injury through suppression of HBV DNA, achievement of HBeAg loss and seroconversion, and loss of HBsAg and seroconversion. The secretion of viral antigens, especially HBsAg, may play a key role in modulating the host immune response to infection by promoting T cell exhaustion, suppressing innate immune responses and cytokine production, and altering adaptive immune function (Yuen 2018). A transition to an HBsAg negative, minimally replicative state is rare (occurring spontaneously in only 1-3% of patients per year, and <5% per year in [nucleos(t)ide reverse transcriptase inhibitors] NrtI-treated patients) but usually durable and, if it precedes the development of cirrhosis and HCC, is associated with improved long-term clinical outcomes (EASL 2017). As such, HBsAg seroconversion is considered a "functional cure" and a potential endpoint for cHBV therapy. However, as HBsAg is derived from both cccDNA as well as integrated HBV DNA, sustained undetectable HBV DNA with or without HBsAg loss after stopping treatment ("off-therapy sustained virologic response [SVR]") is considered an intermediate goal (EASL 2017, Cornberg 2019).

Currently, there are 2 clinically accepted treatment options for cHBV, interferon alfa (IFNα) and NrtIs of the HBV polymerase. Of these agents, oral NrtIs are the more broadly used, and have demonstrated success in achieving and maintaining viral suppression in most patients (Lampertico

2012). However, there is a sizable number of individuals who do not achieve viral suppression to levels below quantitation on commercial assays following an adequate course of NrtI therapy. In the Phase 3 studies with entecavir (ETV), 33% of HBeAg positive patients and 10% of HBeAg negative patients did not achieve HBV DNA <lower limit of quantitation (LLOQ; 300 copies/mL) after 48 weeks of treatment, and 2% or less achieved HBsAg loss (Chang 2006, Lai 2006). Similarly, in a Phase 3 study in HBeAg positive patients, 36% of tenofovir alafenamide (TAF) recipients and 33% of tenofovir disoproxil fumarate (TDF) recipients had HBV DNA >LLOQ (29 IU/mL) at Week 48, and 1% or less achieved HBsAg loss (Chan 2016). In the complementary Phase 3 study in HBeAg negative patients, 6% of TAF recipients and 7% of those receiving TDF had HBV DNA >LLOQ (29 IU/mL) at Week 48, and no subjects experienced HBsAg loss (Buti 2016). Importantly, the level of HBV replication as measured by HBV DNA and HBsAg production in those treated with and without complete virologic response (ie, achieving/not achieving HBV DNA <LLOQ with or without HBsAg loss) has been predictive of progression of liver disease and risk of HCC (Papatheodoridis 2015, EASL 2017, Yip 2019). Further, despite suppression of HBV DNA for extended periods of time with NrtIs, the template for ongoing viral replication, cccDNA, is not eliminated in most patients. Patients with HBV DNA below the limit of quantification using commercial assays continue to have low levels of viral replication even after many years of NrtI therapy (Marcellin 2014, Burdette 2019). As a result, off therapy SVR with currently approved agents is rare, necessitating long-term chronic suppressive treatment approaches. There is a need for improved, novel HBV therapies that further reduce HBV replication and result in a higher proportion of patients achieving SVR (HBV DNA <LLOQ with or without HBsAg loss) with a subsequent improvement in long-term patient outcomes, ie, reduction of HBV associated hepatic inflammation leading to reduced morbidity and mortality from end-stage liver disease and HCC (FDA 2018). Additionally, such deeper virologic responses may enable patients to achieve durable virologic and clinical outcomes following finite treatment duration.

2.2 Vebicorvir

2.2.1 Description

Vebicorvir (VBR; formerly ABI-H0731) is an orally administered, potent and selective small molecule inhibitor of the HBV core protein discovered by Assembly Biosciences (Assembly), which is being developed as a therapeutic agent for the treatment of cHBV. Vebicorvir inhibits HBV replication by interfering with essential functions of the HBV core protein, and therefore inhibits HBV replication by different mechanisms than NrtIs. Thus, inhibition of HBV core protein functions by VBR, when used in combination with currently approved HBV antivirals has the potential to immediately improve current therapy for chronic HBV infection and in combination with additional agents, ultimately provide patients with enhanced rates of SVR following a finite treatment period.

General information concerning VBR is described in the VBR Investigator's Brochure (IB).

2.2.2 Nonclinical Studies

Refer to the VBR IB for a complete summary of the nonclinical and toxicology studies performed to date.

2.2.3 Clinical Studies

A complete summary of all clinical studies performed to date is provided in the VBR IB. The VBR IB also includes preliminary safety and efficacy information for the ongoing Phase 2 studies, Study ABI-H0731-201 (Study 201) and Study ABI-H0731-202 (Study 202), for which the study conduct has been completed. Following completion of treatment in Study 202 and Study 201, eligible subjects were able to participate in Study ABI-H0731-211 (Study 211), a long-term extension study and receive open-label, 300 mg VBR+NrtI for up to an additional 100 weeks. In Study 211, treatment with VBR is ongoing and the overall summary of exposure is based on a data cut-off date of 12 March 2020. The available preliminary efficacy and safety results from Study 211 are provided in Sections 2.2.3.1, 2.2.3.2, and 2.2.3.3.

2.2.3.1 Study 211 Preliminary Disposition

In the open-label treatment extension Study 211, 92 subjects, who participated in Studies 201 and 202 (ie, 23 subjects from Study 202 [12 subjects from the VBR+ETV group; 11 subjects from the Placebo (PBO)+ETV group] and 69 subjects from Study 201 [43 subjects from the VBR+NrtI group; 26 subjects from the PBO+NrtI group]), were enrolled to receive 300 mg VBR for up to 100 additional weeks. Through the first 24 weeks of Study 211, 90 (98%) subjects who enrolled continued on study treatment, one subject discontinued study drug due to a Grade 1 adverse event (AE) of rash and one subject discontinued study drug due to virologic resistance in the setting of noncompliance with study drug.

2.2.3.2 Study 211 Preliminary Safety

In Study 211, preliminary safety data are available for all subjects through 24 weeks of treatment with VBR+NrtI and demonstrate that 300 mg VBR daily continues to be generally well-tolerated in the open-label treatment extension study (Table 1). No subjects discontinued treatment due to treatment-emergent adverse events (TEAEs) in Study 211. One subject discontinued treatment due to a Grade 1 AE of rash which began in Study 201. Overall, 42 of 92 subjects (46%) have experienced TEAEs, the majority of which were Grade 1. The only AEs reported by >5% of subjects in the first 24 weeks of Study 211 are rash (5/92, 5%) and upper respiratory tract infection (5/92, 5%). All the AEs of rash were Grade 1 and 2 AEs were considered not related to study drug. Two subjects have reported Grade 3 AEs. One subject experienced Grade 3 elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were reported as Grade 3 AEs not considered related to study drug and resolved on continued treatment. Another subject experienced a Grade 3 elevation in ALT, which was reported as a Grade 3 AE and considered possibly related to study drug by the Investigator who noted increased alcohol use by the subject at the time; this was associated with a Grade 2 elevation in AST and improved to Grade 2 on continued treatment. No Grade 4 AEs or serious adverse events (SAEs) have been reported and no

deaths have occurred. Most treatment-emergent laboratory abnormalities which occurred have been Grade 1. In addition to the Grade 3 elevations in ALT and AST reported as AEs, one subject had a Grade 3 prolonged prothrombin time and another subject had a Grade 3 elevation in AST (not reported as an AE). There have been no Grade 4 laboratory abnormalities.

Table 1. Overall Summary of Treatment-Emergent Adverse Events Through Week 24 (Study 211)

Characteristic [n, (%)]	Vebicorvir+NrtI (N=92)
Any Treatment-Emergent AE [a]	42 (46)
Grade 1	26 (28)
Grade 2	14 (15)
Grade 3 or 4	2 (2)
Serious adverse events	0
TEAEs leading to study drug discontinuation [b]	0

Abbreviations: AE=adverse event; n=number of subjects with event; N=Number of subjects in the Safety population; NrtI=nucleos(t)ide analog reverse transcriptase inhibitor; TEAE=treatment-emergent adverse event.
Source: Study 211 Table 6.1.1.1.
Data cut through 12 March 2020 including AE data for the first 6 months of exposure in Study 211.
Adverse events were graded according to Division of AIDS (DAIDS) criteria.
[a] Subjects with more than 1 TEAE were reported in the highest TEAE grade.
[b] One non-TEAE (began in Study 201) led to study drug discontinuation in Study 211.

2.2.3.3 Study 211 Preliminary Efficacy

This section summarizes the antiviral activity for subjects continuing treatment from Study 202 or Study 201 into Study 211. During Study 202 and Study 201, subjects received either VBR+NrtI or PBO+NrtI for 24 weeks in a blinded fashion, and, during Study 211, all subjects received open-label treatment with VBR+NrtI. The analyses for Study 211 reported below are based on the subject's characteristics and the initial study into which they enrolled, with treatment naïve subjects with HBeAg positive cHBV originating from Study 202 and virologically-suppressed subjects with HBeAg positive or HBeAg negative cHBV originating from Study 201.

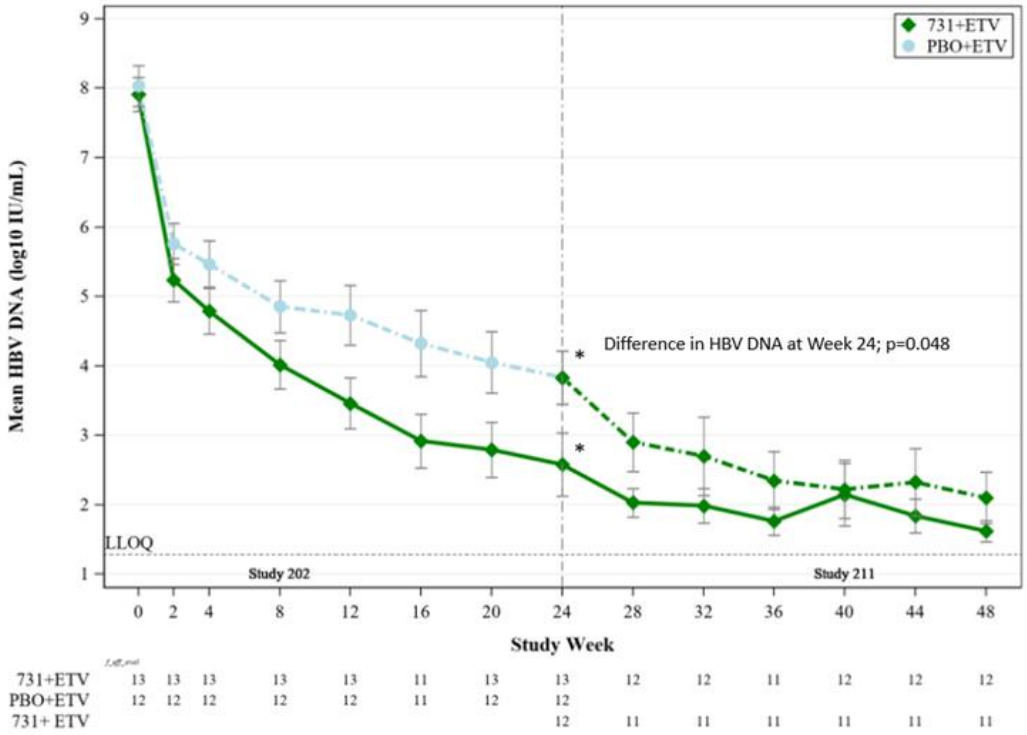
2.2.3.3.1 Treatment-Naïve Subjects with HBeAg Positive cHBV (Originating from Study 202)

The changes in HBV DNA and HBV pgRNA from the beginning of Study 202 through Week 24 in Study 211 are presented in graphical form in Figure 1 and Figure 2. In both figures, each line represents a treatment group originating in Study 202 (either VBR+ETV or PBO+ETV) with green representing VBR+ETV and blue representing PBO+ETV. The numbers of subjects contributing data at each timepoint are presented below the x-axes. These figures demonstrate the different declines in HBV nucleic acids over time in the treatment groups. At Week 24 in Study 202, the

VBR+ETV group had statistically significant lower levels of HBV DNA and pgRNA compared to group receiving PBO+ETV (p=0.048 and p=0.002, respectively). In addition, there is a change in trajectory of HBV DNA and HBV pgRNA following the addition of VBR to ETV at the end of Study 202 in the group who were initially assigned to PBO+ETV. Of note, there is a clear 2-phase decline in pgRNA observed in both treatment groups observed upon initiation of VBR treatment. The initial rapid phase decline of pgRNA is thought to be primary mechanism-based inhibition (ie, core inhibition preventing encapsidation of pgRNA and secretion into serum), while the second slower phase decline of pgRNA is believed to reflect reduction in the cccDNA pool over time.

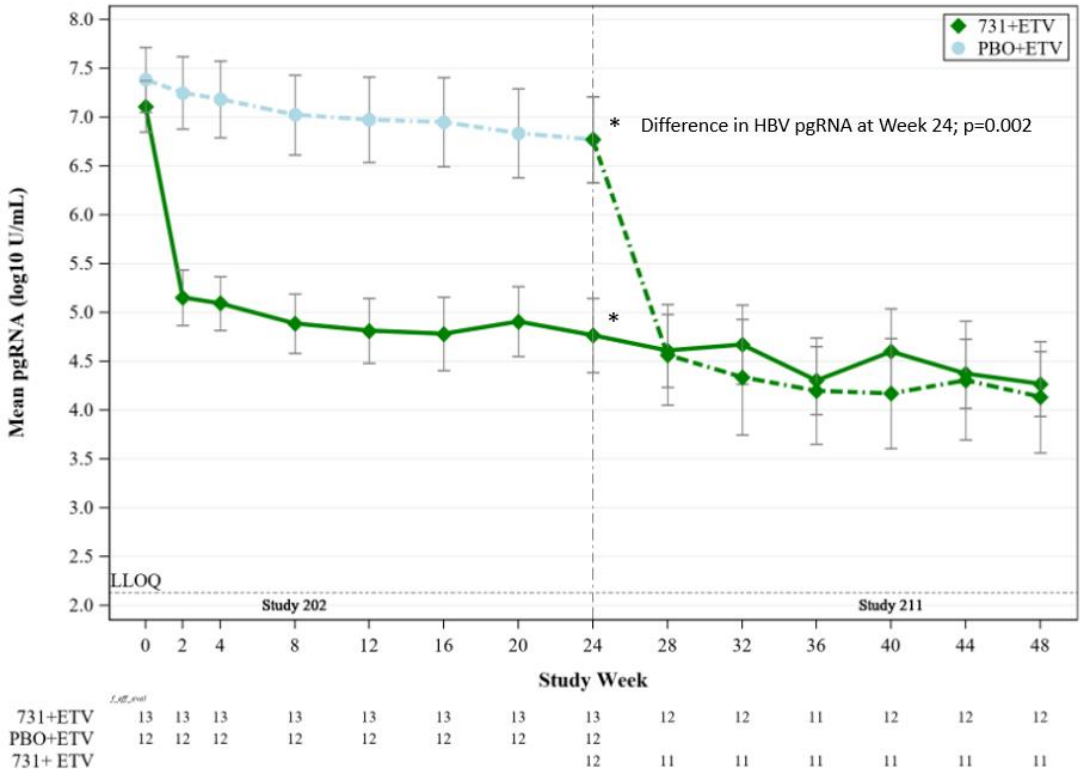
Although all subjects receive VBR+ETV in Study 211, pooling of data in this study is not appropriate given the differing treatments received during Study 202. The Study 202 treatment assignments (VBR+ETV and PBO+ETV) lead to different starting points for markers of HBV infection at the beginning of Study 211. Consequently, the remainder of this section will focus on the subjects who received 48 weeks of VBR+ETV from the beginning of Study 202 through Week 24 in Study 211.

Figure 1. Mean Log_{10} HBV DNA for Treatment-Naïve Subjects with cHBV (Study 202/211)



Abbreviations: 731=vebicorvir; cHBV=chronic hepatitis B virus infection; ETV=entecavir; HBV=hepatitis B virus; IU=international units; PBO=placebo.
Includes subjects in the Intent-to-Treat population. HBV DNA lower limit of quantitation=20 IU/mL (1.30 log_{10} IU/mL).

Figure 2. Mean Log_{10} HBV pgRNA for Treatment-Naïve Subjects with cHBV (Study 202/211)



Abbreviations: 731=vebicorvir; cHBV=chronic hepatitis B virus infection; ETV = entecavir; HBV=hepatitis B virus; PBO=placebo; pgRNA=pregenomic RNA; U=units.
Includes subjects in the Intent-to-Treat population. HBV pgRNA lower limit of quantitation=135 U/mL (2.13 log_{10} U/mL).

For subjects who have received 48 cumulative weeks of VBR+ETV in Study 202/211, Table 2 summarizes the absolute value and change from Baseline in HBV DNA (COBAS® TaqMan®; LLOQ=20 IU/mL) and HBV pgRNA (Assembly quantitative reverse transcription PCR [RT-qPCR]; LLOQ=135 U/mL) by week of treatment. In these subjects, the mean (minimum, maximum) Baseline HBV DNA was 7.9 (5.5, 8.7) log_{10} IU/mL which declined to 1.6 (1.0, 2.7) log_{10} IU/mL after 48 weeks of treatment with VBR+ETV, representing a mean (minimum, maximum) change of -6.3 (-7.2, -4.2) log_{10} IU/mL. Further, the proportion of subjects in this group who had HBV DNA <LLOQ increased from 0% at Baseline to 42% (5/12) at Week 48. The mean (minimum, maximum) HBV pgRNA at Baseline was 7.1 (4.8, 8.6) log_{10} U/mL which declined to 4.3 (2.1, 5.8) log_{10} U/mL after 48 weeks of treatment with VBR+ETV, representing a mean (minimum, maximum) change of -2.8 (-4.9, -1.9) log_{10} U/mL.

Table 2. HBV DNA and pgRNA for Treatment-Naïve Subjects with cHBV by Week of Treatment with Vebicorvir+ETV (Study 202/211)

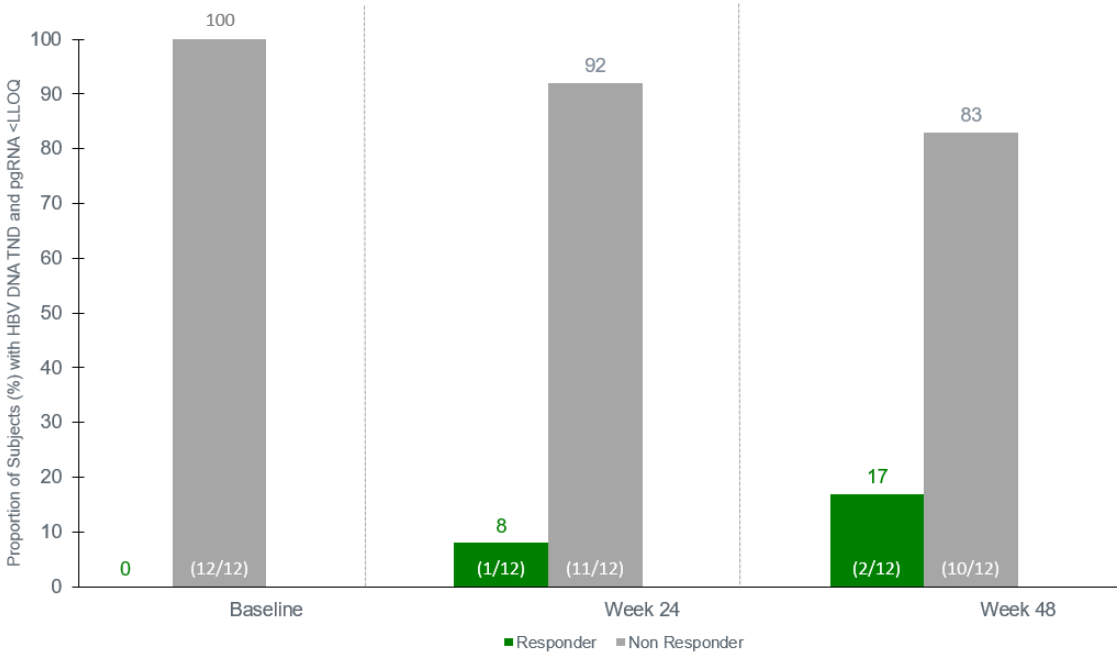
Week of Treatment	HBV DNA[a] Log_{10} IU/mL (N=12)	HBV pgRNA[a] Log_{10} U/mL (N=12)
Baseline		
n	12	12
Mean (Min, Max)	7.9 (5.5, 8.7)	7.1 (4.8, 8.6)
Week 12		
n	12	12
Mean (Min, Max)	3.4 (1.3, 5.3)	4.7 (2.5, 6.3)
Change from Baseline (Min, Max)	-4.5 (-6.2, -3.2)	-2.4 (-4.2, -1.6)
Week 24		
n	12	12
Mean (Min, Max)	2.2 (1.3, 3.4)	4.6 (2.6, 6.2)
Change from Baseline (Min, Max)	-5.7 (-6.8, -4.2)	-2.5 (-4.3, -1.6)
Week 36		
n	11	11
Mean (Min, Max)	1.8 (1.3, 3.4)	4.3 (2.1, 5.8)
Change from Baseline (Min, Max)	-6.1 (-7.3, -4.2)	-2.7 (-4.5, -1.8)
Week 48		
n	12	12
Mean (Min, Max)	1.6 (1.0, 2.7)	4.3 (2.1, 5.8)
Change from Baseline (Min, Max)	-6.3 (-7.2, -4.2)	-2.8 (-4.9, -1.9)

Abbreviations: ETV=entecavir; HBV=hepatitis B virus; IU=international units; Max=maximum; Min=minimum; n=number of subjects at each visit; N=Number of subjects in the Intent-to-Treat population; pgRNA=pregenomic RNA; U=units.
Source: Study 211 Trends Analysis Table 4.1.1, 4.2.
HBV DNA lower limit of quantitation (LLOQ)=20 IU/mL (1.30 log_{10} IU/mL); HBV pgRNA LLOQ=135 U/mL (2.13 log_{10} U/mL).
[a] Subjects who received vebicorvir+ETV in Study 202

The addition of VBR to NrtI has the potential to more effectively inhibit HBV replication than NrtI alone. In addition to reductions in HBV DNA, VBR also reduces HBV pgRNA which is considered to be a direct assessment of cccDNA transcription (Wang 2016). The measurement of a combined meaningful reduction in both HBV DNA and HBV pgRNA is therefore important in assessing the overall treatment effect on HBV replication. Figure 3 summarizes the proportions of subjects who attained both HBV DNA <LLOQ and either HBV pgRNA ≥3 log_{10} reduction from Baseline or HBV pgRNA <LLOQ (considered responders) at key study visits through 48 weeks of treatment with VBR+ETV.

In these subjects, 17% (2/12) attained the combined endpoint of HBV DNA <LLOQ and either HBV pgRNA >3 log_{10} reduction from Baseline or HBV pgRNA <LLOQ. While the number of subjects in this subgroup is relatively low and there is no direct comparator of ETV alone for the full treatment duration, Figure 1 and Figure 2 provide context for estimated reductions in HBV DNA and HBV pgRNA that would likely be observed with ETV monotherapy.

Figure 3. Proportions of Treatment-Naïve Subjects with HBV DNA <LLOQ and HBV pgRNA Decrease ≥ 3 log_{10} U/mL from Baseline or HBV pgRNA <LLOQ by Week of Treatment with Vebicorvir+ETV (Study 202/211)



Abbreviations: ETV=entecavir; HBV=hepatitis B virus; LLOQ=lower limit of quantitation; pgRNA=pregenomic ribonucleic acid; TND=target not detected.

As HBV DNA and HBV pgRNA decline over time, it is anticipated that reductions in HBV antigens may be observed reflective of a lower viral replicative state. Table 3 summarizes the absolute and change from Baseline in HBeAg, HBcrAg and HBsAg by week of treatment. The Baseline values for HBeAg, HBcrAg and HBsAg were 2.5 log_{10} IU/mL, 5.5 log_{10} kU/mL and 4.5 log_{10} IU/mL, respectively. The change from Baseline at Week 48 was -0.4 log_{10} IU/mL, -0.8 log_{10} kU/mL and -0.2 log_{10} IU/mL for HBeAg, HBcrAg and HBsAg, respectively.

Table 3. HBV Antigens for Treatment-Naïve Subjects with cHBV by Week of Treatment with Vebicorvir+ETV (Study 202/211)

Week of Treatment	HBeAg[a] Log_{10} IU/mL (N=12)	HBcrAg[a] Log_{10} kU/mL (N=12)	HBsAg[a] Log_{10} IU/mL (N=12)
Baseline			
n	12	12	12
Mean (Min, Max)	2.5 (0.6, 3.1)	5.5 (3.6, 6.2)	4.5 (3.3, 4.9)
Week 12			
n	12	12	12
Mean (Min, Max)	2.2 (0.2, 3.1)	5.1 (3.1, 5.9)	4.3 (3.4, 4.9)
Change from Baseline (Min, Max)	-0.3 (-1.5, 0.1)	-0.4 (-2.0, 0.0)	-0.1 (-1.5, 0.5)
Week 24			
n	12	11	12
Mean (Min, Max)	2.1 (0.1, 3.1)	4.9 (3.0, 6.0)	4.3 (3.3, 4.8)
Change from Baseline (Min, Max)	-0.4 (-1.1, 0.0)	-0.5 (-2.1, -0.1)	-0.2 (-1.6, 0.7)
Week 36			
n	11	11	11
Mean (Min, Max)	2.0 (0.1, 3.1)	4.6 (2.6, 5.7)	4.2 (3.4, 4.8)
Change from Baseline (Min, Max)	-0.4 (-1.1, 0.1)	-0.8 (-2.5, -0.1)	-0.20 (-1.5, 0.7)
Week 48			
n	12	12	12
Mean (Min, Max)	2.1 (0.0, 3.1)	4.7 (2.5, 5.8)	4.2 (3.3, 4.8)
Change from Baseline (Min, Max)	-0.4 (-1.2, 0.1)	-0.8 (-2.6, 0.0)	-0.2 (-1.5, 0.7)

Abbreviations: cHBV=chronic hepatitis B virus infection; ETV=entecavir; HBcrAg=hepatitis B core-related antigen; HBeAg=hepatitis B e antigen; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; IU=international units; kU=kilounits; Max=maximum; Min=minimum; n=number of subjects at each visit; N=Number of subjects in the Intent to Treat population.
Source: Trends Analysis Tables 4.3, 4.4, 4.5
Lower limit of quantitation (LLOQ) HBeAg=0.11 IU/mL (-0.96 log_{10} IU/mL); LLOQ for HBcrAg=1 kU/mL (0 log_{10} kU/mL); LLOQ for HBsAg=0.05 IU/mL (-1.30 log_{10} IU/mL).
[a] Subjects who received vebicorvir+ETV in Study 202.

Table 4 summarizes the absolute and change from Baseline in serum ALT and proportions of subjects who were >ULN of ALT at key study visits. Treatment with VBR+NrtI led to rapid and sustained normalization of ALT with a mean (minimum, maximum) change from Baseline at Week 48 of -40.8 (-286.0, 148.0).

Table 4. Alanine Aminotransferase for Treatment-Naïve Subjects with cHBV by Week of Treatment with Vebicorvir+ETV (Study 202/211)

Week of Treatment	Vebicorvir+ETV [a] (N=12) U/L
Baseline	
n	12
Mean (Min, Max)	70.3 (17, 295)
>ULN, n (%)	7 (58)
Week 12	
n	12
Mean (Min, Max)	22.3 (13.0, 33.0)
Change from Baseline (Min, Max)	-48.1 (-272.0, 6.0)

Week of Treatment	Vebicorvir+ETV [a] (N=12) U/L
>ULN, n (%)	0
Week 24	
n	12
Mean (Min, Max)	19.2 (10.0, 37.0)
Change from Baseline (Min, Max)	-51.2 (-282.0, 17.0)
>ULN, n (%)	1 (8)
Week 36	
n	11
Mean (Min, Max)	26.5 (9.0, 128.0)
Change from Baseline (Min, Max)	-48.6 (-286.0, 108.0)
>ULN, n (%)	1 (9)
Week 48	
n	12
Mean (Min, Max)	29.6 (9.0, 168.0)
Change from Baseline (Min, Max)	-40.8 (-286.0, 148.0)
>ULN, n (%)	1(8)

Abbreviations: cHBV=chronic hepatitis B virus infection; ETV=entecavir; Max=maximum; Min minimum; n=number of subjects at each visit; N=number of subjects in the Intent-to-Treat population.; U=units; ULN = upper limit of normal.
Source: Study 211 Trends Analysis Table 4.6
ULN (Covance)=34 U/L for females and 43 U/L for males.
No subjects in Study 202/211 have had evidence of treatment-emergent resistance.
[a] Subjects who received vebicorvir+ETV in Study 202.

2.2.3.3.2 Virologically-Suppressed Subjects with HBeAg Positive or HBeAg Negative cHBV (Originating from Study 201)

The virologically-suppressed subjects with cHBV who enrolled in Study 201 had low HBV DNA at Baseline, thus HBV DNA in this population is reported in Study 201 and Study 211 by a sensitive Assembly semi-quantitative polymerase chain reaction (PCR) assay with a Limit of detection=5 IU/mL. Table 5 summarizes the proportions of HBeAg positive and HBeAg negative subjects with undetectable HBV DNA (target not detected; [TND]) at Baseline, Week 24, and Week 48 of treatment with VBR+NrtI in Study 201/211.

To be eligible for participation in the Study 201, subjects must have had HBV DNA ≤20 IU/mL on NrtI treatment for at least 6 months before screening. As shown in Table 5, despite this eligibility criterion, only 7% (2/27) HBeAg positive and 63% (10/16) HBeAg negative subjects had HBV DNA TND (LOD=5 IU/mL) at Baseline by the high sensitivity Assembly assay. This is consistent with prior reports in which virologically-suppressed individuals with cHBV on standard-of-care NrtI treatment who had HBV DNA <20 IU/mL still harbored low levels of infectious virus (Marcellin 2014, Burdette 2019). Following 48 weeks of treatment with VBR+NrtI, 81% (21/26) HBeAg positive subjects and 93% (13/14) of HBeAg negative subjects had achieved HBV DNA TND by the high sensitivity Assembly assay. These data provide evidence that the addition of VBR to NrtI results in deeper virologic suppression in virologically-suppressed subjects with HBeAg positive or HBeAg negative cHBV who have received chronic NrtI therapy for some time.

Table 5. HBV DNA for Virologically-Suppressed Subjects with cHBV by Week of Treatment with Vebicorvir+NrtI (Study 201/211)

	HBV DNA Patients with TND [n/N, (%)]	
Week of Treatment	**HBeAg Positive[a] (N=27)**	**HBeAg Negative[a] (N=16)**
Baseline	2/27 (7)	10/16 (63)
Week 24	22/27 (81)	15/16 (94)
Week 48	21/26 (81)	13/14 (93)

Abbreviations: HBeAg=hepatitis B e antigen; HBV=hepatitis B virus; N=number of subjects in the intent-to-treat population; n=number of patients at each visit; TND=target not detected.
HBV DNA LOD=5 IU/mL.
[a] Subjects who received ABI-H0731+NrtI in Study 201

As described above, the virologically-suppressed subjects with cHBV who enrolled in Study 201 had low HBV pgRNA at Baseline and so HBV pgRNA in this population is reported in Study 201 and Study 211 by a sensitive Assembly RT-qPCR assay with LLOQ <35 U/mL. Table ***6*** summarizes the absolute value and change from Baseline in HBV pgRNA by week of treatment. In HBeAg positive subjects, the mean (minimum, maximum) Baseline HBV pgRNA was 3.6 (1.5, 6.1) $\log_{10}$ U/mL which decreased to 1.9 (1.5, 4.6) $\log_{10}$ U/mL after 48 weeks of treatment, representing a mean (minimum, maximum) change of -1.7 (-3.7, 0) $\log_{10}$ U/mL. Compared to HBeAg positive subjects, pgRNA was lower in HBeAg negative subjects and showed less change over 48 weeks of treatment with VBR+NrtI. In HBeAg negative subjects, the mean (minimum, maximum) Baseline HBV pgRNA was 1.7 (1.5, 2.6) $\log_{10}$ U/mL which decreased to 1.5 (1.5, 1.6) $\log_{10}$ U/mL at Week 48.

Table 6. HBV pgRNA for Virologically-Suppressed Subjects with cHBV by Week of Treatment with Vebicorvir+NrtI (Study 201/211)

	HBV pgRNA Log_{10} U/mL	
Week of Treatment	**HBeAg Positive[a] (N=27)**	**HBeAg Negative[a] (N=16)**
Baseline		
n	27	16
Mean (Min, Max)	3.6 (1.5, 6.1)	1.7 (1.5, 2.6)
Week 12		
n	27	16
Mean (Min, Max)	1.9 (1.5, 3.7)	1.5 (1.5, 1.5)
Change from Baseline (Min, Max)	-1.7 (-3.5, 0.0)	-0.1 (-1.0, 0.0)
Week 24		
n	27	16
Mean (Min, Max)	1.9 (1.5, 3.4)	1.5 (1.5, 1.7)
Change from Baseline (Min, Max)	-1.7 (-3.1, 0.0)	-0.1 (-1.0, 0.0)
Week 36		
n	27	14
Mean (Min, Max)	1.9 (1.5, 3.6)	1.6 (1.5, 1.9)
Change from Baseline (Min, Max)	-1.7 (-3.6, 0.0)	-0.1 (-1.0, 0.3)
Week 48		
n	26	14
Mean (Min, Max)	1.9 (1.5, 4.6)	1.5 (1.5, 1.6)
Change from Baseline (Min, Max)	-1.7 (-3.7, 0.0)	-0.1 (-1.0, 0.1)

Abbreviations: HBeAg=hepatitis B e antigen; HBV=hepatitis B virus; Max=maximum; Min=minimum; n=number of subjects at each visit; N=number of subjects in the Intent-to-Treat population; NrtI=Nucleos(t)ide/reverse transcriptase inhibitor; pgRNA=pregenomic ribonucleic acid.
Source: Trends Analysis Table 4.2
pgRNA LLOQ=35 U/mL.
[a] Subjects who received vebicorvir+NrtI in Study 201.

The measurement of combined reduction in both HBV DNA and HBV pgRNA is important in assessing the overall treatment effect of VBR+NrtI on HBV replication. Figure 4 summarizes the proportions of virologically-suppressed subjects originally enrolled in Study 201 who attained both HBV DNA TND and HBV pgRNA <LLOQ (considered responders) through 48 weeks of treatment with VBR+NrtI. In HBeAg positive subjects, 4% (1/27) attained the combined endpoint of HBV DNA TND and HBV pgRNA <LLOQ at Baseline which increased to 73% (19/26) at Week 48. In HBeAg negative subjects, 63% (10/16) attained the combined endpoint of HBV DNA TND and HBV pgRNA <LLOQ at Baseline which increased to 86% (12/14) at Week 48. Together, these results suggest that treatment with VBR+NrtI leads to deeper virologic suppression through more effective inhibition HBV replication.

Figure 4. Proportion of Virologically-Suppressed Subjects With HBV DNA TND and HBV pgRNA <LLOQ by Week of Treatment with Vebicorvir+ETV (Study 201/211)

Abbreviations: ETV=entecavir; HBV=hepatitis B virus; LLOQ=lower limit of quantitation; pgRNA=pregenomic ribonucleic acid; TND=target not detected.

Subjects in Study 201 had low mean serum ALT was at Baseline (25.0-26.7 U/L) as would be expected for virologically-suppressed individuals on chronic NrtI therapy. Analyses of ALT over the 48 weeks of treatment with VBR+NrtI in this patient population are not included in this summary since it is not meaningful to show change or normalization.

One subject in Study 201/211 experienced virologic rebound and had evidence of treatment-emergent resistance. This subject had been virologically-suppressed with HBV DNA <LLOQ through Week 12 in Study 201 but had low-level viremia with HBV DNA 22-74 IU/mL between Week 16 and Week 24. In Study 211, the subject reported noncompliance with study drug which began around Week 12, intermittently taking NrtI (tenofovir) with continuous VBR, and then intermittently taking VBR. The subject experienced virologic rebound with HBV DNA levels of 4.68 $\log_{10}$ IU/mL at Week 16 at which time the resistance-associated substitution T109I was observed in 100% of the circulating viral population. Per protocol, the subject discontinued VBR treatment, and restarted NrtI treatment. The subject's HBV DNA declined to <20 IU/mL at the first follow-up visit 1 month later and HBV DNA was not detected at a follow-up visit 3 months later.

2.3 AB-729

2.3.1 Description

AB-729 is a novel subcutaneously administered small interfering ribonucleic acid (siRNA) inhibitor of HBV that induces cleavage and degradation of HBV ribonucleic acid (RNA) through

the mechanism of RNA interference (RNAi). The AB-729 drug substance is a *N*-Acetylgalactosamine (GalNAc)-conjugated siRNA duplex composed of single antisense (AB-729-AS) and sense (AB-729-S) strands. In each duplex, the AB-729-AS and AB-729-S strands are present at a nominal 0.49:0.51 (weight:weight) ratio and are bound together by Watson-Crick base pairing over a 17-base region of complementarity.

General information concerning AB-729 is described in the AB-729 IB.

2.3.2 Nonclinical Studies

Refer to the AB-729 IB for a complete summary of the nonclinical and toxicology studies performed to date.

2.3.3 Clinical Studies

Preliminary data from the ongoing first-in-human Study AB-729-001 (A Single and Multiple Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AB-729 Administered by Subcutaneous Injection to Healthy Subjects and Subjects with Chronic Hepatitis B Infection), including Part 1 healthy subject safety and PK, are available in the AB-729 IB. Additional preliminary safety and efficacy data from fully enrolled cohorts in Part 2 (single doses of 60 mg, 90 mg, or 180 mg in virologically-suppressed cHBV subjects) and Part 3 (repeat doses of 60 mg administered every 4 weeks or every 8 weeks in cHBV subjects) are described in Sections 2.3.3.1, 2.3.3.2, and 2.3.3.3. The summary of preliminary safety and efficacy data is based on a data cut-off date of 23 September 2020.

2.3.3.1 Study AB-729-001 Preliminary Disposition

To date, 22 subjects have been dosed amongst 4 cohorts in Part 2 (single doses of AB-729 at either 60 mg [n=6], 90 mg [n=6], or 180 mg [n=4]), and 16 subjects have been dosed amongst 4 cohorts in Part 3 (repeat doses of AB-729 at either 60 mg administered every 4 or 8 weeks [n=7 per cohort], or 90 mg administered every 8 or 12 weeks [n=1 per cohort]) of the study. Cohort A (180 mg single dose) has been completed, but the remainder of the cohorts are ongoing. No subjects have discontinued due to AEs, but 2 subjects (Cohort C, 90 mg single dose) withdrew consent after the Week 12 follow-up visit for personal reasons.

2.3.3.2 Study AB-729-001 Preliminary Safety

In Part 2 of Study AB-729-001, preliminary safety data are available for Cohort A (180 mg single dose), Cohort B (60 mg single dose), and Cohort C (90 mg single dose). There have been no deaths, SAEs, or AEs leading to discontinuation. In Cohort A, 8 TEAEs were observed in 4 subjects including 5 related AEs (Grade 1 ALT [n=2] and AST; Grade 2 headache [n=2]). One subject had an unrelated Grade 2 foodborne toxic illness that was accompanied by Grade 3 ALT and AST changes (without bilirubin changes or changes in markers of liver synthetic function), which returned to baseline levels. In Cohort B, 6 Grade 1 TEAEs have been observed in 3 subjects, including 2 related AEs of Grade 1 injection site redness and injection site pruritis, both transient.

In Cohort C, 8 Grade 1 or 2 TEAEs have been observed in 6 subjects, including 5 related AEs of Grade 1 or 2 injection site pain lasting less than 1 hour (including 2 subjects whose doses were split into 2 injections erroneously). There were no other clinically significant changes in laboratory parameters, ECGs, vital signs, or physical exam findings.

In Part 3 of Study AB-729-001, preliminary safety data are available for Cohort E (60 mg administered every 4 weeks) and Cohort F (60 mg administered every 8 weeks). There have been no deaths, SAEs, or AEs leading to discontinuation. In Cohort E, 7 Grade 1 or 2 TEAEs have been observed in 4 subjects, including 4 related Grade 1 injection site AEs (bruising and transient redness) and 2 related Grade 1 ALT elevations. In Cohort F, 2 Grade 1 TEAEs have been observed in 2 subjects, both related (fatigue and injection site redness). There were no other clinically significant changes in laboratory parameters, ECGs, vital signs, or physical exam findings.

2.3.3.3 Study AB-729-001 Preliminary Efficacy

While clinical efficacy is not an objective of Study AB-729-001, preliminary pharmacodynamic data are available from 4 subjects in Part 2, Cohort A (180 mg single dose), 6 subjects in Part 2, Cohort B (60 mg single dose), 6 subjects in Part 2, Cohort C (90 mg single dose), and 6 subjects in Part 3, Cohort E (60 mg every 4 weeks).

After administration of single subcutaneous doses of 60 mg, 90 mg, or 180 mg of AB-729, all subjects demonstrated >0.5 $\log_{10}$ IU/mL declines in HBsAg by the follow-up Week 12 visit: mean (SEM) HBsAg declines were similar at -0.989 (0.238) $\log_{10}$ IU/mL, -1.23 (0.180) $\log_{10}$ IU/mL, and 0.980 (0.217) $\log_{10}$ IU/mL and 3/6, 5/6, and 3/4 subjects achieved ≥1 $\log_{10}$ decline in HBsAg, respectively.

In Part 3, HBV DNA negative cHBV subjects are currently receiving AB-729 60 mg every 4 weeks. At Week 12 (4 weeks after the third dose of AB-729), mean (SEM) HBsAg decline was -1.10 (0.154) $\log_{10}$ IU/mL, similar to that observed at Week 12 following single subcutaneous doses of 60 mg to 180 mg.

2.4 Study Rationale

2.4.1 Rationale for Combination Treatment of Vebicorvir and AB-729

Chronic hepatitis B virus infection is a major cause of liver-related morbidity and mortality affecting >250 million people worldwide. While SOC therapy with NrtIs is able to achieve adequate viral suppression in most HBeAg negative patients and three quarters of HBeAg positive patients, SVR off-treatment and loss of HBsAg are rare (<5%). Compared to NrtIs, finite treatment with Peg-IFNα leads to lower rates of viral suppression although small increases in the rate of HBsAg loss (5-10%) have been observed. However, any advantages associated with immunomodulation are offset by poor tolerability of Peg-IFNα. New therapeutic modalities are required to improve the depth of suppression and provide the potential for cure. Combination regimens utilizing agents with complementary mechanisms of action and resistance profiles will likely be required to support finite treatment durations.

Vebicorvir is an orally administered, potent and selective small molecule inhibitor of the HBV core protein. Through this mechanism, VBR interferes with multiple steps in the viral lifecycle including capsid disassembly and DNA delivery to the nucleus, pgRNA encapsidation, capsid assembly, and DNA recirculation preventing de novo establishment of cccDNA.

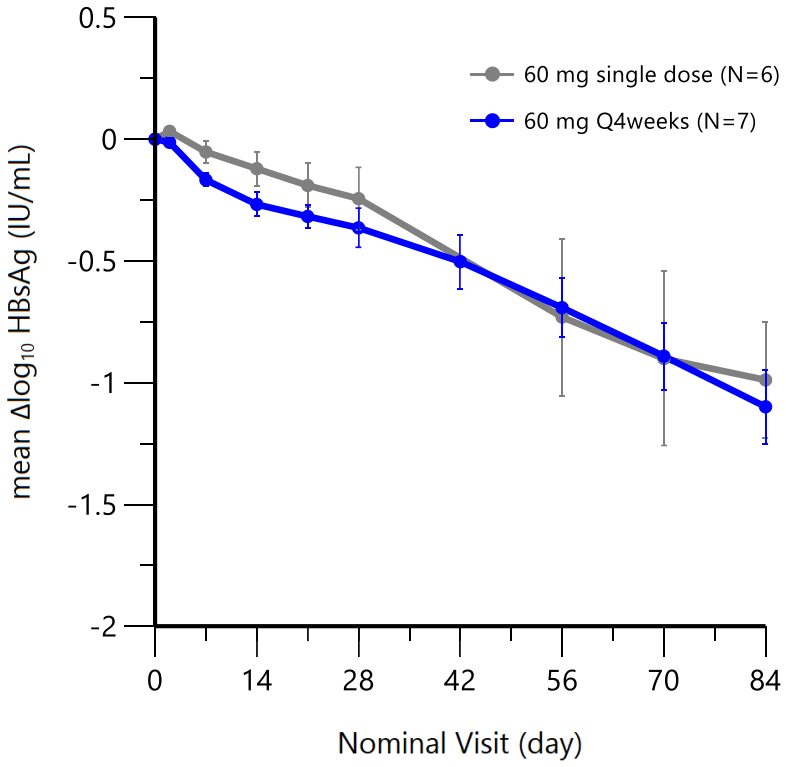
AB-729 is a subcutaneously administered novel GalNAc-conjugated siRNA, which cleaves and degrades HBV RNA, inhibiting production of all viral proteins including HBsAg. Suppression of HBsAg production by AB-729 may contribute to breaking immune tolerance to HBV and restoring T-cell activity directed toward HBV, thereby promoting functional cure. The addition of VBR and AB-729 to other treatments for cHBV will provide multiple complementary antiviral mechanisms, with potential collateral immunological consequences, that may act synergistically to increase cure rates. This Phase 2a study will explore the safety and antiviral activity of VBR and AB-729 in combination with other cHBV treatments (NrtIs).

2.4.2 Rationale for Dose Selection

In the Phase 1 clinical studies, VBR was well-tolerated in healthy subjects at single doses of up to 1000 mg daily, at twice daily doses of 800 mg for 7 days, and at single daily doses of up to 300 mg for 14 days. All TEAEs were considered mild (Grade 1) and reversible. In subjects with cHBV, VBR was well tolerated at doses of up to 300 mg daily for 28 days. Final data indicate that there is a dose dependent decrease in viral load at doses of 100 mg, 200 mg, and 300 mg daily in subjects with cHBV. Phase 2 studies (Studies 201, 202, and 211) demonstrate that 300 mg VBR administered once daily in combination with NrtI for 48 weeks is well-tolerated and leads to continued reductions in HBV DNA and HBV pgRNA (see Section 2.2.3). It is expected that this regimen will be safe, well-tolerated, and demonstrate improved HBV suppression in subjects with cHBV compared to SOC NrtI therapy.

In the AB-729 Phase 1 clinical study (Study AB-729-001), single and repeat 60 mg subcutaneous doses administered every 4 weeks were well tolerated in healthy subjects and subjects with cHBV. In subjects with cHBV, there were no SAEs or AEs leading to discontinuation; all AEs were considered mild (Grade 1). As described previously and displayed in Figure 5, preliminary pharmacodynamic data from this study showed similar mean HBsAg declines at Week 12 following administration of AB-729 60 mg every 4 weeks as that following a single dose of AB-729 60 mg. Furthermore, the slopes of mean HBsAg decline appear similar between single and multiple doses of AB-729 60 mg and taken together, these data suggest that dosing AB-729 as frequently as every 4 weeks is not necessary to achieve substantial HBsAg decline. Thus, AB-729 60 mg will be administered every 8 weeks in this study.

Figure 5. Mean (±SEM) Log_{10} HBsAg Declines up to 12 Weeks Post Single Dose of AB-729 60 mg or AB-729 60 mg Administered Every 4 Weeks



Abbreviations: HBsAg=hepatitis B surface antigen; Q4weeks=every 4 weeks.

The cumulative safety, tolerability, and antiviral activity data generated to date with both VBR and AB-729 support the conduct of the proposed study.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of Cohort 1 is:

- To evaluate the safety and tolerability of combination treatment with VBR, AB-729, and NrtI

3.1.2 Secondary Objectives

The secondary objectives of Cohort 1 are:

- To evaluate the effect of adding VBR and AB-729 to NrtI on reduction in and loss of HBsAg
- To evaluate the effect of adding VBR and AB-729 to NrtI in reducing HBV DNA levels
- To evaluate the effect of adding VBR and AB-729 to NrtI in reducing HBV RNA levels
- To evaluate the effect of adding VBR and AB-729 to NrtI in reducing other HBV antigens (ie, HBcrAg)
- To evaluate the effect of adding VBR and AB-729 to NrtI on HBsAg seroconversion
- To evaluate the effect of adding VBR and AB-729 to NrtI on normalization of ALT
- To evaluate the off-treatment durability of response to treatment with VBR and AB-729
- To evaluate the PK of VBR and AB-729 when coadministered with NrtI

3.1.3 Exploratory Objectives

The exploratory objectives of Cohort 1 are:

- To evaluate the emergence of resistance to VBR and AB-729 when coadministered with NrtI
- To evaluate the effect of VBR, AB-729, and NrtI on immunological biomarkers, where applicable
- To evaluate the effect of VBR, AB-729, and NrtI on HBsAg isoforms and immune complexes, where applicable

- To evaluate the effect of AB-729 on an HBV-derived RNA interference biomarker, where applicable

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint of Cohort 1 is:

- Proportion of subjects with AEs, premature treatment discontinuation due to AEs, and abnormal laboratory results

3.2.2 Secondary Endpoints

The secondary endpoints of Cohort 1 are:

- Mean change in $\log_{10}$ HBsAg from Baseline at each timepoint
- Proportion of subjects with HBsAg <LLOQ at each timepoint
- Proportion of subjects with HBV DNA TND (<5 IU/mL) at Week 48
- Proportion of subjects with HBV RNA <LLOQ at Week 48
- Mean change in $\log_{10}$ HBV RNA from Baseline at each timepoint
- Mean change in $\log_{10}$ HBcrAg from Baseline at each timepoint
- Proportion of subjects with HBsAg seroconversion at Week 48
- Proportion of subjects with abnormal ALT at Baseline who have normal ALT (by central laboratory and American Association for the Study of Liver Diseases [AASLD] criteria) at each timepoint
- Proportion of subjects achieving Treatment Stopping Criteria at end of treatment (EOT)
- Proportion of subjects who remain off-treatment at end of study (EOS)
- Analysis of VBR and AB-729 drug concentrations. NrtI concentrations may be analyzed, as needed

3.2.3 Exploratory Endpoints

The exploratory endpoints of Cohort 1 are:

- Proportion of subjects who continued NrtI after Week 48 and subsequently met the Treatment Stopping Criteria

- The incidence of HBV variants with reduced susceptibility to VBR and AB-729
- The evaluation of immune response markers, where applicable
- The evaluation of the effect on HBsAg isoforms, where applicable
- The evaluation of the effect on HBsAg immune complexes, where applicable
- The evaluation of the effect on an HBV-derived RNAi biomarker over time, where applicable

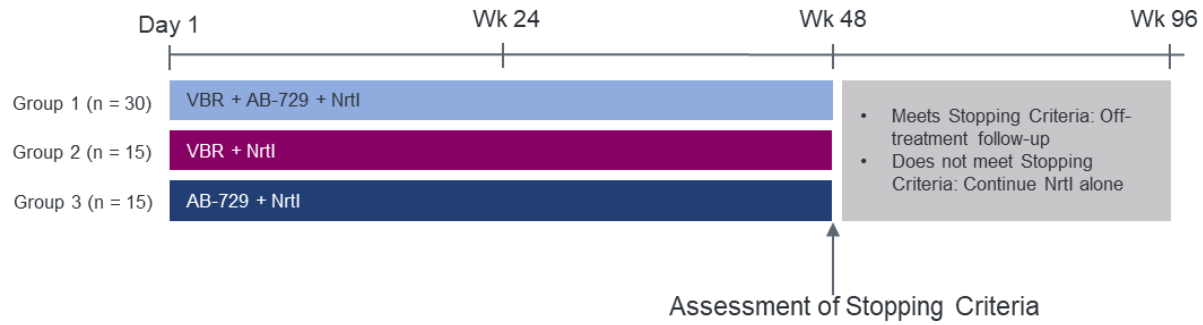
4 STUDY DESIGN

4.1 Overview

This is a randomized Phase 2a, multicenter, open-label, multiple-cohort study evaluating the safety and antiviral activity of VBR and AB-729 in combination with other cHBV treatments in subjects with cHBV.

