Study Title: A Randomized Phase 2a, Multicenter, Open-label Study Evaluating ABI-H0731-Containing Regimens in Patients with Chronic Hepatitis B

NCT Number: 04781647

Date of Document: 29 July 2021

CLINICAL RESEARCH PROTOCOL

PROTOCOL TITLE:	A Randomized Phase 2a, Multicenter, Open-Label Study Evaluating ABI-H0731-Containing Regimens in Patients with Chronic Hepatitis B
STUDY NUMBER:	ABI-H0731-203
DRUG:	ABI-H0731
SPONSOR:	Assembly Biosciences 331 Oyster Point Boulevard, 4th Floor South San Francisco, California 94080, USA (833) 509-4583
AMENDMENT 3.0, DATE:	29 July 2021
AMENDMENT 2.0, DATE:	09 December 2020
AMENDMENT 1.0, DATE:	20 July 2020
ORIGINAL PROTOCOL DATE:	07 December 2018

CONFIDENTIALITY STATEMENT

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Randomized Phase 2a, Multicenter, Open-Label Study Evaluating ABI-H0731-Containing Regimens in Patients with Chronic Hepatitis B

Protocol Number: ABI-H0731-203

Protocol Date: Amendment 3.0, 29 July 2021

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) harmonised tripartite guideline E6(R2) 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.
- China GCP (2020)

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] Assembly Biosciences	[redacted]

INVESTIGATOR STATEMENT

Protocol Title:	A Randomized Phase 2a, Multicenter, Open-Label Study Evaluating ABI-H0731-Containing Regimens in Patients with Chronic Hepatitis B
Protocol Number:	ABI-H0731-203
Protocol:	Amendment 3.0, 29 July 2021

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[R2]) 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 Statement page in your records and provide a copy to your site monitor for archival in the Trial Master File.

1. SYNOPSIS

Protocol Number:	ABI-H0731-203
Title:	A Randomized Phase 2a, Multicenter, Open-label Study Evaluating ABI-H0731-Containing Regimens in Patients with Chronic Hepatitis B
Phase:	2a
Number of Subjects:	Approximately 60
Study Duration:	Up to 45 days for Screening, 48 weeks of treatment and 12 weeks of follow-up
Rationale:	Chronic hepatitis B (CHB) is a major cause of liver-related morbidity and mortality worldwide. ABI-H0731 (731) is an orally administered, direct-acting antiviral agent targeting the hepatitis B virus (HBV) core protein. Through its interaction with core protein, 731 interferes with multiple steps in the viral lifecycle including early events (capsid disassembly and DNA delivery to the nucleus for formation of covalently closed circular [cccDNA]) and late events (assembly of pregenomic (pg) RNA-containing capsids which are required for HBV replication). ABI-H0731 may also prevent newly formed DNA-containing nucleocapsids from delivering HBV DNA to the nucleus to amplify the pool of cccDNA in infected cells. Entecavir (ETV) is an approved, orally administered direct-acting antiviral that inhibits the reverse transcription of HBV pgRNA to DNA. Pegylated (Peg)-interferon alpha (IFNα) is an approved, subcutaneously administered biologic which has both antiviral and immunomodulatory activities. While the specific mechanisms by which Peg-IFNα exerts its antiviral activity against HBV are not fully understood, it is thought to inhibit multiple steps in the viral lifecycle and to augment the host immune response. The combination of 731 with ETV and Peg-IFNα will provide multiple complementary antiviral mechanisms that may act synergistically to increase CHB cure rates. It is anticipated that the combination of 731 and ETV with or without Peg-IFNα will be safe, reduce viral nucleic acids (ie, HBV pgRNA and HBV DNA) and reduce viral antigens (ie, hepatitis B "e" antigen [HBeAg], hepatitis B core-related antigen [HBcrAg], and hepatitis B surface antigen [HBsAg]) in subjects with CHB. This Phase 2a study will explore the safety of the 731+ETV+Peg-IFNα combination, its antiviral activity, as measured by effects on serum HBV pgRNA, HBV DNA, and HBV antigens, and pharmacokinetics (PK).
Target Population:	Male or female, 18 to 65 years (inclusive) of age, treatment naïve with HBeAg positive CHB and no evidence of cirrhosis or end-stage liver disease. Eligible subjects must be candidates to receive Peg-IFNα according to approved prescribing information.
Test Product(s):	731 100 mg tablets + ETV 0.5 mg tablets + Peg-IFNα 180 µg solution
Reference Product(s):	• 731 100 mg tablets + ETV 0.5 mg tablets

- ETV 0.5 mg tablets + Peg-IFNα 180 µg solution

Study Design:

This is a randomized Phase 2a, multicenter, open-label study evaluating the safety, antiviral activity, and PK of 731 administered in addition to ETV with or without Peg-IFNα in treatment-naïve Chinese subjects with CHB.

Approximately 60 eligible subjects with HBeAg positive CHB will be randomly assigned in a 1:1:1 ratio to the treatment groups described in the following figure.

Abbreviations: BL = Baseline; ETV = entecavir; Peg-IFNα = pegylated-interferon alpha; Wk = week.

Treatment with 731 (where applicable) and ETV will be administered orally, once daily; treatment with Peg-IFNα (where applicable) will be administered subcutaneously, once weekly.

- Group 1 will receive 731+ETV for 24 weeks
- Group 2 will receive 731+ETV+Peg-IFNα for 24 weeks
- Group 3 will receive ETV+Peg-IFNα for 24 weeks

All subjects will receive 731+ETV from Week 24 through Week 48 and then ETV alone from Week 48 through Week 60 during the 12-week follow-up period.

Treatment assignments will be stratified by the HBV genotype (GT; ie, HBV GT A or B vs GT C or D vs other GTs) and baseline alanine aminotransferase (ALT; ie, ALT <5 × upper limit of normal [ULN] vs ALT ≥5 × ULN) during the Screening visits.

Objectives:

Primary Objective:

- To evaluate the safety and tolerability of 731 when administered in combination with ETV with or without Peg-IFNα in subjects with CHB

Secondary Objectives:

- To evaluate the effect of 731 when administered in combination with ETV with or without Peg-IFNα in reducing HBV pgRNA levels in subjects with CHB
- To evaluate the effect of 731 when administered in combination with ETV with or without Peg-IFNα in reducing HBV DNA levels in subjects with CHB
- To evaluate the effect of 731 when administered in combination with ETV with or without Peg-IFNα in reducing HBV antigens (ie, HBeAg, HBcrAg, and HBsAg) in subjects with CHB
- To evaluate the effect of 731 when administered in combination with ETV with or without Peg-IFNα on normalization of ALT

- To evaluate the PK of 731 and future PK evaluation of Peg-IFNα and ETV in subjects with CHB
- To evaluate the emergence of resistance to 731 when administered with ETV with or without Peg-IFNα

Primary Endpoint:

Primary Endpoint:

- Proportion of subjects with adverse events, premature treatment discontinuation, and abnormal laboratory results

Secondary Endpoints:

Secondary Endpoints:

- Mean change in $\log_{10}$ HBV pgRNA from Baseline at each timepoint
- Mean change in $\log_{10}$ HBV DNA from Baseline 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 normal ALT at each timepoint
- Analysis of 731 and ad hoc analysis of Peg-IFNα and ETV drug concentrations
- The incidence of HBV variants with reduced susceptibility to 731

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 treatment groups. Continuous endpoints will be described using the mean, standard deviation, median, minimum, and maximum. Categorical endpoints will be described using the number and percent of subjects who meet the endpoint criterion.

Due to sample size limitations, no formal statistical inference is planned. Assessment of antiviral activity will be evaluated 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 must be non-pregnant and have a negative serum pregnancy test at Screening and a negative urine pregnancy test predose on Day 1
5. Chronic hepatitis B infection, defined as HBV infection for ≥6 months documented, for example, by at least 2 measurements of HBsAg positivity and/or detectable HBV DNA ≥6 months apart (inclusive of Screening). For subjects without clear documentation of CHB, serum immunoglobulin M (IgM) antibody to the HBV core antigen (HBcAb) must be negative at Screening to exclude acute HBV infection.

6. HBeAg positive with HBV DNA ≥2 × 10^4 IU/mL at Screening
7. Lack of cirrhosis or advanced liver disease as documented by the following:
    - Liver biopsy results demonstrating absence of cirrhosis (eg, METAVIR F0-F3 or equivalent) within 1 year of Screening

      OR

    - Fasting FibroScan® ≤12 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 (eg, F0-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
8. A candidate for interferon-based therapy
9. Agreement to comply with protocol-specified contraceptive requirements (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, be willing to receive subcutaneous injections of Peg-IFNα (if applicable), and in the opinion of the Investigator, be willing to adhere to study treatment and procedures

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
    - A nucleos(t)ide reverse transcriptase inhibitor of the HBV polymerase (NrtI) (ETV, tenofovir disoproxil fumarate or tenofovir alafenamide) for >4 weeks at any time. Note, NrtI treatment of ≤4 weeks duration cannot be within 6 months prior to Screening
    - Interferon-based therapy within 6 months prior to Screening
    - Liver-protecting and/or ALT-lowering treatment including traditional Chinese medicine within 1 month of Screening
    - Lamivudine, telbivudine or adefovir (of any duration)
    - Previous treatment with siRNA within 9 months prior to Screening
    - HBV core inhibitors (any duration)
    - Previous treatment with any other investigational agent for HBV infection within 6 months prior to Screening
2. *Deleted per protocol amendment 3*

3. Co-infection with HIV, 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 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 psychiatric disease, including severe depression, history of suicidal ideation or suicide attempt
8. Clinically significant 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
9. History of hepatocellular carcinoma (HCC)
10. 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
11. History or presence at Screening of electrocardiogram abnormalities deemed clinically significant, in the opinion of the Investigator
12. History of hypersensitivity or idiosyncratic reaction to any components or excipients of the investigational drug
13. History of any significant food or drug-related allergic reactions such as, anaphylaxis or Stevens-Johnson syndrome
14. The following are exclusionary laboratory results at Screening:
    - Hemoglobin <12g/dL for males or <11g/dL for females
    - Platelet count <100,000/mm^3
    - White blood cell count <2,500/mm^3
    - Absolute neutrophil count <1,500/mm^3
    - Albumin <lower limit of normal
    - History of thyroid disease poorly controlled on prescribed medications, with thyroid-stimulating hormone, free triiodothyronine or free thyroxine outside the normal limits

- Total bilirubin >1.2 × 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 ≤1 × ULN or ≥10 × ULN
- Serum alpha fetoprotein (AFP) ≥100 ng/mL. If AFP at Screening is > ULN but <100 ng/mL, the subject is eligible if hepatic imaging prior to initiation of study drug reveals no lesions indicative of possible HCC
- International Normalized Ratio >1.5 × ULN (unless on a stable anticoagulant regimen)
- Glomerular filtration rate <60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation
- Serum creatinine >1.5 × ULN
- Any other laboratory abnormality deemed clinically significant by the Sponsor or the Investigator

15. Subjects receiving prohibited concomitant medications or medications that should be avoided (as outlined in Section 6.6 and Appendix 5) within 7 days or 5 half-lives (if known), whichever is longer, prior to administration of the first dose of study drug (Day 1) and for the duration of the study period. Please refer to Exclusion Criterion #1 for criteria regarding liver protecting and/or ALT lowering agents
16. Participation in another clinical study of any non-HBV-related 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 (Day 1), whichever is longer.
17. Subjects who have received, in the previous 4 weeks, a treatment likely to alter the immune response (ie, 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
ABI-H0731	731
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
cHBV	chronic hepatitis B virus infection
CRO	Clinical Research Organization
CSR	clinical study report
CYP	cytochrome P450
DAIDS	Division of AIDS
ECG	electrocardiogram
eCRF	electronic case report form
ETV	entecavir
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GT	genotype
HAV	hepatitis A virus
HBcAb	antibody to the HBV core protein
HBcrAg	hepatitis B core-related antigen
HBeAb	antibody to HBeAg
HBeAg	hepatitis B “e” antigen
HBsAb	antibody to HBsAg
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E 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
IFNα	interferon alpha

Abbreviation	Term or Definition
IgM(s)	immunoglobulin M(s)
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NrtI	nucleos(t)ide reverse transcriptase inhibitor of the HBV polymerase
Peg	pegylated
pgRNA	[HBV] pregenomic RNA
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
SVR	sustained virologic response
T4	thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
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 (Colvin & Mitchell 2010; EASL 2017; El-Serag 2012). There are 4 major HBV genotypes (A, B, C, and D). Genotype A is regarded as pandemic and is predominantly found in North America, Northern/Western Europe, and Central Africa. HBV genotype B is most common in Asia including China, Vietnam, Japan, Taiwan, and Indonesia. Genotype C is predominant in East Asia and Oceania. Genotype D (also pandemic) is most highly prevalent in North America, Asia (including India), the Mediterranean, India, and the Middle East (Guettouche & Hnatyszyn 2005). The global prevalence of chronic HBV infection shows wide geographic variation, with a prevalence of >6% of the population in highly endemic regions such as the Western Pacific and African Regions, 1.6% to 3.3% of people in moderately endemic regions (eg, Eastern Mediterranean, South-East Asia, and European Regions), and <1% in locales of low endemicity such as the Region of the Americas (WHO 2019).

In China, the pooled estimated prevalence of HBV infection in the general population from 2013 to 2017 was close to 7% (Wang et al 2019). Despite the implementation of HBV vaccination programs in China, new cases of HBV infection are still common; it is estimated that in 2018, 84 million people were HBsAg positive (Wang et al 2019). A recent report estimates that 97 million people in China are HBV carriers and, of these, at least 20 million suffer from active cHBV with or without cirrhosis and/or HCC (Cui et al 2013). Although significant improvements in liver disease prevention, diagnosis, management, and treatment have been made, HCC is the second most common cancer in China. This translates to death due to liver cancer in approximately 383,000 people every year in China, which accounts for more than half of the deaths from liver cancer worldwide (Wang et al 2014).

The clinical stages of HBV infection 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 et al 2015; Hoofnagle et al 2007; Lok & McMahon 2009; Pungpapong & Kim 2013; Sorrell et al 2009; Yim & Lok 2006; WHO 2019). 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 pregenomic RNA (pgRNA) and HBV core-related antigen (b

) have also been used as markers of infection. Historically, treatment goals included prevention of HBV-related liver injury through suppression of HBV replication to low levels, achievement of HBeAg loss 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 has been 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 (Podlaha et al 2019), sustained undetectable HBV DNA without HBsAg loss after stopping treatment ("sustained virologic responses [SVR]") may be considered as an intermediate goal (Cornberg et al 2020).

Currently, there are 2 clinically accepted, first-line treatment options for CHB: nucleos(t)ide reverse transcriptase inhibitors of the HBV polymerase (NrtIs) and interferon alfa (IFNα). The NrtIs are orally administered, potent, direct-acting antivirals targeting the reverse transcription of HBV pgRNA to DNA. They are broadly used, generally safe and well-tolerated and have demonstrated success in achieving and maintaining viral suppression in most patients (Lampertico & Liaw 2012). However, despite suppression of HBV DNA for extended periods of time with NrtI treatment, HBeAg and HBsAg loss is uncommon and the template for ongoing viral replication, cccDNA, is not eliminated in most patients. As a result, off-treatment SVR with NrtIs is rare, necessitating long-term chronic suppressive treatment. In contrast, IFNα is an approved, subcutaneously administered protein which directly and indirectly targets HBV. While the specific mechanism of action is not fully understood, it is thought that IFNα inhibits multiple steps in the viral lifecycle resulting in modest antiviral activity (Konerman & Lok 2016). In addition, IFNα augments innate immunity and triggers HBV-specific T cell responses. Pegylated (Peg)-IFNα is the preferred formulation due to increased pharmacokinetic (PK) and pharmacodynamic half-life supporting weekly dosing. The recommended treatment duration is 48 weeks. Compared with NrtIs, IFNα is poorly tolerated due to common side effects, including flu-like symptoms, mood disturbances, and cytopenias. With a finite treatment duration, IFNα results in a higher rate of durable virologic response and modest HBeAg and HBsAg loss. However, even with the incremental improvements in virologic response of Peg-IFNα monotherapy, this regimen remains suboptimal and is offset by its safety and tolerability profile.

There is a need for improved, novel HBV therapies, including combination regimens that result in a higher proportion of patients achieving durable virologic response and clinical outcomes following finite treatment duration. Ideally, components of a combination regimen for cHBV should have additive or synergistic antiviral activity, promote restoration of the immune response and have no added toxicity. Combination therapy with NrtIs and IFNα or Peg-IFNα has been shown to be safe in multiple small studies with potential therapeutic value in select patient subgroups (Brouwer et al 2016; Viganò et al 2018); however, none of these combination approaches have been approved for use or recommended by guidelines due to limited evidence that the combination is superior to either monotherapy (Xie et al 2014).

ABI-H0731 (731) is a novel, HBV core inhibitor 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. Thus, inhibition of HBV core protein functions by 731, when used in combination with currently approved HBV antivirals, has the potential to immediately improve current therapy for cHBV 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 731 is described in the Investigator's Brochure (IB).

2.2.2. Preclinical Pharmacology and Toxicology

Refer to the 731 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, including the Phase 2a studies, Study ABI-H0731-201 (Study 201) and Study ABI-H0731-202 (Study 202), and preliminary data from the ongoing Phase 2a Study ABI-H0731-211 are provided in the 731 IB.

2.3. Study Rationale

In the treatment of chronic viral infections, combinations of antiviral agents that inhibit viral replication by different and complementary mechanisms can afford improved efficacy. There are 2 first-line recommended therapies for CHB: NrtIs, which directly target reverse transcription of HBV pgRNA to HBV DNA, and IFNα, which has both antiviral and immunomodulatory activities. Despite distinct and complementary mechanisms of action, combination therapies of NrtIs and IFNα has not been adopted by HBV treatment guideline committees. A number of studies have demonstrated the potential benefit for interferon combination regimens in selected patient subgroups (Brouwer et al 2016; Viganò et al 2018) while other studies indicate limited evidence that combination regimens are superior to monotherapy (Xie et al 2014).

The HBV core protein is involved in multiple steps in the HBV life cycle, including early events (capsid disassembly and DNA delivery to the nucleus for formation of cccDNA) and late events (assembly of pgRNA-containing capsids which are required for HBV replication); 731 may also prevent newly formed DNA-containing nucleocapsids from delivering HBV DNA to the nucleus to amplify the pool of cccDNA in infected cells (Belloni et al 2013; Levrero et al 2009). Inhibition of HBV core protein represents a novel therapeutic strategy for the treatment of CHB (Yang et al 2019). Analyses of Phase 2a studies, including ongoing open-label study, Study 211, demonstrate that treatment-naïve and virologically suppressed subjects treated with 731+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 731 to ETV and Peg-IFNα therapy may increase suppression of HBV DNA, HBV pgRNA, and viral antigens. The present Phase 2a study (ABI-H0731-203) will explore the safety of combination therapy with 731, ETV and Peg-IFNα and evaluate the antiviral activity as measured by viral nucleic acids (ie, HBV pregenomic pgRNA and HBV DNA) and viral antigens (ie, HBeAg, HBcrAg, and HBsAg).

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

- To evaluate the safety and tolerability of 731 when administered in combination with ETV with or without Peg-IFNα in subjects with CHB

3.1.2. Secondary Objectives

- To evaluate the effect of 731 when administered in combination with ETV with or without Peg-IFNα in reducing HBV pgRNA levels in subjects with CHB
- To evaluate the effect of 731 when administered in combination with ETV with or without Peg-IFNα in reducing HBV DNA levels in subjects with CHB

- To evaluate the effect of 731 when administered in combination with ETV with or without Peg-IFNα in reducing HBV antigens (ie, HBeAg, HBcrAg, and HBsAg) in subjects with CHB
- To evaluate the effect of 731 when administered in combination with ETV with or without Peg-IFNα on normalization of alanine aminotransferase (ALT)
- To evaluate the PK of 731 and future PK evaluation of Peg-IFNα and ETV in subjects with CHB
- To evaluate the emergence of resistance to 731 when administered with ETV with or without Peg-IFNα

3.2. Study Endpoints

3.2.1. Primary Endpoint

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

3.2.2. Secondary Endpoints

- Mean change in $\log_{10}$ HBV pgRNA from Baseline at each timepoint
- Mean change in $\log_{10}$ HBV DNA from Baseline 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 normal ALT at each timepoint
- Analysis of 731 and ad hoc analysis of Peg-IFNα and ETV drug concentrations
- The incidence of HBV variants with reduced susceptibility to 731

4. STUDY PLAN

4.1. Study Design

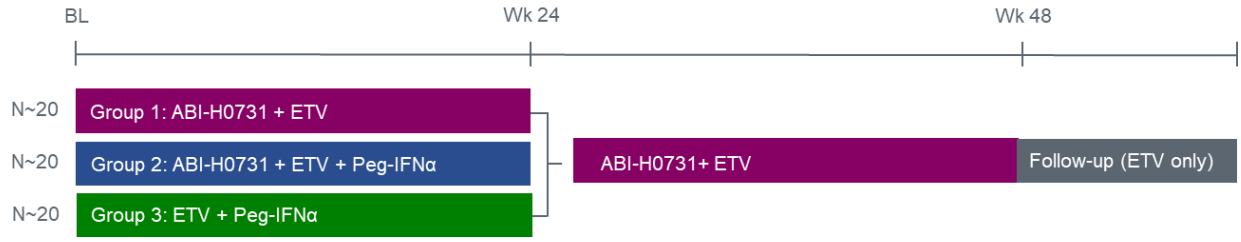
This is a randomized Phase 2a, multicenter, open-label study evaluating the safety, antiviral activity, and PK of 731 administered in addition to ETV with or without Peg-IFNα in treatment-naïve, Chinese subjects with CHB. The study will be conducted at approximately 5 to 10 study sites in China.

Approximately 60 eligible subjects with HBeAg positive CHB will be randomly assigned in a 1:1:1 ratio to the treatment groups shown in the study overview presented in Figure 1.

Treatment with 731 and/or ETV will be administered orally, once daily; treatment with Peg-IFNα will be administered subcutaneously, once weekly. Group 1 will receive 731+ETV for 24 weeks, Group 2 will receive 731+ETV+Peg-IFNα for 24 weeks. Group 3 will receive ETV+Peg-IFNα for 24 weeks. All subjects will receive 731+ETV from Week 24 through Week 48 and then ETV alone from Week 48 through Week 60 during the 12-week follow-up period.

Treatment assignments will be stratified by the HBV genotype (GT; ie, GT A or B vs GT C or D, vs other GTs) and baseline ALT (ie, ALT <5 × upper limit of normal [ULN] vs ALT ≥5 × ULN) during the Screening visits.

Figure 1: Study Overview



Abbreviations: BL = Baseline; ETV = entecavir; Peg-IFNα = pegylated-interferon alpha; Wk = week.

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 7.11.

4.2. Dose Justification

In the Phase 1 clinical studies, 731 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 once-daily doses of up to 300 mg for 14 days. All treatment-emergent adverse events (TEAEs) were considered mild (Grade 1) and reversible. In subjects with CHB, 731 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, 200, and 300 mg daily in subjects with CHB. Phase 2 studies (Studies 201, 202, and 211) demonstrate that 300 mg 731 administered once daily 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 731 300 mg administered in addition to ETV with or without Peg-IFNα will be safe, well tolerated and demonstrate improved antiviral activity in subjects with CHB. The cumulative safety, tolerability, and antiviral activity data generated to date support the conduct of the proposed study. In this study, ETV and Peg-IFNα will be administered in accordance with the approved product labeling.

4.3. Duration of Treatment

All subjects will receive their randomized treatment for 24 weeks. After completion of the assigned treatment, all subjects will receive 731+ETV for an additional 24 weeks and then ETV only during the 12-week follow-up period. After completion of the 12-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 60 male or female subjects between the ages of 18 and 65 years inclusive will be enrolled in the study. Subjects will be treatment-naïve, have HBeAg positive CHB, and no evidence of cirrhosis or end-stage liver disease.

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/m^2 and a minimum body weight of 45 kg (inclusive)
4. Female subjects must be non-pregnant and have a negative serum pregnancy test at Screening and a negative urine pregnancy test predose on Day 1
5. Chronic hepatitis B infection, defined as HBV infection for ≥6 months documented, for example, by at least 2 measurements of HBsAg positivity and/or detectable HBV DNA ≥6 months apart (inclusive of Screening). For subjects without clear documentation of CHB, serum immunoglobulin M (IgM) antibody to the HBV core antigen (HBcAb) must be negative at Screening to exclude acute HBV infection.
6. HBeAg positive with HBV DNA ≥2 × 10^4 IU/mL at Screening
7. Lack of cirrhosis or advanced liver disease as documented by the following:
   - Liver biopsy results demonstrating absence of cirrhosis (eg, METAVIR F0-F3 or equivalent) within 1 year of Screening

     OR
   - Fasting FibroScan® ≤12 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 (eg, F0-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
8. A candidate for interferon-based therapy
9. Agreement to comply with protocol-specified contraceptive requirements (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, be willing to receive subcutaneous injections of Peg-IFNα (if applicable), and in the opinion of the Investigator, be willing to adhere to study treatment and procedures

5.3. Exclusion Criteria

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

1. Current or prior treatment for CHB with
    - NrtI class (ETV, tenofovir disoproxil fumarate or tenofovir alafenamide) for >4 weeks at any time. Note, NrtI treatment of ≤4 weeks duration cannot be within 6 months prior to Screening
    - Interferon-based therapy within 6 months prior to Screening
    - Liver-protecting and/or ALT-lowering treatment, including traditional Chinese medicine, within 1 month of Screening
    - Lamivudine, telbivudine or adefovir (of any duration)
    - Previous treatment with siRNA within 9 months prior to Screening
    - HBV core inhibitors (any duration)
    - Previous treatment with any other investigational agent for HBV infection within 6 months prior to Screening
2. *Deleted per protocol amendment 3*
3. Co-infection with 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 psychiatric disease, including severe depression, history of suicidal ideation or suicide attempt
8. Clinically significant 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
9. History of HCC
10. 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

11. History or presence at Screening of electrocardiogram (ECG) abnormalities deemed clinically significant, in the opinion of the Investigator
12. History of hypersensitivity or idiosyncratic reaction to any components or excipients of the investigational drug
13. History of any significant food or drug-related allergic reactions such as, anaphylaxis or Stevens-Johnson syndrome
14. The following exclusionary laboratory results at Screening:
    - Hemoglobin <12g/dL for males or <11g/dL for females
    - Platelet count <100,000/mm^3
    - White blood cell count <2,500/mm^3
    - Absolute neutrophil count <1,500/mm^3
    - Albumin <lower limit of normal
    - History of thyroid disease poorly controlled on prescribed medications, with thyroid-stimulating hormone (TSH), free triiodothyronine or free thyroxine (T4) outside the normal limits
    - Total bilirubin >1.2 × 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 ≤1 × ULN or ≥10 × ULN
    - Serum alpha fetoprotein (AFP) ≥100 ng/mL. If AFP at Screening is > ULN but <100 ng/mL, the subject is eligible if hepatic imaging prior to initiation of study drug reveals no lesions indicative of possible HCC
    - International Normalized Ratio (INR) >1.5 × ULN (unless on a stable anticoagulant regimen)
    - Glomerular filtration rate <60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (Levey et al 2009)
    - Serum creatinine >1.5 × ULN
    - Any other laboratory abnormality deemed clinically significant by the Sponsor or the Investigator
15. Subjects receiving prohibited concomitant medications or medications that should be avoided (as outlined in Section 6.6 and Appendix 5) within 7 days or 5 half-lives (if known), whichever is longer, prior to administration of the first dose of study drug (Day 1) and for the duration of the study period. Please refer to Exclusion Criterion #1 for criteria regarding liver protecting and/or ALT lowering agents

16. Participation in another clinical study of any non-HBV-related 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 (Day 1), whichever is longer.
17. Subjects who have received, in the previous 4 weeks, a treatment likely to alter the immune response (intravenous immunoglobulins [IgMs], 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. The IRT system will assign eligible subjects in a 1:1:1 ratio to receive either 731+ETV, 731+ ETV+Peg-IFNα or ETV+Peg-IFNα for 24 weeks. Treatment assignments will be stratified by the HBV GT (ie, GT A or B vs GT C or D, vs other GTs) and baseline ALT (ie, ALT <5 × ULN vs ≥5 × ULN) collected at Screening. Additional information on the use of the IRT is provided in the IRT User Manual.

6.1.2. Blinding

Not applicable as this is an open-label study.

6.2. Study Treatments

Details concerning dose and administration of the study drugs (731, ETV and Peg-IFNα) are provided in the following sections.

6.2.1. ABI-H0731

ABI-H0731 will be administered orally, once daily as three 100-mg tablets (ie, 300 mg/day).

ABI-H0731 will be taken at the same time as ETV and consequently will be administered on an empty stomach (Section 6.2.2).

6.2.2. Entecavir

Entecavir will be administered as a single oral 0.5-mg tablet once daily. Entecavir should be administered on an empty stomach (ie, at least 2 hours after a meal and 2 hours before the next meal). Further dosing information for ETV is provided in the package insert for the commercially available product used in this study.

6.2.3. Pegylated-Interferon Alpha

The starting dose of Peg-IFNα will be 180 µg administered once weekly as a subcutaneous injection. Dose adjustment to lower doses (135 µg, 90 µg, or 45 µg) for adverse reactions is described in Section 8.6. Further dosing information for Peg-IFNα is provided in the package insert for the commercially available product used in this study.

6.2.4. Study Drug Administration

ABI-H0731 (where applicable) and ETV tablets will be administered orally as a single dose, once daily, and Peg-IFNα (where applicable) will be administered as a subcutaneous injection, once weekly. Subjects should be instructed to take 731 and ETV at the same time of the day with the possible exception of in-clinic visit days (Appendix 1). Pegylated-interferon alpha should be administered at approximately the same time each week; while not required, Peg-IFNα may be administered in the evening prior to sleeping to help manage AEs.

The study staff will administer 731 (if applicable) and ETV (if possible) to the subject at each study visit and the subject will take 731 (if applicable) on all other days as per the Schedule of Assessments (Appendix 1).

Subjects receiving Peg-IFNα as part of their assigned regimen must be trained in the proper injection technique for self-administration. The first dose of Peg-IFNα may be administered in the clinic for training purposes; however, in-clinic administration is not required at subsequent visits in order to support nighttime administration for AE management. If a subject prefers to have a caregiver to administer Peg-IFNα, the caregiver will need to present at the clinic on Day 1 for injection training.

6.3. Description and Handling of Study Drugs

Details concerning formulation, dose strength, packaging, storage, and handling of study drugs (731, ETV, and Peg-IFNα) are presented in the following sections. Further details for ETV and Peg-IFNα are provided in the respective package inserts.

6.3.1. ABI-H0731

Formulation

[redacted]

Packaging and Labeling

[redacted]

Storage and Handling

[redacted]

6.3.2. Entecavir

Formulation

Commercially available ETV will be supplied by Assembly Biosciences for this study. Entecavir is a guanosine nucleoside analogue with selective activity against HBV. Film-coated tablets are available for oral administration at 0.5 mg strength and contain the following inactive ingredients: lactose

monohydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. The tablet coating contains titanium dioxide, hypromellose, polyethylene glycol 400, and polysorbate 80.

Packaging and Labeling

Tablets are packaged in film/foil blister strips or plastic bottles with closures. Entecavir supplied will be commercial product labeled for the China market.

Storage and Handling

Tablets should be stored in a tightly closed container at 25°C; excursions permitted between 15°C-30°C. Further details for packaging, labeling, storage, and handling of ETV are described in the package insert.

6.3.3. Pegylated-Interferon Alpha

Formulation

Commercially available Peg-IFNα will be supplied by Assembly Biosciences for this study. The active ingredient is prepared by modifying recombinant human IFNα expressed in yeast system with polyethylene glycol (40kD Y-type). Excipients include sodium chloride, sodium acetate, mannitol, aspartic acid, water for injection, sodium hydroxide for adjusting pH. Injectable solution is available in prefilled syringes of different strengths. For this study, Peg-IFNα will be supplied as 180 µg prefilled syringes.

Packaging and Labeling

The product is packaged in prefilled syringes. Pegylated-interferon alpha supplied will be commercial product labeled for the China market.

Storage and Handling

Syringes should be refrigerated between 2°C-8°C. Further details for packaging, labeling, storage, and handling of Peg-IFNα are described in the package insert.

6.4. Study Drug Accountability

Regulatory requirements stipulate accounting of all investigational drug received by the study site. Records of drug disposition must include the date received by the site, date administered, quantity administered, and the subject to whom study drug was administered. The Investigator is responsible for the accountability of all study drugs at his or her site. This includes all used and unused study drug containers (ie, syringes for Peg-IFNα and bottles for 731 and ETV) and unused study drug (ie, 731, ETV, or Peg-IFNα).

Each study site is to use a study drug accountability record to document study drug disposition. All items on this form are to be fully completed. The Sponsor or the Clinical Research Organization (CRO) will confirm if the method of recording study drug accountability by the site and the location of study drug records at the site is appropriate.

Each time designated site personnel dispense study drug for a subject, he or she is to record the date dispensed, the quantity of study drug 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 study drug. The site monitor will review the study drug accountability records during monitoring visits. The site pharmacist or designated staff member will keep accurate records of drug dispensation routinely

during the study. Study drug dispensation is planned for Day 1 and at each scheduled visit thereafter during the treatment and follow-up periods (Section 7; Appendix 1).

On days when study drugs are administered in the clinic, study personnel will document the date and time of study drug administration in the subject's medical record. When study drugs are administered outside the clinic, subjects will be required to record the dates and times of each dose of study drug (ie, 731 and Peg-IFNα [if applicable], and ETV) in the dosing diary, which will be provided as indicated in the Schedule of Assessments (Appendix 1).

Subjects will also be asked to return used packaging (syringes for Peg-IFNα) and any unused study drug along with the dosing diary for accountability and compliance assessment at each study visit (except Day 1). Returned 731, ETV, and Peg-IFNα 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 study drugs at a given visit will be asked to return them at the next study visit.

6.5. Return or Disposal of Study Drug

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

6.6. 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 subjects randomized to the study, 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 study (completion of follow-up period or the Premature Termination Visit [in the event of discontinuation from treatment or study]) 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.

6.6.1. Prohibited Concomitant Therapy

Systemic (oral, injectable, or implanted) hormonal birth control is not considered as an acceptable means of contraception for female subjects of child-bearing potential. Additional details on acceptable means of contraception are provided in Appendix 4.

Other treatments for CHB as defined in Exclusion Criterion #1, Section 5.3 are prohibited.

Since 731 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 of 731 in humans is not fully understood so inhibitors and inducers of CYP3A4 should be avoided. Examples of representative medications that should be avoided due to drug-drug interaction potential with 731 is provided in Appendix 5. 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.

The details of permitted concomitant medications and prohibited medications for ETV and Peg-IFNα are provided in the respective package inserts for the commercially available products used in this study.

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 predose 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 should be retained on all screen failures including demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) information.

Individuals who do not meet the protocol eligibility criteria for participation in this study (ie, screen failures) may not be rescreened; however, retest for some 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). Subjects who meet all study eligibility requirements but are not able to complete the Day 1 visit within the prespecified 45-day window may be rescreened for the study.

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
- Record demographics and medical history, including HBV history and HBV treatment history
- Liver staging (as required per inclusion criteria, ie, fasting FibroScan)
- 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
- Laboratory analyses (additional details are provided in the Laboratory Manual):
    - Safety labs: chemistry, hematology, coagulation, serum AFP, follicle-stimulating hormone (FSH) (females only), TSH and T4, serum pregnancy test, urinalysis, urine drug test (Appendix 2)
    - Virology: HBV genotype, HBV DNA, HBsAg, HBeAg, HBsAb, HBeAb, sample for HBV nucleic acids, HIV Ab, HCV Ab, HDV Ab, HAV (IgM), HEV (IgM), HBcAb (IgM; see Inclusion Criterion #5, Section 5.2) (Appendix 2)
    - HBV sequencing: a blood sample for sequencing of the HBV polymerase coding region will be collected and stored for analysis only in the event of any observed viral breakthrough or blunted response (Appendix 2)

7.3. Day 1

The following assessments must be completed predose on Day 1:

- Update medical history, including HBV history and HBV treatment 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 and serum pregnancy tests, urinalysis, urine drug test (Appendix 2)
    - Virology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb, HBeAb, sample for HBV sequencing and HBV nucleic acids (Appendix 2)
- PK samples: predose samples for 731, Peg-IFNα, and ETV

Dosing:

- Study drug administration (731, ETV and Peg-IFNα [as applicable])

The following assessments must be completed postdose on Day 1:

- Provide dosing diary to subjects
- Study drug dispensation (731, ETV, and Peg-IFNα [as applicable])
- PK samples: postdose samples for 731, Peg-IFNα, and ETV between 2 and 4 hours following study drug administration (Section 7.11)

7.4. Study Week 1

The following assessments are performed at Study Week 1:

- Symptom-directed physical examination
- Review concomitant medications
- Review AEs
- Laboratory analyses (additional details are provided in the Laboratory Manual):
    - Virology: HBV DNA, HBV pgRNA, sample for HBV sequencing and HBV nucleic acids (Appendix 2)
- Review dosing diary and assess drug accountability

7.5. Study Weeks 2 Through 24

The following assessments are performed at Study Weeks 2, 4, 6, 8, 12, 16, 20, and 24 (inclusive) unless otherwise indicated. Subjects who discontinue treatment before Week 24 should immediately undergo the assessments listed for the Premature Termination Visit and then continue the scheduled follow-up assessments. A visit window of ±3 days is applied to each visit through Week 20. A visit window of -3 days is applied to Week 24 (Appendix 1).

- