Study Title: A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled Study Evaluating Treatment Intensification with ABI-H0731 in Subjects with Chronic Hepatitis B Infection on Nucleos(t)ide Reverse Transcriptase Inhibitors

NCT Number: NCT04454567

Date of Document: 08 September 2020

CLINICAL RESEARCH PROTOCOL

PROTOCOL TITLE:	A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled Study Evaluating Treatment Intensification with ABI-H0731 in Subjects with Chronic Hepatitis B Infection on Nucleos(t)ide Reverse Transcriptase Inhibitors
STUDY NUMBER:	ABI-H0731-205
DRUG:	ABI-H0731
REFERENCE NUMBERS:	US IND 136780
SPONSOR:	Assembly Biosciences 331 Oyster Point Boulevard, 4th Floor South San Francisco, California 94080, USA (833) 509-4583
PROTOCOL:	Amendment 1 – 08 September 2020
PROTOCOL HISTORY:	Original – 29 April 2020

CONFIDENTIALITY STATEMENT

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title:	A Phase 2a, Multi-Center, Single-Blind, Placebo-Controlled Study Evaluating Treatment Intensification with ABI-H0731 in Subjects with Chronic Hepatitis B Infection on Nucleos(t)ide Reverse Transcriptase Inhibitors
Protocol Number:	ABI-H0731-205
Protocol Date:	Amendment 1 – 08 September 2020

This 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 product.
- 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), united States (US) Title 21 of the Code of Federal Regulations (CFR) parts 50, 54, 56, and 312, and other applicable local requirements.

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

Name and Title	Approval Signature and Date
[redacted] Chief Medical Officer Assembly Biosciences	[redacted]

INVESTIGATOR STATEMENT

Protocol Title:	A Phase 2a, Multi-Center, Single-Blind, Placebo-Controlled Study Evaluating Treatment Intensification with ABI-H0731 in Subjects with Chronic Hepatitis B Infection on Nucleos(t)ide Reverse Transcriptase Inhibitors
Protocol Number:	ABI-H0731-205
Protocol:	Amendment 1 – 08 September 2020

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.

1. SYNOPSIS

Protocol Number:	ABI-H0731-205
Title:	A Phase 2a, Multi-Center, Single-Blind, Placebo-Controlled Study Evaluating Treatment Intensification with ABI-H0731 in Subjects with Chronic Hepatitis B Infection on Nucleos(t)ide Reverse Transcriptase Inhibitors
Phase:	2a
Number of Subjects:	Approximately 40
Study Duration:	Up to 45 days for Screening, 96 weeks treatment, and 24 weeks of follow-up
Rationale:	Chronic hepatitis B infection (CHB) is a major cause of liver-related morbidity and mortality worldwide. While standard-of-care nucleos(t)ide reverse transcriptase inhibitors (NrtI) targeting the hepatitis b virus (HBV) polymerase are able to suppress viral replication (ie, HBV DNA below the limitation of quantification [LLOQ]), around 30% of hepatitis B 'e' antigen (HBeAg) positive patients and 10% of HBeAg negative patients have only a partial virologic response and are not able to reach this goal by treatment Week 48. Combination approaches are needed to provide adequate viral suppression in these patients. ABI-H0731 is a direct-acting antiviral agent targeting the HBV core protein. Through this mechanism, ABI-H0731 interferes with multiple steps in the viral lifecycle including capsid disassembly and HBV DNA delivery to the nucleus, HBV pregenomic RNA (pgRNA) encapsidation, capsid assembly and HBV DNA recirculation preventing de novo cccDNA establishment. It is anticipated that ABI-H0731 administered in combination with NrtI will be safe and result in complete viral suppression in subjects unable to attain this status on NrtI alone. This Phase 2a study will explore the safety of ABI-H0731 when added to NrtI and evaluate the antiviral activity of the ABI-H0731+NrtI combination as measured by the proportions of partially virologically suppressed subjects achieving HBV DNA <LLOQ at Week 48.
Target Population:	Male or female, aged 18 to 65 years (inclusive), with HBeAg positive or HBeAg negative CHB and no evidence of cirrhosis or end-stage liver disease who are not adequately suppressed on NrtI therapy.
Test Product:	300 mg ABI-H0731 as three 100 mg tablets and NrtI, oral administration
Reference Product:	ABI-H0731-matching placebo (PBO) (as 3 tablets) and NrtI, oral administration
Study Design:	This is a Phase 2a, multi-center, randomized, single-blind, PBO-controlled study, evaluating the safety, antiviral activity, and pharmacokinetics (PK) of ABI-H0731 administered in addition to standard of care NrtI in subjects with CHB who have not achieved adequate virologic suppression of HBV DNA <LLOQ on NrtI alone. For this

study, HBV DNA is analyzed by COBAS® TaqMan Version 2.0 at the central laboratory (lower limit of quantification [LLOQ]=20 IU/mL).

Approximately 40 eligible subjects will be randomized in a 1:1 ratio to the treatment groups described below.

Abbreviations: NrtI=nucleos(t)ide reverse transcriptase inhibitor; PBO=placebo; QD=once daily; Wk=week.

Treatment with ABI-H0731 or PBO and NrtI will be administered orally, once daily

- Group 1 will receive ABI-H0731+NrtI for 96 weeks
- Group 2 will receive PBO+NrtI for 48 weeks, and then ABI-H0731+NrtI until Week 96

All subjects will continue to receive NrtI alone from Week 96 through Week 120 (during the 24-week follow-up period).

The study will enroll up to 75% subjects on entecavir (ETV). Treatment assignments will be stratified by the concurrent NrtI administered (ie, ETV) versus tenofovir (alafenamide versus [TAF] or disoproxil fumarate [TDF]) and HBV DNA (HBV DNA ≥500 IU/mL versus <500 IU/mL) during the Screening visits.

Objectives:

Primary Objectives:

- To evaluate the safety and tolerability of ABI-H0731 when administered in combination with NrtI in subjects with CHB
- To evaluate the effect of the addition of ABI-H0731 to NrtI in fully suppressing HBV DNA in subjects with CHB

Secondary Objectives:

- To evaluate the effect of the addition of ABI-H0731 to NrtI in reducing HBV pgRNA levels in subjects with CHB
- To evaluate the effect of the addition of ABI-H0731 to NrtI in reducing HBV antigens (ie, HBeAg, hepatitis B core-related antigen [HBcrAg], and hepatitis B surface antigen [HBsAg]) in subjects with CHB
- To evaluate the effect of the addition of ABI-H0731 to NrtI on normalization of alanine aminotransferase (ALT) in subjects with abnormal ALT
- To evaluate the PK of ABI-H0731 and NrtI in subjects with CHB
- To evaluate the emergence of resistance to ABI-H0731 when administered in combination with NrtI

Exploratory Objectives:

- To assess the relationship between immunological and/or viral biomarkers with virologic and/or clinical outcomes
- For subjects who provide an optional pharmacogenomic sample, to evaluate the potential contribution of host genomics to clinical or virologic outcomes and/or drug disposition

Primary Endpoint:

Primary Endpoints:

- Proportion of subjects with adverse events, premature treatment discontinuation, and abnormal laboratory results
- Proportion of subjects with HBV DNA <LLOQ at Week 48 for PBO+NrtI and ABI-H0731+NrtI

Secondary Endpoints:

Secondary Endpoints:

- Mean change in $\log_{10}$ HBV DNA from Baseline at each timepoint
- Proportion of subjects with HBV DNA is <LLOQ at each timepoint
- Proportion of subjects with HBV DNA is <level of detection (target not detected) at each timepoint
- Mean change in $\log_{10}$ HBV pgRNA from Baseline at each timepoint
- Proportion of subjects with HBV pgRNA <LLOQ at each timepoint
- Mean change in $\log_{10}$ serum viral antigens (ie, HBeAg, HBcrAg, and HBsAg) from Baseline at each timepoint
- Proportion of subjects with abnormal ALT at Baseline who have normal ALT at each timepoint
- Analysis of ABI-H0731 and NrtI drug concentrations:
  - PK on study visit days of ABI-H0731 on ABI-H0731+NrtI
  - PK on study visit days of NrtI on PBO+NrtI and ABI-H0731+NrtI
- The incidence of HBV variants with reduced susceptibility to ABI-H0731

Exploratory Endpoints:

Exploratory Endpoints:

- Proportion of subjects with loss of serum viral antigens (defined as <LLOQ) in HBeAg, HBcrAg, and HBsAg
- Proportion of subjects with HBeAg seroconversion (defined as loss of HBeAg and appearance of HBeAg antibody [HBeAb]) or HBsAg seroconversion (defined as loss of HBsAg and appearance of HBsAg antibody [HBsAb]) at each timepoint
- Immunologic outcomes, including changes in humoral and cellular immunity to PBO+NrtI and ABI-H0731+NrtI
- Pharmacogenomic correlations may be performed with clinical or virologic outcomes for subjects who provide optional informed consent
- For subjects who provide an optional pharmacogenomic sample, to evaluate known gene variants and ABI-H0731, its metabolites, and PK and/or safety

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, antiviral activity, and PK endpoints will be summarized using descriptive statistics by dose groups within cohorts. 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.

Due to sample size limitations, no formal statistical inference is planned. Assessment of antiviral activity will be compared by treatment groups using 95% confidence intervals where appropriate.

Key Eligibility Criteria:

Inclusion Criteria:

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

1. Willing and able to provide informed consent
2. Male or female between the ages 18 and 65 years (inclusive)
3. Body mass index (BMI) 18 to 36 kg/m^2 and a minimum body weight of 45 kg (inclusive)
4. Female subjects of child-bearing potential (Appendix 4) must be non-pregnant and have a negative serum pregnancy test at Screening and a negative urine pregnancy test predose on Day 1
5. HBeAg positive or HBeAg negative CHB, defined as HBV infection documented for ≥12 months
6. HBV DNA >LLOQ (using a commercially available assay with LLOQ=20 IU/mL) from 2 samples drawn on 2 separate occasions during the Screening period approximately 10-14 days apart. If the results from these 2 samples indicate a numeric decline in HBV DNA, then a third sample will be collected at least a week later for Sponsor review and approval prior to randomization
7. On a stable NrtI regimen (ETV, TDF or TAF) for more than 12 months, without evidence of resistance and while known to be adherent to therapy
8. Lack of cirrhosis or advanced liver disease as documented by the following:
   - Liver biopsy results of METAVIR F0-F3 (absence of cirrhosis) within 1 year of Screening

     OR

   - Fasting FibroScan® ≤14 kPa within 3 months of Screening (including the Screening visit) or other Sponsor-approved hepatic imaging method within 6 months of Screening indicating lack of cirrhosis (F0 to F3 or equivalent)

     If results from both 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
9. Agreement to comply with protocol-specified contraceptive requirements (Refer to Appendix 4)

10. Agreement to abstain from alcohol abuse (defined as alcohol consumption exceeding 2 standard drinks per day on average [1 standard drink=14 grams of alcohol]) and the use of illicit substances for the duration of the trial
11. In good general health, except for CHB (in the opinion of the Investigator).
12. Have the ability to take oral medication and, in the opinion of the Investigator, be willing to adhere to trial treatment

Exclusion Criteria:

Subjects who meet any of the following exclusion criteria will not be eligible for the trial.

1. Current or prior treatment for CHB with
    - Lamivudine, telbivudine or adefovir (any duration)
    - HBV core inhibitor (any duration)
    - Previous treatment with an investigational agent for HBV infection
2. Presence of substitutions in the HBV polymerase coding region which may confer reduced susceptibility to NrtIs (Appendix 2)
3. Co-infection with human immunodeficiency virus, hepatitis A virus, hepatitis C virus, hepatitis E virus, or hepatitis D virus
4. Females who are lactating or wish to become pregnant during the course of the trial
5. History or evidence of advanced liver disease 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
6. 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
7. 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 CHB; 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 trial participation
8. History of hepatocellular carcinoma (HCC)
9. A 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
10. History or presence at Screening of electrocardiogram abnormalities deemed clinically significant, in the opinion of the Investigator
11. History of hypersensitivity or idiosyncratic reaction to any components or excipients of the investigational drug or PBO formulation

12. History of any significant food or drug-related allergic reactions such as, anaphylaxis or Stevens-Johnson syndrome
13. The following are exclusionary laboratory results at the Screening visit:
    - Platelet count <100,000/mm^3
    - Albumin <lower limit of normal
    - Total bilirubin >1.2 × upper limit of normal (ULN) unless known Gilbert's syndrome; subjects with Gilbert's syndrome are eligible for trial participation if the direct bilirubin is within the normal range
    - Direct bilirubin >1.2 × ULN
    - ALT >10 × ULN
    - Serum alpha fetoprotein (AFP) ≥100 ng/mL. If AFP at Screening is >ULN but <100 ng/mL, the subject is eligible if a hepatic imaging trial prior to initiation of study drug reveals no lesions indicative of possible HCC.
    - International Normalized Ratio >1.5 × ULN
    - Glomerular filtration rate <50 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation
    - Any other laboratory abnormality deemed clinically significant by the Sponsor or the Investigator
14. Subjects receiving prohibited concomitant medications, as defined in Section 6.4.1 of the protocol, grapefruit juice, or prohibited herbal/over-the-counter medications within 7 days or 5 half-lives (if known), whichever is longer, prior to administration of the first dose of study drug and for the duration of the trial period
15. Participation in another clinical trial 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. However, subjects receiving any prior investigational therapy for HBV, will be excluded
16. Subjects who have received, in the previous 4 weeks, a treatment likely to alter the immune response (intravenous immunoglobulins, blood-derived products, or high-dose steroids, or other immunosuppressants)

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Term or Definition
AE	adverse event
AFP	alpha fetoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
cccDNA	covalently closed circular DNA
CFR	Code of Federal Regulations
CHB	chronic hepatitis B infection
CI	core inhibitor
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRO	Contract Research Organization
CSR	clinical study report
CYP	cytochrome P450
DAIDS	Division of AIDS
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
ETV	entecavir
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GMP	Good Manufacturing Practices
HAV	hepatitis A virus
HBcAb	antibody to the HBV core protein
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
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee

Abbreviation	Term or Definition
IFNα	Interferon alpha
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
LLOQ	lower limit of quantification
LOD	level of detection
MedDRA	Medical Dictionary for Regulatory Activities
NrtI	nucleos(t)ide reverse transcriptase inhibitor of the HBV polymerase; also called nucleos(t)ide analogues or nucleos(t)ides
PBMC	peripheral blood mononuclear cell
pgRNA	[HBV] pre-genomic RNA
PK	pharmacokinetic(s)
PBO	placebo
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SVR	sustained virologic response
TEAE	Treatment-emergent adverse event
TAF	tenofovir alafenamide
TD	target detected
TDF	tenofovir disoproxil fumarate
TND	target not detected
ULN	upper limit of normal
US	United States
WHO	World Health Organization

2. INTRODUCTION

2.1. Background

Worldwide >240 million people are chronically infected with the hepatitis B virus (HBV), and chronic hepatitis B infection (CHB) 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 CHB (EASL 2017, WHO 2016, El-Serag 2012, Colvin 2010). 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, WHO 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 more than 4 million acute HBV infections worldwide each year (WHO 2015).

The clinical stages of HBV represent different risks for ongoing liver injury depending on the degree of HBV replication and individuals' concurrent immune responses to HBV infection (EASL 2012, Gish 2015, Hoofnagle 2007, Lok 2009, Pungpapong 2013, Sorrell 2009, Yim 2006). The standard virologic and serologic markers for HBV infection include HBV DNA, hepatitis B surface antigen (HBsAg), antibody to HBsAg (HBsAb), hepatitis B "e" antigen (HBeAg), antibody to HBeAg (HBeAb), and in almost all patients, antibody to the HBV core protein (HBcAb). More recently, HBV pre-genomic RNA (pgRNA) and HBV core-related antigen (HBcrAg) have also been used as markers of infection. Historically, treatment goals include prevention of HBV-related liver injury through suppression of HBV DNA to low levels, achievement of HBeAg loss and seroconversion, and loss of HBsAg and seroconversion. A transition to an HBsAg negative, minimally replicative state is rare but usually durable and, if it precedes the development of cirrhosis and HCC, is associated with improved long-term clinical outcomes (EASL 2012). As such, HBsAg seroconversion is considered a "functional cure" and a potential endpoint for HBV therapy. However, as HBsAg is derived from both covalently closed circular DNA (cccDNA) as well as integrated HBV DNA, sustained undetectable HBV DNA without HBsAg loss after stopping treatment ("sustained virologic responses [SVR]") may be considered as an intermediate goal (Cornberg 2020).

Currently, there are 2 clinically accepted treatment options for CHB: interferon alfa (IFNα) and nucleos(t)ide reverse transcriptase inhibitors of the HBV polymerase (NrtI). Of these agents, oral NrtIs are 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 complete viral suppression to levels below quantification on commercially available assays following an adequate course of NrtI therapy. In the Phase 3 studies with entecavir (ETV), 33% of HBeAg positive subjects and 10% of HBeAg negative subjects did not achieve HBV DNA <lower limit of quantification (LLOQ) (300 copies/mL) after 48 weeks of treatment (Chang 2006; Lai 2006). Similarly, in a Phase 3 trial in HBeAg positive subjects, 36% of tenofovir alafenamide (TAF) recipients and 33% of subjects receiving tenofovir disoproxil fumarate (TDF) had HBV DNA >LLOQ (29 IU/mL) at Week 48 (Chan 2016). In the complementary Phase 3 trial in HBeAg negative subjects, 6% of TAF recipients and 7% of those receiving TDF had HBV DNA >LLOQ (29 IU/mL) at Week 48 (Buti 2016). Importantly, the level of HBV replication as measured by HBV DNA in those treated with and without complete virologic response (ie, achieving/not achieving HBV DNA <LLOQ) has been predictive of progression of liver disease and risk of hepatocellular carcinoma (EASL 2017,

Paptheodoridis 2015, Yip 2020). Further, despite suppression of HBV DNA for extended periods of time, the template for ongoing viral replication, cccDNA, is not eliminated in most patients. As a result, off-treatment 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 virologic response (ie, HBV DNA <LLOQ) 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). Additionally, such deeper virologic responses may enable patients to achieve durable virologic and clinical outcomes following finite treatment duration.

ABI-H0731 is a novel, HBV core inhibitor (CI) discovered by Assembly Biosciences, which is being developed as a therapeutic agent for the treatment of CHB. ABI-H0731 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 ABI-H0731, when used in combination with currently approved HBV antivirals, has the potential to immediately improve current therapy for chronic HBV infection and ultimately provide patients with enhanced rates of SVR following a finite treatment period.

2.2. ABI-H0731

2.2.1. General Information

General information concerning ABI-H0731 is described in the Investigator's Brochure (IB).

2.2.2. Preclinical Pharmacology and Toxicology

Refer to the ABI-H0731 IB for a complete summary of the preclinical and toxicology studies performed to date.

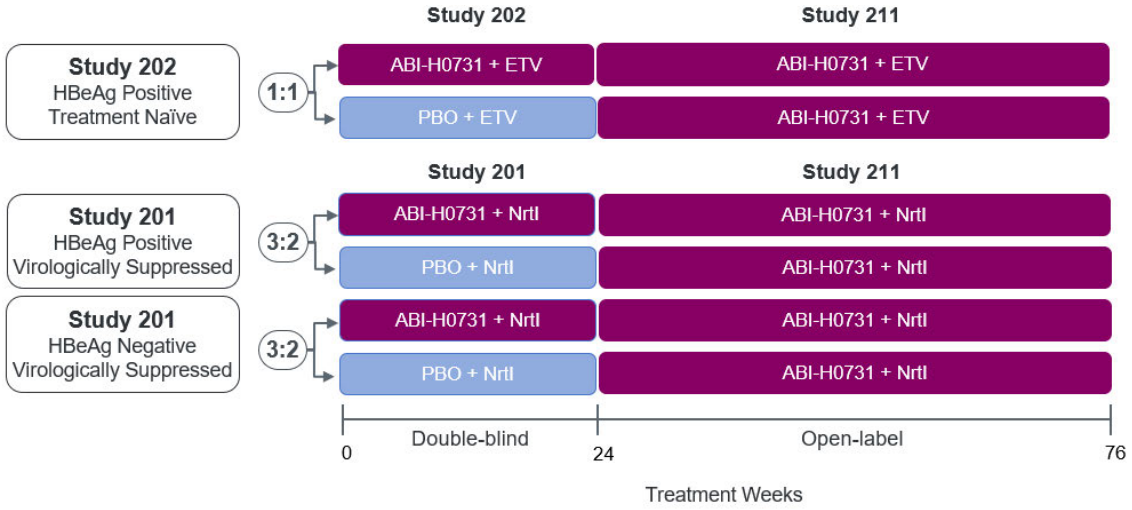
2.2.3. Clinical Studies with ABI-H0731

Summaries of the clinical studies completed to date and the Phase 2a studies, Study ABI-H0731-201 (Study 201) and Study ABI-H0731-202 (Study 202), are provided in the ABI-H0731 IB. In addition, the ongoing Phase 2a trial, ABI-H0731-211 is summarized below in Section 2.2.3.1.

2.2.3.1. Ongoing Study ABI-H0731-211 (Open-label Treatment Extension)

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 trial and receive open-label, 300 mg ABI-H0731+NrtI for up to an additional 76 weeks (Figure 1).

Figure 1: Study Design for Open-Label Extension (Study 211)



Abbreviations: ETV=entecavir; NrtI= nucleos(t)ide reverse transcriptase inhibitor of the HBV polymerase; also called nucleos(t)ide analogues or nucleos(t)ides; PBO=placebo.

2.2.3.2. Summary of Exposure

Overall, 92 subjects have been enrolled in ongoing open-label treatment extension Study 211. The overall summary of exposure based on a data cut date of 12 March 2020 is summarized in Table 1. For the purposes of this summary (unless otherwise noted), preliminary safety and efficacy data through Week 24 in Study 211 are presented. Through the first 24 weeks of Study 211, 90 (98%) of subjects who enrolled continued on study treatment, 1 subject discontinued study drug due to a Grade 1 AE or rash and 1 subject discontinued study drug due to virologic resistance in the setting of non-compliance with study drug.

Table 1: Duration of ABI-H0731+NrtI Treatment (Weeks) in Study 211 by Parent Study

	Study 202	Study 201	
	HBeAg	HBeAg	
Treatment duration in weeks	Positive (N=23)	Positive (N=43)	Negative (N=26)
Mean (SD)	50.6 (7.40)	45.1 (7.65)	40.3 (10.26)
Median	50.1	45.3	43.2
Minimum, maximum	36.4, 64.1	27.7, 61.6	1.1, 48.4

Source: Data on file.
Abbreviations: HBeAg=hepatitis B "e" antigen; N=Number of subjects in the Intent-to-Treat population; N=number of subjects in the Intent-to-Treat population; NrtI=nucleos(t)ide reverse transcriptase inhibitor of the HBV polymerase; SD=standard deviation
Duration of Treatment=(Date of Last Reported Exposure – Date of First Exposure in Study 211)/7

2.2.3.2.1. Summary of Safety

In Study 211, preliminary safety data are available for all subjects through 24 weeks of treatment with ABI-H0731+NrtI and demonstrate that ABI-H0731 300 mg daily continues to be generally well-tolerated in the open-label treatment extension trial (Table 2). No subjects discontinued treatment due to 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 were considered not related to study drug. Two subjects reported Grade 3 AEs. One subject experienced Grade 3 elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) which were 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; this was associated with a Grade 2 elevation in AST and improved to Grade 2 on continued treatment. No Grade 4 AEs or serious AEs (SAEs) were reported and no deaths occurred. Most treatment-emergent laboratory abnormalities were Grade 1. In addition to the Grade 3 elevations in ALT and AST reported as AEs, 1 subject had a Grade 3 prolonged prothrombin time and another subject had a Grade 3 elevation in AST (not reported as an AE). There were no Grade 4 laboratory abnormalities.

Table 2: Overall Summary of TEAEs Through Week 24 (Study 211)

Characteristic [n, (%)]	**ABI-H0731+NrtI (N=92)**
Any treatment-emergent AE[a]	44 (48)
Grade 1	27 (29)
Grade 2	15 (16)
Grade 3 or 4	2 (2)
Serious adverse events	0
TEAEs leading to study drug discontinuation[b]	0

Source: Data on file.
Abbreviations: AE=adverse event; DAIDS=Division of Aids; N=number of subjects in the Safety population; NrtI=nucleos(t)ide analog reverse transcriptase inhibitor; TEAE=treatment-emergent adverse event.
Adverse events were graded according to DAIDS criteria.
[a] Subjects with more than 1 TEAE were reported in the highest TEAE grade
[b] One non-TEAE (which began in Study 201) led to study drug discontinuation in Study 211.

2.2.3.2.2. Summary of Efficacy

This section summarizes the antiviral activity for subjects continuing treatment from Study 202 or Study 201 into Study 211 through 24 weeks of treatment. The preliminary analyses for Study 211 reported below are based on subject characteristics and the initial study into which they enrolled, with treatment-naïve subjects with HBeAg positive CHB originating from Study 202 and virologically-suppressed subjects with HBeAg positive or HBeAg negative CHB originating from Study 201.

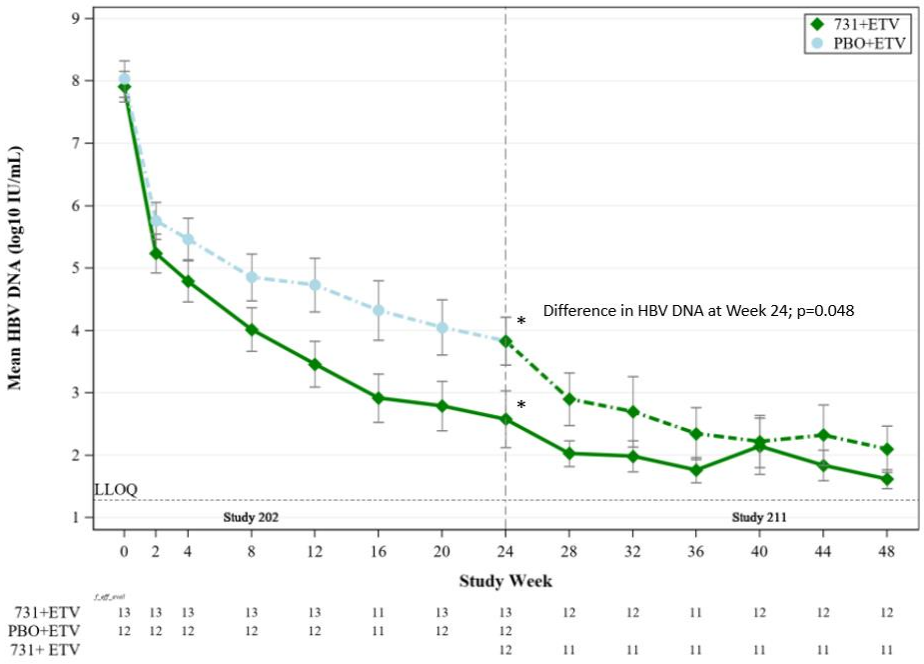
Treatment-Naïve Subjects with HBeAg Positive CHB in ABI-H0731-211 (Originating from Study 202)

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 2 and Figure 3. In both figures, each line represents a treatment group originating in Study 202 (either ABI-H0731+ETV or PBO+ETV) with green representing ABI-H0731+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 ABI-H0731+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 was a change in trajectory of HBV DNA and HBV pgRNA following the addition of ABI-H0731 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 ABI-H0731 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.

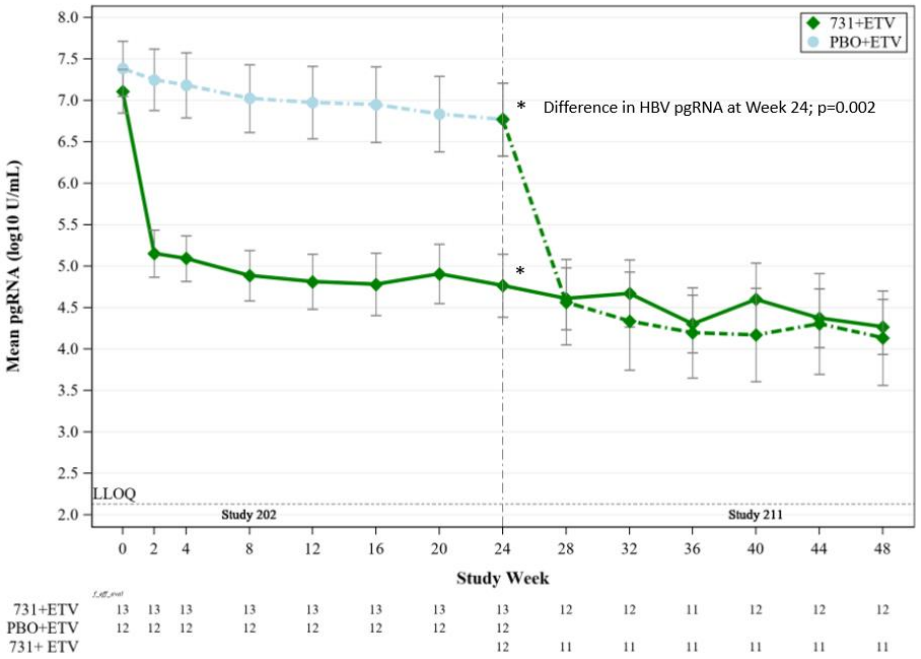
Although all subjects received ABI-H0731+ETV in Study 211, pooling data of data in this study is not appropriate given the differing treatments received during Study 202. The Study 202 treatment assignments (ABI-H0731+ETV and PBO+ETV) led to different starting points for markers of HBV infection at the beginning of Study 211. Consequently, the remainder of this section will focus on the subjects who received 48 weeks of ABI-H0731+ETV from the beginning of Study 202 through Week 24 in Study 211.

Figure 2: Mean Change from Baseline in HBV DNA for Treatment-Naïve Subjects with CHB (Study 202/211)



Source: Data on file.
Abbreviations: 731=ABI-H0731, CHB=chronic hepatitis B infection; ETV=entecavir; HBV=hepatitis B virus; IU=international units; PBO=placebo.
Includes subjects in the Intent-to-Treat population. HBV DNA LLOQ=20 IU/mL (1.20 $\log_{10}$ IU/mL).

Figure 3: Mean Change from Baseline in HBV pgRNA for Treatment-Naïve Subjects with CHB (Study 202/211)



Source: Data on file.
Abbreviations: 731=ABI-H0731, CHB=chronic hepatitis B infection; ETV=entecavir; HBV=hepatitis B virus; LLOQ=lower limit of quantification; PBO=placebo; pgRNA=pregenomic RNA; U=units.
Includes subjects in the Intent-to-Treat population. HBV pgRNA LLOQ 135 U/mL (1.54 log_{10} U/mL).

For subjects who have received 48 cumulative weeks of ABI-H0731+ETV in Study 202/211, Table 3 summarizes the mean (minimum, maximum) absolute value and change from Baseline in HBV DNA (COBAS® TaqMan; LLOQ=20 IU/mL) and HBV pgRNA (Assembly 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 ABI-H0731+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} IU/mL which declined to 4.3 (2.1, 5.8) log10 IU/mL after 48 weeks of treatment with ABI-H0731+ETV, representing a mean (minimum, maximum) change of -2.8 (-4.9, -1.9) log_{10} IU/mL. The proportion of subjects in this group who had HBV pgRNA <LLOQ was 0% at Baseline to 8% (1/12) at Week 48.

Table 3: HBV DNA and pgRNA for Treatment-Naïve Subjects with CHB by Week of Treatment with ABI-H0731+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)

Mean 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)
Mean 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)
Mean 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)
Mean change from Baseline (min, max)	-6.3 (-7.2, -4.2)	-2.8 (-4.9, -1.9)

Source: Study 211 Trends Analysis Table 4.1.1, 4.2.
N = Number of subjects in the Intent-to-Treat population. HBV DNA LLOQ = 20 IU/mL (1.30 $\log_{10}$ IU/mL); HBV pgRNA LLOQ 135 U/mL (2.13 $\log_{10}$ U/mL).
Abbreviations: ETV = entecavir; H; HBV = hepatitis B virus; IU = international units; Min = minimum; Max = maximum; pgRNA = pregenomic RNA; U = units.
[a]Subjects who received ABI-H0731+ETV in Study 202

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 4 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 Log10 IU/mL, -0.8 $\log_{10}$ kU/mL and -0.2 $\log_{10}$ IU/mL for HBeAg, HBcrAg and HBsAg, respectively.

Table 4: HBV Antigens for Treatment-Naïve Subjects with CHB by Week of Treatment with ABI-H0731+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)	-0.50 (-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)

Source: Study 211 Trends Analysis Tables 4.3, 4.4, 4.5
HBeAg LLOQ = 0.11 IU/mL (-0.96 $\log_{10}$ IU/mL); HBcrAg LLOQ = 1 kU/mL (0 $\log_{10}$ kU/mL); HBsAg LLOQ = 0.05 IU/mL (-1.30 $\log_{10}$ IU/mL).
Abbreviations: CHB=chronic hepatitis 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; Min = minimum;

Max = maximum; N=number of subjects in the Intent-to-Treat population.
[a]Subjects who received ABI-H0731+ETV in Study 202

Virologically-suppressed Subjects with HBeAg Positive or HBeAg Negative CHB in ABI-H0731-211 (Originating from Study 201)

Virologically-suppressed subjects with CHB 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 high sensitivity Assembly semi-quantitative polymerase chain reaction assay with a LOD=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 ABI-H0731+NrtI in Study 201/211.

To be eligible for participation in the Study 201, subjects must have had HBV DNA ≤ LLOQ (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 CHB on standard of care NrtI treatment who had HBV DNA <20 IU/mL still harbored low levels of infectious virus (Burdette 2019). Following 48 weeks of treatment with ABI-H0731+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 ABI-H0731 to NrtI results in deeper virologic suppression in virologically-suppressed subjects with HBeAg positive or HBeAg negative CHB who have received chronic NrtI therapy for some time.

Table 5: HBV DNA for Virologically-Suppressed Subjects with CHB by Week of Treatment with ABI-H0731+NrtI (Study 201/211)

	HBV DNA Subjects 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)

Source: Study 211 Table 7
HBV DNA LOD=5 IU/mL.
Abbreviations: HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; N=number of subjects in Intent-to-Treat population; NrTI=nucleos(t)ide reverse transcriptase inhibitor of the HBV polymerase; TD=target detected; TND = target not detected.
[a] Subjects who received ABI-H0731+NrtI in Study 201

The virologically-suppressed subjects with CHB 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 high sensitivity Assembly RT-qPCR assay with LLOQ <35 U/mL. Table 6 summarizes the absolute value, change from Baseline in HBV pgRNA and proportion of subjects with HBV pgRNA <LLOQ by week of treatment. In HBeAg positive subjects, the mean (minimum, maximum) Baseline HBV pgRNA was 3.6 (1.5, 6.1) $\log_{10}$ IU/mL which decreased to 1.9 (1.5, 4.6) $\log_{10}$ IU/mL after 48 weeks, representing a mean (minimum, maximum) change of -1.7 (-3.7, 0) $\log_{10}$ IU/mL. Compared to HBeAg positive subjects, HBV pgRNA was lower in HBeAg negative subjects and showed less change over 48 weeks of treatment with ABI-H0731+NrtI. In HBeAg negative subjects, the mean (minimum, maximum) Baseline HBV pgRNA was 1.7 (1.5, 2.6) $\log_{10}$ IU/mL which decreased to 1.5 (1.5, 1.6) $\log_{10}$ IU/mL at

Week 48. In both HBeAg positive and negative subjects, the proportion of subjects <LLOQ generally increased over time during treatment with ABI-H0731+NrtI.

Table 6: HBV pgRNA for Virologically-Suppressed Subjects with CHB by Week of Treatment with ABI-H0731+NrtI (Study 201/211)

Week of treatment	HBV pgRNA log_{10} U/mL	
	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)
<LLOQ, n (%)	4 (15)	13 (81)
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)	-0.1 (-1.0, 0)
<LLOQ, n (%)	15 (56)	16 (100)
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)	-0.1 (-1.0, 0)
<LLOQ, n (%)	16 (59)	15 (94)
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)	-0.1 (-1.0, 0.3)
<LLOQ, n (%)	16 (59)	11 (79)
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)	-0.1 (-1.0, 0.1)
<LLOQ, n (%)	20 (77)	13 (93)

Source: Trends Analysis Study 211 Table 4.2
HBV pgRNA LLOQ = 35 U/mL.
Abbreviations: CHB=chronic hepatitis B infection; HBeAg = hepatitis B e antigen; HBV=hepatitis B virus; LL0Q=lower limit of quantification; Max=maximum; Min = minimum; N=number of subjects in Intent-to-Treat population; NrtI= nucleos(t)ide reverse transcriptase inhibitor of the HBV polymerase; pgRNA = pregenomic RNA; U=units.
[a]Subjects who received ABI-H0731+NrtI in Study 201

The initial results from the ongoing Phase 2a, open-label, treatment extension study, Study 211 demonstrate that ABI-H0731 administered in combination with NrtI has an efficacy benefit over NrtI therapy alone, leading to more complete viral inhibition as measured most directly by HBV DNA and HBV pgRNA, and are consistent with results of Study 201 and Study 202 presented in the IB.

2.3. Study Rationale

While standard of care NrtIs targeting the HBV, polymerase are able to suppress HBV DNA in most patients, around 30% of HBeAg positive patients and up to 10% of HBeAg negative patients are not able to reach HBV DNA <LLOQ by treatment Week 48. Treatment intensification approaches are needed to increase the proportion of patients able to achieve complete viral suppression (ie, proportion of subjects achieving HBV DNA <LLOQ at Week 48). The HBV core protein is involved in multiple steps in the HBV life cycle, including both viral replication and the establishment of new cccDNA (Belloni 2013; Levrero 2009). Inhibition of HBV core protein represents a novel therapeutic strategy

for the treatment of CHB (Yang 2019). Analyses of Phase 2a studies, including ongoing open-label study, Study 211, demonstrate that treatment-naïve and virologically suppressed subjects treated with ABI-H0731 + NrtI, compared to those treated with NrtI alone, achieve deeper declines in HBV DNA (Section 2.2.3).

Based on these data, the addition of ABI-H0731 to NrtI therapy may increase the proportions of subjects with partial virologic suppression able to achieve complete viral suppression, a status that has been shown to correlate with long-term clinical outcomes (EASL 2017, Paptheodoridis 2015, Yip 2020). The present Phase 2a study (ABI-H0731-205) will explore the safety of ABI-H0731 when added to NrtI and evaluate the antiviral activity of the combination as measured by the proportions of subjects achieving HBV DNA <LLOQ at Week 48. At Week 48 all subjects will receive ABI-H0731+NrtI through Week 96. Following completion of treatment with ABI-H0731 in this study, eligible subjects will undergo follow-up evaluation while continuing standard of care therapy with NrtI until Week 120.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

- To evaluate the safety and tolerability of ABI-H0731 when administered in combination with NrtI in subjects with CHB
- To evaluate the effect of the addition of ABI-H0731 to NrtI in fully suppressing HBV DNA in subjects with CHB

3.1.2. Secondary Objectives

- To evaluate the effect of the addition of ABI-H0731 to NrtI in reducing HBV pgRNA levels in subjects with CHB
- To evaluate the effect of the addition of ABI-H0731 to NrtI in reducing HBV antigens (ie, HBeAg, HBcrAg, and HBsAg) in subjects with CHB
- To evaluate the effect of the addition of ABI-H0731 to NrtI on normalization of ALT in subjects with abnormal ALT
- To evaluate the pharmacokinetics (PK) of ABI-H0731 and NrtI in subjects with CHB
- To evaluate the emergence of resistance to ABI-H0731 when administered in combination with NrtI

3.1.3. Exploratory Objectives:

- To assess the relationship between immunological and/or viral biomarkers with virologic and/or clinical outcomes
- For subjects who provide an optional pharmacogenomic sample, to evaluate the potential contribution of host genomics to clinical or virologic outcomes and/or drug disposition

3.2. Study Endpoints

3.2.1. Primary Endpoint

- Proportion of subjects with AEs, premature treatment discontinuation, and abnormal laboratory results
- Proportion of subjects with HBV DNA <LLOQ at Week 48 for PBO+NrtI and ABI-H0731+NrtI

3.2.2. Secondary Endpoints

- Mean change in $\log_{10}$ HBV DNA from Baseline at each timepoint
- Proportion of subjects with HBV DNA is <LOQ at each timepoint
- Proportion of subjects with HBV DNA is <LOD (TND) at each timepoint
- Mean change in $\log_{10}$ HBV pgRNA from Baseline at each timepoint

- Proportion of subjects with HBV pgRNA <LLOQ at each timepoint
- Mean change in $\log_{10}$ serum viral antigens (ie, HBeAg, HBcrAg, and HBsAg) from Baseline at each timepoint
- Proportion of subjects with abnormal ALT at Baseline who have normal ALT at each timepoint
- Analysis of ABI-H0731 and NrtI drug concentrations:
- PK on study visit days of ABI-H0731 on ABI-H0731+NrtI
- PK on study visit days of NrtI on PBO+NrtI and ABI-H0731+NrtI
- The incidence of HBV variants with reduced susceptibility to ABI-H0731

3.2.3. Exploratory Endpoints

- Proportion of subjects with loss of serum viral antigens (defined < LLOQ) in HBeAg, HBcrAg, and HBsAg
- Proportion of subjects with HBeAg seroconversion (defined as loss of HBeAg and appearance of HBeAb) or HBsAg seroconversion (defined as loss of HBsAg and appearance of HBsAb) at each timepoint
- Immunologic outcomes, including changes in humoral and cellular immunity to PBO+NrtI and ABI-H0731+NrtI
- Pharmacogenomic correlations may be performed with clinical or virologic outcomes for subjects who provide optional informed consent
- For subjects who provide an optional pharmacogenomic sample, to evaluate known gene variants and ABI-H0731, its metabolites, and PK and/or safety

4. STUDY PLAN

4.1. Study Design

This is a Phase 2a, multi-center, randomized, single-blind, PBO-controlled study, evaluating the safety, antiviral activity, and PK of ABI-H0731 administered in addition to standard of care NrtI in subjects with CHB who have not achieved adequate virologic suppression of HBV DNA <LLOQ on NrtI alone. For this study, HBV DNA is analyzed by COBAS TaqMan® Version 2.0 at the central laboratory (LLOQ=20 IU/mL).

The study will be conducted at approximately 10 study centers worldwide. Approximately 40 eligible subjects will be randomized in a 1:1 ratio to the treatment groups shown in the study overview presented in Figure 4.

Study investigational drugs, ie, 300 mg (3×100 mg tablets) ABI-H0731 or matching PBO (3 tablets) and subjects' background NrtI therapy will be administered orally, once daily (QD). Group 1 will receive ABI-H0731+NrtI for 96 weeks, Group 2 will receive PBO+NrtI for 48 weeks followed by ABI-H0731+NrtI for 48 weeks until Week 96. All subjects will continue to receive NrtI alone during the 24-week follow-up period from Week 96 through Week 120.

Treatment assignments will be stratified by the concurrent NrtI administered (ie, ETV) versus tenofovir (alafenamide versus [TAF] or disoproxil fumarate [TDF]) and HBV DNA (HBV DNA ≥500 IU/mL versus <500 IU/mL) during the Screening visits. The study will enroll up to 75% subjects on ETV. Safety, antiviral activity, and PK will be assessed during treatment and the 24-week follow-up period.

Figure 4: Study Overview

NrtI=nucleos(t)ide reverse transcriptase inhibitor; PBO=placebo; QD=once daily [administration]

The schedule of study procedures is described in Section 7 and presented in tabular form in Appendix 1. A detailed review of the planned PK analyses is provided in Section 7.10.

4.2. Dose Justification

In the Phase 1 clinical studies, ABI-H0731 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 CHB, ABI-H0731 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 CHB. Phase 2 studies, Study 201, Study 202 and Study 211, demonstrate that 300 mg ABI-H0731 administered QD in combination with NrtI for 48 weeks is well-tolerated and leads to continued reductions in HBV DNA and HBV pgRNA. It is expected that this regimen will be safe, well tolerated and demonstrate improved HBV suppression in subjects with CHB compared to standard of care NrtI therapy. The cumulative safety, tolerability, and antiviral activity data generated to date support the conduct of the proposed study.

4.3. Study Treatments

This is a Phase 2a, multicenter, randomized, single-blind, PBO-controlled study, evaluating the safety, antiviral activity, and PK of ABI-H0731+NrtI in subjects with CHB who are not suppressed to HBV DNA <LLOQ on NrtI alone. See Section 4.1 for a detailed summary of the study design.

Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups. Group 1 will receive ABI-H0731+NrtI for 96 weeks, Group 2 will receive PBO+NrtI for 48 weeks followed by ABI-H0731+NrtI for 48 weeks until Week 96. All subjects will continue to receive NrtI alone during the 24-week follow-up period from Week 96 through Week 120.

Both ABI-H0731 (3×100 mg tablets) or matching PBO (3 tablets) should be taken together at approximately the same time each day as the NrtI. ABI-H0731 and matching PBO may be administered with or without food, depending on the NrtI with which they are administered. Entecavir should be administered on an empty stomach (ie, at least 2 hours after a meal and 2 hours before the next meal), whereas TDF or TAF may be administered either with or without food. Further information is provided in the respective package insert.

On study visit days, ABI-H0731 or matching PBO will be administered in the clinic; subjects will self-administer assigned treatment on all other days. On study visit days which include PK sample collection (Table 7), subjects will administer ABI-H0731 or PBO in the clinic, and if possible, also administer NrtI in the clinic and study personnel will document the time of study drug administration in subject's medical record. Subjects will be required to record the dates and times of each dose of ABI-H0731 or PBO and NrtI they self-administer in the dosing diary provided to them. Additional information concerning study treatments and the management of missed or incorrect doses is provided in the Study Pharmacy Manual.

4.4. Duration of Treatment

All subjects will receive their randomized treatment in a blinded manner for up to 96 weeks. Following completion of the assigned treatment, all subjects will continue to receive NrtI during the 24-week follow-up period. Following completion of the 24-week follow-up period, subjects will exit the study and resume standard of care oversight by their physicians.

5. POPULATION

5.1. Number of Subjects

Approximately 40 male or female subjects between the ages of 18 and 65 will be enrolled in the study. Subjects will have HBeAg positive or negative CHB, no evidence of cirrhosis or end-stage liver disease and will not be adequately suppressed on NrtI therapy.

5.2. Inclusion Criteria

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

1. Willing and able to provide informed consent
2. Male or female between the ages 18 and 65 years (inclusive)
3. Body mass index (BMI) 18 to 36 kg/m2 and a minimum body weight of 45 kg (inclusive)
4. Female subjects of child-bearing potential (Appendix 4) must be non-pregnant and have a negative serum pregnancy test at Screening and a negative urine pregnancy test predose on Day 1.
5. HBeAg positive or HBeAg negative CHB Chronic hepatitis B infection, defined as HBV infection documented for ≥12 months.
6. HBV DNA >LLOQ (using a commercially available assay with LLOQ=20 IU/mL) from 2 samples drawn on 2 separate occasions during the Screening period approximately 10-14 days apart. If the results from these 2 samples indicate a decline in HBV DNA then a third sample will be collected at least a week later for Sponsor review and approval prior to randomization.
7. On a stable NrtI regimen (ETV, TDF, or TAF) for more than 12 months, without evidence of resistance and while known to be adherent to therapy
8. Lack of cirrhosis or advanced liver disease as documented by the following:
    - Liver biopsy results of METAVIR F0-F3 (absence of cirrhosis) within 1 year of Screening

      OR
    - Fasting FibroScan® ≤14 kPa within 3 months of Screening (including the Screening visit) or other Sponsor-approved hepatic imaging method within 6 months of Screening indicating lack of cirrhosis (F0 to F3 or equivalent).

      If the results from both 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.
9. Agreement to comply with protocol-specified contraceptive requirements (Refer to Appendix 4).
10. Agreement to abstain from alcohol abuse (defined as alcohol consumption exceeding 2 standard drinks per day on average (1 standard drink=14 grams of alcohol) and the use of illicit substances from Screening through the duration of the study

11. In good general health, except for CHB (in the opinion of the Investigator)
12. Have the ability to take oral medication and, in the opinion of the Investigator, be willing to adhere to study treatment

5.3. Exclusion Criteria

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

1. Current or prior treatment for CHB with
    - Lamivudine, telbivudine or adefovir (any duration)
    - HBV core inhibitor (any duration)
    - Previous treatment with an investigational agent for HBV infection
2. Presence of substitutions in the HBV polymerase coding region which may confer reduced susceptibility to NrtIs (Appendix 2)
3. Co-infection with human immunodeficiency virus (HIV), hepatitis A virus (HAV) hepatitis C virus (HCV), hepatitis E virus (HEV), or hepatitis D virus (HDV)
4. Females who are lactating, or wish to become pregnant during the course of the study
5. History or evidence of advanced liver disease 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
6. 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
7. 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 CHB; 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
8. History of HCC
9. A 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
10. History or presence at Screening of electrocardiogram (ECG) abnormalities deemed clinically significant in the opinion of the Investigator.
11. History of hypersensitivity or idiosyncratic reaction to any components or excipients of the investigational drug or PBO formulation
12. History of any significant food or drug-related allergic reactions such as, anaphylaxis or Stevens-Johnson syndrome

13. The following exclusionary laboratory results at the Screening and Baseline visit:
    - Platelet count <100,000/mm^3
    - Albumin <lower limit of normal
    - Total bilirubin >1.2 × upper limit of normal (ULN) unless known Gilbert's syndrome; subjects with Gilbert's syndrome are eligible for study participation if the direct bilirubin is within the normal range
    - Direct bilirubin >1.2 × ULN
    - ALT >10 × ULN
    - Serum alpha fetoprotein (AFP) ≥100 ng/mL. If AFP at Screening is >ULN but <100 ng/mL, the subject is eligible if a hepatic imaging study prior to initiation of study drug reveals no lesions indicative of possible HCC.
    - International Normalized Ratio >1.5 × ULN
    - GFR <50 mL/min/1.73 m2 by CKD-EPI equation (Levey 2009)
    - Any other laboratory abnormality deemed clinically significant by the Sponsor or the Investigator
14. Subjects receiving prohibited concomitant medications , grapefruit juice, or prohibited herbal/over-the-counter medications (Section 6.4.1) within 7 days or 5 half-lives (if known), whichever is longer, prior to administration of the first dose of study drug and for the duration of the study period.
15. 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. However, subjects receiving any prior investigational therapy for HBV, will be excluded.
16. Subjects who have received, in the previous 4 weeks, a treatment likely to alter the immune response (intravenous immunoglobulins, blood-derived products, or high -dose steroids, or other immunosuppressants).

6. INVESTIGATIONAL MEDICAL PRODUCTS

6.1. Randomization, Blinding and Treatment Codes

6.1.1. Randomization

Randomization of eligible subjects to their respective treatment assignments will be performed centrally using an Interactive Response Technology (IRT) system. Following successful completion of Screening assessments and confirmation of subject eligibility, site personnel will enter the subject specific information in the IRT system and receive a subject number at the Screening visit. Upon confirmation of subject eligibility on Day 1, the IRT system will assign eligible subjects in a 1:1 ratio to receive either 300 mg ABI-H0731+NrtI for 96 weeks (n=20) or PBO+NrtI for 48 weeks followed by 300 mg ABI-H0731+NrtI for 48 weeks (n=20). Individual treatment assignments will be stratified by the concurrent NrtI administered (ie, ETV versus TDF or TAF) and HBV DNA (HBV DNA ≥500 IU/mL versus <500 IU/mL). The study will enroll approximately 75% subjects receiving ETV. Additional information on the use of the IRT is provided in the IRT user manual.

6.1.2. Blinding

Study subjects, Investigators and other site personnel administering the study drug, performing the clinical assessments and handling data on the study subjects, will be blinded to individual subject treatments assignments (ie, PBO+NrtI or ABI-H0731+NrtI) throughout the duration of the study. To support maintenance of the study blind, HBV pgRNA results will not be provided to the study subjects, Investigators or other site personnel until completion of the study.

A limited internal Sponsor team will be unblinded to individual subjects' treatment assignments throughout the study to ensure timely analysis of any emergent safety/tolerability issues, and completion of the prespecified safety data reviews. The unblinded individuals will be identified in the Statistical Analysis Plan (SAP) along with their specific roles and responsibilities. All other Sponsor personnel will remain blinded until completion of the study. The contract research organization's (CRO's) Medical Monitor may be unblinded to individual subjects' treatment assignments where required for assessment of emergent safety/tolerability issues.

6.1.3. Unblinding in Emergency Situations

Requests can be made to unblind an individual study subject for emergencies or urgent situations. Prior to unblinding, and if the situation permits, the Investigator should first contact the Sponsor and/or authorized Medical Monitor to discuss the case. However, the final decision whether to unblind a subject will be the Investigator's decision, and the Investigator need not wait for the unblinding permission to be granted by the Sponsor/CRO Medical Monitor in emergency situations where identification of the individual treatment assignment is required for the immediate medical management of the subject. Access to the unblinded treatment assignment should be limited to the minimum number of people required for emergent management of the subject. The actual treatment assignment must not be disclosed to the subject and/or other study personnel, including site monitors and office staff; nor should there be any written or verbal disclosure of the code in the subject's study documents.

The request for unblinding should include the protocol number, site number, subject number, treating Investigator's contact info, a detailed reason for the unblinding, and date the information is needed. All

key correspondence between the requestor and Sponsor or CRO Medical Monitor should be saved in the Trial Master File.

The IRT system will be used as the unblinding tool. In the event that an individual subject's treatment assignment is unblinded, the date and reason that the blind was broken must be recorded in the source documentation. Any treatment assignments that are unblinded must be immediately reported to the CRO Medical Monitor and the Sponsor. Code-break IRT access is given to the Investigator/designated person at the site and to the designated Medical Monitor(s) for the study.

Following unblinding, the subject will discontinue ABI-H0731 or matching PBO and continue with the study follow-up assessments.

6.2. Description and Handling of ABI-H0731 and Matching Placebo (Investigational Medicinal Product)

The investigational medicinal products (IMPs) to be used in this study are ABI-H0731 and matching PBO.

6.2.1. Formulation

The drug product is a tablet containing ABI-H0731 formulated in a solid dispersion which is produced by spray drying a solution of ABI-H0731 with an inert polymer HPMCP HP-55. This spray-dried dispersion has been mixed with standard pharmaceutical excipients, such as microcrystalline cellulose, calcium phosphate, croscarmellose sodium, and magnesium stearate, and compressed into a tablet containing approximately 100 mg of ABI-H0731, manufactured according to Good Manufacturing Practices (GMP).

6.2.2. Packaging and Labeling

ABI-H0731 tablets and matching PBO tablets are packaged in high density polyethylene bottles fitted with child-resistant screw caps, induction sealed and shipped to sites under ambient conditions.

The IMP will be labelled in accordance with US Food and Drug Administration (FDA) requirements and European Union GMP Annex 13, Investigational Medicinal Products. Additional local labelling requirements in countries of study conduct will be incorporated in the IMP label(s).

6.2.3. Storage and Handling

Bottled drug product at the study site should be stored at controlled room temperature (15 °C to 30 °C [59 °F to 86 °F]) in a secure, locked location at the sites, accessible only to study personnel.

6.3. Description and Handling of NrtI (Non-Investigational Medicinal Product)

All subjects will enter the study receiving standard-of-care NrtI monotherapy of either ETV, TDF or TAF. The NrtIs used by subjects in this study are designated as non-investigational medicinal products (NIMP) (background therapy). Subjects taking a NrtI other than ETV, TDF, or TAF are excluded from study participation. Subjects will continue to administer their same standard-of-care NrtI used prior to and during Screening and continue for the entire duration of the study including follow-up. If a subject's access to concurrent standard of care NrtI therapy should change while on-study, then the Investigator should first contact the Sponsor and/or authorized Medical Monitor to discuss the case-

Details describing the packaging, labelling, storage and handling of the NrtI are described in the respective package insert.

6.4. Prior and 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 administered to a study subject during the conduct of the clinical trial. For randomized subjects, concomitant medications are discouraged, unless they are prescribed by the Investigator for treatment of an emergent medical event occurring during the course of the study. No concomitant procedures will be performed during the study unless approved by the Investigator.

All concomitant medications taken from the date the Informed Consent Form (ICF) is signed, through end of the study (completion of the follow-up period) must be recorded in the subject's source documentation. This information should include the name of the medication or treatment, the dose and regimen, the start and stop dates, and the indication for which the concomitant medication was administered.

6.4.1. Prohibited Concomitant Therapy

Systemic (oral, injectable, or implanted) hormonal birth control is not permitted as an acceptable means of contraception for female subjects of child-bearing potential. Additional details on acceptable means of contraception are provided in Appendix 5.

Since ABI-H0731 is a weak inhibitor of cytochrome P450 (CYP) 2C9, concomitant use with narrow index CYP2C9 substrates such as warfarin and phenytoin are prohibited. Use of other CYP2C9 substrates should be avoided. Those taking sulfonylureas for controlled diabetes mellitus should monitor blood sugar levels and adjust dosage as appropriate. To the extent possible, other medications with narrow therapeutic indices should be avoided.

The route of elimination in humans is not fully understood so inhibitors and inducers of CYP3A4 should be avoided. Refer to Appendix 5 for details on prohibited CYP2C9 substrates as well as inhibitors and inducers of CYP3A4.

Provisions regarding concomitant medications described in the respective NrtI product labeling must also be followed during the study through the end of the follow up period.

The designated Medical Monitor may be consulted for any questions regarding acceptable or prohibited concomitant medication use during the study. As previously described, concomitant medications, over-the-counter medications, and supplements must be recorded in the subject's source documentation.

6.5. Drug Accountability

Regulatory requirements stipulate accounting of all IMP (ie, ABI-H0731 and matching PBO) received by the study site. Records of IMP disposition must include the date received by the site, date administered, quantity administered, and the subject to whom the IMP was administered. The Investigator is responsible for the accountability of all IMP at his or her site. This includes all used and unused IMP bottles and unused IMP.

Each 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 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 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 monitoring visits. The site pharmacist or designated staff member will keep accurate records of IMP dispensation routinely during the study (Section 7; Appendix 1).

NrtI accountability will be captured by the subjects in dosing diaries.

6.6. Study Drug Administration and Compliance

Subjects participating in this study will receive ABI-H0731 or PBO in addition to standard-of-care treatment with a NrtI. ABI-H0731 (3 × 100 mg tablets) or PBO tablets should be administered as a single dose, once daily. Subjects will self-administer assigned treatment and should be instructed to take ABI-H0731 or PBO at the same time of the day with the possible exception of in-clinic visit days. To monitor IMP compliance and to facilitate IMP accountability at the study site, subjects will be required to record each dose/quantity of tablets taken of ABI-H0731 or matching PBO in a dosing diary provided to the subject at visits shown in the Schedule of Assessments (Appendix 1). Subjects will also be asked to return used bottles and any unused IMP at study visits for accountability and compliance assessment at each visit. Returned IMP will be counted and reconciled against the diary entries by study site personnel preferably in the presence of the subject. Subjects who forget to return IMPs at a given visit will be asked to return them at the next study visit. The IMP dosing dates and time for doses given at the PK collection study visits will be entered in the subject's eCRF.

For assessment of compliance to the NrtI (NIMP) regimen, subjects will be provided dosing diaries at each study visit and will be asked to record the dosing dates, times, and quantity for NrtI administration. The dosing dates and time of NrtI at the PK collection study visits will be entered in the subject's eCRF by study site personnel.

Additional information concerning study treatments and the management of missed or incorrect doses is provided in the Study Pharmacy Manual.

6.7. Return or Disposal of Study Drug

Procedures for the return of IMP or provisions for onsite destruction (where approved prospectively by the Sponsor) are described separately in the Study Pharmacy Manual.

7. STUDY PROCEDURES

The schedule of assessments to be conducted in the study is provided in tabular form in Appendix 1.

7.1. 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 6.1.1. Protocol waivers will not be granted.

7.1.1. 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 (if applicable).

Individuals who do not meet the protocol eligibility criteria for participation in this study (ie, screen failures) may not be rescreened, however, a single retest for a laboratory parameter(s) is permitted if there is considered to be 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).

7.2. Screening Assessments (Day -45 to Day -1)

It is recommended, though not mandated, that invasive procedures, such as a liver biopsy (if required) are not conducted until it has been determined that the subject is broadly eligible for study participation.

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

- Obtain written informed consent
- A separate consent is required for the subject to provide an optional pharmacogenomic sample
- Record demographics and medical history, including HBV history
- Measure height and body weight
- 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 (as required per inclusion criteria, ie, fasting FibroScan)
- Laboratory analyses (additional details are provided in the Laboratory Manual):

- Safety labs: chemistry, hematology, coagulation, serum AFP, follicle-stimulating-hormone (FSH) (females only), HbA1c, serum pregnancy test for females of child-bearing potential only, urinalysis, urine drug test (Appendix 2)
- Virology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBsAb, HBeAb, sample for HBV sequencing and HBV nucleic acids, HIV Ab, HCV Ab, HDV Ab, HAV (immunoglobulin M [IgM]), HEV (IgM) (see Appendix 2)
    - A second HBV DNA sample will be drawn approximately 10 to 14 days after the initial Screening Visit. If the results from the 2 HBV DNA samples indicate a numeric decline in HBV DNA during the Screening assessment period, then a third sample at least a week later will be collected for Sponsor review and approval prior to randomization.
- HBV sequencing: a blood sample for sequencing of the HBV polymerase coding region will be collected and analyzed. The presence of specific base substitutions which may confer reduced susceptibility to NrtIs would exclude subjects from participating in the study (see Appendix 2)
- HBV immunology: whole blood sample for collection of peripheral blood mononuclear cells (PBMCs) followed by serum cytokine sample collection for immunologic testing at selected sites only (Appendix 2)

7.3. Day 1

The following assessments must be completed at Day 1:

- Update medical history, including HBV history
- Measure body weight
- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated)
- 12-lead ECG
- Review concomitant medications
- Review AEs
- Confirm subject eligibility
- Complete randomization
- Laboratory analyses (additional details are provided in the Laboratory Manual):
- Safety labs: chemistry, hematology, coagulation, urine pregnancy test for females of child-bearing potential only, urinalysis, urine drug test (see Appendix 2)
- Virology: HBV genotype, HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb, HBeAb, sample for HBV sequencing and HBV nucleic acids (see Appendix 2)
- Immunology (For subjects who provided PBMCs at Screening at selected sites ONLY): PBMCs collection followed by serum cytokine sample and PaxGene® DNA and PaxGene® RNA sample collection (see Appendix 2).

- PK samples: predose samples for ABI-H0731 or PBO and NrtI. Postdose samples for ABI-H0731 and NrtI between 2 and 4 hours following study drug administration (see Section 7.10)
- Pharmacogenomic Sample: Optional and only collected in subjects who provide additional informed consent.
- Dispense dosing diary
- ABI-H0731 or PBO dispensation
- ABI-H0731 or PBO administration
- NrtI administration

7.4. Study Weeks 2 Through 48

The following assessments are performed at Study Weeks 2, 4, 8, 12, 16, 20, 24 and then every 4 weeks thereafter through Week 48 (inclusive) unless otherwise indicated. Subjects who discontinue treatment before Week 48 should immediately undergo the assessments listed for the Premature Termination visit and then continue the scheduled follow-up assessment. A visit window of ±3 days is applied to each visit through Week 44. A visit window of -3 days is applied to Week 48. (Appendix 1)

- Measure body weight (Week 48 only)
- Vital signs (temperature, heart rate, respiration rate, and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated; Week 48 only)
- Symptom-directed physical examination (not at Week 48)
- 12-lead ECG (Weeks 12, 24, 36, and 48 only)
- Review concomitant medications
- Review AEs
- Laboratory analyses (additional details are provided in the Laboratory Manual):
- Safety labs: chemistry, hematology, coagulation (not at Week 2), urinalysis (not at week 2), urine pregnancy test for females of child-bearing potential only (see Appendix 2)
- Virology: HBV DNA, HBV pgRNA, HBsAg (not at Week 2), HBeAg (not at Week 2), HBcrAg (not at Week 2), HBsAb and HBeAb (Weeks 12, 24, and 48 only), sample for HBV sequencing and HBV nucleic acids (Weeks 20 to 44 and Week 48) (see Appendix 2)
- Immunology (For subjects who provided PBMCs at Screening at selected sites ONLY): PBMCs collection followed by serum cytokine sample collection at Weeks 2, 4, 12, 24, 36, and 48 (see Appendix 2)
- PK samples: samples for ABI-H0731 or PBO and NrtI may be collected from 2 to 4 hours postdose on Day 1, between 30 min to 2 hours postdose at Weeks 2, 8, 12, 24, and 28, and between 4 and 6 hours postdose at Weeks 16 and 20. Predose samples for ABI-H0731 or PBO and NrtI will be collected at Week 4, and Week 48 only (see Section 7.10)
- Review dosing diary and assess ABI-H0731 or PBO accountability

- ABI-H0731 or PBO dispensation
- ABI-H0731 or PBO administration
- NrtI administration
- Dispense dosing diary

7.5. Study Weeks 52 to 96

The following assessments are performed every 4 weeks unless otherwise indicated. A visit window of ±5 days is applied from Weeks 52 through 96.

- Measure body weight (Week 96 only)
- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated; Week 96 only)
- Symptom-directed physical examination (Weeks 52 to 92only)
- 12-lead ECG (Week 96 only)
- Review concomitant medications
- Review AEs
- Laboratory analyses (additional details are provided in the Laboratory Manual):
- Safety labs: chemistry, hematology, coagulation, urinalysis, urine pregnancy test for females of child-bearing potential only (see Appendix 2)
- Virology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb, and HBeAb (Weeks 72 and 96 only), sample for HBV sequencing and HBV nucleic acids (see Appendix 2)
- Immunology (For subjects who provided PBMCs at Screening at selected sites ONLY): PBMCs collection followed by serum cytokine sample collection at Weeks 60, 72, 84, and 96 (see Appendix 2). Additionally, these subjects will provide PaxGene® RNA sample at Week 96 only.
- Review dosing diary
- Assess ABI-H0731 accountability (final ABI-H0731 accountability performed at Week 96)
- ABI-H0731 dispensation (final ABI-H0731 dispensation performed at Week 92)
- ABI-H0731 administration
- NrtI administration
- Dispense dosing diary

7.6. Follow-up Assessments

All subjects who prematurely discontinue treatment or complete treatment per protocol will enter a 24-week follow-up period during which they will have the following assessments performed between

4 weeks and 20 weeks and at 24 weeks (±5 days) after the last dose of study drug unless otherwise stated. Subjects will remain on standard of care NrtI during the follow-up period:

- Measure body weight (24 Weeks post only)
- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Complete physical examination (24 Weeks post only)
- Symptom-directed physical examination (not at 24 Weeks post)
- 12-lead ECG (24 Weeks post only)
- Review concomitant medications
- Review AEs
- Laboratory analyses (additional details are provided in the Laboratory Manual):
- Safety labs: chemistry, hematology, coagulation, urinalysis (4 Weeks post and 24 Weeks post only), urine pregnancy test (only at 4 Weeks post and for female of child-bearing potential) (see Appendix 2)
- Virology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb, and HBeAb (24 Weeks post only), sample for HBV sequencing and HBV nucleic acids (see Appendix 2)
- Immunology (For subjects who provided PBMCs at Screening at selected sites ONLY): PBMCs collection followed by serum cytokine sample collection at 4-, 12-, and 24-Weeks post (see Appendix 2). Additionally, these subjects will also provide a PaxGene® RNA sample at 24 Weeks post only.
- PK sample: samples for ABI-H0731 or PBO and NrtI collected at 4 Weeks post. See Section 7.10 for additional information on PK sampling.
- Review dosing diary for NrtI ONLY
- NrtI administration at 4 Weeks post ONLY
- Dispense dosing diary (EXCEPT at 24 Weeks Post)

7.7. 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:

- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Symptom-directed physical examination
- Review concomitant medications
- Review AEs
- Laboratory analyses (additional details are provided in the Laboratory Manual):

- Safety labs: chemistry, hematology, coagulation, urinalysis, urine drug test, urine pregnancy test for females of child-bearing potential only (see Appendix 2)
- Virology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, sample for HBV sequencing, and HBV nucleic acids (see Appendix 2)
- PK samples: samples for ABI-H0731 or PBO and NrtI. See Section 7.10 for additional information on PK sampling.

Assessments performed should be documented in the subject's source documentation. Clinical laboratory assessments should be conducted through the central laboratory.

7.8. Premature Termination Visit

Should a subject prematurely discontinue treatment (Section 7.9.1) or discontinue from the study (Section 7.9.2), 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:

- Vital signs (temperature, heart rate, respiration rate, and blood pressure)
- Complete physical examination (excluding breast and genitalia unless indicated)
- 12-lead ECG
- Review concomitant medications
- Review AEs
- Laboratory analyses (additional details are provided in the Laboratory Manual):
- Safety labs: chemistry, hematology, coagulation, urinalysis, urine drug test, urine pregnancy test for females of child-bearing potential only (see Appendix 2)
- Virology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb, and HBeAb, sample for HBV sequencing and HBV nucleic acids (see Appendix 2)
- PK samples: samples for ABI-H0731 or PBO and NrtI. See Section 7.10 for additional information.
- Immunology (For subjects who provided PBMCs at Screening at selected sites ONLY): PBMCs collection followed by serum cytokine and PaxGene® RNA sample collection (see Appendix 2).
- Review dosing diary and assess IMP accountability (if applicable)

7.9. Discontinuation

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 discontinuation from the study, if possible, a Premature Termination visit should be conducted (Section 7.8). If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, he/she may

request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.9.1. Discontinuation from Treatment

If an individual subject is, in the judgement of the Investigator, not satisfactorily tolerating study drug treatment due to AEs, then in consultation with the Sponsor, the subject may discontinue treatment with ABI-H0731 or PBO. NrtI may be continued at the discretion of the Investigator. Discontinuation from treatment does not mean discontinuation from the study. Subjects who prematurely discontinue treatment should immediately undergo the assessments listed for the Premature Termination visit (Section 7.8) and then continue scheduled follow-up assessments (Section 7.6).

In this study, subjects will be closely monitored for ALT elevations and declining hepatic function. Procedures to be followed for these subjects are described in Section 9.4. Study treatment will be discontinued in subjects with confirmed evidence of declining hepatic function during treatment, a Premature Termination visit (Section 7.8) will be completed, and subjects will subsequently undergo the follow-up assessments described in Section 7.6.

Any subjects negative by urine pregnancy test at Baseline (Day 1) who are subsequently found to be positive on serum pregnancy test should immediately discontinue treatment with ABI-H0731 or PBO. NrtI may be continued if indicated based on Investigator judgment in accordance with local practice and the approved NrtI package insert. These subjects may be replaced at the discretion of the Sponsor.

7.9.2. Discontinuation from Study

Discontinuation from study (ie, withdrawal of consent) means that the subject does not wish to receive further protocol-required treatments or undergo protocol-required procedures, and the subject does not wish to, or is unable to, continue further study participation. Subjects who discontinue from the study during follow-up should undergo the assessments listed for the Premature Termination visit (Section 7.8). It is recommended, though not mandated, that the additional follow-up assessments described in Section 7.6 be conducted, with the consent of the subject. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent.

7.9.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a 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, he/she will be considered to have withdrawn from the study.

7.10. PK Assessments

During the study, predose plasma samples will be collected from all subjects to explore the PK profile of ABI-H0731 and NrtI following combination treatment in subjects with CHB. Additionally, postdose and post-treatment samples will be collected. The timing of PK sample collection is outlined in Table 7. Additional details regarding the collection, processing, storage, and shipment of PK samples is described in the Laboratory Manual.

Table 7: Pharmacokinetic Sample Collection

Time period	Time relative to study drug administration [a]	Time relative to study drug administration [b]
Treatment	Predose	Day 1, Weeks 4, and 48
	30 min to 2 hours postdose	Weeks 2, 8, 12, 24, and 28
	2 to 4 hours postdose	Day 1
	4 to 6 hours postdose	Weeks 16 and 20
Follow-up	Collect at same time with other central labs	At Unscheduled and Premature Termination [c] Visits and the Week 4 Post Treatment Follow-up visit

[a] If the subject self-administers the study drug outside the study clinic, a pharmacokinetic sample should be collected during the next in-clinic visit with documentation of date and time of the dose in the subject's source documents.
[b] Sample collection times are targeted times. Samples collected outside of these targeted times will not be considered protocol deviations. The actual sample collection date/time should be accurately recorded on source documentation.
[c] A pharmacokinetic sample should also be collected if an unscheduled or premature termination visit is performed.

7.11. End of Study Definition

The study will be completed when the last subject completes the 24-week, post-treatment follow-up period, or is considered "lost to follow-up," (Section 7.9.3) whichever is later.

7.12. Resistance Monitoring

During the Screening procedures, all subjects will be evaluated for HBV polymerase mutations as described in Appendix 2. Subjects having any of these mutations will be excluded from study participation.

To assess for viral resistance during the study, serum samples from subjects at each visit will be collected (Section 7). Samples from those subjects with evidence of nonresponse to treatment, such as viral breakthrough (ie, >1 $\log_{10}$ increase in HBV DNA from on-treatment nadir) will be selected for HBV gene sequencing, with sequence comparisons to Baseline sequences, as well as comparisons to HBV gene sequences from subjects who received PBO and HBV database sequences.

8. ADVERSE EVENTS

An AE is any untoward medical occurrence in a study subject administered an investigational product(s) regardless of the causal relationship with treatment.

An AE, therefore, can be any unfavorable and unintended sign (including laboratory finding), symptom, or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs the ICF for participation is considered an adverse event. This includes any side effect, injury, toxicity, or sensitivity reaction.

8.1. Documenting Adverse Events

Adverse events will be monitored throughout the entire study. 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 provided: a description of the event, severity, time of occurrence, duration, any action (eg, treatment and follow-up tests), and the outcome should be provided along with the Investigator's assessment of the relationship to the study treatment (refer to the eCRF completion guidelines).

Adverse events will be recorded from the date informed consent is signed through end of study (completion of follow-up period).

8.2. 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 Table for Grading the Severity of Adult and Pediatric AEs (Appendix 3), which grades the severity of clinical AEs and laboratory abnormalities in a 4-category system.

For AEs not included in Appendix 3, 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 and 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

Note that an AE or laboratory abnormality that is life-threatening as it exists constitutes an SAE.

8.3. 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.

8.4. Expectedness

An AE is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed. The CRO and Sponsor Medical Monitors will be responsible for determining whether an AE is expected or unexpected.

8.5. Abnormal Laboratory Test Values

In the event of abnormal laboratory test values, the tests should be repeated immediately. If the Investigator considers the abnormality to be clinically significant, it should be reported as an AE and followed up until it returns to the normal range and/or an adequate explanation of the abnormality is found.

8.6. Adverse Event Follow-up

After the initial AE or SAE report, the Investigator will follow-up proactively on each subject and provide further information to the CRO/Sponsor on the subject's condition. During the study, all AEs or SAEs should be followed 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.

8.7. Pregnancy

8.7.1. Female subjects who become pregnant

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

The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study, including the 24-week follow-up period. The initial information will be recorded on the Pregnancy Reporting form and submitted to the CRO Pharmacovigilance group 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. 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 post-study pregnancy related SAE considered reasonably related to the study drug(s) by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

8.7.2. Male subjects with partners who become pregnant

The Investigator will conduct due diligence to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is participating in this study. This applies only to male subjects who receive the study drug.

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 CRO Pharmacovigilance group 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 Pharmacy Manual for contact information for reporting a pregnancy.

9. SERIOUS ADVERSE EVENTS

9.1. Definition of SAE

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 who received ABI-H0731
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse

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 pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either “serious” or “non-serious” according to the usual criteria.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

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.

9.2. Reporting Serious Adverse Events

All SAEs must be reported within 24 hours of learning about the event using the SAE Report form to the 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. This additional information will be requested, if necessary, by the responsible monitor within 5 days of receipt of the alert report. This is to ensure that the initial reporting of SAEs is made to regulatory authorities within the required time period.

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 regulatory 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.

9.3. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. 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.

9.4. Management of On-treatment and Post-treatment ALT Elevations

All subjects participating in the study will be closely monitored for ALT elevations and/or signs of potential decline in hepatic function. Subjects experiencing ALT elevations ≥2 × Baseline 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. For these subjects, at each timepoint, an Unscheduled Visit should be conducted with completion of assessments as described in Section 7.7. Additionally, the following guidance is provided for management of subjects with ALT elevations:

- 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. To confirm the ALT finding, the subject should return to the clinic for an Unscheduled Visit and undergo all assessments as noted in Section 7.7 (Unscheduled Visit).
- 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, HBV DNA, and quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]), HAV IgM, HCV RNA, HDV RNA, and HEV IgM.
    - 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, HBV DNA, and quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]). Subjects whose ALT has stabilized should continue to be monitored weekly (or more frequently, as deemed necessary by the treating physician) 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
- Subjects with confirmed ALT elevation with 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 >2 × 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.
- Post-treatment ALT Elevation

  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 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.

  All subjects with ALT elevation without or with declining hepatic function (on or off-treatment) should continue to be followed on their regular study visit schedule, with the addition of unscheduled visits as described above. If the post-treatment 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 Principal Investigator, in consultation with the Sponsor, and the unscheduled visit module in the case report form should be utilized as needed to gather additional clinical and laboratory data 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.

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

10. STATISTICAL CONSIDERATIONS

This section provides the key details of the statistical analyses for a final analysis to be performed using data captured according to this protocol. No interim analysis is planned for this study. A complete SAP describing all planned analyses will be finalized prior to database lock.

10.1. Determination of Sample Size

Approximately, 40 subjects with CHB will be enrolled in the study. Subjects will be randomized to receive either 300 mg ABI-H0731 or matching PBO in a 1:1 ratio in addition to standard of care NrtI. Since this is a proof-of-concept study, sample size is similar to that previously utilized for this type of study and is not based upon statistical considerations.

10.2. Analysis Populations

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

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

Full Analysis Set: It is the main analysis population for the efficacy analysis. It includes all randomized subjects, classified according to the treatment arm into which they were randomized regardless of the actual treatment received, who used any amount of study drug and have at least 1 post-baseline efficacy assessment.

Safety Set: It includes all subjects, classified according to the actual treatment received regardless of random assignment, who used any amount of study drug and have at least 1 post-baseline safety evaluation. This is the main analysis population for all safety analyses.

PK-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. A Baseline and at least 1 PK blood sample following a dose of study treatment is required for inclusion in this analysis. This is the main analysis population for all PK 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.

10.3. Planned Analyses

As a general strategy, continuous efficacy and safety endpoints will be summarized using the five-number summary (mean, standard deviation, median, minimum, and maximum). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints.

Analyses by treatment group will be presented as follows:

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

The primary analysis of the study will be performed when all subjects complete Week 48 evaluations.

10.3.1. 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 set will be used to produce this analysis.

10.3.2. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized and compared by treatment group. Results will be reported using subjects in the randomized, full analysis, per protocol and PK analysis sets.

Prior and concomitant medications will be classified according to the anatomical therapeutic chemical codes in the WHO Drug dictionary. The incidence rate of each coded medication will be tabulated by treatment group. The table will be sorted by the incidence use of the entire sample.

10.3.3. Exposure to Study Treatment and Compliance

Frequency distributions of the number of doses received will be presented by treatment group. Treatment duration and treatment compliance for all randomized subjects will also be described by treatment group.

10.3.4. Analysis of Primary Efficacy Endpoints

The primary efficacy endpoint is the proportion of subjects with HBV DNA <LLOQ at Week 48.

The proportion of subjects achieving the primary efficacy endpoint will be reported along with the corresponding 95% asymptotic confidence interval by treatment group. The proportion of responders will be compared between the 2 treatment groups using a *Cochran-Mantel-Haenszel* test accounting for stratification factors.

10.3.5. Analysis of Secondary Efficacy Endpoints

A similar approach will be used to describe and compare the proportion of subjects with reduction in HBV DNA < LLOQ, HBV DNA <LOD, HBV pgRNA <LLOQ and subjects with abnormal ALT at Baseline who have normal ALT for ABI-H0731+NrtI and PBO+NrtI.

Change in mean $\log_{10}$ HBV DNA and in mean $\log_{10}$ HBV pgRNA from Baseline for ABI-H0731+NrtI and PBO+NrtI will be compared using a linear model with Baseline values and stratification as covariates.

10.3.6. PK Analysis

Drug concentrations of ABI-H0731 or PBO and NrtI will be listed at end of study:

- ABI-H0731 on ABI-H0731+NrtI therapy stratified by collection time window and collection day.
- NrtI on ABI-H0731+NrtI therapy as compared with PBO+NrtI therapy stratified by collection time window and study day.

Application to a population PK model may be applied, details of which will be provided in the pharmacometrics analysis plan. Results from of the population PK work will be reported outside of the clinical study report (CSR).

10.3.7. Safety Analysis

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

10.3.7.1. TEAEs

Treatment-emergent adverse events reported during the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidence of TEAEs will be summarized by treatment group and the following:

- Preferred term
- System organ class and preferred term
- System organ class, preferred term, and severity

These summaries will be presented for the following subsets:

- All adverse events
- Serious adverse events
- Drug-related adverse events

For tables reporting adverse events by severity, if a subject has multiple occurrences of an adverse event with the same organ class and preferred term, the most severe event will be presented.

10.3.7.2. Clinical Laboratory Evaluation

Laboratory parameters will be summarized by treatment group at each visit. Each summary will include the values of the laboratory parameters and their change from Baseline. Shift tables from Baseline will be presented for laboratory values in the chemistry and hematology panels. Parameters will be classified according to the laboratory reference normal ranges. A listing will be provided for out of normal range as well as clinically significant abnormal laboratory values.

10.3.7.3. Vital Signs

Vital signs, including heart rate, blood pressure, temperature, height, and body weight will be summarized by treatment group and time point. For each assessment of vital signs, change and percent change in vital signs from Baseline will be summarized by treatment group.

10.4. Interim Analysis

No formal interim analysis is planned.

10.5. Independent Data Monitoring Committee

An independent Data Monitoring Committee is not planned for this study.

10.6. Handling of Missing Data

For the analysis of primary efficacy endpoint, missing HBV DNA data will be imputed using a multiple imputation method appropriate to the pattern of missingness. Details of the considered patterns and associated sensitivity analyses will be described 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; 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 clinical study, the Investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC, as well as for study protocol amendment(s), written ICF, any ICF updates, subject recruitment procedures (eg, advertisements), and any written information to be provided to subjects and a statement from the IRB/IEC that complies 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 and the IRB/IEC and will contain all elements in the sample form, in language readily understood by the subject. Each subject's original ICF 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 physicians 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 his/her respective site in accordance with this protocol. Protocol compliance assessments will be conducted during routine site monitoring visits and ongoing data review by the Sponsor and CRO.

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 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 CSRs according to the applicable regulatory requirements. CSRs 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 when preparing publications associated with clinical studies (ICMJE 2018, Battisti 2015).

12. REFERENCES

Battisti WP, Wager E, Baltzer L, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Annals Internal Medicine. 2015 Sep 15;163(6)L:461-4.

Belloni L, Li L, Palumbo GA, et al. HAPs hepatitis B virus (HBV) capsid inhibitors block core protein interaction with the viral minichromosome and host cell genes and affect cccDNA transcription and stability. Hepatology. 2013;58(4 suppl 1):277A.

Burdette D, Cathcart A, Shauf A, et al. Evidence for the presence of infectious virus in the serum from chronic hepatitis B patients suppressed on nucleos (t)ide therapy with detectable but not quantifiable HBV DNA; Hepatology: 2019 Apr;70(1):e95.

Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016 Nov;1(3):196-206.

Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016 Nov;1(3):185-95.

Chang TT, Gish RG, de Man R et al.A Comparison of Entecavir and Lamivudine for HBeAg-Positive Chronic Hepatitis B. N Engl J Med. 2006 Mar 9;354(10):1001-10.

Colvin HM, Mitchell AE. Hepatitis and liver cancer: A National Strategy for Prevention and Control of Hepatitis B and C. Washington DC: The National Academies Press; 2010.

Cornberg M, Lok AS-F, Terrault NA, and Zoulim F. Guidance for design and endpoints of clinical trials in chronic hepatitis B – Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference. Hepatology. 2020 Mar;71(3):1070-92.

El-Serag HB. Epidemiology of Viral Hepatitis and Hepatocellular Carcinoma. Gastroenterology. 2012;142(6):1264-73.

European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012 Jul;57(1):167-85.

European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-98.

Gish RG, Given BD, Lai CL, et al. Chronic hepatitis B: Virology, natural history, current management and a glimpse at future opportunities. Antiviral Res. 2015 Sep;121:47-58.

Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. Hepatology. 2007 Apr;45(4):1056-75.

Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE). http://www.icmje.org/recommendations/ Accessed: January 2019.

Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Zet, al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med. 2006 Mar 9;354(10):1011-20.

Lampertico P and Liaw YF. New Perspectives in the Therapy of Chronic Hepatitis B. Gut. 2012 May;61 Suppl 1:i18-24.

Levey AS1, Stevens LA, Schmide CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12.

Levrero M, Pollicino T, Petersen J, Belloni L, Raimondo G, Dandri M. Control of cccDNA function in hepatitis B virus infection. J. Hepatol. 2009 Sep;51(3):581-92.

Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009 Sep;50(3):661-2.

Paptheodoridis GV, Chan H L-Y, Hansen BE, Janssen HLA, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. J Hepatol. 2015 Apr;62(4):956-67.

Pungpapong S, Kim WR. In the Eye of the B-holder: natural history of chronic hepatitis B. Hepatology. 2013 Jul;58(1):6-8.

Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet, 2015 Oct;386(10003):1546-55.

Sorrell MF, Belongia EA, Costa J, et al. National Institutes of Health consensus development conference statement: management of hepatitis B. Ann Intern Med. 2009 Jan 20;150(2):104-10.

World Health Organization (WHO) Scientific Group Technical Report. Assessment of osteoporosis at the primary health-care level. University of Sheffield, United Kingdom: World Health Organization; 2007.

World Health Organization (WHO). Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection. Geneva Switzerland: World Health Organization; 2015.

World Health Organization (WHO). Hepatitis B: fact sheet. Geneva Switzerland: World Health Organization; 2016.

World Health Organization (WHO). Hepatitis B: fact sheet. Geneva Switzerland: World Health Organization; 2019.

Yang L, Liu F, Tong X, Hoffman D, Zuo J, Lu M. Treatment of chronic hepatitis B virus infection using small molecule modulators of nucleocapsid assembly: recent advances and perspectives. ACS Infect Dis. 2019 May 10;5(5):713-724.

Yim HJ, Lok ASF. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology. 2006 Feb;43(2 Suppl 1):S173-81.

Yip TC, Wong WW, Chan HL, Tse YK, Lui GC, Wong GL. Tenofovir is associated with lower risk of hepatocellular carcinoma than entecavir in patients with chronic HBV infection in China. Gastroenterology. 2020 Jan;158(1):215-225.e6.

13. APPENDICES

APPENDIX 1 SCHEDULE OF ASSESSMENTS TABLE

Period or Visit	**Screening**		**On Treatment**									**Follow-up**		**Premature Termination[2]**	**Unscheduled Visit [3]**
	Day -45 to Day -1														
Study Day or Week	**Visit 1**	**Visit 2**	**Day 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wks 20-44 [1]**	**Wk 48**	**Wks 52-96 [1]**	**4-20 Wks Post [1]**	**24 Wks Post**		
Visit Window (days)			0	±3	±3	±3	±3	±3	±3	-3	±5	±5	±5	NA	NA
Informed Consent(s) [4]	X														
Demographics, medical history, and HBV history	X		X												
Liver staging [5]	X														
Height and weight [6]	X		X							X	X [8]		X		
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination [7]	X		X							X	X [8]		X	X	
Symptom-directed physical				X	X	X	X	X	X		X [9]	X			X
12-lead ECG [10]	X		X				X		X [10]	X	X [10]		X	X	
Concomitant medications and AEs[22]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm subject eligibility			X												
Complete randomization (IRT)			X												
Chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X		X		X	X	X	X	X	X	X	X	X	X	X
HbA1c	X														
Serum AFP	X														
FSH (females only)	X														
Pregnancy Test [11]	X		X	X	X	X	X	X	X	X	X	X		X	X
Urinalysis	X		X		X	X	X	X	X	X	X	X [12]	X	X	X
Urine drug test	X		X											X	X
HBV genotype			X												
HBV DNA	X	X [13]	X	X	X	X	X	X	X	X	X	X	X	X	X

Period or Visit		Screening		On Treatment									Follow-up		Premature Termination[2]	Unscheduled Visit [3]
		Day -45 to Day -1														
Study Day or Week		Visit 1	Visit 2	Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wks 20-44 [1]	Wk 48	Wks 52-96 [1]	4-20 Wks Post [1]	24 Wks Post		
Visit Window (days)				0	±3	±3	±3	±3	±3	±3	-3	±5	±5	±5	NA	NA
HBV pgRNA		X		X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg, HBeAg [14]		X		X		X	X	X	X	X	X	X	X	X	X	X
HBcrAg				X		X	X	X	X	X	X	X	X	X	X	X
HBsAb, HBeAb		X		X				X		X[15]	X	X [15]		X	X	
Sample for HBV DNA sequencing and HBV nucleic acids		X		X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Ab, HCV Ab, HDV Ab, HAV (IgM), HEV (IgM)		X														
Dosing diary				X	X	X	X	X	X	X	X	X	X	X		
IMP (ABI-H0731/PBO) accountability					X	X	X	X	X	X	X	X[16]			X	
IMP (ABI-H0731/PBO) dispensation				X	X	X	X	X	X	X	X	X[16]				
In-clinic IMP (ABI-H0731/PBO) dosing				X	X	X	X	X	X	X	X	X				
In-clinic NrtI dosing				X	X	X	X	X	X	X	X	X	X[23]			
PK Sample Collections [17, 18]	ABI-H0731			X	X	X	X	X	X	X	X		X [19]		X	X
	NrtI			X	X	X	X	X	X	X	X		X [19]		X	X
Immunology (PBMC followed by serum cytokine sample collection) [24]		X		X	X	X		X		X [20]	X	X [20]	X [20]	X	X	
PaxGene® DNA and PaxGene® RNA samples [24]				X								X [21]		X [21]	X	
Optional pharmacogenomic sample collection				X												

Abbreviations: Ab=antibody; AE=adverse event; AFP=alpha fetoprotein; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; FSH=follicle-stimulating hormone; HAV=hepatitis A virus; 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; HCV=hepatitis C virus; HDV=hepatitis D virus; HEV=hepatitis E virus; HIV=human immunodeficiency virus; IgM=immunoglobulin M; INR=international normalized ratio; IRT=Interactive Response Technology; NA=not applicable; PBO=placebo; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic; pgRNA= pre-genomic RNA; ULN=upper limit of normal; Wk=week; Wks=weeks.

[1] Study visits occur every 4 weeks between Weeks 20 and 96 on treatment and between Weeks 4 and 20 Post Treatment.
[2] Subjects who discontinue treatment before Week 48 should immediately undergo the assessments listed for the Premature Termination visit and then continue the scheduled follow-up assessments.
[3] Any subjects with alanine aminotransferase (ALT) elevation (defined as ALT≥2 × Baseline and ≥10 × ULN) should return to the clinic for an Unscheduled Visit to confirm the findings within 3 days of receipt of the original results. At the Unscheduled Visit, subjects should undergo the assessments described in Section 7.7. If the ALT elevation is confirmed, the subject will return for an additional Unscheduled Visit at which the following tests: HBV DNA, HBV serologies (quantitative HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]), HAV IgM, HCV RNA, HDV RNA, and HEV IgM, will be performed. If the ALT is rising, the subject will return for additional Unscheduled Visits every 2-5 days until the ALT has stabilized. At these visits the following tests will be performed: HBV DNA, HBV serologies (quantitative HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]).
[4] In addition to the study specific Informed Consent Form, a separate consent is required for the subject to provide an optional pharmacogenomic sampling.
[5] Liver staging is to be performed to determine lack of cirrhosis or advanced liver disease as required by inclusion criteria and should be performed in a fasted state by FibroScan or other Sponsor-approved hepatic imaging method within 3 months of Screening.
[6] Height is measured at the Screening visit only.
[7] For the complete physical examination, assessment of the breasts and genitalia are not required unless indicated.
[8] Complete physical exam and weight measurement are performed only at Weeks 48 and 96 visits, and at 24 Week post-treatment visit (if applicable).
[9] A Symptom-directed physical exam is performed only at the visits when a complete physical exam is not performed.
[10] During the study, any clinically significant ECG result or change from Baseline (Day 1) should be confirmed, and if confirmed, should be recorded as an AE. 12-lead ECG to be also performed at Weeks 24, 36, 48, and 96.
[11] A serum pregnancy test for females of child-bearing potential is required at Screening. On Day 1 both urine and serum should 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 and may be replaced). All post-Day 1 pregnancy tests may be conducted by urine dipstick. If positive on dipstick, reflex to serum.
[12] Urinalysis will be conducted 4 and 24-Weeks Post Treatment
[13] A second, confirmatory HBV DNA should be drawn 10 to14 days after the initial Screening visit during the Screening assessment period. If the results from these 2 samples indicate a decline in HBV DNA then a third sample will be collected to ensure virologic plateau prior to randomization.
[14] If quantitative HBsAg or HBeAg are negative at any visit subsequent to Screening, reflex to qualitative.
[15] HBsAb and HBeAb tests are performed at Weeks 24, 48, 72, and 96.
[16] Final study drug dispensation is performed at Week 92, and final study drug accountability is performed at Week 96. NrtI will be continued throughout the 24-week follow-up period.
[17] If the subject inadvertently administers study drug prior to collection, a PK sample should still be drawn. Refer to Section 10.3.6.
[18] Predose PK samples for ABI-H0731 or PBO and NrtI on Day 1 and Weeks 4 and 48. Postdose PK samples for ABI-H0731 and NrtI may be collected from 2 to 4 hours postdose on Day 1, and between 30 min and 2 hours after in-clinic study drug + NrtI administration at Weeks 2, 8, 12, 24, and 28. Postdose samples on Weeks 16 and 20 may be collected between 4 and 6 hours after in-clinic study drug + NrtI administration.
[19] Collect a PK sample with other central labs at week 4 Post-treatment follow-up visit.
[20] Immunology (PBMCs and serum cytokine sample) collections occur every 12 weeks at Weeks 24, 36, 48, 60, 72, 84, and 96 visits, at selected sites only. At follow-up, collect at 4 Weeks Post-treatment, 12 Weeks Post-treatment, and 24 Weeks Post-treatment visits, and at the premature termination visit.
[21] PaxGene® RNA only at Week 96, 24-Weeks post treatment visit, and on premature termination visit.
[22] Concomitant medications must be recorded in the subjects' source documentation until the end of study (completion of follow-up period); NrtIs should be followed through to the end of the follow-up period.
[23] In-clinic NrtI administration only required at 4 weeks post visit.

[24] Only the subjects that provide PBMCs at Screening at selected sites will undergo additional PBMCs, serum cytokine, PaxGene® DNA and PaxGene® RNA sample collection at the specified timepoints. Note that PaxGene® DNA sample will only be collected on Day 1.

APPENDIX 2 CLINICAL AND LABORATORY ASSESSMENTS

Clinical Laboratory Tests

Clinical laboratory tests will be performed at the designated central laboratories at the timepoints indicated in Section 7 and the Schedule of Assessments table in Appendix 1. 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. Urgent local laboratory testing results conflicting with the central laboratory results should be discussed between the Investigator and the study Medical Monitor.

The specific components of the clinical laboratory tests are listed below in Table 8.

Table 8: Clinical Laboratory Tests

Panel	Tests
Clinical chemistry	Blood glucose levels, serum or plasma electrolytes (sodium, potassium, chloride, bicarbonate), calcium, blood urea nitrogen, serum creatinine, creatine kinase, GFR, uric acid, total and direct bilirubin [a], ALT, AST, GGT, alkaline phosphatase, LDH, amylase, triglycerides, total cholesterol, inorganic phosphate or total phosphate, total protein, albumin, lipase, and total serum or plasma globulins
In case of elevated ALT	ALT, AST, total bilirubin, serum albumin, and INR
Hematology	Complete blood counts: hemoglobin, hematocrit, RBC indices (MCV, MCHC), reticulocyte counts, leukocyte counts (total and differential), and platelet counts
Coagulation	Prothrombin time/INR and aPTT
Urinalysis	pH, specific gravity, protein, glucose, ketones, and occult blood
Other	AFP, HbA1c, and FSH
Pregnancy tests	For females of child-bearing potential only; a serum or plasma pregnancy test must be performed at Screening, and both serum/plasma and urine are required at Day 1; a serum, plasma, or urine pregnancy test must be performed at all subsequent visits. A positive result disqualifies the subject for study treatment
Urine drug screening	Amphetamine/methamphetamine, barbiturates, benzodiazepines, cocaine metabolite, ecstasy, ethanol, opiates, phencyclidine, and propoxyphene.
Antibodies	HCV, HDV, HAV IgM, HEV IgM, and HIV

Abbreviations: AFP=alpha fetoprotein; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transpeptidase; GFR=glomerular filtration rate; HAV=hepatitis A virus; HbA1c=hemoglobin A1c; HCV=hepatitis C virus; HDV=hepatitis D virus; HEV=hepatitis E virus; HIV=human immunodeficiency virus; IgM=immunoglobulin M; INR=International Normalized Ratio; LDH=lactate dehydrogenase; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; ULN=upper limit of normal.

[a] Perform fractionated bilirubin, if total bilirubin >ULN.

HBV Virology

To provide an assessment of the antiviral efficacy of ABI-H0731 in subjects with CHB, this study will evaluate treatment effects on the following parameters:

- HBV genotyping
- HBV DNA
- HBV pgRNA

- HBsAg
- HBeAg
- HBcrAg, HBsAb, HBeAb
- HBV sequence analysis for assessment of resistance

To assure standardization of the virologic methodologies utilized in this study, HBV DNA-related, HBV antigen-related and HBV antibody-related virologic assessments will be conducted at a central reference laboratory. Subject serum samples for resistance-related sequencing and HBV pgRNA testing will be shipped frozen to the Sponsor or a designated third-party laboratory for testing. The HBV virology tests will be performed at the timepoints indicated in Section 7 and the Schedule of Assessments table in Appendix 1. HBV pgRNA results could unblind individual subject's treatment assignments and therefore will not be reported to investigative sites or other blinded personnel until completion of the study, the database has been locked and the study has been unblinded.

Additional details concerning the collection and processing of HBV virology samples are described in the Laboratory Manual.

HBV Resistance Testing:

Specific base substitutions in the HBV polymerase coding region may confer reduced susceptibility to NrtIs. During the Screening period HBV sequencing will be performed for all subjects. Subjects with base substitutions commonly associated with decreased susceptibility to treatment with NrtI will be excluded from participation in the study.

HBV Immunology

Subjects will provide whole blood PBMCs samples at Screening at selected sites only. These subjects will provide additional whole blood PBMCs samples followed by serum cytokine samples for immunologic testing at timepoints specified in Appendix 1. Additionally, these subjects will also provide PaxGene® RNA and PaxGene® DNA samples at timepoints specified in Appendix 1.

Other Safety Assessments

12-lead ECG:

Prior to the conduct of 12-lead ECGs, subjects should rest in a supine position for 10 minutes. ECGs 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 sub-investigator 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 sub-investigator 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).

Complete Physical Examination:

Complete physical examinations will be performed by the Investigator or qualified sub-investigator at the time points indicated in the Study Procedures section (Section 7, Appendix 1). 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 7; Appendix 1). Additional symptom-directed of complete physical examinations made 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 sub-investigator will examine the appropriate body system(s).

APPENDIX 3 TOXICITY GRADING SCALE FOR ADVERSE EVENTS AND LABORATORY ABNORMALITIES

Adapted from the US National Institutes of Health (DAIDS) 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

Cardiovascular				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-threatening**
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)	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 subject not previously diagnosed with hypertension (eg, 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 (eg, hypoxemia) OR Intervention indicated (eg, oxygen)	Life-threatening consequences OR Urgent intervention indicated (eg, vasoactive medications, ventricular assist 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 indicated

Cardiovascular				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-threatening**
Prolonged PR Interval or AV Block	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 QT^{c} Interval[a]	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds OR ≥0.06 seconds above Baseline	Life-threatening consequences (eg, 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 (eg, pulmonary embolism, thrombus)

Abbreviations: ECG=electrocardiogram; IV=intravenous; NA=not applicable; QTc=corrected QT interval; RBC=red blood cell

[a] As per Bazett's formula.

Dermatologic				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life- threatening**
Alopecia (scalp only)	Detectable by study subject, caregiver, or physician AND Causing no or minimal interference with usual social and functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social and functional activities	NA	NA
Bruising	Localized to 1 area	Localized to more than 1 area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (eg, oral antibiotics, antifungals, antivirals)	IV treatment indicated (eg, IV antibiotics, antifungals, antivirals)	Life-threatening consequences (eg, sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social and functional activities	Marked or generalized causing greater than minimal interference with usual social and functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social and functional activities	Marked or generalized causing greater than minimal interference with usual social and functional activities	NA	NA
Petechiae	Localized to 1 area	Localized to more than 1 area	Generalized	NA
Pruritus [b] (without skin lesions)	Itching causing no or minimal interference with usual social and functional activities	Itching causing greater than minimal interference with usual social and functional activities	Itching causing inability to perform usual social and 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 1 site	Extensive or generalized bullous lesions **OR** Ulceration of mucous membrane involving 2 or more distinct mucosal sites **OR** Stevens-Johnson syndrome **OR** Toxic epidermal necrolysis

Abbreviations: IV=intravenous; NA=not applicable.
[b] For pruritus associated with injections or infusions, see the Site Reactions to Injections and Infusions section.

Endocrine and Metabolic				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life- Threatening**
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 (eg, ketoacidosis, hyperosmolar non- ketotic coma, end organ failure)
Gynecomastia	Detectable by study subject, caregiver, or physician AND Causing no or minimal interference with usual social and functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social and functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social and functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social and functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social and functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social and functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social and functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy[c]	Detectable by study subject, caregiver, or physician AND Causing no or minimal interference with usual social and functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social and functional activities	Disfiguring changes	NA
Lipohypertrophy[d]	Detectable by study subject, caregiver, or physician AND Causing no or minimal interference with usual social and functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social and functional activities	Disfiguring changes	NA

Abbreviation: NA=not applicable

[c] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

[d] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life- threatening**
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 (eg, tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (eg, diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea	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 (eg, hypotensive shock)
Dysphagia or Odynophagia *Report only 1 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 (eg, hypotensive shock)
Mucositis or Stomatitis *Report only 1 and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (eg, 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 indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Perforation *(colon or rectum)*	NA	NA	Intervention indicated	Life-threatening consequences

Gastrointestinal				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life- threatening**
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social and functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social and functional activities OR Operative intervention indicated	Life-threatening consequences (eg, 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 (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)

Abbreviations: IV=intravenous; NA=not applicable.

Musculoskeletal				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life- threatening**
Arthralgia	Joint pain causing no or minimal interference with usual social and functional activities	Joint pain causing greater than minimal interference with usual social and functional activities	Joint pain causing inability to perform usual social and 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 and functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social and functional activities	Stiffness or joint swelling causing inability to perform usual social and 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 and functional activities	Muscle pain causing greater than minimal interference with usual social and functional activities	Muscle pain causing inability to perform usual social and functional activities	Disabling muscle pain causing inability to perform basic self-care functions
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 [e] *≥30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
<30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis [e] *≥30 years of age*	NA	BMD t-score <-2.5	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
<30 years of age	NA	BMD z-score <-2	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

Abbreviations: BMD=bone mineral density; NA=not applicable; WHO=World Health Organization.

[e] Bone mineral density t and z scores can be found in WHO 2007.

Neurologic				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-threatening**
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (eg, 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 and functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social and functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and 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 and functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social and functional activities OR Specialized resources on part- time basis indicated	Disability causing inability to perform usual social and functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Headache	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and 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 and functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social and functional activities	Muscle weakness causing inability to perform usual social and 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 and functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures *New Onset Seizure*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)

Neurologic				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-threatening**
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 (eg, severity or focality)	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Syncope	Near syncope without loss of consciousness (eg, presyncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Abbreviations: CNS=central nervous system; NA=not applicable.

Pregnancy, Puerperium, and Perinatal				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-threatening**
Stillbirth (report using mother's subject ID) *Report only one*	NA	NA	Fetal death occurring at ≥20 weeks gestation	NA
Preterm Birth (report using mother's subject 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 [f] (report using mother's subject ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

Abbreviations: ID=identification; NA=not applicable.

[f] Definition: A pregnancy loss occurring at <20 weeks gestational age.

Psychiatric				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-threatening**
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social and functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social and functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social and 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 and functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social and functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social and 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

Abbreviations: NA=not applicable.

Respiratory				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-threatening**
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 and functional activities	Forced expiratory volume in 1 second or peak flow 25 to <50% OR Symptoms causing inability to perform usual social and 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 and functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social and functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to <95%	Dyspnea at rest causing inability to perform usual social and functional activities OR Pulse oximetry <90%	Respiratory failure with ventilator support indicated (eg, CPAP, BPAP, intubation)

Abbreviations: CPAP=Continuous positive airway pressure, BPAP=Bilevel Positive Airway Pressure

Sensory				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life- threatening**
Hearing Loss	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 (ie, >50 dB audiogram and <50% speech discrimination)
Tinnitus	Symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated	Symptoms causing inability to perform usual social and functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social and functional activities	Vertigo causing greater than minimal interference with usual social and functional activities	Vertigo causing inability to perform usual social and 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 and functional activities	Visual changes causing greater than minimal interference with usual social and functional activities	Visual changes causing inability to perform usual social and functional activities	Disabling visual loss in affected eye(s)

Abbreviations: NA=not applicable.

Systemic				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-threatening**
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 and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	NA
Cytokine Release Syndrome [g]	Mild signs and symptoms AND Therapy (ie, antibody infusion) interruption not indicated	Therapy (ie, 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 (eg, requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
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 [h] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social and functional activities	Pain causing greater than minimal interference with usual social and functional activities	Pain causing inability to perform usual social and functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness [i]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (eg, antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (eg, steroids or IV fluids)	Life-threatening consequences (eg, requiring pressor or ventilator support)
Underweight [j]	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 (eg, tube feeding, total parenteral nutrition)

Abbreviations: BMI=body mass index; IV=intravenous; NA=not applicable; WHO=World Health Organization.

[g] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[h] For pain associated with injections or infusions, see the Site Reactions to Injections and Infusions section.

[i] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

[j] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URL: http://www.who.int/growthref/who2007_bmi_for_age/en/ for subjects >5 to 19 years of age

Urinary				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-threatening**
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

Abbreviations: NA=not applicable.

Laboratory Values[k]: 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×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×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, High***	NA	NA	>ULN with other signs and symptoms of hepatotoxicity.	>ULN with life- threatening consequences (eg, signs and symptoms of liver failure)
Total Bilirubin, High	1.1 to <1.6×ULN	1.6 to <2.6×ULN	2.6 to <5.0×ULN	≥5.0×ULN
Calcium, High (mg/dL; *mmol/L*)	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*)	7.8 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*
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×ULN	6 to <10×ULN	10 to <20×ULN	≥20×ULN
Creatinine, High [l]*Report only one*	1.1 to 1.3×ULN	>1.3 to 1.8×ULN OR Increase to 1.3 to <1.5×subject's Baseline	>1.8 to <3.5×ULN OR Increase to 1.5 to <2.0×subject's Baseline	≥3.5×ULN OR Increase of ≥2.0×subject's Baseline

Laboratory Values[k]: Chemistries[*]				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-threatening**
Creatinine Clearance [m] or eGFR, Low [l]*Report only one*	NA	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to <30% decrease from subject's Baseline	<60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to <50% decrease from subject's Baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from subject's Baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to <6.95*	>125 to 250 *6.95 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Nonfasting, High	116 to 160 *6.44 to <8.89*	>160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*)	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×ULN without acidosis	≥2.0×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×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High***	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	NA
LDL, Fasting, High	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 [n], 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*
Phosphate, Low (mg/dL; *mmol/L*)	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*

Abbreviations; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LLN=lower limit of normal; NA=not applicable; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; ULN=upper limit of normal.

[k] 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.

[l] Reminder: Choose the method that selects for the higher grade.
[m] 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.
[n] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Laboratory Values: Hematology				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *(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*) *(not HIV infected)*	600 to <650 *0.600×10^9 to <0.650×10^9*	500 to <600 *0.500×10^9 to <0.600×10^9*	350 to <500 *0.350×10^9 to <0.500×10^9*	<350 *<0.350×10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)	800 to 1,000 *0.800×10^9 to 1.000×10^9*	600 to 799 *0.600×10^9 to 0.799×10^9*	400 to 599 *0.400×10^9 to 0.599×10^9*	<400 *<0.400×10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00×LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75×LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50×LLN	<50 *<0.50* OR <0.25×LLN OR Associated with gross bleeding
Hemoglobin [o], Low (g/dL; *mmol/L*)[n] *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*
Hemoglobin [p], Low (g/dL; *mmol/L*)[n] *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×ULN	1.5 to <2.0×ULN	2.0 to <3.0×ULN	≥3.0×ULN
Methemoglobin (% hemoglobin)	5.0 to <10.0%	10.0 to <15.0%	15.0 to <20.0%	≥20.0%
PTT, High (not on anticoagulation therapy)	1.1 to <1.66×ULN	1.66 to <2.33×ULN	2.33 to <3.00×ULN	≥3.00×ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <125,000 *100.000×10^9 to <125.000×10^9*	50,000 to <100,000 *50.000×10^9 to <100.000×10^9*	25,000 to <50,000 *25.000×10^9 to <50.000×10^9*	<25,000 *<25.000×10^9*
PT, High (not on anticoagulation therapy)	1.1 to <1.25×ULN	1.25 to <1.50×ULN	1.50 to <3.00×ULN	≥3.00×ULN
WBC, Decreased (cells/mm^3; *cells/L*)	2,000 to 2,499 *2.000×10^9 to 2.499×10^9*	1,500 to 1,999 *1.500×10^9 to 1.999×10^9*	1,000 to 1,499 *1.000×10^9 to 1.499×10^9*	<1,000 *<1.000×10^9*

[o] Male and female sex are defined as sex at birth. For transgender subjects 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).

[p] 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.

Laboratory Values: Urinalysis				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
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

Abbreviations: NA=not applicable; RBC=red blood cells

APPENDIX 4 PREGNANCY PRECAUTIONS AND THE DEFINITION OF CHILDBEARING POTENTIAL AND CONTRACEPTIVE REQUIREMENTS

Pregnancy Precautions

Embryofetal development studies with ABI-H0731 have not been conducted in animals, therefore effects of ABI-H0731 on pregnancy are unknown. Contraceptive requirements for female subjects of childbearing potential are required as described below.

Definition of Female Subjects of Childbearing Potential

A female subject is considered of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Female subjects in the following categories are not considered of childbearing potential

- Premenopausal with one of the following:
- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- Postmenopausal: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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 childbearing 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 (DDI) study with ABI-H0731 and oral contraceptive has not been completed, and therefore, oral contraceptives are not acceptable as a form of effective birth control.

Female subjects of childbearing potential (defined above) must agree to use dual effective birth control methods for the duration of the study and follow-up. Effective birth control methods include male or female condom (may not be used together due to increased risk of breakage), vasectomy, tubal

sterilization, intrauterine device (IUD), diaphragm, or cervical cap. Note that the DDI of ABI-H0731, and systemic (oral/injectable) hormonal birth control has not been assessed and so systemic hormonal birth control is not considered effective birth control method for female subjects for the purposes of this study. Female subjects must have a negative serum pregnancy test at Screening and a negative urine pregnancy test prior to receiving the first dose of study drug at Baseline (Day 1).

All male subjects must agree to use dual effective birth control methods with their female partners if they are of childbearing potential for the duration of the study and follow-up. In this case, effective birth control methods include systemic (oral/injectable) hormonal birth control, male or female condom (may not be used together due to increased risk of breakage), 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, and for at least 30 days after administration of the last dose of study drug.

APPENDIX 5 CYTOCHROME P450 3A4 INHIBITORS AND INDUCERS AND CYP2C9 SUBSTRATES

The following drugs are known inhibitors of CYP3A4 and CYP2C9 substrates and should be avoided when taking ABI-H0731:

CYP3A4 Inhibitors	
HIV antivirals	indinavir, nelfinavir, ritonavir, saquinavir
Other	clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, idelalisib, ribociclib, telithromycin, aprepitant, erythromycin, fluconazole, grapefruit juice, netupitant/palonosetrone, verapamil, diltiazem, voriconazole cimetidine, amiodarone, NOT azithromycin, chloramphenicol, boceprevir, ciprofloxacin, delaviridine, diethyl-dithiocarbamate, fluvoxamine, gestodene, imatinib, mibefradil, mifepristone, norfloxacin, norfluoxetine, starfruit, telaprevir, voriconazole

The following drugs are known substrates of CYP2C9:

CYP2C9 Substrates	
Narrow therapeutic index substrates that are prohibited while taking ABI-H0731	Warfarin, phenytoin
Substrates that should be avoided while taking ABI-H0731	Amitriptyline, capecitabine, celecoxib, clopidogrel, diclofenac, doxepin, fluoxetine, Fluvastatin, glibenclamide, glimepiride, glipizide, glyburide, ibuprofen, irbesartan, lesinurad, lornixicam, losartan, meloxicam, nateglinide, piroxicam, rosiglitazone, naproxen, suprofen, tamoxifen, tolbutamide, torsemide, valproic acid, venlafaxine, voriconazole, zakirlukast

The following drugs are known inducers of CYP3A4 and should be avoided when taking ABI-H0731:

CYP3A4 Inducers	
	Barbiturates, brigatinib, carbamazepine, efavirenz, enzalutamide, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, st. john's wort, troglitazone

Source: The Flockhart Table. http://medicine.iupui.edu/clinpharm/ddis/main-table# (Accessed 6 March 2020).
Abbreviations: CYP=cytochrome P450.

APPENDIX 6 SUMMARY OF CHANGES

The primary purpose of Amendment 1 is to clarify the distinction between the investigational medicinal products (IMPs) to be used in this study, ie, ABI-H0731 and matching placebo (PBO), and the subjects' background NrtI therapy (non-IMP [NIMP]). This has implications for the procedures for IMP accountability and compliance activities to be performed by site personnel. Further clarifications and minor corrections have been applied. A table of summary of major changes included in Amendment 1 is provided below.

Amendment 1 Summary of Changes

Section Number and Name	Description of Change	Brief Rationale
Section 2.3	Reference Yang 2009 has been corrected to Yang 2019.	Minor correction.
Sections 4.1, 4.3 Synopsis	The number of study centers has been updated from approximately 5 to 10. ABI-H0731 and matching placebo have been defined as IMPs to make the distinction from NrtIs, which are defined as NIMP (background therapy) in this study.	To update planned sites for the study. To clarify that the use of NrtI therapy in this study is considered background therapy.
Section 5.2, Synopsis	Inclusion #4: "of child-bearing potential" has been added. Inclusion #6: "at least 2 weeks apart" has been updated to "approximately 10-14 days apart." Inclusion #7: Phrase "but <5 years" has been deleted.	Inclusion #4 has been modified to clarify that only female subjects of child-bearing potential will have to undergo a serum pregnancy test at Screening and a urine pregnancy test predose on Day 1 to qualify for the study participation. Inclusion #6 has been modified to clarify that 2 samples from the Screening period have been to be collected approximately 10-14 days apart. Inclusion #7 has been modified to expand enrollment criteria.
Section 5.3, Synopsis	Exclusion #7: "diseases or conditions, such as," has been added. Exclusion #14: "prohibited" has been added.	Exclusion #7 has been modified to clarify that "clinically significant" applies to all items listed in the criterion (minor modification). Exclusion #14 has been modified to clarify that subjects receiving prohibited herbal/over-the-counter-medications will not be eligible for study participation.

Section Number and Name	Description of Change	Brief Rationale
Section 6.1.1	Phrases "at the Screening visit" and "upon confirmation of subject eligibility on Day 1," have been added.	To clarify the sequence of events with respect to randomization and treatment assignment.
Sections 6.2, 6.3, 6.5, 6.6	This section has been modified with several edits that clarify the distinction between IMP (ABI-H0731 and PBO) and NIMP background therapy (NrtIs).	The designation of NrtIs as NIMP (background therapy) has been added to clarify how NrtIs should be handled.
Section 6.4.1	The phrase "concomitant prescription medications, over-the-counter medications, and supplements will be reported in the electronic case report form (eCRF) from the date informed consent is obtained to 30 days following the last dose of all study drug(s) – with the exception of NrtI medications used to manage CHB. Medications for management of CHB should be captured until the last study visit," has been deleted.	The deletion has been made to clarify that concomitant medications must be recorded in the subjects' source documentation until the end of study (completion of follow-up period), and that administration of NrtIs should continue to the end of the follow-up period.
Sections 7.2-7.8	The following modifications have been made: Serum and urine pregnancy testing will be conducted only for females of child-bearing potential. Immunology testing will include collection of PBMCs at Screening for subjects at selected sites only. PBMCs, serum cytokine samples, and PaxGene® DNA and RNA samples will be collected from subjects at the selected sites. Immunology samples will be collected from these subjects at premature termination visits as well. A dosing diary will be provided at all scheduled study visits. Only the IMPs will be dispensed at scheduled visits. Specified accountability by site for the IMPs. A pharmacogenomic sample will not be collected at Week 96 visit.	The modifications have been made to clarify tests and sample collections from subjects, and to clarify the distinction between handling of IMPs from that of NrtIs.

Section Number and Name	Description of Change	Brief Rationale
Section 9.4	Text has been updated to indicate the laboratory tests to be performed during an Unscheduled Visit in the event of an ALT elevation.	To clarify the laboratory tests to be performed.
Appendix 1	The 'x' for complete randomization has been deleted from Screening.	To clarify that randomization will be completed on Day 1.
	A row for HbA1c at Screening has been added.	To correct for an omission.
	'x's' have been added for dosing diary for 4-20- and 24-Weeks post.	To reflect that diaries will be provided for subjects during this follow-up period to record NrtI dosing.
	"Study drug" has been updated to "IMP (ABI-H0731/PBO)".	To clarify the distinction between IMPs and NrtIs (NIMPs).
	Footnotes 3, 11, 20, 21 have been updated.	To align with updates in Section 9.4 and Section 7.1-7.7.
	Footnotes 22, 23, and 24 have been added.	To clarify the follow up period of concomitant medications and NrtIs; to clarify that in-clinic NrtI during the follow-up period will be conducted only at the 4-Weeks Post visit; and to clarify the timepoints and conditions for immunologic testing.
	'x' has been deleted from Week 96 for pharmacogenomic sampling.	Week 96 pharmacogenomic sampling will not be conducted.
Appendix 2	Sentences "Subjects will provide whole blood PBMCs samples at Screening at selected sites only. These subjects will provide additional whole blood PBMCs samples followed by serum cytokine samples for immunologic testing at timepoints specified in Appendix 1. Additionally, these subjects will also provide PaxGene® RNA and PaxGene® DNA samples at timepoints specified in Appendix 1" have been added.	To clarify the conditions for immunologic testing.
	HbcrAb has been deleted from "HBV Virology."	Correction.

Section Number and Name	Description of Change	Brief Rationale
Appendix 3	A row for "Prolonged PR Interval or AV Block" has been added to align with standard DAIDS table. Minor corrections have been made to acidosis, calcium high, and sodium low.	Corrections were made to align with the DAIDS 2017 Corrected Version 2.1.
Appendix 4	Tubal sterilization has been added as an effective birth control method. Statement "Male subjects must avoid sperm donation from the time of the first dose of study drug and throughout the study period, and for at least 30 days after administration of the last dose of study drug," has been added.	Text has been added for comprehensive instructions.

Study Title: A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled Study Evaluating Treatment Intensification with ABI-H0731 in Subjects with Chronic Hepatitis B Infection on Nucleos(t)ide Reverse Transcriptase Inhibitors

NCT Number: NCT04454567

Date of Document: 06 May 2021

STATISTICAL ANALYSIS PLAN

Sponsor:	Assembly Biosciences, Inc 331 Oyster Point Blvd South San Francisco, CA 94030
Protocol Number:	ABI-H0731-205
Protocol Title:	A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled Study Evaluating Treatment Intensification with ABI-H0731 in Subjects with Chronic Hepatitis B Infection on Nucleos(t)ide Reverse Transcriptase Inhibitors
Product:	Vebicorvir (formerly ABI-H0731)
Protocol Version (Date):	Amendment 1 (08 September 2020)
Indication:	Chronic Hepatitis B Virus Infection
Analysis Type:	Final Analysis for Early Termination
Analysis Plan Version (Date):	Version 1.0 (06 May 2021)
Analysis Plan Author(s):	[redacted] Contractor, Biostatistics

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN APPROVAL FORM

Protocol Title:	A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled Study Evaluating Treatment Intensification with ABI-H0731 in Subjects with Chronic Hepatitis B Infection on Nucleos(t)ide Reverse Transcriptase Inhibitors
Protocol Number:	ABI-H0731-205
SAP Version (Date):	Version 1.0 (06 May 2021)

The SAP was subject to critical review and has been approved by the participating members.

Name and Title	Approval Signature	Date
[redacted] Vice President, Biometrics Assembly Biosciences	See e-signature page	
[redacted] Chief Medical Officer Assembly Biosciences	See e-signature page	

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
cHBV	chronic hepatitis B virus infection
CK	creatine kinase
CRF	case report form
CSR	clinical study report
ECG	Electrocardiogram
ET	early termination
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 infection
HLT	high-level term
LOQ	limit of quantitation
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NrtI	nucleos(t)ide reverse transciptase inhinitors
pgRNA	pergenomic RNA
PK	pharmacokinetic
PT	preferred term
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia’s formula
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAP	statistical analysis plan
SI (units)	international system of units
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

Study ABI-H0731-205 is a Phase 2a, multi-center, randomized, single-blind, placebo (PBO)-controlled study to assess the safety, antiviral activity, and pharmacokinetics (PK) of once daily dose of 300 mg vebicorvir (VBR, formerly ABI-H0731) (3 × 100 mg tablets) administered in addition to standard of care nucleos(t)ide reverse transciptase inhibitors (NrtI) in subjects with chronic hepatitis B virus infection (cHBV) who have not achieved adequate virologic suppression of hepatitis B virus (HBV) DNA less than the limit of quantitation (<LLOQ) on NrtI alone. Due to a change in the Sponsor's development strategy, Study ABI-H0731-205 has been terminated early. At the time of early termination, a total of 2 subjects were randomized in the entire study.

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the synoptic clinical study report (CSR) for Study ABI-H0731-205. This SAP is based on the study protocol Amendment 1 dated 08 September 2020 and the electronic case report form (eCRF). The SAP will be finalized before database lock. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of VBR when administered in combination with NrtI in subjects with cHBV
- To evaluate the effect of the addition of VBR to NrtI in fully suppressing HBV DNA in subjects with cHBV

The secondary objectives of this study are as follows:

- To evaluate the effect of the addition of VBR to NrtI in reducing HBV pregenomic RNA (pgRNA) levels in subjects with cHBV
- To evaluate the effect of the addition of VBR to NrtI in reducing HBV antigens (ie, hepatitis B "e" antigen [HBeAg], hepatitis B core-related antigen [HBcrAg], and hepatitis B surface antigen [HBsAg]) in subjects with cHBV
- To evaluate the effect of the addition of VBR to NrtI on normalization of alanine aminotransferase (ALT) in subjects with abnormal ALT
- To evaluate the PK of VBR and NrtI in subjects with cHBV
- To evaluate the emergence of resistance to VBR when administered in combination with NrtI

The exploratory objectives of this study are as follows:

- To assess the relationship between immunological and/or viral biomarkers with virologic and/or clinical outcomes

- For subjects who provide an optional pharmacogenomic sample, to evaluate the potential contribution of host genomics to clinical or virologic outcomes and/or drug disposition

1.2. Study Design

This is a Phase 2a, multi-center, randomized, single-blind, PBO-controlled study. This study will assess the safety, antiviral activity, and PK of VBR administered in addition to standard of care NrtI in subjects with cHBV who have not achieved adequate virologic suppression of HBV DNA <LLOQ on NrtI alone.

Approximately 40 eligible subjects will be randomized in a 1:1 ratio to the two treatment groups as below.

Treatment with VBR or PBO and NrtI will be administered orally, once daily:

- Group 1 will receive VBR+NrtI for 96 weeks
- Group 2 will receive PBO+NrtI for 48 weeks, and then VBR+NrtI until Week 96

All subjects will continue to receive NrtI alone during the 24-week follow-up period from Week 96 through Week 120. Treatment assignments will be stratified by the concurrent NrtI administered (ie, entecavir, ETV) versus tenofovir (alafenamide versus [TAF] or disoproxil fumarate [TDF]) and HBV DNA (HBV DNA ≥500 IU/mL versus <500 IU/mL) during the Screening visits. The study will enroll up to 75% subjects on ETV.

The schedule of study procedures is presented in tabular form in Appendix 1 of the study protocol.

1.3. Sample Size and Power

Approximately 40 subjects with cHBV will be enrolled in the study. Subjects will be randomized to receive either 300 mg VBR (3×100 mg tablets) or matching PBO in a 1:1 ratio in addition to standard of care NrtI. Since 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

Randomization of eligible subjects to their respective treatment assignments will be performed centrally using an Interactive Response Technology (IRT) system. Following successful completion of Screening assessments and confirmation of subject eligibility, site personnel will enter the subject specific information in the IRT system and receive a subject number and

treatment assignment. The IRT system will assign eligible subjects in a 1:1 ratio to receive either 300 mg VBR+NrtI for 96 weeks (n=20) or PBO+NrtI for 48 weeks followed by 300 mg VBR+NrtI for 48 weeks (n=20). Individual treatment assignments will be stratified by the concurrent NrtI administered (ie, ETV versus TDF or TAF) and HBV DNA (HBV DNA ≥500 IU/mL versus <500 IU/mL) during the Screening visits. The study will enroll approximately 75% subjects receiving ETV. Additional information on the use of the IRT is provided in the IRT user manual.

1.4.2. Blinding

Study subjects, Investigators, and other site personnel administering the study drug, performing the clinical assessments and handling data on the study subjects, will be blinded to individual subject treatments assignments (ie, PBO+NrtI or VBR+NrtI) throughout the duration of the study. To support maintenance of the study blind, HBV pgRNA results will not be provided to the study subjects, Investigators, or other site personnel until completion of the study.

Except for the personnels with standard unblinded roles, all other study team members remain blinded prior to the database lock.

2. TYPE OF PLANNED ANALYSIS

2.1. Final Analysis

The study is being terminated early. The final analysis will be performed after the enrolled subjects have been terminiated from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data has been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Statistical analysis will not be performed for this study. Only listings will be provided.

By-subject listings will be presented for all subjects in the All Randomized Analysis Set and sorted by subject ID number, visit date, and time (if applicable) in chronological order within the subject. The treatment group to which subjects were randomized will be used in the listings.

3.1. Analysis Sets

Analysis set defines the subjects to be included in an analysis. Analysis set and its definition is provided in this section. The analysis set will be identified and included as a subtitle of each listing.

3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all subjects who were randomized in the study.

3.2. Data Handling Conventions and Transformations

3.2.1. General

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, imputed month and day (January 1st), and informed consent date.

3.2.2. Non-PK Data

The laboratory data that are below the LLOQ or above the upper limit of quantitation (LOQ) will be listed as such.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A subject disposition listing will be provided by subject identification (ID) number in ascending order based on All Randomized Analysis Set. The treatment group, date of randomiazation, date of first and last dose, the status of study drug and study completion, and reasons for premature discontinuation will be presented in the by-subject listing.

4.2. Extent of Study Drug Administration

A study drug administration listing will be provided by subject ID number in ascending order based on All Randomized Analysis Set. The planned treatment group and actual drug received, dose amount and unit, dose frequency, route, dose start date, dose end date, and discontinuation from the study drug will be included in the listing.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, sex, race, and ethnicity), baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be provided for all subjects in the All Randomized Analysis Set.

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

5.2. Baseline Disease Characteristics

A by-subject listing of baseline disease characteristics based on the All Randomized Analysis Set will be provided by subject ID number in ascending order. The following baseline disease characteristics will be included in the listing:

- Years positive for HBV
- HBV Genotype
- Type of nucleoside/nucleotide treatment at Baseline
- Years on current HBV treatment (years)
- Baseline HBeAg status (positive, negative)
- Baseline HBV DNA (log_{10} IU/mL) and HBV DNA group (< LLOQ)
- Baseline HBV pgRNA (log_{10} U/mL) and HBV pgRNA group (< LLOQ)
- Baseline HBeAg (log_{10} IU/mL) and HBV HBeAg group (< LLOQ)
- Baseline HBcrAg (log_{10} kU/mL) and HBV HBcrAg group (< LLOQ)
- Baseline HBsAg (log_{10} IU/mL) and HBV HBsAg group (< LLOQ)
- Baseline ALT (U/L) and ALT group (>ULN [Covance], >ULN [AASLD])
- Baseline HBeAg antibody (HBeAb)
- Baseline HBsAg antibody (HBsAb)
- Liver biopsy staging
- Fibroscan result

6. EFFICACY ANALYSES

No formal efficacy analysis will be performed. A listing of virology parameters will be provided by subject ID number and visit in ascending order based on the All Randomized Analysis Set. The following virology parameters will be included in the listing:

- HBV DNA
- HBV pgRNA
- HBsAg
- HBeAg
- HBcrAg
- HBeAb
- HBsAb

7. SAFETY ANALYSES

7.1. Adverse Events

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). 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 the data listing.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the Investigator selected "Related" on the AE CRF to the question of "Relationship to ABI-H0731/Placebo" based on the Investigator's choice. Events for which the Investigator did not record relationship will show the relationship as missing in the by-subject data listing.

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 on or after the study drug start date and no later than 28 days after permanent discontinuation of study drug.

7.1.6. Adverse Events Results

All AEs will be provided in a by-subject listing based on the All Randomized Analysis Set.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be presented based on the All Randomized Analysis Set. The lab values that are below LLOQ or above the upper LOQ will be listed as such. A by-subject listing for all laboratory test results (including hematology, serum chemistry, and urinalysis) will be provided by subject ID number and time visit in chronological order.

7.2.1. Graded Laboratory Values

The criteria specified in the study protocol will be used to grade laboratory results as normal (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3) or potentially life threatening (Grade 4). See Appendix 3 of the study protocol for detailed DAIDS grading criteria on the relevant laboratory tests. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1.

The relevant reference range and DAIDS severity grade will also be provided in the laboratory test listing.

7.3. Body Weight and Vital Signs

A by-subject listing of vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min], respiration [breaths/min], and body temperature [ºC]), body weight, height, and BMI 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 the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

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

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

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

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug.

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

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

- A medication started after the first dosing date but prior to or on the last dosing date of study drug.

- 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 medication started and stopped on the same day as the first dosing date or the last dosing date of study drug

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

All prior and concomitant medications will be provided based on All Randomized Analysis Set in a by-subject listing sorted by subject ID number and administration date in chronological order. The Anatomical Therapeutic Chemical (ATC) drug class Level 2, preferred name of medications will be included in the listing.

7.5. Electrocardiogram Results

A by-subject listing for overall ECG assessment results will be provided by subject ID number and visit in chronological order. The ECG date, overall interpretation of the ECG, significance of abnormality will be presented.

7.6. Other Safety Measures

For female subjects in the All Randomized Analysis Set, results from urine pregnancy tests will be presented in a data listing.

8. PHARMACOKINETIC (PK) ANALYSES

PK analysis will not be performed for this study.

9. REFERENCES

None.

10. SOFTWARE

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

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

None.

Signature Page for VV-TMF-04911 v1.0

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