Cohort 1 is prespecified and will enroll virologically-suppressed subjects on NrtI therapy with HBeAg negative cHBV. Approximately 60 eligible subjects will be randomized 2:1:1 in 1 of 3 treatment groups as shown in Figure 6. Up to 2 additional cohorts may be added in future protocol amendments to evaluate other populations and/or treatment regimens.

Figure 6. Study Design Schematic for Study ABI-H0731-204



Abbreviations: VBR=vebicorvir; NrtI= nucleos(t)ide /reverse transcriptase inhibitor; Wk=week.

Treatment assignments will be stratified by HBsAg level (ie, HBsAg ≤1000 IU/mL vs >1000 IU/mL) during the Screening visit.

Treatment with VBR and NrtI will be administered orally, once daily; treatment with AB-729 will be administered subcutaneously, once every 8 weeks, for a total of 6 doses (Figure 6).

4.1.1 Treatment Stopping Criteria

At Week 48, all subjects will have an assessment of Treatment Stopping Criteria. Any subjects who meet the below Treatment Stopping Criteria, will discontinue their assigned treatment including NrtI, and continue with off-treatment follow-up through Week 96, unless they meet the NrtI-restart criteria (see Section 4.1.2). Decisions to discontinue assigned treatment and undergo off-treatment follow-up will be based on laboratory results from blood samples collected at the Week 48 visit. Subjects will remain on their assigned oral agents (ie, VBR+NrtI for Groups 1 and 2; NrtI for Group 3) until Week 48 laboratory results required for Treatment Stopping Criteria assessment are available.

Treatment Stopping Criteria are:

- ALT < 2 × ULN, *and*

- HBV DNA < LLOQ, *and*
- HBsAg < 100 IU/mL

Subjects who do not meet the Treatment Stopping Criteria with Week 48 laboratory results will continue treatment with NrtI alone and will remain in follow-up through Week 96.

4.1.2 NrtI-Restart Criteria

Subjects who meet the Treatment Stopping Criteria at the Week 48 assessment but subsequently meet **ANY** of the below NrtI-Restart Criteria, will restart treatment with NrtI and remain in follow-up through Week 96.

NrtI-Restart Criteria are:

- ALT > 10 ×ULN, confirmed by repeat
- ALT > Baseline and > ULN, confirmed by repeat, and
  - Direct bilirubin > 2.0 × ULN, confirmed by repeat, or
  - International Normalized Ratio > 1.5, confirmed by repeat
- ALT ≥ 2 – 5 × ULN AND HBV DNA > 2000 IU/mL for 12 weeks
- ALT elevations ≥ 5 – 10 ×ULN AND HBV DNA > 2000 IU/mL for 4 weeks
- Any clinical decompensation, regardless of HBV DNA level
- Investigator discretion

4.2 Study Treatments

Approximately 60 subjects will be randomized in Cohort 1 as shown in Table 7. Up to 2 additional cohorts may be subsequently enrolled by future protocol amendments.

Table 7. Subject Treatment Assignment for Study ABI-H0731-204 Cohort 1

Treatment Group	Study Treatment	Mode of Delivery	Number of Subjects per Group
1	VBR+AB-729+NrtI	VBR and NrtI: Oral; AB-729: Subcutaneous	30
2	VBR+NrtI	Oral	15
3	AB-729+NrtI	AB-729: Subcutaneous; NrtI: Oral	15

Treatment Group	Study Treatment	Mode of Delivery	Number of Subjects per Group
		Total Subjects Planned:	60

Abbreviations: NrtI=nucleos(t)ide/reverse transcriptase inhibitor; VBR=vebicorvir.

For detailed information regarding dosing and administration, refer to Sections 6.1.1.4 and 6.1.2.4.

4.3 Duration of Treatment

All subjects will receive their assigned treatment for 48 weeks. Subjects will continue to receive assigned oral agents (ie, VBR+NrtI for Groups 1 and 2, and NrtI for Group 3) until all laboratory results from the Week 48 visit are available to determine each individual subject treatment action, based on Treatment Stopping Criteria (discontinuation of all treatment or continuation of NrtI; see Section 4.1.1).

4.4 End of Study Definition

The study will end when the last subject completes the last visit of the follow-up period or is considered "lost to follow-up," whichever is later.

5 STUDY POPULATION

5.1 Number of Subjects

Approximately 60 subjects will be enrolled in Cohort 1 of this study. Up to 2 additional cohorts, with approximately 60 subjects per cohort, may be added in future protocol amendments, for a maximum sample size of approximately 180 subjects.

5.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria in order to be eligible for enrollment into Cohort 1:

1. Willing and able to provide Informed Consent
2. Male or female between the ages 18 and 50 years (inclusive) at Screening
3. Body mass index (BMI) 18 to 36 kg/m^2 and a minimum body weight of 45 kg (inclusive) at Screening
4. Female subjects of child-bearing potential (Appendix 2) must be non-pregnant and have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Day 1 predose
5. cHBV defined as HBV infection documented for ≥6 months prior to Screening
6. Must be HBeAg negative at least 3 months prior to the Screening Visit (historical documentation) AND at the Screening Visit to be eligible
7. Virologically suppressed on NrtI therapy with nonquantifiable HBV DNA for at least 6 months prior to and including Screening
8. On a stable NrtI regimen of entecavir (ETV), tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF) for >12 months
9. HBsAg ≥100 IU/mL at Screening
10. Lack of bridging fibrosis or cirrhosis as documented by the following:

    - Fasting FibroScan® ≤8 kPa within 3 months prior to Screening (including the Screening visit) or other Sponsor-approved hepatic imaging method within 6 months prior to Screening (eg, Meta-analysis of Histological Data in Viral Hepatitis [METAVIR] F0-F2 or equivalent)

      OR

- Liver biopsy results (eg, METAVIR F0-F2 or equivalent) within 1 year prior to Screening

  If results from liver biopsy and FibroScan® are available, then the diagnostic method reporting the most advanced liver disease will be used to determine eligibility for the study

11. Agreement to comply with protocol-specified contraceptive requirements (Appendix 2)
12. In good general health, except for cHBV, in the opinion of the Investigator
13. Able to take oral medication, be willing to receive subcutaneous injections of AB-729, and in the opinion of the Investigator, be willing to adhere to study treatment and procedures

5.3 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible for Cohort 1 of the study:

1. Co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis D virus (HDV), acute hepatitis A virus (HAV), or acute hepatitis E virus (HEV)
2. Females who are lactating or wish to become pregnant during the course of the study
3. History of liver transplant or evidence of advanced liver disease, cirrhosis, or hepatic decompensation (including jaundice, ascites, portal hypertension, gastrointestinal bleeding esophageal varices, hepatic encephalopathy) at any time prior to, or at the time of Screening
4. History of persistent alcohol abuse (alcohol consumption exceeding 2 standard drinks per day on average [1 standard drink=14 grams of alcohol]) or illicit drug abuse within 3 years prior to Screening
5. Clinically significant diseases or conditions, such as cardiac disease, including poorly-controlled or unstable hypertension; pulmonary disease; chronic or recurrent renal or urinary tract disease; liver disease other than cHBV; endocrine disorder; autoimmune disorder; poorly controlled diabetes mellitus; neuromuscular, musculoskeletal, or mucocutaneous conditions requiring frequent treatment, seizure disorders requiring treatment; ongoing infection or other medical conditions requiring frequent medical management or pharmacologic or surgical treatment that, in the opinion of the Investigator or the Sponsor, makes the subject unsuitable for study participation
6. History of hepatocellular carcinoma (HCC)

7. History of malignancy other than HCC unless the subject's malignancy has been in complete remission off chemotherapy and without additional medical or surgical interventions during the 3 years before Screening

8. History or presence at Screening of electrocardiogram (ECG) abnormalities deemed clinically significant, in the opinion of the Investigator

9. History of hypersensitivity or idiosyncratic reaction to any components or excipients of the investigational drugs

10. History of any significant food or drug-related allergic reactions such as anaphylaxis or Stevens-Johnson syndrome

11. The following are exclusionary laboratory results at Screening:

    a. Platelet count <100,000/mm^3

    b. Albumin <3 g/dL

    c. Direct bilirubin >1.2× ULN

    d. ALT ≥5× ULN

    e. Serum alpha fetoprotein (AFP) ≥100 ng/mL. If AFP at Screening is > ULN but <100 ng/mL, the subject is eligible if hepatic imaging prior to initiation of study drug reveals no lesions indicative of possible HCC

    f. INR >1.5× ULN

    g. Estimated creatinine clearance (CrCl) <50 mL/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight at Screening

    h. Any other laboratory abnormality deemed clinically significant by the Investigator

12. Current or prior use of prohibited concomitant medications from 28 days prior to Day 1 (Section 6.3.1)

13. Current or prior treatment for cHBV with:

    - Lamivudine, telbivudine or adefovir (any duration)

    - HBV core inhibitor (any duration)

    - siRNA or other oligonucleotide therapeutic (any duration)

    - Interferon in the 6 months prior to Screening

- Any investigational agent for cHBV in the 6 months prior to Screening

14. Participation in another clinical study of a drug or device whereby the last investigational drug/device administration is within 60 days or 5 half-lives prior to the first study drug administration, whichever is longer

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized to study treatment. Minimal information to be retained on all screen failures includes demography, screen failure details, eligibility criteria, and any SAE information. Data regarding HBV genotype and HBV viral variants, if generated, will also be retained to further our understanding of the epidemiology of HBV and the natural frequency of polymorphisms present in the HBV sequences around the core and polymerase regions and the AB-729 target site.

Individuals who do not meet the protocol eligibility criteria for participation in this study (screen failure) may be allowed to rescreen (once). Rescreening may occur following resolution of acute exclusionary conditions or stabilization of conditions that were exclusionary and reversible (eg, unstable hypothyroidism, electrolyte abnormalities) and with the approval of the study Medical Monitor.

A single retest for a laboratory parameter(s) is permitted if there is a specific issue related to the collection, shipping, processing or analysis of a sample (eg, receipt of a hemolyzed sample at the testing laboratory, or samples received by the testing laboratory outside of the acceptable temperature range, or resolved intercurrent illness). If more than 45 days are required to obtain a result of a screening procedure and/or test conducted within the permitted window, the screening period may be extended until results are obtained. However, the clinical safety laboratory tests may need to be repeated under the instruction of the study Medical Monitor if the screening period is beyond 45 days.

6 STUDY DRUGS

6.1 Investigational Medicinal Product(s) (IMPs)

The investigational medicinal products (IMPs) to be used in this study are VBR and AB-729.

6.1.1 Vebicorvir

6.1.1.1 Formulation

[redacted]

6.1.1.2 Packaging and Labeling

[redacted]

6.1.1.3 Storage and Handling

[redacted]

6.1.1.4 Dosage and Administration

Vebicorvir is administered once daily as a 300 mg oral dose (3×100 mg tablets); VBR and the NrtI (Groups 1 and 2 in Figure 6) should be taken together at approximately the same time each day.

Additional information concerning VBR dosing and the management of missed or incorrect doses of VBR is provided in the Pharmacy Manual.

6.1.2 AB-729

6.1.2.1 Formulation

[redacted]

6.1.2.2 Packaging and Labeling

[redacted]

6.1.2.3 Storage and Handling

[redacted]

6.1.2.4 Dosage and Administration

AB-729 is administered once every 8 weeks as a 60 mg subcutaneous injection at specified clinic visits.

Additional information concerning AB-729 dosing and the management of missed or incorrect doses is provided in the Pharmacy Manual.

6.1.3 Accountability of IMP

Regulatory requirements stipulate accounting of all IMPs received by the study site. Records of drug disposition must include the date received by the site, date administered, quantity administered, and the subject to whom IMP was administered. The Investigator is responsible for the accountability of all IMPs at their site. The study site is to use an IMP accountability record to document IMP disposition. All items on this form are to be fully completed. The Sponsor or the Clinical Research Organization (CRO) will confirm if the method of recording IMP accountability by the site and the location of IMP records at the site is appropriate.

Each time designated site personnel dispense IMP (ie, VBR and AB-729) for a subject, he or she is to record the date dispensed, the quantity of IMP dispensed, and his or her initials. Study site personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused IMP. The site monitor will review the IMP accountability records during the monitoring visits. The site pharmacist or designated staff member will keep accurate records of drug dispensation routinely during the study.

For VBR, subjects will be asked to return used bottles and any unused IMP at study visits for accountability and compliance assessment. Returned VBR will be counted by study site personnel preferably in the presence of the subject. Subjects who forget to return VBR at a given visit will be asked to return them at the next study visit. Dose administration of VBR will be recorded in the subject diary.

As AB-729 will be administered in the clinic by qualified study personnel, the study site will be responsible for performing IMP accountability following administration of each injection of AB-729.

6.1.3.1 Return or Disposal of IMP

Procedures for the return of VBR or provisions for onsite destruction (where approved prospectively by Assembly) are described in the Pharmacy Manual.

6.2 Non-Investigational Medicinal Products(s) (NIMPs)

6.2.1 Nucleos(t)ide/Reverse Transcriptase Inhibitor (NrtI)

The non-investigational medicinal product (NIMP) to be used in this study is NrtI. Acceptable NrtIs for administration in this study are TAF, TDF, or ETV. The NrtI will not be provided by the Sponsor unless required by the country or study site.

6.2.1.1 Formulation

Details of the NrtI formulations are specified in the respective package inserts.

6.2.1.2 Packaging and Labeling

Details of the NrtI packaging and labeling are specified in the respective package inserts.

6.2.1.3 Dosage and Administration

Details for the NrtI dosage and administration are specified in the respective package inserts. The NrtI should be taken with VBR at approximately the same time each day.

6.2.1.4 Storage and Handling

Details for the NrtI storage and handling are specified in the respective package inserts.

6.2.2 Accountability for NIMPs

Oversight of background medication (NrtI) according to product label will be provided by the Investigator. Dose administration of NIMPs will be recorded in the subject diary.

6.3 Concomitant Medications

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins, medications, vaccinations, herbal preparations and supplements that is taken by a subject during the conduct of the clinical trial.

All concomitant medications taken from the date the informed consent is signed through end of study or “lost to follow-up” must be recorded in the subject’s source documentation. This information should include the name of the medication, the dosage, the start and stop dates, and the indication for which the concomitant medication was administered.

6.3.1 Prohibited Concomitant Therapy

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters [ie, P-glycoprotein] or metabolizing enzymes [ie, cytochrome P450s]) may result in PK interactions that increase or decrease the exposure of VBR or the concomitant medication. Examples of representative medications which are prohibited from 28 days prior to Day 1 through 2 weeks after the last dose of VBR or "lost to follow-up" are listed in Table 8. Investigational agents are also prohibited. Provisions regarding concomitant medications described in the respective NrtI package inserts must also be followed during the study through the end of the follow-up period.

Medications with narrow therapeutic indices should be avoided or used with caution (representative medications are shown in Table 8). Narrow therapeutic drugs that are substrates for CYP2C9 are prohibited.

Should subjects need treatment with any prohibited concomitant medication, the Medical Monitor must be consulted prior to initiation of the new medication. In instances where a prohibited concomitant medication is initiated prior to discussion with the Medical Monitor, the Investigator must notify the Sponsor as soon as he/she is aware.

Note that systemic (oral, injectable, or implanted) hormonal contraceptives are not considered as an acceptable means of contraception for female subjects of child-bearing potential (Appendix 2) up to 28 days after the last dose of VBR (Groups 1 and 2 in Figure 6). For AB-729, the use of hormonal contraceptives is acceptable for female subjects of child-bearing potential as long as they use a second non-hormonal form of contraception during the study and up to 6 months after the last dose of AB-729 (Group 3 in Figure 6).

Table 8. Prohibited Concomitant Therapies

Drug Class	Prohibited Medications	Use with Caution
Antiarrhythmics		Quinidine
Anticonvulsants	Phenytoin, carbamazepine, phenobarbital, oxcarbazepine	Digoxin
Antidepressants		Amitriptyline, doxepin, fluoxetine, venlafaxine
Antimycobacterials	Rifamycins	
Cardiac Medications	Warfarin, digoxin	Irbesartan, losartan
Hypoglycemics	Troglitazone	Glimepiride, glipizide, glyburide, nateglinide, rosiglitazone, tolbutamide, chlorpropamide, nateglinide
Herbal/Natural Supplements	St. John's Wort, echinacea, milk thistle, grapefruit/grapefruit juice	

Drug Class	Prohibited Medications	Use with Caution
Nonsteroidal anti-inflammatory drugs (NSAIDs)		Celecoxib, diclofenac, ibuprofen, lornoxicam, meloxicam, naproxen, piroxicam, suprofen
Others	Barbiturates, modafinil	

6.4 Randomization, Blinding, and Treatment Codes

6.4.1 Randomization

All subjects will be assigned a unique Subject identification (ID) at Screening and will be randomized upon successful completion of the Screening assessments. Upon confirmation of subject eligibility on Day 1, an Interactive Response Technology (IRT) system will assign eligible subjects to a study treatment, as shown in Table 7. Additional information on the use of the IRT system is provided in the IRT User Manual.

6.4.2 Blinding

This is an open-label study.

7 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

With the exception of treatment cessation based on Treatment Stopping Criteria (see Section 4.1.1), if an individual subject is not satisfactorily tolerating their assigned treatment due to any AEs in the judgment of the Investigator, then, upon consultation with the Sponsor, the Investigator may discontinue treatment with VBR and/or AB-729 depending on the treatment group assignment. Discontinuation from treatment does not mean discontinuation from the study. Subjects who prematurely discontinue their assigned treatment regimen should immediately undergo the assessments listed for the Premature Termination visit (Section 8.5) and then continue scheduled follow-up assessments (Table 11).

- If both or either IMP is discontinued, the subject may remain on NrtI as clinically indicated at the discretion of the Investigator.

- For subjects in Group 1, if the NrtI is discontinued, then VBR must also be discontinued; treatment with AB-729 may be continued following discussion with the Medical Monitor. In this event, subjects will not be required to undergo a premature termination visit, and will continue with their scheduled visits, as planned.

7.2 Criteria for Discontinuation of Study Treatment

With the exception of treatment cessation based on Treatment Stopping Criteria (see Section 4.1.1), study drug treatment may be discontinued in the following instances:

- Intercurrent illness that would, in the judgement of the Investigator, affect assessments of clinical status to a significant degree

- Unacceptable toxicity as defined in Section 9.10 (Toxicity Management), or toxicity that, in the judgment of the Investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest

- Lack of efficacy (virologic failure)

- Subject noncompliance

- Pregnancy during the study

- Discontinuation of the study at the request of the Sponsor, a regulatory agency or an Institutional Review Board or Independent Ethics Committee (IRB/IEC)

7.3 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. At the time of discontinuing from the study, if possible, a Premature Termination visit should be conducted (Section 8.5).

7.3.1 Subject Lost to Follow-Up

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject, reschedule the missed visit as soon as possible, and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

Should the subject continue to be unreachable, they will be considered lost to follow-up.

8 STUDY PROCEDURES AND ASSESSMENTS

8.1 Schedule of Assessments

All procedures for Cohort 1 of this study are outlined in Table 9.

Table 9. Schedule of Assessments (Cohort 1) – On-Treatment for All Subjects

Period or Visit	**Screen**	**On Treatment**													**PT [a]**	**UV [b]**
Study Day or Week	**D-45 to D-1**	**D 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**NA**	**NA**
Visit Windows (days)	**NA**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**NA**	**NA**
Informed Consent(s)	X																
Demographics, medical history & HBV history	X	X															
Height	X																
Weight	X	X							X						X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical exam	X	X							X						X	X	
Symptom-directed physical exam			X	X	X	X	X	X		X	X	X	X	X			X
12-lead ECG [c]	X	X				X			X			X			X	X	
Review of concomitant medications & AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver staging	X [d]																
Fibroscan® (if available)	X								X						X	X	
FibroTest®, APRI	X								X						X	X	
Chemistry, hematology, coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CrCl	X	X							X						X	X	X
AFP, HbA1c	X																
Pregnancy test [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug test	X																
HBV genotype	X [f]																
HBV DNA (COBAS® TaqMan®)	X	X				X			X			X			X	X	X
HBV RNA (COBAS®)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV TNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Qualitative HBeAg	X	X													X	X	
HBeAb	X	X													X	X	
Quantitative HBsAg [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAb [g]	X	X													X		
HBcrAg	X	X													X	X	

Period or Visit	**Screen**	**On Treatment**														**PT [a]**	**UV [b]**
Study Day or Week	**D-45 to D-1**	**D 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**NA**	**NA**
Visit Windows (days)	**NA**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**NA**	**NA**
HBsAg isoforms and immune complexes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sample for HBV resistance monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Virology back-up sample [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immune biomarkers/cytokines		X	X	X	X	X		X		X		X		X		X	X
PBMCs [i]		X	X	X	X	X		X		X		X		X		X	X
RNAi biomarker sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV Ab, HDV Ab, HIV Ab, HAV Ab, HEV Ab	X																
Confirm subject eligibility	X	X															
Randomization		X															
Dispense VBR		X		X	X	X	X	X	X	X	X	X	X	X			
VBR administration (Groups 1, 2)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
NrtI administration (All subjects)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AB-729 administration (Group 1, 3)		X			X		X		X		X		X				
VBR accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review subject dosing diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review injection site reaction diary (Groups 1 and 3)			X			X		X		X		X		X		X	
Sparse PK of VBR (Groups 1, 2)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sparse PK of NrtI (All subjects)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sparse PK of AB-729 (Group 1, 3) [j]		X [j]			X		X		X		X		X [j]				
Optional intensive PK substudy of AB-729		X [k]											X [k]				
Optional pharmacogenomic sample							X [l]										

Period or Visit	Screen	On Treatment													PT [a]	UV [b]
Study Day or Week	D-45 to D-1	D 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	NA	NA
Visit Windows (days)	NA	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	NA	NA
Assessment of Treatment Stopping Criteria (see Section 4.1.1)															X [m]		

Abbreviations: Ab=antibody; AE=adverse event; AFP=alpha fetoprotein; APRI=aspartate aminotransferase to platelet ratio index; CrCl=creatinine clearance; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; HbA1c=glycated hemoglobin; HBcrAg=hepatitis B core-related antigen; HBeAb=anti-hepatitis B e antigen antibody; HBeAg=hepatitis B e antigen; HBsAb=anti-hepatitis B surface antigen antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDV=hepatitis D virus; HEV=hepatitis E virus; HIV=human immunodeficiency virus; IRT= Interactive Response Technology; NA=not applicable; NrtI=nucleos(t)ide/reverse transcriptase inhibitor; PK=pharmacokinetic(s); PT=Premature Termination visit; RNA=ribonucleic acid; TNA=total nucleic acids; UV=Unscheduled visit; Wk(s)=week(s); VBR=vebicorvir.

[a] Subjects who prematurely discontinue their assigned treatment regimen before the Week 48 visit should immediately undergo the assessments listed for the Premature Termination visit and then continue with Weeks 52 to 96 follow-up assessments (see Table 11).

[b] Any subject with ALT elevation as defined in Section 9.10.4 should return to the clinic for an Unscheduled visit.

[c] Any clinically significant ECG result will be confirmed.

[d] At Screening, liver staging will be done EITHER via FibroScan ® (if available)/ other Sponsor-approved hepatic imaging method OR via liver biopsy.

[e] A serum pregnancy test is required at Screening for female subjects of child-bearing potential. On Day 1, both urine and serum will be performed (subjects may begin treatment based on urine results; any subjects negative by urine subsequently found to be positive on serum should immediately discontinue treatment). All post-Day 1 pregnancy tests may be conducted by urine dipstick. If positive on dipstick, reflex to serum.

[f] HBV genotype samples will be collected and stored for analysis by sequence methodology.

[g] Quantitative HBsAg assay will be performed at Screening and all study visits. If quantitative HBsAg is <LLOQ, then reflex to qualitative HBsAg. HBsAb is performed at Screening, Day 1, and Week 48. Additionally, if HBsAg is <LLOQ then reflex testing of HBsAb will also be performed.

[h] The virology back-up sample will be used for retesting the specified HBV parameters.

[i] PBMC collection at selected sites only; not to be collected at subsequent timepoints if not collected at Day 1.

[j] A sparse PK sample will be collected for AB-729 at 2 hours (±1 hour) postdose at Weeks 8, 16, 24, and 32 visits. At Day 1 and Week 40, a sparse PK sample will be collected at 2 hours (±1 hour) postdose from subjects who do not participate in the intensive PK substudy.

[k] Optional intensive PK substudy of AB-729. Samples will be collected predose, and at 0.5 (±3 min), 1 (±6 min), 2 (±10 min), 4 (±10 min), and 6 (±10 min)- hours postdose (see Section 8.9.1.2).

[l] Pharmacogenomic sample will be obtained only from subjects who provide an additional informed consent. The sample can be collected at a later visit if not collected at Week 16.

[m] Subjects will either stop their treatment altogether or continue with NrtI administration based on assessment of Treatment Stopping Criteria (Section 4.1.1) utilizing laboratory results from the Week 48 Visit. Subjects will remain on assigned oral agents (ie, VBR+NrtI for groups 1 and 2, and NrtI for Group 3) beyond the Week 48 visit until all laboratory results are available to adjudicate the Treatment Stopping Criteria.

Table 10. Schedule of Assessments (Cohort 1) – Off-treatment Follow-Up for Subjects Meeting Treatment Stopping Criteria

Study Day or Week	**Wk 50**	**Wk 52**	**Wk 54**	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**
Visit Windows (days)	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Weight								X						X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical exam								X						X
Symptom-directed physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG [a]					X									X
Review of concomitant medications & AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fibroscan® (if available)								X						X
FibroTest®, APRI								X						X
Chemistry, hematology, coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CrCl								X						X
Pregnancy test [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA (COBAS® TaqMan®)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV RNA (COBAS®)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV TNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Qualitative HBeAg					X			X			X			X
HBeAb					X			X			X			X
Quantitative HBsAg [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBcrAg					X			X			X			X
HBsAg isoforms	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immune complexes		X		X	X	X		X			X			X
Sample for HBV resistance monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Virology back-up sample [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immune biomarkers/cytokines				X		X		X			X			X
PBMCs [e]				X		X		X			X			X
RNAi biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sparse PK of VBR (off-treatment; Groups 1, 2)	X													

Study Day or Week	Wk 50	Wk 52	Wk 54	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96
Visit Windows (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
VBR Accountability (Groups 1, 2) [f]	X													

Abbreviations: Ab=antibody; AE=adverse event; APRI=aspartate aminotransferase to platelet ratio index; CrCl=creatinine clearance; DNA=deoxyribonucleic acid; ECG=electrocardiogram; HBcrAg=hepatitis B core-related antigen; HBeAb=anti-hepatitis B e antigen antibody; HBeAg=hepatitis B e antigen; HBsAg=hepatitis B surface antigen; NrtI=nucleos(t)ide/reverse transcriptase inhibitor; PK=pharmacokinetic(s); RNA=ribonucleic acid; TNA=total nucleic acids; UV=Unscheduled visit; Wk(s)=week(s); VBR=vebicorvir.

[a] Any clinically significant ECG result will be confirmed.

[b] Pregnancy tests may be conducted by urine dipstick. If positive on dipstick, reflex to serum.

[c] If quantitative HBsAg is <LLOQ, then reflex to qualitative HBsAg. HBsAb is performed at Screening, Day 1, and Week 48. Additionally, if HBsAg is <LLOQ then reflex testing of HBsAb will also be performed.

[d] The virology back-up sample will be used for retesting the specified HBV parameters.

[e] PBMC collection at selected sites only; not to be collected at subsequent timepoints if not collected at Day 1.

[f] Subjects will either stop their treatment altogether or continue with NrtI administration based on assessment of Treatment Stopping Criteria (Section 4.1.1) utilizing laboratory results from the Week 48 Visit. Subjects will remain on assigned oral agents (ie, VBR+NrtI for groups 1 and 2, and NrtI for Group 3) beyond the Week 48 visit until all laboratory results are available to adjudicate the Treatment Stopping Criteria.

Table 11. Schedule of Assessments (Cohort 1) – Follow-up for Rest of the Subjects

Study Day or Week	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96
Visit Windows (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Weight						X						X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical exam						X						X
Symptom-directed physical exam	X	X	X	X	X		X	X	X	X	X	
12-lead ECG [a]			X									X
Review of concomitant medications & AEs	X	X	X	X	X	X	X	X	X	X	X	X
Fibroscan® (if available)						X						X
FibroTest®, APRI						X						X
Chemistry, hematology, coagulation	X	X	X	X	X	X	X	X	X	X	X	X
CrCl						X						X
Pregnancy test [b]	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA (COBAS® TaqMan®)			X			X			X			X

Study Day or Week	**Wk 52**	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**
Visit Windows (days)	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
HBV RNA (COBAS®)	X	X	X	X	X	X	X	X	X	X	X	X
HBV TNA	X	X	X	X	X	X	X	X	X	X	X	X
Qualitative HBeAg			X			X			X			X
HBeAb			X			X			X			X
Quantitative HBsAg [c]	X	X	X	X	X	X	X	X	X	X	X	X
HBcrAg			X			X			X			X
HBsAg isoforms	X	X	X	X	X	X	X	X	X	X	X	X
Immune complexes	X	X	X	X		X			X			X
Sample for HBV resistance monitoring	X	X	X	X	X	X	X	X	X	X	X	X
Virology back-up sample [d]	X	X	X	X	X	X	X	X	X	X	X	X
Immune biomarkers/cytokines		X		X		X			X			X
PBMCs [e]		X		X		X			X			X
RNAi biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X
NrtI administration (see Sections 4.1.1, 4.1.2)	X	X	X	X	X	X	X	X	X	X	X	X
Review subject dosing diary	X	X	X	X	X	X	X	X	X	X	X	X
Sparse PK of VBR (Groups 1, 2)	X											
VBR accountability (Groups 1, 2) [f]	X											

Abbreviations: Ab=antibody; AE=adverse event; APRI=aspartate aminotransferase to platelet ratio index; CrCl=creatinine clearance; DNA=deoxyribonucleic acid; ECG=electrocardiogram; HBcrAg=hepatitis B core-related antigen; HBeAb=anti-hepatitis B e antigen antibody; HBeAg=hepatitis B e antigen; HBsAg=hepatitis B surface antigen; NrtI=nucleos(t)ide/reverse transcriptase inhibitor; PK=pharmacokinetic(s); RNA=ribonucleic acid; TNA=total nucleic acids; UV=Unscheduled visit; Wk(s)=week(s); VBR=vebicorvir.

[a] Any clinically significant ECG result will be confirmed.

[b] Pregnancy tests may be conducted by urine dipstick. If positive on dipstick, reflex to serum.

[c] If quantitative HBsAg is <LLOQ, then reflex to qualitative HBsAg. HBsAb is performed at Screening, Day 1, and Week 48. Additionally, if HBsAg is <LLOQ then reflex testing of HBsAb will also be performed.

[d] The virology back-up sample will be used for retesting the specified HBV parameters.

[e] PBMC collection at selected sites only; not to be collected at subsequent timepoints if not collected at Day 1.

[f] Subjects will either stop their treatment altogether or continue with NrtI administration based on assessment of Treatment Stopping Criteria (Section 4.1.1) utilizing laboratory results from the Week 48 Visit. Subjects will remain on assigned oral agents (ie, VBR+NrtI for groups 1 and 2, and NrtI for Group 3) beyond the Week 48 visit until all laboratory results are available to adjudicate the Treatment Stopping Criteria.

8.2 Study Visit Assessments

To reduce the risk of potential exposure to COVID-19, study visits may be conducted by home health personnel in the home of the subject and study drug may be shipped by courier directly from the study site to the subject or provided via other alternative mechanisms of provision. Subjects must provide prior consent (verbal or written) for home visits and direct shipment of study drug to their home. Telemedicine visits may be allowed if the clinical site or subject is directly affected by local COVID restrictions. Blood sampling for telemedicine visits may be drawn by home health personnel or via subject visit to a local laboratory.

8.3 Subject Enrollment and Treatment Assignment

Following provision of informed consent and completion of all Screening and Day 1 assessments, if a subject meets all protocol eligibility requirements the Investigator or designee will randomize the subject using the IRT system described in Section 6.4.1 and Table 7. Protocol waivers will not be granted for any reason.

8.3.1 Screening Visits

The following Screening assessments must be completed within 45 days of the scheduled Day 1 visit:

- Obtain written informed consent prior to the initiation of any Screening procedures
- Record demographics and medical history, including HBV history
- Measure height and weight
- Record vital signs (temperature, heart rate, respiration rate, and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated)
- 12-lead ECG
- Review of concomitant medications
- Review of AEs occurring after provision of informed consent
- Liver staging (via FibroScan (if available)/other Sponsor-approved hepatic imaging method OR via liver biopsy)
- FibroTest®, APRI
- Obtain blood samples for the following:
  - Safety laboratory tests: chemistry, hematology, coagulation, CrCl

  - Virology: HBV genotype sample, HBV total nucleic acids (TNA), HBV DNA, HBV RNA, HBsAg, qualitative HBeAg, HBsAb, HBeAb, HBsAg isoforms and immune complexes, HBcrAg, HBV resistance monitoring sample
  - Virology back-up sample (to be used for retesting HBV parameters)
  - Serology: HAV, HCV, hepatitis D virus (HDV), hepatitis E virus (HEV), HIV
  - Other: AFP, glycated hemoglobin (HbA1c), pregnancy test for female subjects of child-bearing potential

- Obtain urine sample for:
  - Urine drug test
- Confirm subject eligibility

8.3.2 Day 1 Visit

The following procedures must be completed at Day 1, prior to the first dose of study drug:

- Update medical history, including HBV history
- Measure weight
- Vital signs (temperature, heart rate, respiration rate, and blood pressure)
- Complete physical examination
- 12-lead ECG
- Review AEs and concomitant medications
- Obtain blood samples for the following:
  - Safety laboratory tests: chemistry, hematology, coagulation, CrCl
  - Virology: HBV TNA, HBV DNA, HBV RNA, HBsAg, HBeAg, HBsAb, HBeAb, HBsAg isoforms and immune complexes, HBcrAg, HBV resistance monitoring sample
  - Virology back-up sample (to be used for retesting HBV parameters)
  - Other:
    - Pregnancy test for female subjects of child-bearing potential
    - Sparse PK samples for VBR and NrtI

  - Sparse PK samples for AB-729 at 2 hours (±1 hour) postdose (for subjects who are not participating in the AB-729 optional intensive PK substudy only)
  - Blood samples for AB-729 intensive PK substudy (optional) will be collected at the timepoints listed in Section 8.8.5
  - Cytokines/Immune biomarkers
  - PBMCs (at selected sites only)
  - RNAi biomarker

- Obtain urine samples for the following:
  - Pregnancy test for female subjects of child-bearing potential
  - Urinalysis
- Confirm subject eligibility
- Complete randomization (IRT)
- IMP (VBR and AB-729) and NIMP (NrtI) administration during clinic visit
- Dispense VBR bottles
- Provide dosing diary to the subject and record first dose administration
- Provide injection site reaction diary for subjects in Groups 1 and 3

8.3.3 Week 2 Through Week 48 Visits (±3 Days)

The following assessments will be performed at Study Weeks 2, 4, 8, 12, 16, and every 4 weeks thereafter through Week 48 (inclusive) unless otherwise indicated:

- Measure body weight (Weeks 24 and 48 only)
- Record vital signs (temperature, heart rate, respiration rate and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated; Weeks 24 and 48 only); all other visits, symptom-directed physical examination
- 12-lead ECG (Weeks 12, 24, 36, and 48 only)
- FibroScan (if available; Weeks 24 and 48 only)
- Review AEs and concomitant medications

- Obtain blood samples for the following:
  - Safety laboratory tests:
    - chemistry, hematology, coagulation
    - CrCl (Weeks 24 and 48 only)
  - Virology:
    - HBV TNA, HBV RNA, HBsAg, HBsAb (only if HBsAg <LLOQ), HBsAg isoforms and immune complexes, HBV resistance monitoring sample
    - HBV DNA (at Weeks 12, 24, 36, and 48 only)
    - HBeAg, HBeAb, HBsAb, HBcrAg (at Week 48 only)
    - Virology back-up sample (to be used for retesting HBV parameters)
  - Other:
    - FibroTest, APRI (both at Weeks 24 and 48 only)
    - Sparse PK samples for VBR and NrtI
    - Sparse PK samples for AB-729 at 2 hours (±1 hour) postdose (at Weeks 8, 16, 24, and 32 only) and also at Week 40 from subjects who are not participating in the optional intensive PK substudy
    - Blood samples for AB-729 intensive PK substudy (optional) will be collected after the last dose (at Week 40 only) at the timepoints listed in Section 8.8.5
    - Cytokines/Immune biomarkers (at Weeks 2, 4, 8, 12, 20, 28, 36, and 44 only)
    - PBMCs (at selected sites at Weeks 2, 4, 8, 12, 20, 28, 36, and 44 only; not to be collected at subsequent timepoints if not collected at Day 1)
    - RNAi biomarker
    - Pharmacogenomics sample (optional, at Week 16 only); collected only in subjects who provide additional informed consent and can be collected at a later visit if not collected at Week 16
- Obtain urine samples for the following:
  - Pregnancy test for female subjects of child-bearing potential
  - Urinalysis

- Review subject injection site reaction diary (Groups 1 and 3) at Weeks 2, 12, 20, 28, 36, and 44
- Subject dosing diary
- Assess VBR accountability (Groups 1 and 2)
- Dispense VBR bottles (excluding Week 2); final dispensation at Week 44
- Assessment of Treatment Stopping Criteria (see Section 4.1.1 for details)
- VBR and NrtI administration once daily at home; Subjects will continue to receive VBR and NrtI beyond the Week 48 visit, until all laboratory results are available to adjudicate individual subject Treatment Stopping Criteria (see Section 4.1.1).
- AB-729 administration in clinic at Weeks 8, 16, 24, 32, and 40; last administration of AB-729 at Week 40

8.3.4 Week 50 Through Week 96 Off-Treatment Follow-Up Visits for Subjects Meeting Treatment Stopping Criteria (±5 Days)

The following follow-up assessments will be performed from Study Weeks 50 through 96 for subjects meeting Treatment Stopping Criteria (see Table 10). Note: If a subject is determined to meet the NrtI-restart criteria at any time during the follow-up, he/she should follow the schedule of visits specified in Section 8.3.5 and Table 11:

- NrtI and VBR will continue to be administered at home until laboratory results from the Week 48 visits are available to determine if an individual subject meets Treatment Stopping Criteria (see Section 4.1.1). Once a subject meets the Treatment Stopping Criteria and is notified by the site, subject will discontinue treatment with NrtI and VBR.
- Measure body weight (Weeks 72 and 96 only)
- Record vital signs (temperature, heart rate, respiration rate, and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated; Week 72 and 96 only); all other visits, symptom-directed physical examination
- 12-lead ECG (Weeks 60 and 96 only)
- Review AEs and concomitant medications
- FibroScan (if available; Weeks 72 and 96 only)
- Obtain blood samples for the following:
  - Safety laboratory tests:

- chemistry, hematology, coagulation
- CrCl (Weeks 72 and 96 only)

- Virology:
  - HBV DNA, HBV TNA, HBV RNA
  - HBsAg, HBsAb (only if HBsAg <LLOQ), HBsAg isoforms, HBV resistance monitoring sample
  - Immune complexes (Weeks 52, 56, 60, 64, 72, 84, and 96 only)
  - HBeAg, HBeAb, HBcrAg (Weeks 60, 72, 84, and 96 only)
  - Virology back-up sample (to be used for retesting HBV parameters)
- Other:
  - FibroTest, APRI (both at Week 72 and 96 only)
  - A single off-treatment blood sample for sparse PK of VBR (Groups 1 and 2; Week 50 only)
  - Cytokines/Immune biomarkers (Weeks 56, 64, 72, 84, and 96 only)
  - PBMCs (at selected sites at Weeks 56, 64, 72, 84, and 96; not to be collected at subsequent timepoints if not collected at Day 1)
  - RNAi biomarker

- Obtain urine samples for the following:
  - Pregnancy test for female subjects of child-bearing potential
  - Urinalysis
- VBR accountability (Groups 1 and 2; Week 50 only)

8.3.5 Week 52 Through Week 96 Follow-Up Visits for Rest of the Subjects (±5 Days)

The following follow-up assessments will be performed every 4 weeks from Study Weeks 52 through 96, for subjects who do NOT meet the Treatment Stopping Criteria, or subjects who meet the NrtI-restart criteria after having met Treatment Stopping Criteria, or subjects who prematurely discontinue treatment with VBR/AB-729 at any time (see Table 11):

- NrtI and VBR will continue to be administered at home until laboratory results from the Week 48 visits are available to adjudicate the individual subject Treatment Stopping Criteria (see Section 4.1.1). Once a subject is determined to not meet the Treatment Stopping Criteria, he/she will be notified by the site, and the subject will discontinue treatment with VBR.

- NrtI administration once daily at home through Week 96

- Measure body weight (Weeks 72 and 96 only)

- Record vital signs (temperature, heart rate, respiration rate, and blood pressure)

- Complete physical examination (excluding breast and genitalia, unless indicated; Week 72 and 96 only); all other visits, symptom-directed physical examination

- 12-lead ECG (Weeks 60 and 96 only)

- Review AEs and concomitant medications

- FibroScan (if available; Weeks 72 and 96 only)

- Obtain blood samples for the following:
  - Safety laboratory tests:
    - chemistry, hematology, coagulation
    - CrCl (Weeks 72 and 96 only)
  - Virology:
    - HBV TNA, HBV RNA
    - HBV DNA (Weeks 60, 72, 84, and 96 only)
    - HBsAg, HBsAb (only if HBsAg <LLOQ), HBsAg isoforms, HBV resistance monitoring sample
    - Immune complexes (Weeks 52, 56, 60, 64, 72, 84, and 96 only)
    - HBeAg, HBeAb, HBcrAg (Weeks 60, 72, 84, and 96 only)
    - Virology back-up sample (to be used for retesting HBV parameters)
  - Other:
    - FibroTest, APRI (both at Week 72 and 96 only)

  - A single off-treatment blood sample for sparse PK of VBR (Groups 1 and 2; Week 52 only)
  - Cytokines/Immune biomarkers (Weeks 56, 64, 72, 84, and 96 only)
  - PBMCs (at selected sites at Weeks 56, 64, 72, 84, and 96; not to be collected at subsequent timepoints if not collected at Day 1)
  - RNAi biomarker

- Obtain urine samples for the following:
  - Pregnancy test for female subjects of child-bearing potential
  - Urinalysis
- Subject dosing diary
- VBR accountability (Groups 1 and 2; Week 52 only)

8.4 Unscheduled Visit

An unscheduled visit may be performed at any time at the discretion of Investigator in order to further evaluate a subject. The specific assessments to be performed at these visits would be determined by the Investigator according to nature of the subject specific follow-up required, however at a minimum the assessments would include the following:

- Record vital signs (temperature, heart rate, respiration rate, and blood pressure)
- Symptom-directed physical examination
- Review AEs and concomitant medications
- Obtain blood samples for the following, as applicable:
  - Safety laboratory tests: chemistry, hematology, coagulation, CrCl
  - Virology: HBV TNA, HBV DNA, HBV RNA, HBsAg, HBsAg isoforms and immune complexes, HBV resistance monitoring sample
  - Virology back-up sample (to be used for retesting HBV parameters)
  - Other:
    - Sparse PK sample for VBR and NrtI
    - Cytokines/immune biomarkers

    - PBMCs (at selected sites, if feasible)
    - RNAi biomarker

- Obtain urine samples, as applicable for:
    - Pregnancy test for female subjects of child-bearing potential
    - Urinalysis
- Assess VBR accountability and review subject dosing diary, as applicable

Assessments performed should be documented in the subject's source documentation. Clinical laboratory assessments should be conducted through the central laboratory. The minimum Unscheduled Visit assessments to be completed when managing ALT elevations are noted in Section 9.10.4.

8.5 Premature Termination Visit

Should a subject prematurely discontinue their assigned treatment regimen (Section 7.1) or discontinue from the study (Section 7.2), a Premature Termination visit should be scheduled. While the Investigator may include additional assessments and evaluations determined by the status of the individual subject, at the minimum, the following assessments should be performed as soon as feasibly possible:

- Record vital signs (temperature, heart rate, respiration rate, and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated)
- 12-lead ECG
- Review AEs and concomitant medications
- FibroScan (if available)
- Obtain blood samples for the following:
    - Safety laboratory tests: chemistry, hematology, coagulation, CrCl
    - Virology: HBV TNA, HBV DNA, HBV RNA, HBeAg, HBeAb, HBsAg, HBsAb (only if HBsAg <LLOQ), HBcrAg, HBsAg isoforms and immune complexes, HBV resistance monitoring sample
    - Virology back-up sample (to be used for retesting HBV parameters)
    - Other:
        - FibroTest, APRI

  - Sparse PK sample for VBR and NrtI
  - Cytokines/Immune biomarkers
  - PBMCs (at selected sites only)
  - RNAi biomarker

- Obtain urine samples for the following:
  - Pregnancy test for female subjects of child-bearing potential
  - Urinalysis
- Subject injection site reaction diary for subjects in Groups 1 and 3
- Subject dosing diary
- Assess VBR accountability

8.6 Assessment of Efficacy

8.6.1 Quantification of HBV Total Nucleic Acids (TNA)

HBV TNA will be quantified by an in-house assay at Assembly. For this assay, HBV nucleic acids are extracted from plasma using commercially available purification kits following the manufacturer's instructions. HBV nucleic acids are then quantified by RT-qPCR with dual pan-genotypic primer probes that amplify sequences in the HBc and HBx genes. Additional details concerning the methodology, collection and processing of the samples are described in the Study Laboratory Manual. HBV TNA will be measured at the timepoints indicated in Section 8 and the Schedule of Assessments (Table 9, Table 10, Table 11).

8.6.2 Quantification of HBV DNA

HBV DNA will be quantified using a commercially available HBV test with LLOQ of 10 IU/mL, at a central reference laboratory. Additional details concerning the collection and processing of the samples are described in the Study Laboratory Manual. HBV DNA will be measured at the timepoints indicated in Section 8 and the Schedule of Assessments (Table 9, Table 10, Table 11). Additional higher sensitivity assays for HBV DNA may also be implemented dependent upon virologic response to treatment. The Sponsor also reserves the right to use alternate HBV virology assays with comparable LLOQ if the (originally) specified assays become unavailable.

8.6.3 Quantification of HBV RNA

HBV RNA will be quantified using the commercially available COBAS assay (Roche Diagnostics, US) at a central reference laboratory. Additional details concerning the methodology, collection and processing of the samples are described in the Study Laboratory Manual. HBV RNA will be

measured at the timepoints indicated in Section 8 and the Schedule of Assessments (Table 9, Table 10, Table 11). Additional higher sensitivity assays for HBV RNA may also be implemented dependent upon virologic response to treatment.

8.6.4 Quantification of HBV Antigens and Antibodies

To ensure standardization of the analytical methodologies utilized in this study, HBV antigens (ie, HBeAg, HBcrAg, HBsAg) and HBV antibodies (ie, HBeAb, HBsAb) will be measured by quantitative and/or qualitative assays at a central reference laboratory. In cases where a quantitative assay is negative or <LLOQ, reflex qualitative testing will be done. Details regarding the specific methodologies, collection and processing of samples are described in the Study Laboratory manual. These parameters will be measured at the timepoints indicated in Section 8 and the Schedule of Assessments (Table 9, Table 10, Table 11).

8.7 Resistance Monitoring

To monitor for HBV resistance, serum samples will be collected at Screening and on Day 1 and at each visit thereafter (Section 8 and the Schedule of Assessments [(Table 9, Table 10, Table 11]). The core protein gene and polymerase coding region and the region containing the AB-729 target site will be sequenced for all subjects on Day 1 and will be attempted for all viremic subjects at Week 48 and Week 72. Samples from those subjects with evidence of virologic failure, such as confirmed virologic breakthrough (2 consecutive visits with a ≥1 $\log_{10}$ IU/mL increase in on-treatment HBV DNA from on-treatment nadir or 2 consecutive visits with HBV DNA ≥LLOQ after having been <LLOQ) will also be sequenced.

8.8 Assessment of Safety

8.8.1 Physical Examination

A complete or symptom-directed physical examination will be performed at timepoints specified in (Table 9, Table 10, Table 11). Height and weight will also be measured and recorded.

Complete physical examinations will be performed by the Investigator or qualified subinvestigator at the time points indicated in the Study Procedures section (Section 8; Table 9, Table 10, Table 11). The complete physical examination will consist of the following body systems: head, eyes, ears, nose, and throat; cardiovascular; respiratory; gastrointestinal; dermatologic; musculoskeletal; nervous; extremities; and lymph nodes. Additional body systems may be evaluated at the Investigator's discretion. Examination of the breast and genitalia are not required unless clinically indicated.

Additional symptom-directed physical examinations will be performed at the time points indicated in the Study Procedures section (Section 8; Table 9, Table 10, Table 11). Additional symptom-directed or complete physical examinations may be performed at the Investigator's discretion throughout the course of the study. If the subject reports feeling unwell or has ongoing AEs, the Investigator or qualified subinvestigator will examine the appropriate body system(s).

8.8.2 Vital Signs

Vital sign assessments will include temperature, heart rate, respiration rate, and blood pressure at timepoints specified in the Schedule of Assessments (Table 9, Table 10, Table 11).

8.8.3 Electrocardiograms

A standard 12-lead ECG will be obtained as specified in the Schedule of Assessments (Table 9, Table 10, Table 11). Prior to the conduct of 12-lead ECGs, subjects should rest in a supine position for 10 minutes. Electrocardiograms should be conducted in accordance with local practice and equipment. The ECG assessment will include interpretation of the tracings (eg, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T-wave, and Uwave abnormalities). The Investigator or a physician subinvestigator is responsible for reviewing and overreading the ECG interpretation, for assessing whether the ECG machine interpretation findings are accurate, appropriate, normal or abnormal, and for providing corrected interpretations as appropriate. In addition, any abnormal ECGs will be assessed for clinical significance.

Additional ECGs may be obtained if clinically indicated and will be obtained if abnormal and clinically significant or thought to be an error (eg, lead placement error, movement artifact, etc.). Any additional relevant data obtained by the Investigator during the course of this study will be recorded in the subject's source documentation. The Investigator or a physician subinvestigator will review all ECGs, evaluate the results, and sign/date the tracing or report. For any ECG abnormality that the Investigator considers clinically significant, the Investigator will:

- Repeat the ECG;
- Obtain follow-up ECG(s) if any significant abnormalities are detected after study drug administration to document resolution and as clinically indicated;
- Record as an AE any ECG abnormality that: (1) is confirmed and the Investigator considers clinically significant; (2) requires a subject to be discontinued from the study; or (3) the abnormality requires a subject to receive treatment (Section 8).

8.8.4 Clinical Safety Laboratory Assessments

Clinical laboratory tests will be performed at the designated central laboratories at the timepoints indicated in Section 8 and the Schedule of Assessments (Table 9, Table 10, Table 11). Should any laboratory parameter require urgent testing to support immediate medical care of a subject, samples should be collected for both local and central laboratory assessment. The local result may be used to manage the emergent medical situation, however only the results from the central laboratory will be reported in the study database for analysis purposes.

The specific components of the clinical laboratory tests are listed below in Table 12.

Table 12. Clinical Laboratory Tests

Panel	Tests
Chemistry	Glucose, sodium, potassium, chloride, bicarbonate, calcium, blood urea nitrogen, creatinine, creatine kinase, uric acid, total and direct bilirubin, ALT, AST, GGT, alkaline phosphatase, LDH, triglycerides, total cholesterol, phosphorous (inorganic), total protein, albumin, amylase, lipase
Hematology	Hemoglobin, hematocrit, red blood cell count, RBC indices (MCV), reticulocyte count, white blood cell count including, lymphocytes (total and differential), monocytes, neutrophils, eosinophils, basophils, platelet counts
ALT Elevation Management (Section 9.10.4)	ALT, AST, total bilirubin, serum albumin, creatine kinase, INR, HBV DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]), HAV immunoglobulin M (IgM), HCV RNA, HDV RNA, HEV IgM, ANA, smooth muscle antibodies and anti-LKM1 antibodies, EBV DNA, CMV DNA, HSV DNA, and total IgG.
Coagulation	Prothrombin time/INR and aPTT
Urinalysis	pH, specific gravity, protein, glucose, ketones, and occult blood
FibroTest	alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total Bilirubin, ALT
APRI	AST, platelet count
Other	AFP, HbA1c, creatinine clearance calculated by Cockcroft-Gault (Cockcroft 1976)
Pregnancy Tests	For females of child-bearing potential only; a serum pregnancy test must be performed at Screening, and both serum and urine are required at Day 1; a urine pregnancy test must be performed at all subsequent visits, if positive, confirm with a serum pregnancy test
Urine Drug Test	Amphetamine/methamphetamine, barbiturates, benzodiazepines, cocaine metabolite, ethanol, opiates, phencyclidine, and propoxyphene
Serology [a]	HAV, HCV, HDV, HEV, and HIV
Virology	HBV DNA, HBV RNA, HBsAg [b], HBeAg, HBcrAg, HBsAb and HBeAb, HBV resistance monitoring

Abbreviations: AFP=alpha fetoprotein; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; DNA=deoxynucleic acid;; GGT=gamma-glutamyl transferase; HAV=hepatitis A virus; HbA1c=glycated hemoglobin; HBcrAg=hepatitis B core-related antigen; HBeAb=anti-hepatitis B e antigen antibody; HBeAg=hepatitis B e antigen; HBsAb=anti-hepatitis B surface antigen antibody; HBsAg= hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDV=hepatitis D virus; HEV=hepatitis E virus; INR=international normalized ratio; MCV=mean corpuscular volume; RBC=red blood cell; RNA=ribonucleic acid.

[a] If antibody positive, reflex to DNA or RNA (as applicable)

[b] Quantitative HBsAg assay will be performed at Screening and all study visits. If quantitative HBsAg is <LLOQ, then reflex to qualitative HBsAg. HBsAb is performed at Screening, Day 1, and Week 48. Additionally, if HBsAg is <LLOQ then reflex testing of HBsAb will also be performed.

8.8.5 Injection Site Reaction Diary

Subjects enrolled in Groups 1 and 3 will be provided an injection site reaction diary to capture information regarding the nature of any changes at the site of the AB-729 subcutaneous injection(s) occurring while as an outpatient, including the resolution of these events. These subjects will be instructed to contact the clinical site with any new AEs they observe at the injection site(s) to determine if an unscheduled clinic visit is needed for formal assessment of the AEs.

8.9 Assessment of Pharmacokinetics

The details of PK blood sampling procedures and sample management will be provided in the Study Laboratory Manual.

8.9.1.1 Vebicorvir Pharmacokinetic Assessment

Single PK blood samples will be collected for all subjects receiving VBR at each on-treatment visit and at a single timepoint off treatment at Week 52 for sparse PK analysis of VBR (Table 9, Table 10, Table 11). Note the Day 1 PK sample collection should be done prior to the first dose of study drug.

8.9.1.2 AB-729 Pharmacokinetic Assessment

An optional intensive PK substudy of AB-729 will be performed after the first 60 mg subcutaneous dose on Day 1 and after the last dose at Week 40. The plasma PK parameters to be estimated are listed in Section 10.4.6. Blood samples will be collected at the following timepoints: predose, and at 0.5 (±3 min), 1 (±6 min), 2 (±10 min), 4 (±10 min), and 6 (±10 min)-hours postdose.

Single PK blood samples will be collected from all subjects receiving AB-729 at Weeks 8, 16, 24, and 32 at 2 hours (±1 hour) postdose for sparse PK analysis of AB-729 (Table 9).

A sparse PK sample will also be collected at Day 1 and Week 40 at 2 hours (±1 hour) postdose from those subjects who do not participate in the optional intensive PK substudy.

8.9.1.3 NrtI Pharmacokinetic Assessment

Single PK blood samples will be collected for all subjects receiving NrtI at each on-treatment visit for sparse PK analysis of NrtI (Table 9). Note the Day 1 PK sample collection should be done prior to the first dose of study drug.

8.10 Exploratory Biomarkers

HBsAg isoforms, immune complexes, immune biomarkers, cytokines and characterization of PBMC function and immune cell phenotypes may be conducted using validated assays. Additional details concerning the methodology, collection and processing of the samples are described in the Study Laboratory Manual.

An RNAi biomarker to indicate RNAi activity may be assessed using a validated Rapid Amplification of complementary DNA ends (RACE) assay. Additional details concerning the methodology, collection and processing of the samples are described in the Study Laboratory Manual.

These exploratory assessments may be evaluated at the timepoints indicated in Section 8 and the Schedule of Assessments (Table 9, Table 10, Table 11).

8.11 Use of Residual Samples for Optional Future Research

In addition to the study-specific Informed Consent Form (ICF) to be signed by each subject, a separate consent form, or a separate specific signature within the main ICF, will be required to document a subject's agreement to allow the use of unused or residual biomarker and/or virologic samples collected as part of the protocol assessments for optional future research.

The specimens collected for optional future research will be used to increase knowledge and understanding of the biology of HBV and related diseases and to study the association of biomarkers with disease pathogenesis, progression, and/or treatment outcomes, including efficacy, AEs, and the process of drug absorption and disposition.

These specimens may be used also to develop biomarker or diagnostic assays for HBV and establish the performance characteristics of these assays. The collection and analysis of optional future research specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future. Residual samples will not be used for genetic testing.

Samples will be securely stored by the Sponsor or at a Sponsor-approved third-party storage management facility. Samples will be stored in a coded fashion, and no researcher will have access to the key. The key will be securely held by the Investigator at the clinical site such that there will be no direct ability for a researcher to connect a sample to a specific individual. Additional research samples will be retained for the maximum time allowed by applicable law.

Further details of sample collection and processing will be provided to the site in the Study Laboratory Manual.

9 ADVERSE EVENTS AND TOXICITY MANAGEMENT

9.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a study subject administered a study drug regardless of the causal relationship with treatment.

An AE, therefore, can be any unfavorable and unintended sign, symptom, or disease temporally associated with participation in an investigational study, whether or not considered study drug related. In addition to new events, any increase in the severity or frequency of a preexisting condition that occurs after the subject signs the ICF for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction. AEs may also include complications associated with protocol mandated procedures.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or clinically significant laboratory abnormalities present or detected before the screening visit that do not worsen during the study
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented on the medical history electronic Case Report Form (eCRF).

9.2 Documenting Adverse Events

Adverse events will be monitored and recorded from the written informed consent obtained through end of study (completion of follow-up period or “lost to follow-up”). Investigators will ask the subject at each visit if they have experienced any untoward effects since the last study visit. All AEs will be entered in the eCRFs; refer to the eCRF Completion Guidelines for additional information.

9.3 Assessment of Intensity

The severity of each AE and laboratory abnormality is to be assessed by the Investigator according to the modified Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric AEs (Appendix 1), which grades the severity of clinical AEs and laboratory abnormalities in a 4-category system.

For AEs not included in Appendix 1, the following guidelines will be used to describe severity:

- Mild (Grade 1): Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated
- Moderate (Grade 2): Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
- Severe (Grade 3): Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated (Of note, the term "severe" does not necessarily equate to "serious")
- Life-Threatening (Grade 4): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

9.4 Assessment of Causality

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. Each AE must be recorded in the source documentation, whether serious or not serious. For the purposes of this study each event is to be assessed with regard to the following causality categorizations, in the Investigator's considered judgment:

- Not related: An AE with sufficient evidence to accept that there was no causal relationship to administration of study drug (eg, no temporal relationship because the study drug was administered after the onset of the event, an investigation showed that study drug was not administered, another cause was proven).
- Related: An AE occurred in a plausible time relationship to administration of study drug and that could not be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) was clinically reasonable.

9.5 Adverse Event Follow-up

All AEs should be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve due to the subject's underlying disease, or the subject is lost to follow-up.

9.6 Serious Adverse Events

9.6.1 Definition of Serious Adverse Event

An SAE is any event that meets any of the following criteria:

- Death
- Life-threatening

- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject.
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    - Development of drug dependency or drug abuse

9.6.2 Definition of Terms

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

9.6.3 Reporting Serious Adverse Events

All SAEs must be reported by the investigational staff within 24 hours of learning about the event using the SAE Report form to the Sponsor or its designee (eg, CRO Pharmacovigilance group). Refer to the Study Reference Manual for contact information for reporting SAEs.

The initial report should be promptly followed by detailed, written reports, which will include copies of relevant hospital case reports, autopsy reports, and other documents when requested and applicable.

For a follow-up report to the authorities, the monitor may be required to collect further information for a final evaluation of the case. Reporting to the respective country Health Authorities will be the responsibility of the Sponsor and the CRO.

The CRO will be responsible for informing all central Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of SAEs as required. It will be the responsibility of the individual Investigators to inform any local IRBs/IECs of SAEs as required. Correspondence with the IRB(s)/IEC(s) relating to the reporting of SAEs will be retained in the study file.

9.7 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs or SAEs

Laboratory abnormalities are usually not recorded as AEs or SAEs. Clinical laboratory abnormalities that require medical or surgical intervention or lead to study drug interruption or discontinuation must be recorded as an AE or SAE, if applicable. The modified DAIDS Table for Grading the Severity of Adult and Pediatric AEs (Appendix 1) will be used to assess the severity of clinical laboratory abnormalities. In addition, clinical laboratory or other abnormal assessments (eg, ECG and 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 described in Sections 9.1 and 9.6. If the clinical laboratory abnormality or abnormal assessment is part of a syndrome or diagnosis, record the syndrome or diagnosis (eg, anemia), not the clinical laboratory result (ie, decreased hemoglobin).

9.8 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). The Medical Monitor may be contacted for questions concerning potential cases of overdose. An overdose is not in and of itself considered to be an AE unless it results in untoward medical effects. Any AE associated with an overdose or incorrect administration of study drug should be entered in the subject's source documentation and Adverse Event eCRF. If the associated AE fulfills the criteria of an SAE, then the event should be reported to the Sponsor or CRO within 24 hours after the site learns of the event.

9.9 Pregnancy

9.9.1 Female Subjects Who Become Pregnant

The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The initial information will be recorded on the Pregnancy Reporting form and submitted to the Sponsor or its designee within 24 hours of learning of a subject's pregnancy. Refer to the Study Reference Manual for contact information for reporting a pregnancy.

The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor or its designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any female subject who becomes pregnant while participating in the study will discontinue the study drug immediately.

9.9.2 Male Subjects With Partners Who Become Pregnant

The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is participating in this study.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the Pregnancy Reporting form and submit it to the Sponsor or its designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure. Refer to the Study Reference Manual for contact information for reporting a pregnancy.

9.10 Toxicity Management

Administration of study drug may be interrupted or discontinued due to a clinical event or laboratory abnormality. The Medical Monitor should be consulted prior to dose interruption or discontinuation of study drug unless the Investigator believes that immediate action is warranted to ensure the continued safety of subject.

Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 days of receipt of results and before study drug interruption or discontinuation, unless such a delay is not consistent with good medical practice.

Any questions regarding toxicity management should be directed to the Medical Monitor.

9.10.1 Grades 1 and 2 Clinical Event or Laboratory Abnormality

- Continue study drug at the discretion of the Investigator.

9.10.2 Grade 3 Clinical Event or Laboratory Abnormality

- For Grade 3 clinical event or clinically significant laboratory abnormality, the study drug may be continued if considered to be unrelated to investigational medicinal product.

- For a Grade 3 clinical event or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to the study drug, the study drug should be withheld until the toxicity returns to ≤Grade 2.

- If a laboratory abnormality recurs to ≥Grade 3 following rechallenge with the study drug and is considered related to the study drug, then the study drug should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to the study drug may not require permanent discontinuation.

9.10.3 Grade 4 Clinical Event or Laboratory Abnormality

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to the study drug, the study drug should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to Baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

- The study drug may be continued without dose interruption for a clinically nonsignificant Grade 4 laboratory abnormality (eg, Grade 4 creatine kinase after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to the study drug.

9.10.4 Management of Alanine Aminotransferase (ALT) Elevations

All subjects participating in the study will be closely monitored for ALT elevations and/or signs of potential decline in hepatic function (see Figure 7). Subjects experiencing ALT elevations ≥2× Baseline (Day 1) or on-treatment nadir and >2× ULN during study treatment or during post-treatment follow-up should be closely monitored with regular Unscheduled Visits every 1 to 2

weeks at the discretion of the Investigator. At these visits, the following laboratory tests will be performed: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum albumin, INR and creatine kinase. The Investigator will determine if other Unscheduled Visit assessments should be performed. Additionally, the following guidance is provided for management of subjects with ALT elevations:

- ALT Elevation Without Declining Hepatic Function

o All subjects with an ALT elevation on treatment, defined as ALT >2× Baseline or on treatment nadir and ≥10× ULN, should have the ALT findings confirmed within 3 days of receipt of the original results. All subjects should return for an Unscheduled Visit.

o If the ALT elevation is confirmed, then an additional Unscheduled Visit will be performed to further evaluate the subject. At this visit, the following laboratory tests will be performed: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum albumin, INR, creatine kinase, HBV DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]), HAV immunoglobulin M (IgM), HCV RNA, HDV RNA, HEV IgM, ANA, smooth muscle antibodies and anti-LKM1 antibodies, EBV DNA, CMV DNA, HSV DNA, and total IgG. The Investigator will determine if other Unscheduled Visit assessments should be performed.

  - If an intercurrent illness is determined to be causal, subjects with an ALT elevation without declining hepatic function and without contraindications may continue treatment and the intercurrent illness should be treated as deemed medically appropriate by the Investigator.

  - Subjects with an ALT elevation without declining hepatic function and without contraindications may continue treatment with study drug under close observation.

  - If ALT is rising at the confirmatory visit, subjects should return for an Unscheduled Visit every 2 to 5 days until the ALT elevation has stabilized. At these visits, the following laboratory tests will be performed: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum albumin, INR, creatine kinase, HBV DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]). The Investigator will determine if other assessments specified in Section 8.4 should be performed. Subjects whose ALT has stabilized should continue to be monitored weekly (or more frequently, as deemed necessary by the Investigator) until ALT values return to normal or Baseline levels.

  - Subjects with an ALT elevation without declining hepatic function and without contraindications should discontinue study drug if the ALT remains persistently elevated for >4 weeks

- ALT Elevation With Declining Hepatic Function

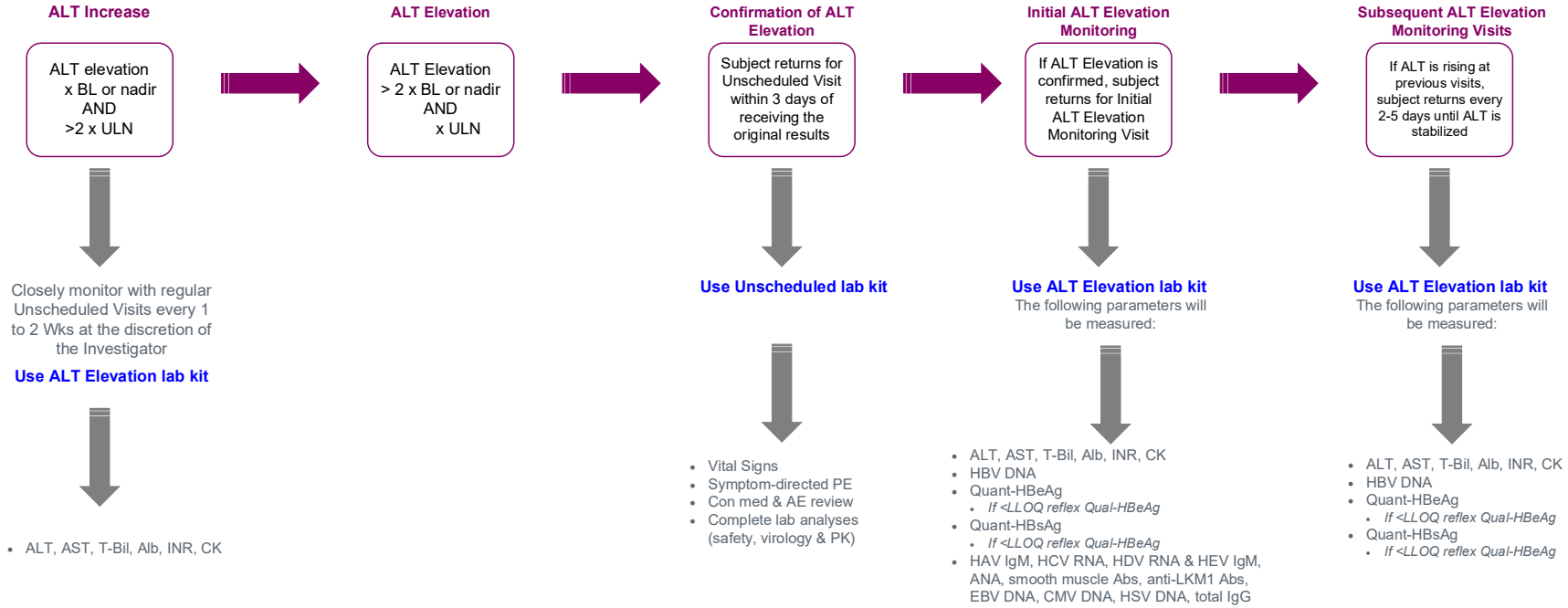
- Subjects with confirmed ALT elevation with biochemical evidence of declining hepatic function should be discontinued from study treatment. This is defined as:
    - ALT elevation ≥2× Baseline or nadir and >2× ULN AND
        - Direct bilirubin increase to ≥2× Baseline and ≥2× ULN OR
        - Albumin decline ≥0.5 g/dL OR INR >1.5× Baseline OR
        - Symptoms of liver inflammation (eg, fatigue, weakness, lack of appetite, nausea, vomiting, jaundice, or discolored feces)
- Subjects with evidence of declining hepatic function should return for an Unscheduled Visit every 2 to 5 days until the relevant laboratory values stabilize. Subjects whose hepatic function has stabilized should continue to be monitored weekly (or more frequently as deemed necessary by the Investigator) until the relevant laboratory values return to normal or Baseline.

All subjects with ALT elevation without or with declining hepatic function should continue to be followed on their regular study visit schedule, with the addition of unscheduled visits as described above. If the posttreatment ALT elevation has not substantially resolved by the last study follow-up visit, subjects should continue to return to clinic as deemed medically appropriate by the Investigator, in consultation with the Sponsor until the ALT elevation is documented to be either resolved or resolving (defined as consistent ALT declines of 10% or more or normalization of ALT) on at least 2 successive visits.

Following cessation of study drug treatment under this protocol, all subjects will be closely followed for ALT elevations and/or signs of potential decline in hepatic function. This applies to all subjects whether they prematurely discontinue study drug or complete the study treatment per protocol. Any subject with a post-treatment ALT elevation without evidence of declining hepatic function or a post-treatment ALT elevation with evidence of declining hepatic function as defined above, will be evaluated as noted above.

If 5 or more subjects meet these flare management criteria, the relevant regulatory agencies will be notified, and subsequent steps will be determined after consultation with these agencies.

Figure 7. Schematic for Safety Management of ALT Elevation



10 STATISTICAL CONSIDERATIONS

10.1 General Considerations

This section provides the key details of the statistical analyses to be performed using data captured according to this protocol. A complete Statistical Analysis Plan (SAP) describing all planned analyses will be finalized prior to database lock.

10.2 Determination of Sample Size

Cohort 1 will enroll virologically suppressed subjects on NrtI therapy with HBeAg negative cHBV. Approximately 60 subjects will be randomized to receive 1 of the following 3 treatments, VBR+AB-729+NrtI, VBR+NrtI, or AB-729+NrtI in a 2:1:1 ratio.

Up to 2 additional cohorts, with approximately 60 subjects per cohort, may be added in future protocol amendments, for a maximum sample size of approximately 180 subjects.

This is a proof-of-concept study. The sample size is similar to that previously utilized for this type of study and is not based upon statistical considerations.

10.3 Analysis Populations

The following populations will be considered for analysis of various endpoints:

- Randomized Analysis Set: It includes all randomized subjects who satisfied the inclusion and exclusion criteria described in this protocol.

- Full Analysis Set: It includes all randomized subjects, classified according to the treatment group into which they were randomized regardless of the actual treatment received, who took at least 1 dose of study drug. It is the main analysis population for the efficacy analysis.

- Safety Analysis Set: It includes all subjects, classified according to the actual treatment received regardless of random assignment, who took at least 1 dose of study drug. This is the main analysis population for all safety analyses.

- Pharmacokinetic-Evaluable Set: It consists of all subjects, classified according to the actual treatment received regardless of random assignment, who receive at least 1 dose of study drug. At least 1 pharmacokinetic blood sample following a dose of study treatment is required for inclusion in this analysis. This is the main analysis population for all pharmacokinetic analyses.

Based on the actual deviations, the criteria for exclusion of subjects from the different data sets will be specified and updated, if necessary, prior to database lock.

10.4 Planned Analyses

All safety, PK, and antiviral activity endpoints will be summarized using descriptive statistics by treatment groups. Continuous endpoints will be described using the mean, standard deviation, median, minimum, and maximum. Categorical endpoints will be described using the number and percent of subjects who meet the endpoint criterion.

Analyses by treatment group will be presented as follows:

- Efficacy analyses: according to the treatment to which subjects were randomized
- Safety and pharmacokinetic analyses: according to the treatment received

Due to sample size limitations, no formal statistical inference is planned.

10.4.1 Disposition of the Study Subjects

The disposition of subjects will be described with summaries by treatment group of the number of subjects in each analysis set described above, the number of subjects who completed the study, and the number of subjects for whom study drug was permanently discontinued (including the reasons for discontinuation). Randomized Analysis Set will be used to produce this analysis.

10.4.2 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using standard descriptive methods by treatment group and overall. Demographic summaries will include age, sex, race, ethnicity, body weight, and body mass index. Baseline disease characteristics data will include, but not limited to, years positive for HBV, HBV genotype, HBV DNA, HBV RNA, HBeAg, HBsAg, HBcrAg, and ALT levels at Baseline.

10.4.3 Extent of Exposure

Extent of exposure to study drug will be examined by assessing the total duration of study drug exposure and the level of adherence to the study drug by treatment group for the Safety Analysis Set.

10.4.4 Analysis of Efficacy Endpoint(s)

The efficacy endpoints are described in Section 3.2.2. The efficacy analysis will be based on the Full Analysis Set.

In addition to the descriptive statistics at each time point, treatment comparisons may be performed. The continuous variables, such as mean change from Baseline, will be evaluated using a regression model with Baseline values and stratification as covariates. The binary variables, such as the proportion of subjects who meet the endpoint criterion, will evaluated using a Cochran-Mantel-Haenszel test adjusting for the stratification factor.

10.4.5 Analysis of Safety Endpoints

All safety endpoints will be summarized using data from the Safety Analysis Set. Safety analyses will involve examination of the incidence, severity and type of TEAEs reported, changes from Baseline in laboratory test results and in vital signs to specified time points throughout the study, and concomitant medications use.

10.4.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE will be defined as any AE that begins on or after the date of first dose of study drug through end of study (completion of follow-up period or "lost to follow-up").

Summaries (number and percentage of subjects) of TEAEs by system organ class and preferred term will be provided by treatment group. Summaries will include all TEAEs, TEAEs considered related to study treatment by investigators, TEAEs by Grade, and SAEs. All AEs, emergent or nonemergent, will be listed by subject. Any TEAEs leading to premature discontinuation from the study intervention and serious TEAEs will be presented as a separate table or a listing.

10.4.5.2 Clinical Laboratory Evaluation

Laboratory values will be graded according to DAIDS criteria (Appendix 1). Laboratory parameters will be summarized by treatment group at each visit. Incidence of graded laboratory abnormalities will be summarized by treatment group. Listings will be provided for clinical laboratory values for each subject grouped by laboratory panel.

10.4.5.3 Other Safety Evaluations

Individual data for physical examination findings, prior and concomitant medications and medical history will be provided. Vital signs measurements and 12-lead ECGs will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistics as appropriate.

10.4.6 Analysis of Pharmacokinetic Endpoints

Population PK analysis may be performed outside the scope of this study.

Pharmacokinetic analysis of AB-729 for an optional intensive PK substudy will be conducted using the Pharmacokinetic-Evaluable Set defined in Section 10.3. Plasma PK parameters of AB-729-AS and the AB-729-AS(N-1)3' and AB-729-AS(N-2)3' metabolites for each subject will be estimated over the sampling interval using noncompartmental analysis and summarized by treatment group using descriptive statistics. Plasma PK parameters to be estimated, as data allow, are listed below in Table 13. Additional parameters may be analyzed, as appropriate. A minimum of 10 subjects from Group 1 and 5 subjects from Group 3 (Figure 6) will need to provide blood samples from Cohort 1 for PK analysis.

Table 13. Pharmacokinetic Parameters and Definitions

Parameter	Definition
C_{max}	maximum observed plasma concentration
T_{max}	time of maximum observed plasma concentration
AUC_{0-t}	area under the concentration time curve from the time of dosing to the last measurable concentration
AUC_{TAU}	area under the concentration time curve from the time of dosing to the end of the dosing interval
C_{TAU}	plasma concentration at the end of the dosing interval
C_{trough}	predose plasma concentration
AI	accumulation index for AUC_{TAU} calculated as final dose/first dose

10.5 Interim Analysis

No formal interim analyses are planned. As an open-label study, the data will be reviewed periodically.

10.6 Handling of Missing Data

Statistical considerations and methodology for handling missing data will be detailed in the SAP.

10.7 Multiplicity Adjustment

No formal inference is planned in this study; hence, no multiplicity adjustment is required.

11 RESPONSIBILITIES

11.1 Investigator Responsibilities

11.1.1 Good Clinical Practice

This study will be conducted in compliance with IRB/IEC and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines; Title 21 Part 56 of the US Code of Federal Regulations (CFR) relating to IRBs/IECs and GCP as described in the US FDA CFR (21 CFR § 50, 56, 312; China GCP; applicable ICH guidelines regarding clinical safety data management (E2A, E2B(R3)); European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). In addition, this study will adhere to all local regulatory requirements, and requirements for data protection.

11.1.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Before initiating a trial/study, the Investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC for the study protocol/amendment(s), written ICF, any consent form updates, subject recruitment procedures (eg, advertisements), and any written information to be provided to subjects and a statement from the IRB/IEC that they comply with GCP requirements. The IRB/IEC approval must identify the protocol version as well as the documents reviewed.

11.1.3 Informed Consent

The Investigator will explain the benefits and risks of participation in the study to each subject or the subject's legally acceptable representative and obtain written informed consent. Written informed consent must be obtained prior to the subject entering the study and before initiation of any study-related procedure (including administration of investigational product).

The Sponsor or its designee will provide a sample ICF. The final, version dated, ICF must be agreed to by the Sponsor or its designees and the IRB/IEC and will contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form must be personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. The original, signed ICF will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed ICF.

The ICF may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. In this instance approval should always be given by the IRB/IEC and existing subjects informed of the changes and reconsented. This is documented in the same way as previously described.

The Investigator should encourage subjects to inform their primary physician about their participation in the clinical study.

11.1.4 Confidentiality

All information generated in this study is considered confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB/IEC personnel, and the Sponsor and the Sponsor's authorized representatives are allowed full access to the records.

Identification of subjects and eCRFs shall be by Subject Number only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

11.1.5 Study Files and Retention of Records

Records must be retained in accordance with the current ICH guidelines on GCP. All essential study documents including records of subjects, source documents, eCRFs, and investigational product inventory must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational products. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor and will give the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities.

If an Investigator moves, withdraws from an investigation, or retires, responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

11.1.6 Audits and Inspections

The Sponsor or their designee, the CRO, may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the site during or after the study. The Investigator or designee should contact the Sponsor and/or the CRO, immediately if this occurs. The site must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethical, regulatory, and quality requirements are fulfilled.

11.1.7 Protocol Compliance

It is the responsibility of the Investigator to ensure that the study is conducted at their respective site in accordance with this protocol. Protocol compliance assessments will be conducted during routine site monitoring visits.

11.2 Sponsor Responsibilities

11.2.1 Protocol Amendments and Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent, significant change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. The Sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

If, in the judgment of the IRB/IEC, the Investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study subject, the currently approved written ICF will require similar modification. In such cases, subjects will be required for to sign the amended informed consent prior to continued participation in the study.

11.2.2 Data Management

A set of data management documents will be created under the responsibility of the Sponsor, or designated CRO, to describe the processes being used to ensure data quality.

The data management plan, and other associated documentations, will specify data capture methods, who is authorized to enter data, decisions about ownership of data, source data storage, which data will be transferred (including timing of transfers), and the origin/destination of data.

11.2.3 Study Report and Publications

The Sponsor or its designee is responsible for preparing and providing the appropriate regulatory authorities with the Clinical Study Report (CSR) according to the applicable regulatory requirements. CSR will be developed in accordance with the ICH E3 Guideline on the ‘Structure and Content of Clinical Study Reports’. Local country requirements will be considered during CSR preparation.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all proposed manuscripts or abstracts to the Sponsor before

submission. This allows the Sponsor to protect proprietary information and to provide comments. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Assembly Biosciences follows the guidelines and recommendations of the International Committee of Medical Journal Editors (ICMJE) and the International Society for Medical Publication Professionals (ISMPP) when preparing publications associated with clinical studies (Battisti 2015, ICMJE 2019).

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APPENDICES

APPENDIX 1. TOXICITY GRADING SCALE FOR ADVERSE EVENTS AND LABORATORY ABNORMALITIES

Adapted from the U.S. National Institutes of Health (Division of AIDS) Table for Grading Severity of Adult Adverse Experiences (Corrected Version 2.1, July 2017) [https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf]

MAJOR CLINICAL CONDITIONS

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
CARDIOVASCULAR				
Arrhythmia (by ECG or physical examination) Specify type, if applicable	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities Hypertension (with the lowest reading taken after repeat testing during a visit) ≥ 18 years of age	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
				device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* > 16 years of age	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval [2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
DERMATOLOGIC				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with	Marked or generalized causing greater than minimal	NA	NA

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
	usual social & functional activities	interference with usual social & functional activities		
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus [3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash Specify type, if applicable	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
ENDOCRINE AND METABOLIC				
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar nonketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or Minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics,	Symptoms recur or persist despite intervention	Life-threatening consequences

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
		therapeutic paracentesis)		
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent Constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea ≥ 1 year of age	Transient or Intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration	Life-threatening consequences (e.g., hypotensive shock)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
			indicated (e.g., IV fluids)	
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
MUSCULOSKELETAL				
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or Minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] ≥ 30 years of age < 30 years of age	BMD t-score -2.5 to -1 BMD z-score -2 to -1	NA NA	NA NA	NA NA
Osteoporosis[6] ≥ 30 years of age < 30 years of age	NA NA	BMD t-score < -2.5 BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height) Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences Pathologic fracture causing life-threatening consequences
NEUROLOGIC				
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status *(for Dementia, see Cognitive, Behavioral, or Attentional Disturbance below)*	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) Specify type, if applicable	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on parttime basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a fulltime basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) Specify type, if applicable	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) Specify type, if applicable	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures New Onset Seizure ≥ 18 years of age	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of	Loss of consciousness with	Loss of consciousness AND Hospitalization or	NA

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
	consciousness (e.g., pre-syncope)	no intervention indicated	intervention required	
PREGNANCY, PUERPERIUM, AND PERINATAL				
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
PSYCHIATRIC				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) Specify disorder	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with Intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with Hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
RESPIRATORY				
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)
SENSORY				
Hearing Loss ≥ 12 years of age	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical	Posterior or panuveitis OR Operative	Disabling visual loss in affected eye(s)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
		intervention indicated	Intervention indicated	
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
SYSTEMIC				
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise Report only one	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life -threatening
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) Specify location	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight > 5 to 19 years of age	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
URINARY				
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

2 As per Bazett's formula.
3 For pruritus associated with injections or infusions, see the Site Reactions to Injections and Infusions section.
4 Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
5 Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.
6 BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.
7 Definition: A pregnancy loss occurring at <20 weeks gestational age.
8 Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
9 For pain associated with injections or infusions, see the Site Reactions to Injections and Infusions section.
10 Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

SITE REACTIONS TO INJECTIONS AND INFUSIONS

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for Injection Site Erythema or Redness, > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

12 Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

LABORATORY VALUES* CHEMISTRIES

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; g/L)	3.0 to < LLN 30 to < LLN	≥ 2.0 to < 3.0 ≥ 20 to < 30	< 2.0 < 20	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; mmol/L)	16.0 to < LLN 16.0 to < LLN	11.0 to < 16.0 11.0 to < 16.0	8.0 to < 11.0 8.0 to < 11.0	< 8.0 < 8.0
Bilirubin Direct Bilirubin[13], High > 28 days of age	NA	NA	> ULN with other signs and symptoms of hepatotoxicity	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Total Bilirubin, High > 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Calcium, High (mg/dL; mmol/L) ≥ 7 days of age	10.6 to < 11.5 2.65 to < 2.88	11.5 to < 12.5 2.88 to < 3.13	12.5 to < 13.5 3.13 to < 3.38	≥ 13.5 ≥ 3.38
Calcium (Ionized), High (mg/dL; mmol/L)	> ULN to < 6.0 > ULN to < 1.5	6.0 to < 6.4 1.5 to < 1.6	6.4 to < 7.2 1.6 to < 1.8	≥ 7.2 ≥ 1.8
Calcium, Low (mg/dL; mmol/L) ≥ 7 days of age	7.8 to < 8.4 1.95 to < 2.10	7.0 to < 7.8 1.75 to < 1.95	6.1 to < 7.0 1.53 to < 1.75	< 6.1 < 1.53
Calcium (Ionized), Low (mg/dL; mmol/L)	< LLN to 4.0 < LLN to 1.0	3.6 to < 4.0 0.9 to < 1.0	3.2 to < 3.6 0.8 to < 0.9	< 3.2 < 0.8

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance [14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; mmol/L) Fasting, High Nonfasting, High	110 to 125 6.11 to < 6.95 116 to 160 6.44 to < 8.89	> 125 to 250 6.95 to < 13.89 > 160 to 250 8.89 to < 13.89	> 250 to 500 13.89 to < 27.75 > 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75 ≥ 500 ≥ 27.75
Glucose, Low (mg/dL; mmol/L) ≥ 1 month of age	55 to 64 3.05 to <3.55	40 to < 55 2.22 to < 3.05	30 to < 40 1.67 to < 2.22	< 30 < 1.67
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; mmol/L) Cholesterol, Fasting, High ≥ 18 years of age	200 to < 240 5.18 to < 6.19	240 to < 300 6.19 to < 7.77	≥ 300 ≥ 7.77	NA
LDL, Fasting, High ≥ 18 years of age	130 to < 160 3.37 to < 4.12	160 to < 190 4.12 to < 4.90	≥ 190 ≥ 4.90	NA
Triglycerides, Fasting, High	150 to 300 1.71 to 3.42	>300 to 500 >3.42 to 5.7	>500 to < 1,000 >5.7 to 11.4	> 1,000 > 11.4
Magnesium[15], Low (mEq/L; mmol/L)	1.2 to < 1.4 0.60 to < 0.70	0.9 to < 1.2 0.45 to < 0.60	0.6 to < 0.9 0.30 to < 0.45	< 0.6 < 0.30

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
Phosphate, Low (mg/dL; mmol/L) > 14 years of age	2.0 to < LLN 0.65 to < LLN	1.4 to < 2.0 0.45 to < 0.65	1.0 to < 1.4 0.32 to < 0.45	< 1.0 < 0.32
Potassium, High (mEq/L; mmol/L)	5.6 to < 6.0 5.6 to < 6.0	6.0 to < 6.5 6.0 to < 6.5	6.5 to < 7.0 6.5 to < 7.0	≥ 7.0 ≥ 7.0
Potassium, Low (mEq/L; mmol/L)	3.0 to < 3.4 3.0 to < 3.4	2.5 to < 3.0 2.5 to < 3.0	2.0 to < 2.5 2.0 to < 2.5	< 2.0 < 2.0
Sodium, High (mEq/L; mmol/L)	146 to < 150 146 to < 150	150 to < 154 150 to < 154	154 to < 160 154 to < 160	≥ 160 ≥ 160
Sodium, Low (mEq/L; mmol/L)	130 to < 135 130 to < 135	125 to < 130 125 to < 130	121 to < 125 121 to < 125	≤ 120 ≤ 120
Uric Acid, High (mg/dL; mmol/L)	7.5 to < 10.0 0.45 to < 0.59	10.0 to < 12.0 0.59 to < 0.71	12.0 to < 15.0 0.71 to < 0.89	≥ 15.0 ≥ 0.89
HEMATOLOGY				
Absolute CD4+ Count, Low (cell/mm^3; cells/L) > 5 years of age (not HIV infected)	300 to < 400 300 to < 400	200 to < 300 200 to < 300	100 to < 200 100 to < 200	< 100 < 100
Absolute Lymphocyte Count, Low (cell/mm^3; cells/L) > 5 years of age (not HIV infected)	600 to < 650 0.600 x 10^9 to < 0.650 x 10^9	500 to < 600 0.500 x 10^9 to < 0.600 x 10^9	350 to < 500 0.350 x 10^9 to < 0.500 x 10^9	< 350 < 0.350 x 10^9
Absolute Neutrophil Count (ANC), Low (cells/mm^3; cells/L) > 7 days of age	800 to 1,000 0.800 x 10^9 to 1.000 x 10^9	600 to 799 0.600 x 10^9 to 0.799 x 10^9	400 to 599 0.400 x 10^9 to 0.599 x 10^9	< 400 < 0.400 x 10^9
Fibrinogen, Decreased (mg/dL; g/L)	100 to < 200 1.00 to < 2.00 OR 0.75 to < 1.00 x LLN	75 to < 100 0.75 to < 1.00 OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 0.50 to < 0.75 OR 0.25 to < 0.50 x LLN	< 50 < 0.50 OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; mmol/L)[17] ≥ 13 years of age (male only)	10.0 to 10.9 6.19 to 6.76	9.0 to < 10.0 5.57 to < 6.19	7.0 to < 9.0 4.34 to < 5.57	< 7.0 < 4.34
≥ 13 years of age (female only)	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 < 4.03
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life-threatening
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; cells/L)	100,000 to < 125,000 100.000 x 10^9 to < 125.000 x 10^9	50,000 to < 100,000 50.000 x 10^9 to < 100.000 x 10^9	25,000 to < 50,000 25.000 x 10^9 to < 50.000 x 10^9	< 25,000 < 25.000 x 10^9
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; cells/L) > 7 days of age	2,000 to 2,499 2.000 x 10^9 to 2.499 x 10^9	1,500 to 1,999 1.500 x 10^9 to 1.999 x 10^9	1,000 to 1,499 1.000 x 10^9 to 1.499 x 10^9	< 1,000 < 1.000 x 10^9
URINALYSIS				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

* Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

13 Direct bilirubin >1.5 mg/dL in a participant <28 days of age should be graded as grade 2, if <10% of the total bilirubin.

** Reminder: Choose the method that selects for the higher grade.

14 Use the applicable formula (ie, Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m^2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

15 To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

16 Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (ie, a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

17 The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

APPENDIX 2. PREGNANCY PRECAUTIONS AND THE DEFINITION OF CHILD-BEARING POTENTIAL AND CONTRACEPTIVE REQUIREMENTS

Pregnancy Precautions

The effect of VBR and AB-729 on pregnancy has not been assessed. In preclinical studies, there was no evidence of embryo-fetal toxicity with VBR, while maternal toxicity was observed in initial dose range-finding studies with AB-729 in rats and rabbits (further studies are ongoing); refer to the respective IBs for details. Pregnancy precautions are required and contraceptive requirements for female subjects of child-bearing potential are described below.

Definition of Female Subjects of Child-bearing Potential

A female subject is considered of child-bearing potential unless they are in the following categories:

- Premenarchal
- Premenopausal with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal: A postmenopausal state is defined as age >54 years with no menses for 12 months without an alternative medical cause.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Müllerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Documentation to determine child-bearing potential can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

Contraceptive Requirements

The drug-drug interaction of VBR and systemic (oral/injectable/implantable) hormonal contraceptives has not been assessed and so systemic hormonal contraceptives are not considered an effective contraceptive method for female subjects of child-bearing potential for the purposes of this study.

Female subjects of child-bearing potential (defined above) must agree to use dual effective contraceptive methods for the duration of the study and follow-up, or for at least 28 days after the last dose of VBR (Group 2 in Figure 6) and 6 months after the last dose of AB-729 (Groups 1 and 3 in Figure 6) if the subject prematurely discontinues from the study.

Effective contraceptive methods include male or female condom (may not be used together due to increased risk of breakage), vasectomy, tubal sterilization, intra-uterine device (IUD), diaphragm, or cervical cap. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test prior to receiving the first dose of study drug on Day 1.

All male subjects must agree to use dual effective contraceptive methods with their female partners (if their female partner is of child-bearing potential) for the duration of the study and follow-up, or for at least 28 days after the last dose of VBR (Group 2 in Figure 6) and for 6 months after the last dose of AB-729 (Groups 1 and 3 in Figure 6) if they prematurely discontinue the study. In this case, effective contraceptive methods may include systemic (oral/injectable/implantable) hormonal contraceptives, vasectomy, tubal sterilization, IUD, diaphragm, or cervical cap. Male subjects must avoid sperm donation from the time of the first dose of study drug and throughout the study period or for at least 28 days after the last dose of VBR (Group 2 in Figure 6) and for 6 months after the last dose of AB-729 (Groups 1 and 3 in Figure 6) if they prematurely discontinue the study.

APPENDIX 3. PROTOCOL AMENDMENT SUMMARY OF CHANGES

The changes in Amendment 1 to the Original Protocol for Study ABI-H0731-204 dated 20 Nov 2020, have been summarized in the table below. Deletions are reflected with strikethrough and additions are in bold. A redline version of the protocol amendment with all edits to the original protocol has also been provided.

Section **(In Original Protocol)**	**Change Made**	**Rationale**
Section 3.1.2, Synopsis	The following secondary objective in bold has been added: • **To evaluate the off-treatment durability of response to treatment with VBR and ABI-729**	With the addition of Treatment Stopping Criteria, an additional objective of the study becomes evaluation of off-treatment durability of response to study treatment.
Section 3.2.2, Synopsis	The eight secondary endpoint has been modified as follows: • Proportion of subjects with **abnormal ALT at Baseline** who have normal ALT (by central laboratory and American Association for the Study of Liver Diseases [AASLD] criteria) at each timepoint The following additional endpoints in bold have been added: • **Proportion of subjects achieving Treatment Stopping Criteria at end of treatment (EOT)** • **Proportion of subjects who remain off-treatment at end of study (EOS)** The last secondary endpoint has been modified as follows: • Analysis of VBR~~,~~ **and** AB-729 **drug concentrations**. NrtI ~~drug~~ **concentrations may be analyzed, as needed**	The phrase “abnormal ALT at Baseline” has been added to clarify the endpoint. The additional endpoints address the objective added above. To clarify that NrtI drug concentrations may be evaluated only as needed.

Section (In Original Protocol)	Change Made	Rationale
Section 3.2.3, Synopsis	The following additional endpoint has been added: • **Proportion of subjects who continued NrtI after Week 48 and subsequently met the Treatment Stopping Criteria**	With the addition of Treatment Stopping Criteria, an additional objective of the study becomes evaluation of off-treatment durability of response to study treatment.
Figure 6, Section 4.1, Synopsis	The following statement has been added to the Synopsis to be consistent with Section 4.1: **Up to 2 additional cohorts may be added in future protocol amendments to evaluate other populations and/or treatment regimens.** The study design schematic has been updated to add the planned assessment of Treatment Stopping Criteria on Week 48 and the off treatment follow up of subjects who meet the Treatment Stopping Criteria on Week 48. Sections 4.1.1 and 4.1.2 have been created to add the following in-bold text: **Treatment Stopping Criteria** **At Week 48, all subjects will have an assessment of Treatment Stopping Criteria. Any subjects who meet the below Treatment Stopping Criteria, will discontinue their assigned treatment including NrtI, and continue with off-treatment follow-up through Week 96, unless they meet the NrtI-restart criteria specified below. Decisions to discontinue assigned treatment and undergo off-treatment follow-up will be based on laboratory results from blood samples collected at the Week 48 visit. Subjects will remain on their assigned oral agents (ie, VBR+NrtI for Groups 1 and 2; NrtI for Group 3) until Week 48 laboratory results**	The addition of the Treatment Stopping Criteria enables the assessment of the functional cure after 48 weeks of treatment and the evaluation of the duration of sustained functional cure with 3 different treatment regimens.

Section (In Original Protocol)	Change Made	Rationale

	required for Treatment Stopping Criteria assessment are available.
	
	Treatment Stopping Criteria are:
	
	• **ALT < 2 × ULN, *and***
	• **HBV DNA < LLOQ, *and***
	• **HBsAg < 100 IU/mL**
	
	Subjects who do not meet the Treatment Stopping Criteria with Week 48 laboratory results will continue treatment with NrtI alone and will remain in follow-up through Week 96.
	
	NrtI-Restart Criteria:
	
	Subjects who meet the Treatment Stopping Criteria at the Week 48 assessment but subsequently meet ANY of the below NrtI-Restart Criteria, will restart treatment with NrtI and remain in follow-up through Week 96.
	
	NrtI-Restart Criteria are:
	
	• **Alanine aminotransferase (ALT) > 10 × upper limit of normal (ULN), confirmed by repeat**
	• **ALT > Baseline and > ULN, confirmed by repeat, *and***
	  ○ **Direct bilirubin > 2.0 × ULN, confirmed by repeat, *or***
	  ○ **International Normalized Ratio > 1.5, confirmed by repeat**
	• **ALT ≥ 2 – 5 × ULN AND HBV DNA > 2000 IU/mL for 12 weeks**	

Section (In Original Protocol)	Change Made	Rationale
	• **ALT elevations ≥ 5 – 10 × ULN AND HBV DNA > 2000 IU/mL for 4 weeks** • **Any clinical decompensation, regardless of HBV DNA level** • **Investigator discretion** ~~At Week 48, subjects will discontinue VBR and/or AB-729 (as applicable) and undergo 48 weeks of follow-up while remaining on NrtI.~~	
Section 4.3	The following in-bold text has been added: All subjects will receive their assigned treatment for 48 weeks. **Subjects will continue to receive assigned oral agents (ie, VBR+NrtI for Groups 1 and 2, and NrtI for Group 3) until all laboratory results from the Week 48 visit are available to determine each individual subject treatment action, based on Treatment Stopping Criteria (discontinuation of all treatment or continuation of NrtI; see Section 4.1.1).**	To clarify that subjects should continue to receive their assigned oral agents till the results from their Week 48 laboratory tests are available to enable the subsequent treatment action for the subject.
Section 5.4	The following in-bold text has been added: Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized to study treatment. Minimal information to be retained on all screen failures includes demography, screen failure details, eligibility criteria, and any SAE information. Data regarding HBV genotype and HBV viral variants**, if generated,** will also be retained to further our understanding of the epidemiology of HBV and the natural frequency of polymorphisms present in the HBV sequences around the core	To enable enrollment of subjects who are eligible upon resolution or stabilization of an acute exclusionary condition and to clarify that the screening period may be extended if laboratory results are not available within the 45-day screening period, while ensuring the safety assessment at Baseline remains current.

Section (In Original Protocol)	Change Made	Rationale
	and polymerase regions and the AB-729 target site. Individuals who do not meet the protocol eligibility criteria for participation in this study (screen failure) may~~ not be rescreened, however,~~ **be allowed to rescreen (once). Rescreening may occur following resolution of acute exclusionary conditions or stabilization of conditions that were exclusionary and reversible (eg, unstable hypothyroidism, electrolyte abnormalities) and with the approval of the study Medical Monitor.** **A** single retest for a laboratory parameter(s) is permitted if there is a specific issue related to the collection, shipping, processing or analysis of a sample (eg, receipt of a hemolyzed sample at the testing laboratory, or samples received by the testing laboratory outside of the acceptable temperature range, or resolved intercurrent illness). **If more than 45 days are required to obtain a result of a screening procedure and/or test, the screening period may be extended till results are obtained. However, the clinical safety laboratory tests may need to be repeated under the instruction of the study Medical Monitor if the screening period is beyond 45 days.**	
Section 6.1.2.4	The text in bold has been added: AB-729 is administered once every 8 weeks as a 60 mg subcutaneous injection at **specified** clinic visits.	For clarity.
Section 6.3	The text has been modified as follows: All concomitant medications taken from the date the informed consent is signed through ~~24 weeks after the last dose~~ **end** of study ~~drug~~	To correct and provide the intended follow up of concomitant medications,

Section (In Original Protocol)	Change Made	Rationale
	or "lost to follow-up" must be recorded in the subject's source documentation.	which is through the end of the study.
Section 6.3.1	The text has been modified as follows: Paragraph 1: Examples of representative medications which are prohibited from 28 days prior to Day 1 through ~~24~~ **2** weeks after the last dose of ~~study drug~~ **VBR** or "lost to follow-up" are listed in Table 8. Paragraph 4: Note that systemic (oral, injectable, or implanted) hormonal contraceptives are not considered as an acceptable means of contraception for female subjects of child-bearing potential (Appendix 2) up to ~~30~~ **28** days after the last dose of VBR (Groups 1 and 2 in Figure 6).	The edits to Paragraph 1 are made to correct the duration of prohibited concomitant medications, which should be through 2 weeks after the last dose of VBR, since this is sufficient time for clearance of VBR (as well as ABI-729) from the subjects. In Paragraph 4, the total number of days after last dose of VBR for adherence to study contraceptive guidelines has been changed from 30 to 28 days to align with the current general guidelines from the Sponsor with respect to clinical trials and is not related to any safety concern.
Sections 7.1	The following modifications have been made: Paragraph 1: **With the exception of treatment cessation based on Treatment Stopping Criteria (see Section 4.1.1), ~~I~~if** an individual subject is not satisfactorily tolerating their assigned treatment due to **any** AEs in the judgment of the Investigator, then, upon consultation with the Sponsor, the Investigator may discontinue treatment with VBR and/or AB-729 depending on the treatment group assignment. Discontinuation from treatment does not mean discontinuation from the study. Subjects who prematurely discontinue their assigned	To make the distinction between general criteria for discontinuation of study treatment at any time during the study and the Treatment Stopping Criteria specified to enable assessment of functional cure at Week 48 of treatment. The reference to Table 11 has been added to clarify that such subjects should follow the assessments specified in

Section (In Original Protocol)	Change Made	Rationale
	treatment regimen should immediately undergo the assessments listed for the Premature Termination visit (Section 8.5) and then continue scheduled follow-up assessments **(Table 11).**	Table 11 of Protocol Amendment 1.
Section 7.2	The following modifications have been made: Paragraph 1: "**With the exception of treatment cessation based on Treatment Stopping Criteria (see Section 4.1.1),** ~~S~~study drug treatment may be discontinued in the following instances"	
Table 9	The Table title has been modified as follows: Schedule of Assessments (Cohort 1) – **On-Treatment for All Subjects** The follow up visits column from Table 9 has been removed from the table. In Table 9, the NrtI and VBR administration and NrtI and VBR PK assessments have been separated into distinct rows, instead of being coupled together. The study treatment group numbers have been added in parentheses next to these assessments to clarify which subjects undergo the assessments based on their assigned treatment. A row for assessment of Treatment Stopping Criteria on Week 48 has been added, with the following corresponding footnote m: **[m] Subjects will either stop their treatment altogether or continue with NrtI administration based on assessment of Treatment Stopping Criteria (Section 4.1.1) utilizing laboratory results from the Week 48 Visit. Subjects will remain on assigned oral agents (ie, VBR+NrtI for groups 1 and**	The edits have been made to add clarity to the assessments planned for the follow-up period and to accommodate the Treatment Stopping Criteria evaluation at Week 48.

Section (In Original Protocol)	Change Made	Rationale
	2, and NrtI for Group 3) beyond the Week 48 visit until all laboratory results are available to adjudicate the Treatment Stopping Criteria. The follow up visits have been specified in new tables, ie, Table 10 and Table 11. Table 10 lists the follow up visits and assessments only for subjects who meet the Treatment Stopping Criteria at Week 48 assessment. Table 11 lists the follow up visits and assessments for the rest of the subjects in the study. All footnotes specific to the follow-up period in Table 9 have been deleted and applied as appropriate to Tables 10 and 11. Consequently, the footnote labels in Table 9 have been reordered and re-alphabetized.	
Section 8.3.3	The following edits are made: • **Review** subject injection site reaction diary **(Groups 1 and 3) at Weeks 2, 12, 20, 28, 36, and 44** • Assess VBR accountability **(Groups 1 and 2)** • **Assessment of Treatment Stopping Criteria (see Section 4.1.1 for details)** • VBR and NrtI administration once daily at home; ~~last administration of~~ **Subjects will continue to receive** VBR ~~at~~ **and NrtI beyond the** Week 48 **visit, until all laboratory results are available to adjudicate individual subject Treatment Stopping Criteria (see Section 4.1.1)**	For clarity and alignment with Table 9
Section 8.3.4	The following edits are made:	To align with the addition of assessment of Treatment

Section (In Original Protocol)	Change Made	Rationale
	Section Title: Week ~~52~~ **50** Through Week 96 **Off-treatment** Follow-up Visits **for Subjects Meeting Treatment Stopping Criteria** (± 5 Days) Paragraph 1: ~~At Week 48, subjects will discontinue VBR and/or AB-729 (as applicable) and be observed for 48 weeks of follow-up. During the follow-up period, subjects will remain on NrtI.~~ The following **follow-up** assessments will be performed ~~every 4 weeks~~ from Study Weeks ~~52~~ **50** through 96 ~~up period, unless otherwise stated~~ **for subjects meeting Treatment Stopping Criteria (see Table 10). Note: If a subject is determined to meet the NrtI-restart criteria at any time during the follow-up, he/she should follow the schedule of visits specified in Section 8.3.5 and Table 11.** The following edits have been made to the list of assessments: • **NrtI and VBR will continue to be administered at home until laboratory results from the Week 48 visits are available to determine if an individual subject meets Treatment Stopping Criteria (see Section 4.1.1). Once a subject meets the Treatment Stopping Criteria and is notified by the site, subject will discontinue treatment with NrtI and VBR** • Measure body weight (**Weeks 72 and** 96 only)	Stopping Criteria at Week 48 to the study design.

Section (In Original Protocol)	Change Made	Rationale
	• Complete physical examination (excluding breast and genitalia, unless indicated; Week**s 72 and** 96 only); all other visits, symptom-directed physical examination • Review AEs and concomitant medications~~; concomitant medications up to Week 72 only~~ • **HBV DNA,** HBV TNA, HBV RNA • ~~HBV DNA (Weeks, 60, 72, 84, and 96 only)~~ ▪ FibroTest, APRI (both at Week **72 and** 96 only) ▪ A single off-treatment blood sample for sparse PK of VBR **(Groups 1 and 2;** Week ~~52~~ **50** only**)** • **VBR accountability (Groups 1 and 2; Week 50 only)**	
Section 8.3.5	The section has been added to list assessments during the follow-up period for the rest of the subjects in the study. The following text has been added: **Week 52 Through Week 96 Follow-Up Visits for Rest of the Subjects (±5 Days)** **The following follow-up assessments will be performed every 4 weeks from Study Weeks 52 through 96, for subjects who do NOT meet the Treatment Stopping Criteria, or subjects who meet the NrtI-restart criteria after having met Treatment Stopping**	To align with the addition of assessment of Treatment Stopping Criteria at Week 48 to the study design.

Section (In Original Protocol)	Change Made	Rationale
	Criteria, or subjects who prematurely discontinue treatment with VBR/AB-729 at any time (see Table 11): • **NrtI and VBR will continue to be administered at home until laboratory results from the Week 48 visits are available to adjudicate the individual subject Treatment Stopping Criteria (see Section 4.1.1). Once a subject is determined to not meet the Treatment Stopping Criteria, he/she will be notified by the site, and the subject will discontinue treatment with VBR.** • NrtI administration **once daily** at home **through Week 96** • **Measure body weight (Weeks 72 and 96 only)** • **Record vital signs (temperature, heart rate, respiration rate, and blood pressure)** • **Complete physical examination (excluding breast and genitalia, unless indicated; Week 72 and 96 only); all other visits, symptom-directed physical examination** • **12-lead ECG (Weeks 60 and 96 only)** • **Review AEs and concomitant medications** • **FibroScan (if available; Weeks 72 and 96 only)** • **Obtain blood samples for the following:**	

Section (In Original Protocol)	Change Made	Rationale
	○ **Safety laboratory tests:** ▪ **chemistry, hematology, coagulation** ▪ **CrCl (Weeks 72 and 96 only)** ○ **Virology:** ○ **HBV TNA, HBV RNA** ○ **HBV DNA (Weeks 60, 72, 84, and 96 only)** ○ **HBsAg, HBsAb (only if HBsAg <LLOQ), HBsAg isoforms, HBV resistance monitoring sample** ○ **Immune complexes (Weeks 52, 56, 60, 64, 72, 84, and 96 only)** ○ **HBeAg, HBeAb, HBcrAg (Weeks 60, 72, 84, and 96 only)** ○ **Virology back-up sample (to be used for retesting HBV parameters)** ○ **Other:** ▪ **FibroTest, APRI (both at Week 72 and 96 only)** ▪ **A single off-treatment blood sample for sparse PK of VBR (Groups 1 and 2; Week 52 only)**	

Section (In Original Protocol)	Change Made	Rationale
	▪ **Cytokines/Immune biomarkers (Weeks 56, 64, 72, 84, and 96 only)** ▪ **PBMCs (at selected sites at Weeks 56, 64, 72, 84, and 96; not to be collected at subsequent timepoints if not collected at Day 1)** ▪ **RNAi biomarker** • **Obtain urine samples for the following:** o **Pregnancy test for female subjects of child-bearing potential** o **Urinalysis** • ~~NrtI administration at home~~ • **Subject dosing diary** • **VBR accountability (Groups 1 and 2; Week 52 only)**	
Section 8.4	"As applicable" has been added to collection of blood samples for various tests and urine samples for pregnancy or urinalysis, and for the assessment of VBR accountability and review of subject dosing diary.	To allow for flexibility to the assessments that need to be carried out during an unscheduled visit, based on the judgement of the Investigator.
Section 8.6.2	The following edits have been made: HBV DNA will be quantified using ~~the~~ **a** commercially available ~~COBAS TaqMan~~ HBV test **with LLOQ of 10 IU/mL**, ~~Version 2.0 (Roche Diagnostics, US)~~ at a central reference laboratory.	The central lab has a new commercially available HBV DNA assay (Cobas 6800) with LLOQ 10 IU/mL, replacing the COBAS TaqMan assay. The additional added text

Section (In Original Protocol)	Change Made	Rationale
	The Sponsor also reserves the right to use alternate HBV virology assays with comparable LLOQ if the (originally) specified assays become unavailable.	provides flexibility in case the assays changes during the course of the study
Section 8.6.4	Added the following sentence: **In cases where a quantitative assay is negative or <LLOQ, reflex qualitative testing will be done**	To provide more complete guidance.
Section 8.7	The text in bold has been added: Samples from those subjects with evidence of virologic failure, such as **confirmed** virologic breakthrough **(2 consecutive visits with a** ≥1 $\log_{10}$ IU/mL increase in on-treatment HBV DNA from on-treatment nadir **or 2 consecutive visits with HBV DNA ≥LLOQ after having been <LLOQ**) will also be sequenced.	To provide more complete guidance.
Table 10	The list of laboratory tests under ALT elevation management has been updated as follows: ALT, AST, total bilirubin, serum albumin, creatine kinase, INR, **HBV DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]), HAV immunoglobulin M (IgM), HCV RNA, HDV RNA, HEV IgM, ANA, smooth muscle antibodies and anti-LKM1 antibodies, EBV DNA, CMV DNA, HSV DNA, and total IgG.** The footnote 'a' has been deleted ~~Perform fractionated bilirubin, if total bilirubin >ULN~~	The list of laboratory tests has been updated for completion, despite duplication of some tests specified in other rows of Table 10. Fractionated bilirubin should be performed regardless of total bilirubin levels.

Section **(In Original Protocol)**	**Change Made**	**Rationale**
Sections 8.9.1.1, 8.9.1.3	The following text in bold has been added: **Note the Day 1 PK sample collection should be done prior to the first dose of study drug.**	To clarify that the Day 1 PK sample collection for VBR and NrtI PK assessment should be done prior to the first dose of study drug.
Section 9.10.4	The following changes have been made: Paragraph 2: o All subjects with an ALT elevation on treatment, defined as ALT >2× Baseline or on treatment nadir and ≥10× ULN, should have the ALT findings confirmed within 3 days of receipt of the original results. All subjects should return for an Unscheduled Visit. ~~At this visit subjects will undergo a symptom-directed physical examination, vital signs, review of concomitant medications and AEs, and the following laboratory tests: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum albumin, creatine kinase and INR. The Investigator will determine if other assessments specified in Section should be performed.~~ Paragraph 3: o If the ALT elevation is confirmed, then an additional Unscheduled Visit will be performed to further evaluate the subject. At this visit, the following laboratory tests will be performed: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum albumin, INR, creatine kinase, HBV DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is	The edits clarify the sequence of assessments and laboratory tests to be followed in the event of ALT elevation in subjects. The tests for ANA, smooth muscle antibodies and anti-LKM1 antibodies, EBV DNA, CMV DNA, HSV DNA, and total IgG, have been added to exclude other etiologies for ALT elevation. Albumin decline INR >1.5 is more conservative than >2 and is supported by scientific literature. The reference to the US FDA has been deleted since Study 204 is not being conducted in the USA. The figure has been added for clarity.

Section (In Original Protocol)	Change Made	Rationale
	negative]), HAV immunoglobulin M (IgM), HCV RNA, HDV RNA, ~~and~~ HEV IgM**, ANA, smooth muscle antibodies and anti-LKM1 antibodies, EBV DNA, CMV DNA, HSV DNA, and total IgG.** The Investigator will determine if other **Unscheduled Visit** assessments ~~specified in Section~~ should be performed. The albumin-decline criteria have been modified as follows for subjects with declining hepatic function: • Albumin decline ≥0.5 g/dL OR INR > ~~2~~ **1.5**× Baseline (Day 1) OR If 5 or more subjects meet these flare management criteria, the ~~US FDA and other~~ relevant regulatory agencies will be notified, and subsequent steps will be determined after consultation with these agencies. Figure 7 has been added as a schematic for the safety management plan for ALT elevations.	
Appendix 2	The following changes have been made: Female subjects of child-bearing potential (defined above) must agree to use dual effective contraceptive methods for the duration of the study and follow-up, or for at least ~~30~~ **28** days after the last dose of VBR (Group 2 in Figure 6) and 6 months after the last dose of AB-729 (Groups 1 and 3 in Figure 6 if the subject prematurely discontinues from the study. Effective contraceptive methods include male or female condom (may not be used together due to increased risk of breakage), vasectomy, tubal sterilization, intra-uterine device (IUD), diaphragm, or cervical cap. Female subjects **of**	To clarify that: a. The total number of days after last dose of VBR for adherence to study contraceptive guidelines has been changed from 30 to 28 days to align with the current general guidelines from the Sponsor with respect to clinical trials and is not related to any safety concern

Section (In Original Protocol)	Change Made	Rationale
	childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test prior to receiving the first dose of study drug on Day 1. All male subjects must agree to use ~~a condom and an additional~~ **dual** effective contraceptive method**s** with their female partners (if their female partner is of child-bearing potential) for the duration of the study and follow-up, or for at least ~~30~~ **28** days after the last dose of VBR (Group 2 in Figure 6) and for 6 months after the last dose of AB-729 (Groups 1 and 3 in Figure 6) if they prematurely discontinue the study. In this case, effective contraceptive methods may include systemic (oral/injectable/implantable) hormonal contraceptives ~~(for Group 3 only)~~, vasectomy, tubal sterilization, IUD, diaphragm, or cervical cap. Male subjects must avoid sperm donation from the time of the first dose of study drug and throughout the study period or for at least ~~30~~ **28** days after the last dose of VBR (Group 2 in Figure 6) and for 6 months after the last dose of AB-729 (Groups 1 and 3 in Figure 6) if they prematurely discontinue the study.	b. Only female subjects of childbearing potential (rather than all female subjects) are required to have a negative serum pregnancy test at Screening and a negative urine pregnancy test prior to receiving the first dose of study drug on Day 1. This change aligns with the instruction provided in Section 5.2 and the Schedule of Assessment c. Male subjects do not necessarily have to use a condom with their female partners, rather the use of any dual effective contraceptive methods is acceptable Female partners of male subjects of the study who are of child-bearing potential may use hormonal contraceptives as an effective contraceptive method, regardless of the treatment assigned to their male partners

Study Title: A Randomized Phase 2a, Multicenter, Open-Label, Multiple-Cohort Study Evaluating Regimens Containing Vebicorvir in Subjects with Chronic Hepatitis B Virus Infection

NCT Number: NCT04820686

Date of Document: 22 May 2023

STATISTICAL ANALYSIS PLAN

Sponsor:	Assembly Biosciences, Inc 331 Oyster Point Blvd South San Francisco, CA 94080 (833) 509-4583
Protocol Number:	ABI-H0731-204
Protocol Title:	A Randomized Phase 2a, Multicenter, Open-Label, Multiple-Cohort Study Evaluating Regimens Containing Vebicorvir in Subjects with Chronic Hepatitis B Virus Infection
Product:	Vebicorvir (VBR; formerly ABI-H0731) AB-729
Protocol Version (Date):	Amendment 1 (27 October 2021)
Indication:	Chronic Hepatitis B Virus Infection
Analysis Type:	Final Analysis for Synoptic CSR
Analysis Plan Version (Date):	Version 2.0 (22 May 2023)
Analysis Plan Author:	[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN APPROVAL FORM

Protocol Title: A Randomized Phase 2a, Multicenter, Open-Label, Multiple-Cohort Study Evaluating Regimens Containing Vebicorvir in Subjects with Chronic Hepatitis B Virus Infection

Protocol Number: ABI-H0731-204

SAP Version (Date): Version 2.0 (22 May 2023)

The SAP was subject to critical review and has been approved .

Name and Title	Approval Signature/Date
[redacted] Assembly Biosciences	Signature applied in Veeva eTMF. See e-signature page.
[redacted] Assembly Biosciences	Signature applied in Veeva eTMF. See e-signature page.
[redacted] Assembly Biosciences	Signature applied in Veeva eTMF. See e-signature page.

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LIST OF ABBREVIATIONS

AASLD	american association for the study of liver diseases
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BLOQ	below the limit of quantitation
BMI	body mass index
cHBV	chronic hepatitis B virus infection
CI	confidence interval
CSR	clinical study report
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
ET	early termination
FAS	full Analysis Set
HBcAb	antibody to the HBV core antigen
HBcrAg	hepatitis B core-related antigen
HBeAb	HBeAg antibody
HBeAg	hepatitis B “e” antigen
HBsAb	HBsAg antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HLGT	high-level group term
HLT	high-level term
ID	identification
INR	international normalized ratio
IPD	important protocol deviation(s)
IRT	interactive response technology
LLOQ	lower limit of quantitation
LLT	lower-level term
LOD	limit of detection
LOQ	limit of quantitation
MedDRA	medical dictionary for regulatory activities
NrtI	Nucleos(t)ide reverse transcriptase inhibitor

PD	protocol deviation(s)
PT	preferred term
Q1, Q3	first quartile, third quartile
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TNA	total nucleic acid
ULN	upper limit of normal
VBR	vebicorvir
WHO	world health organization

1. INTRODUCTION

Study ABI-H0731-204 is a randomized Phase 2a, multicenter, open-label, multiple-cohort study evaluating the safety and antiviral activity of Vebicorvir (VBR) and AB-729 in combination with other chronic hepatitis B virus (HBV) infection (cHBV) treatments in subjects with cHBV. The target population is male or female subjects, 18 to 50 years of age, inclusive, with no evidence of cirrhosis or end-stage liver disease. Cohort 1 is prespecified and will enroll virologically-suppressed subjects on nucleos(t)ide reverse transcriptase inhibitor (NrtI) therapy with hepatitis B virus "e" antigen (HBeAg) negative cHBV. Approximately 60 subjects will be enrolled in Cohort 1 of this study. Up to 2 additional cohorts, with approximately 60 subjects per cohort, may be added in future protocol amendments, for a maximum sample size of approximately 180 subjects.

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study ABI-H0731-204. This SAP is based on the study protocol Amendment 1, dated 27 October 2021 and the electronic case report form (eCRF). In February 2023, Assembly and Arbutus jointly made the decision to discontinue study ABI-H0731-204, following the observation that AB-729 in dual combination with NrtI alone and as a triple combination with VBR promoted similar on-treatment declines in HBsAg, as has been observed in other AB-729 studies. Thus, there appears to be limited additional benefit to subjects continuing in the post-treatment study period as currently defined in the protocol. The study was prematurely terminated after every active subject completed 48-week treatment period.

The SAP will be finalized before database lock. Only key safety and efficacy endpoints will be performed. Any changes made after the finalization of the SAP will be documented in the Synoptic CSR.

1.1. Study Objectives

The primary objective of Cohort 1 is:

- To evaluate the safety and tolerability of combination treatment with VBR, AB-729, and NrtI

The secondary objectives of Cohort 1 are:

- To evaluate the effect of adding VBR and AB-729 to NrtI on reduction in and loss of HBsAg
- To evaluate the effect of adding VBR and AB-729 to NrtI in reducing HBV deoxyribonucleic acid (DNA) levels
- To evaluate the effect of adding VBR and AB-729 to NrtI in reducing HBV ribonucleic acid (RNA) levels

- To evaluate the effect of adding VBR and AB-729 to NrtI in reducing other HBV antigens (ie, hepatitis B core-related antigen [HBcrAg])
- To evaluate the effect of adding VBR and AB-729 to NrtI on hepatitis B surface antigen (HBsAg) seroconversion
- To evaluate the effect of adding VBR and AB-729 to NrtI on normalization of alanine aminotransferase (ALT)
- To evaluate the off-treatment durability of response to treatment with VBR and AB-729
- To evaluate the pharmacokinetics (PK) of VBR and AB-729 when coadministered with NrtI

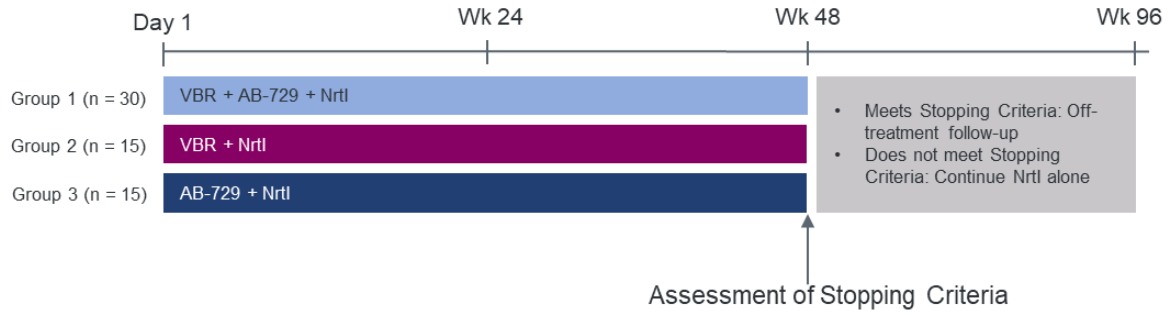
The exploratory objectives of Cohort 1 are:

- To evaluate the emergence of resistance to VBR and AB-729 when coadministered with NrtI
- To evaluate the effect of VBR, AB-729, and NrtI on immunological biomarkers, where applicable
- To evaluate the effect of VBR, AB-729, and NrtI on HBsAg isoforms and immune complexes, where applicable
- To evaluate the effect of AB-729 on an HBV-derived RNA interference biomarker, where applicable

1.2. Study Design

This study will assess the safety, antiviral activity, and PK of VBR and AB-729 administered in combination with other cHBV treatments in subjects with cHBV. Cohort 1 is prespecified and will enroll virologically-suppressed subjects on NrtI therapy with HBeAg negative cHBV. Approximately 60 eligible subjects will be randomized 2:1:1 in 1 of 3 treatment groups as shown in
Figure . Up to 2 additional cohorts may be added in future protocol amendments to evaluate other populations and/or treatment regimens.

Figure 1-1. Study Design Schematic for Study ABI-H0731-204



Abbreviations: VBR=vebicorvir; NrtI= nucleos(t)ide /reverse transcriptase inhibitor; Wk=week.

Treatment with VBR and NrtI will be administered orally, once daily; treatment with AB-729 will be administered subcutaneously, once every 8 weeks, for a total of 6 doses. Group 1 will receive VBR+AB-729+NrtI, Group 2 will receive VBR+NrtI, and Group 3 will receive AB-729+NrtI. Treatment assignments will be stratified by HBsAg level (ie, HBsAg ≤1000 IU/mL vs >1000 IU/mL) during the Screening visit.

Treatment Stopping Criteria

At Week 48, all subjects will have an assessment of Treatment Stopping Criteria. Any subjects who meet the below Treatment Stopping Criteria, will discontinue their assigned treatment including NrtI, and continue with off-treatment follow-up through Week 96, unless they meet the NrtI-restart criteria. Decisions to discontinue assigned treatment and undergo off-treatment follow-up will be based on laboratory results from blood samples collected at the Week 48 visit. Subjects will remain on their assigned oral agents (ie, VBR+NrtI for Groups 1 and 2; NrtI for Group 3) until Week 48 laboratory results required for Treatment Stopping Criteria assessment are available.

Following the announcement of the study early termination in February 2023, Treatment Stopping Criteria were not applicable to the subjects who subsequently reached the Week 48 visit. In this scenario, subjects were to complete the Premature Termination Visit and undergo assessments as outlined in protocol Section 8.5 at the time of the next protocol defined follow up visit. At that time, subjects were to discontinue VBR and study defined NrtI, as applicable, and were to transition to regular standard of care treatment and follow-up outside of the study.

Treatment Stopping Criteria are:

- ALT < 2 × upper limit of normal (ULN), *and*
- HBV DNA < lower limit of quantitation (LLOQ), *and*

- HBsAg < 100 IU/mL

Subjects who do not meet the Treatment Stopping Criteria with Week 48 laboratory results will continue treatment with NrtI alone and will remain in follow-up through Week 96.

NrtI-Restart Criteria

Subjects who meet the Treatment Stopping Criteria at the Week 48 assessment but subsequently meet **ANY** of the below NrtI-Restart Criteria, will restart treatment with NrtI and remain in follow-up through Week 96.

NrtI-Restart Criteria are:

- ALT > 10 ×ULN, confirmed by repeat
- ALT > Baseline and > ULN, confirmed by repeat, and
  - Direct bilirubin > 2.0 × ULN, confirmed by repeat, or
  - International Normalized Ratio > 1.5, confirmed by repeat
- ALT ≥ 2 – 5 × ULN AND HBV DNA > 2000 IU/mL for 12 weeks
- ALT elevations ≥ 5 – 10 ×ULN AND HBV DNA > 2000 IU/mL for 4 weeks
- Any clinical decompensation, regardless of HBV DNA level
- Investigator discretion

The schedule of study procedures is presented in tabular form in Tables 9 through 11 of the study protocol.

1.3. Sample Size and Power

Approximately 60 subjects will be randomized in Cohort 1 as shown in Table 1-2. Up to 2 additional cohorts may be subsequently enrolled by future protocol amendments, for a maximum sample size of approximately 180 subjects.

Table 1-2. Subject Treatment Assignment for Study ABI-H0731-204 Cohort 1

Treatment Group	Study Treatment	Mode of Delivery	Number of Subjects per Group
1	VBR+AB-729+NrtI	VBR and NrtI: Oral; AB-729: Subcutaneous	30
2	VBR+NrtI	Oral	15
3	AB-729+NrtI	AB-729: Subcutaneous;	15

	NrtI: Oral	
	Total Subjects Planned:	60

Abbreviations: NrtI=nucleos(t)ide/reverse transcriptase inhibitor; VBR=vebicorvir.

This is a proof-of-concept study. The sample size is similar to that previously utilized for this type of study and is not based upon statistical considerations.

1.4. Methods of Assigning Subjects to Treatment

1.4.1. Randomization

All subjects will be assigned a unique Subject identification (ID) at Screening and will be randomized upon successful completion of the Screening assessments. Upon confirmation of subject eligibility on Day 1, an Interactive Response Technology (IRT) system will assign eligible subjects to a study treatment. Additional information on the use of the IRT system is provided in the IRT User Manual.

In Cohort 1, the IRT system will assign eligible subjects in a 2:1:1 ratio to receive either VBR+AB-729+NrtI, VBR+ NrtI, or AB-729+NrtI for 48 weeks. Treatment assignments will be stratified by HBsAg level (ie, HBsAg ≤1000 IU/mL vs >1000 IU/mL) during the Screening visit.

1.4.2. Blinding

Not applicable as this is an open-label study.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

No formal interim analyses are planned. As an open-label study, the data will be reviewed periodically.

2.2. Final Analysis

As of 14 February 2023, the study was terminated early. The final analysis to support a Synoptic CSR will be performed after all subjects have discontinued or completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

No formal statistical testing is planned. Hence no multiplicity adjustment is required.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing. For each analysis set, the number and percentage of subjects eligible for inclusion will be summarized by treatment group. A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all subjects who were randomized in the study, classified according to the treatment group into which they were randomized regardless of the actual treatment received.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects, classified according to the treatment group into which they were randomized regardless of the actual treatment received who took at least 1 dose of a study drug. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects, classified according to the actual treatment received regardless of random assignment, who took at least 1 dose of a study drug. This is the primary analysis set for safety analyses.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set and FAS, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set , subjects will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via an IRT system in a 2:1:1 ratio to receive either VBR+AB-729+NrtI, VBR+NrtI, or AB-729+NrtI using a stratified randomization schedule. Stratification will be by HBsAg level (ie, HBsAg ≤1000 IU/mL vs >1000 IU/mL) during the Screening visit.

If there are discrepancies in stratification factor values between the IRT and the clinical database, the values recorded in the clinical database will be used for analyses. Given that the study is early terminated, a sensitivity analysis of the efficacy endpoints will not be performed for the stratification discrepancy.

3.4. Data Handling Conventions and Transformations

Subject age collected at Screening visit will be used for analyses and presented in listings. The age is derived in the electronic data capture (EDC) system based on year of birth and informed consent date.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation (LLOQ), less than the limit of detection (LOD), or above the upper limit of quantitation (LOQ) will be imputed for the purposes of calculating descriptive statistics.

A value that is half of the LLOQ will be used to calculate descriptive statistics if the datum is reported in the form of <x or <=x (where x is considered the LLOQ or LOD), or is reported as not detected. For example, if the reported datum is "<10", then a value of 5 will be assigned. If the LLOQ is reported in log units, the imputed value will be half of the equivalent non-log LLOQ value.

A value that is 1 significant value unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). For example, if the result of a continuous laboratory test is >20, a value of 21 will be assigned. If the result of a continuous laboratory test is >20.1, a value of 20.2 will be assigned.

The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≥ x" (where x is considered the LOQ).

For selected analyses, virology efficacy data will be transformed to the logarithmic (base 10) scale.

Total bilirubin values entered as < 0.2 mg/dL will be analyzed as 0.1 mg/dL; direct bilirubin values entered as < 0.1 mg/dL will be analyzed as 0.05 mg/dL (according to the methods of Nehls and Akland, 1973).

3.5. Missing Data and Outliers

3.5.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dose date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for adverse event (AE) onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.3.2.

3.5.2. Outliers

Outliers will be identified during the data management review process. No sensitivity analyses will be conducted. All data will be included in the data analysis.

3.6. Analytic Definitions

3.6.1. Definition of Study Drug

In this study, study drug is defined as VBR and AB-729.

3.6.2. Definition of Baseline

In general, Baseline will be defined as the last non-missing evaluation prior to the first dose on Day 1. Change from Baseline will be defined as the result at desired timepoint minus the result at Baseline.

3.6.3. Definition of Study Phase and End of Study

The analyses will include all the data collected in this study based on three phases defined as follows.

- **On-Treatment Phase:** when a subject is undergoing treatment with AB-729, VBR, or both per treatment group (ie, from first dose of either study drug through the last dose of VBR +1 day or last dose of AB-729 +56 days, whichever is later)
- **Off-Treatment Phase:** after a subject has discontinued AB-729, VBR, or both per treatment group, and prior to NrtI restart if applicable (ie, after the last dose of VBR +1 day or last dose of AB-729 +56 days, whichever is later, until the end of study or before the first dose of NrtI if it was restarted)
- **NrtI-Restart Phase:** after a subject has restarted NrtI, following the Off-Treatment Phase (ie, from the first dose of restarted NrtI through the end of study)

End of study is defined as when the last subject completes the last follow-up or is considered "lost to follow-up", whichever is later.

Subjects may prematurely discontinue study drug earlier prior to the Week 48 visit. The end dates of the On-Treatment Phase may vary for individual subjects based on their last dose dates as defined in Section 3.6.3.

3.6.4. Definition of Study Day

The first dose date of VBR and of AB-729 will be calculated where applicable. Study Day 1 is defined as the first dose date of study drug, which is the minimum of the first dose dates of VBR and of AB-729 in a treatment group. If the first dose date is missing, the date of randomization will be used.

The last dose date of VBR and of AB-729 will be calculated where applicable. The last dose date of each drug will be the end date on the respective study drug end of treatment eCRF. The last dose date of study drug will be defined as the maximum of the last dose dates of VBR and of AB-729 in a treatment group.

For the On-Treatment Phase, study day will be calculated from Study Day 1 and derived as follows:

- For days prior to the first dose: Assessment Date – Study Day 1
- For postdose study days: Assessment Date – Study Day 1 + 1

For the Off-Treatment Phase, the Off-Treatment Day 1 will be defined as the day after the last dose date of study drug VBR or 56 days after last dose of AB-729, whichever is later. The off-treatment study day will be calculated from the last dose date and derived as Assessment Date – Off-Treatment Day 1 + 1.

For the NrtI-Restart Phase, the NrtI-Restart Day 1 will be defined as the first dose date of restarted NrtI. The NrtI-Restart study day will be calculated from the first dose of NrtI and derived as Assessment Date – First Dose Date of NrtI + 1.

3.6.5. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. For the On-Treatment Phase, data will be summarized up to Week 48 visit or premature termination visit. For the Off-Treatment Phase, the data will be summarized by treatment action up to the end of study, or up to NrtI restart for applicable patients. For the NrtI-Restart Phase, data will be summarized only for applicable subjects who restarted NrtI after having discontinued AB-729, VBR, or both.

The analysis windows for the On-Treatment Phase assessments of HBV TNA, HBV RNA, HBsAg, Vital signs, Chemistry, Hematology, Coagulation, and Urinalysis are provided in Table 3-1.

For the On-Treatment Phase assessments of HBeAg, only the analysis visits of Baseline and Week 48 will be presented in the summary tables. Any non-baseline on-treatment visit will be categorized under analysis visit Week 48.

Table 3-1 On-Treatment Phase Analysis Visit Windows for Efficacy (HBV TNA, HBV RNA, HBsAg), Vital Signs, and Laboratory Assessments

Nominal Visit	On-Treatment Phase Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 2	14	2	21
Week 4	28	22	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	99	126
Week 20	140	127	154
Week 24	168	155	182
Week 28	196	183	210
Week 32	224	211	238
Week 36	252	239	266
Week 40	280	267	294
Week 44	308	295	322
Week 48	336	323	350
Week 52	364	351	378
Week 56	392	379	≥392

The analysis windows for the On-Treatment Phase assessments of HBV DNA, HBcrAg, and electrocardiogram (ECG) are provided in Table 3-2.

Table 3-2 On-Treatment Analysis Visit Windows for HBV DNA, HBcrAg, and ECG

Nominal Visit	On-Treatment Phase Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	84	2	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	≥336

The analysis windows for the Off-Treatment Phase assessments for subjects meeting Treatment Stopping Criteria of HBV DNA, HBV TNA, HBV RNA, HBsAg, Vital signs, Chemistry, Hematology, Coagulation, and Urinalysis are provided in Table 3-3.

Table 3-3 Off-Treatment Phase Analysis Visit Windows for HBV DNA, HBV TNA, HBV RNA, HBsAg, Vital Signs, Chemistry, Hematology, Coagulation, and Urinalysis for Subjects Meeting Treatment Stopping Criteria

Nominal Visit	Off-Treatment Phase Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Off-Treatment Day 1	1	(none)	1
Off-Treatment Week 4	28	2	42
Off-Treatment Week 8	56	43	70
Off-Treatment Week 12	84	71	98
Off-Treatment Week 16	112	99	126
Off-Treatment Week 20	140	127	154
Off-Treatment Week 24	168	155	182
Off-Treatment Week 28	196	183	210
Off-Treatment Week 32	224	211	238
Off-Treatment Week 36	252	239	266

Nominal Visit	Off-Treatment Phase Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Off-Treatment Week 40	280	267	294
Off-Treatment Week 44	308	295	322
Off-Treatment Week 48	336	323	≥ 336

The analysis windows for the Off-Treatment Phase assessments of HBcrAg and HBeAg for subjects meeting Treatment Stopping Criteria are provided in Table 3-4.

Table 3-4 **Off-Treatment Phase Analysis Visit Windows for HBcrAg and HBeAg for Subjects Meeting Treatment Stopping Criteria**

Nominal Visit	Off-Treatment Phase Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Off-Treatment Day 1	1	(none)	1
Off-Treatment Week 12	84	2	126
Off-Treatment Week 24	168	127	210
Off-Treatment Week 36	252	211	294
Off-Treatment Week 48	336	295	≥ 336

The analysis windows for Off-Treatment Phase assessments for subjects meeting Treatment Stopping Criteria of ECG are provided in Table 3-5.

Off-Treatment Phase Analysis Visit Windows for HBcrAg and HBeAg for Subjects Meeting Treatment Stopping Criteria

Table 3-5 Off-Treatment Phase Analysis Visit Windows for Subjects Meeting Treatment Stopping Criteria for ECG

Nominal Visit	Off-Treatment Phase Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Off-Treatment Day 1	1	(none)	1
Off-Treatment Week 12	84	2	210
Off-Treatment Week 48	336	211	≥ 366

The analysis windows for the Off-Treatment Phase assessments for subjects not meeting Treatment Stopping Criteria of HBV TNA, HBV RNA, HBsAg, Vital signs, Chemistry, Hematology, Coagulation, and Urinalysis are provided in Table 3-6.

The analysis windows for the NrtI-Restart Phase assessments of the same categories as the previous paragraph also follow Table 3-6.

Table 3-6 Off-Treatment Phase for Subjects Not Meeting Treatment Stopping Criteria and NrtI-Restart Phase Analysis Visit Windows for HBV TNA, HBV RNA, HBsAg, Vital Signs, Chemistry, Hematology, Coagulation, and Urinalysis

Nominal Visit	Off-Treatment/NrtI-Restart Phase Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Off-Treatment/NrtI-Restart Day 1	1	(none)	1
Off-Treatment/NrtI-Restart Week 4	28	2	42
Off-Treatment/NrtI-Restart Week 8	56	43	70
Off-Treatment/NrtI-Restart Week 12	84	71	98
Off-Treatment/NrtI-Restart Week 16	112	99	126
Off-Treatment/NrtI-Restart Week 20	140	127	154
Off-Treatment/NrtI-Restart Week 24	168	155	182
Off-Treatment/NrtI-Restart Week 28	196	183	210

Nominal Visit	Off-Treatment/NrtI-Restart Phase Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Off-Treatment/NrtI-Restart Week 32	224	211	238
Off-Treatment/NrtI-Restart Week 36	252	239	266
Off-Treatment/NrtI-Restart Week 40	280	267	294
Off-Treatment/NrtI-Restart Week 44	308	295	322
Off-Treatment/NrtI-Restart Week 48	336	323	≥ 336

The analysis windows for the Off-Treatment Phase assessments for subjects not meeting Treatment Stopping Criteria of HBV DNA, HBcrAg, and HBeAg are provided in Table 3-7.

The analysis windows for the NrtI-Restart Phase assessments of the same categories as the previous paragraph also follow Table 3-7.

Table 3-7 Off-Treatment Phase for Subjects Not Meeting Treatment Stopping Criteria and NrtI-Restart Phase Analysis Visit Windows for HBV DNA, HBcrAg, and HBeAg

Nominal Visit	Off-Treatment/NrtI-Restart Phase Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Off-Treatment/NrtI-Restart Day 1	1	(none)	1
Off-Treatment/NrtI-Restart Week 12	84	2	126
Off-Treatment/NrtI-Restart Week 24	168	127	210
Off-Treatment/NrtI-Restart Week 36	252	211	294
Off-Treatment/NrtI-Restart Week 48	336	295	≥ 336

The analysis windows for the Off-Treatment Phase assessments for subjects not meeting Treatment Stopping Criteria of ECG are provided in Table 3-8.

The analysis windows for the NrtI-Restart Phase assessments of the same categories as the previous paragraph also follow Table 3-8.

Table 3-8 Off-Treatment Phase for Subjects Not Meeting Treatment Stopping Criteria and NrtI-Restart Phase Analysis Visit Windows for ECG

Nominal Visit	Off-Treatment/NrtI-Restart Phase Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Off-Treatment/NrtI-Restart Day 1	1	(none)	1
Off-Treatment/NrtI-Restart Week 12	84	2	210
Off-Treatment/NrtI-Restart Week 48	336	211	≥ 366

3.6.6. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. If a single value is needed, but multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules:

- For baseline, the last nonmissing value on or prior to the first dose date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the record with the lowest accession number will be used.
- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day with the same time, the retest record will be selected. If there is no clear indication for which record is the retest record, then the record with the lowest accession number will be used.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group for each country, Investigator within a country, and overall. The summary will present the number and percentage of subjects randomized. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of subjects in the stratum will be the total number of randomized subjects. If there are discrepancies in the value used for stratification assignment between the IRT and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with discrepancies in the value used for stratification assignment between the IRT and the clinical database at the time of data finalization will be provided. The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group. This summary will present the number of subjects in each of the categories listed below:

- All Randomized Analysis Set
- Full Analysis Set
- Safety Analysis Set

The number and percentage of the subjects in the following categories will be summarized using the Safety Analysis Set:

- Completed study drug VBR
- Did not complete study drug VBR with reasons for premature study drug discontinuation
- Completed study drug AB-729
- Did not complete study drug AB-729 with reasons for premature study drug discontinuation
- Completed study
- Did not complete the study with reasons for study discontinuation

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set corresponding to that column.

The following by-subject listings will be provided by subject ID number in ascending order:

- Reasons for premature study drug or study discontinuation
- Dispensed bottle number and lot number for VBR, lot number for AB-729

The proportion of subjects meeting treatment stopping criteria will be summarized. A by-subject listing detailing each subject's treatment stopping decision and the HBV DNA, HBsAg, and ALT results from their last on-treatment (i.e. week 48) study visit will be included.

4.2. Extent of Study Drug Exposure and Compliance

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of compliance relative to the study drug regimen specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to each study drug will be defined as the last dose date minus the first dose date plus 1 for VBR and plus 56 days for AB-729, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). Duration (weeks) = Duration (days) /7. The last dose date of individual study drug is defined in Section 3.6.3. If the last study drug dose date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used for subjects included in the final analyses or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis.

The total duration of exposure to study drug will be summarized using descriptive statistics. Summaries will be provided by treatment group and study drug for the Safety Analysis Set. The expected total duration of on-treatment therapy for all subjects is 48 weeks. The distribution of subjects by the total number of weeks on therapy (ie. ≤4 weeks, >4-8 weeks, >8-12 weeks, >12-16 weeks, >16-20 weeks, >20-24 weeks, >24-36 weeks, and >36-48 weeks, ≥48 weeks) will be presented. The cumulative distribution of subjects will also be presented using the following cutoffs: at least 1 dose, ≥2 weeks, ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥24 weeks, ≥36 weeks, and ≥48 weeks. For AB-729, the distribution of subjects by number of injections will be summarized.

4.2.2. Study Drug Compliance

Compliance will be calculated for study drugs VBR and AB-729.

The total number of tablets (VBR) and injections (AB-729) administered will be summarized using descriptive statistics.

The presumed total number of tablets (VBR) administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

$$\text{Total Number of Tablets Administered} = \left(\sum \text{No. of Tablets Dispensed}\right) - \left(\sum \text{No. of Tablets Returned}\right)$$

The presumed total volume of injections (AB-729) administered to a subject will be determined by summing the volume administered during each visit containing an injection, as reported on each relevant week's study drug administration CRF.

4.2.2.1. On-Treatment Compliance

The level of on-treatment compliance to the study drug will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period.

The level of on-treatment compliance for each study drug will be expressed as a percentage using the following formula:

$$\text{On-Treatment Compliance (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Total Amount of Study Drug Expected to be Administered on Treatment}}\right) \text{ x } 100$$

Per protocol, each subject receiving VBR is expected to take three 100 mg tablets of VBR daily during the on-treatment phase. In a 48-week period, a total of 1008 tablets would be expected. Each subject receiving AB-729 is expected to receive a 60 mg (0.33 mL) injection once every 8 weeks during the on-treatment phase. In a 48-week period, a total of 360 mg (2 mL) over 6 injections would be expected.

For subjects who prematurely discontinue, the denominator will be the total amount of study drug expected to be administered by the date of premature discontinuation.

Descriptive statistics for the level of on-treatment compliance with the number and percentage of subjects belonging to compliance categories (e.g., < =80%, > 80-90%, and ≥ 90%) will be provided by treatment group for the Safety Analysis Set.

A by-subject listing of study drug administration and drug accountability will be provided by subject ID number in ascending order and visit in chronological order.

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry but enrolled in the study will be summarized. The number and percentage of subjects who did not meet at least 1 eligibility criterion will be provided for specific criteria by treatment group based on the All Randomized Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations (PDs) occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important PDs (IPDs) by deviation category will be summarized by treatment group for All Randomized Analysis Set. A table will be provided to summarize any COVID-19 related PDs with the deviation reason by treatment groups. A by-subject listing will be provided for those subjects with any protocol deviations.

A table will be provided to summarize any COVID-19 related PDs with the deviation reason by treatment groups. Any visits that were not performed will be summarized by reason (ie, adverse event, COVID-19 restrictions, and Other). A listing of subjects who had study disruption due to COVID-19 will be provided with a description.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, age group [<40/ ≥ 40 years], sex, race, and ethnicity), baseline characteristics (body weight [in kg], height [in m], body mass index [BMI; in kg/m^2]) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

5.2. Baseline Disease Characteristics

Baseline disease characteristics will be summarized by treatment group and overall. Summary descriptive statistics will be used for continuous variables and the number and percentage of subjects will be used for categorical variables. The following factors will be included, but not limited to:

- Years positive for HBV
- HBV Genotype
- Baseline NrtI type
- Years on current HBV treatment
- Baseline HBV DNA (log_{10} IU/mL)
- Baseline HBV RNA (log_{10} U/mL)
- Baseline HBV total nucleic acid (TNA) (log_{10} IU/mL)
- Baseline HBeAg (log_{10} IU/mL)
- Baseline HBcrAg (log_{10} kU/mL)
- HBcrAg groups (< LLOQ, < 500, < 100, < 10)
- Baseline HBsAg (log_{10} IU/mL)
- HBsAg groups (< LLOQ, ≤ 1000, > 1000 IU/mL)
- Baseline HBeAg antibody (HBeAb)

- Baseline HBsAg antibody (HBsAb)
- Baseline ALT (U/L)
- Baseline ALT groups (>ULN [Covance], >ULN [American Association for the Study of Liver Diseases (AASLD)]
- Liver biopsy staging
- Fibroscan result
- Metavir Fibrosis Stage

A by-subject listing of baseline disease characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

Medical history collected at Screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version (v) 23.1.

Medical history will be summarized by preferred term (PT), treatment group and overall. Subjects who report 2 or more medical history items that are coded to the same PT will be counted only once by the unique coded term in the summary. The summary will be provided for the Safety Analysis Set.

HBV specific medical history will be summarized by mode of HBV infection, treatment group and overall. The summary will be provided for the Safety Analysis Set.

A by-subject listing of medical history will be provided by subject ID number in ascending order.

6. EFFICACY ANALYSES

The primary analysis set for efficacy analyses will be the FAS, defined in Section 3.1.2. All the efficacy analyses will be performed for each cohort separately. The following sections describe the primary and secondary analyses for the efficacy endpoints.

6.1. Efficacy Endpoints

6.1.1. Definition of Efficacy Endpoints

The efficacy endpoints of Cohort 1 are:

- Mean change in $\log_{10}$ HBsAg from Baseline at each timepoint
- Mean change in $\log_{10}$ HBV RNA from Baseline at each timepoint
- Mean change in $\log_{10}$ HBcrAg from Baseline at each timepoint
- Mean change in TNA quantitative from Baseline at each timepoint
- ALT results and change from Baseline

6.1.2. Analysis Methods for Efficacy Endpoints

The observed and mean change in $\log_{10}$ HBV RNA, HBV TNA, HBsAg, HBcrAg, and ALT from Baseline will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by phase, treatment group, and treatment action at each visit.

For the On-Treatment Phase, analysis will be performed to compare the mean changes of $\log_{10}$ HBV RNA, $\log_{10}$ HBV TNA, $\log_{10}$ HBsAg, $\log_{10}$ HBcrAg, and ALT from Baseline to each timepoint between VBR+AB-729+NrtI and VBR+NrtI, and between VBR+AB-729+NrtI and AB-729+NrtI. The primary comparison for mean change endpoints will be made using an analysis of covariance (ANCOVA) model, including baseline value, the stratification factors, and treatment group as covariates. The estimated least square means of treatment effects and estimated difference in treatment effects between treatment groups at Week 48 will be presented along with the 95% CIs and p-values. The analysis will be based on observed data.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version (v) 23.1. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, or 4 according to the toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the Investigator selected "Related" on the AE eCRF to the question of "Relationship to Study Treatment" based on the his/her clinical assessment. Events for which the Investigator fails to record a relationship to an applicable study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met protocol-specified definitions of a SAE.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs with an onset date/time equal to or after the study drug start date/time through end of study .

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dose date of any study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset date is in the same as or after the month and year (or year) of the first dose date of any study drug, and

- The AE onset date is in the same as or before the month and year (or year) of the end of study

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dose date of any study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dose date of any study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set. Tables will be created per study phase (i.e. On-Treatment Phase, Off-Treatment Phase, and NrtI-Restart Phase).

A brief, high-level summary of the number and percentage of subjects who experienced at least 1 TEAE in the categories described below will be provided by treatment group. The brief summary will also include treatment-related TEAEs, treatment-related TE SAEs, and TEAEs leading to premature study discontinuation. All deaths observed in the study will also be included in this summary. In addition, a table for each category showing the number and percentage of subjects will be provided by PT and treatment group in descending order of total frequency:

- TEAEs

- TEAEs by severity grade

- TEAEs related to AB-729

- TEAEs related to VBR

- TE SAEs

- TE SAEs related to AB-729

- TE SAEs related to VBR

- TEAEs leading to premature study drug AB-729 discontinuation

- TEAEs leading to premature study drug VBR discontinuation

- TEAEs leading to study discontinuation

- TEAEs leading to death (ie, outcome of death)

- COVID-19 specific TEAEs
- COVID-19 specific TE SAEs

Multiple events will be counted only once per subject in each summary. For summary by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

A data listing containing all AEs will be provided.

7.2. Laboratory Evaluations

7.2.1. Graded Laboratory Values

The criteria specified in the study protocol will be used to grade laboratory results as normal (no grade), mild (Grade 1), moderate (Grade 2), severe (Grade 3) or potentially life threatening (Grade 4). See Appendix 1 of the protocol for detailed DAIDS grading criteria on the relevant laboratory tests. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.1.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from Baseline at any postbaseline time point. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.1.2. Summaries of Laboratory Abnormalities

A summary (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test.

Treatment-emergent lab abnormalities will be summarized based on the Safety Analysis Set. Tables will be created per study phase (i.e. On-Treatment Phase, Off-Treatment Phase, and NrtI-Restart Phase).

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values in each phase.

The maximum post-baseline grade in each phase will be tabulated for each laboratory test, and percentages will be based on the number of subjects with a post-baseline evaluation of the specific laboratory test. The laboratory abnormalities during the follow-up period will also be summarized.

A by-subject listing of graded laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.2. Ungraded Laboratory Values

Treatment-emergent abnormal direct bilirubin will be summarized by cohort and treatment group. A treatment-emergent abnormal direct bilirubin record is defined as a record with value > baseline and >=ULN in the phase. The highest direct bilirubin measurement will be counted for each subject. A by-subject listing of visits

Treatment-emergent abnormal direct bilirubin will be summarized based on the Safety Analysis Set. Tables will be created per study phase (i.e. On-Treatment Phase, Off-Treatment Phase, and NrtI-Restart Phase).

7.2.3. ALT Elevation

7.2.3.1. ALT Elevation without Declining Hepatic Function

All subjects with an ALT elevation on treatment, defined as ALT >2 × Baseline or on-treatment nadir and ≥10 × ULN, should have the ALT findings confirmed within 3 days of receipt of the original results.

7.2.3.2. ALT Elevation with Declining Hepatic Function

Subjects with confirmed ALT elevation with evidence of declining hepatic function should be discontinued prematurely from study treatment. This is defined as:

- ALT elevation ≥2 × Baseline (Day 1) or nadir and >2 × ULN AND
- Direct bilirubin increase to ≥2 × Baseline (Day 1) and ≥2 × ULN OR
- Albumin decline ≥0.5 g/dL from Baseline OR international normalized ratio (INR) >2 × Baseline (Day 1) OR
- Symptoms of liver inflammation (eg, fatigue, weakness, lack of appetite, nausea, vomiting, jaundice or discolored feces)

The number of subjects meeting the above criteria will be summarized by treatment group. Clinical signs or symptoms of liver inflammation will not be included in the summary. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For the composite criteria, subjects will be counted once when the criteria are met at the same visit. The denominator is the number of subjects in the Safety Analysis Set who have nonmissing postbaseline values. A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Vital Signs

Vital signs will be summarized for the on-treatment phase.

Descriptive statistics will be provided by treatment group for vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min], respiration [breaths/min], and body temperature [ºC]) as follows:

- Baseline value
- Values at each postbaseline time visit
- Change from Baseline at each postbaseline visit

A Baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from Baseline to a postbaseline visit will be calculated for any postbaseline visit including follow-up visits.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.5.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using World Health Organization (WHO) Drug dictionary (WHODrug Global 1 Sep 2020).

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first study drug.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once within each ATC drug class. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

A medication will be considered as a prior medication if it meets one the following criteria:

- A medication with a start date prior to the first dose date of study drug will be included in the prior medication summary regardless of when the stop date is.

- If a partial start date is entered, the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dose date.

- A medication with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by ATC drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once within each ATC drug class will be counted only once when calculating the number and percentage of subjects who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

A medication will be considered as a concomitant medication if it meets one the following criteria:

- A medication with a start date prior to or on the first dose date of study drug, and continued to be taken after the first dose date.

- A medication started after the first dose date

- If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) before the study drug stop date and the stop date after the first dose date of study drug. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the date of first study drug

- A medications started and stopped on the same day as the first dose

- Medications with completely missing start and stop dates, unless otherwise specified.

A medications with a stop date prior to the date of first dose date of study drug will be excluded from the summary.

Summaries of prior and concomitant medications and HBV concomitant medications will be based on the Safety Analysis Set.

All the prior and concomitant medications will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram Results

A shift table of the investigators' assessment of ECG results at each visit compared with baseline values will be presented by treatment group using the following categories:

- normal
- abnormal (not clinically significant)
- abnormal (clinically significant)
- missing/not done

The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

A by-subject listing for ECG assessment results will be provided by subject ID number and visit in chronological order.

7.6. Other Safety Measures

Since the study is terminated early, no additional safety measures specified in the protocol will be performed.

8. REFERENCES

Nehls G, Akland G. Procedures for Handling Aerometric Data. Journal of the Air Pollution Control Association 1973;23 (3):180-4.

9. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

10. DOCUMENT HISTORY

Version	Date (DD MMM YYYY)	Summary of Changes
1.0	17 MAY 2023	Original
2.0	22 MAY 2023	Updated section 4.2.2. for Study Drug Compliance

11. APPENDICES

None

Signature Page for VV-TMF-60087 v2.0

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 23-May-2023 04:57:00 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 23-May-2023 14:52:44 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 23-May-2023 15:24:14 GMT+0000

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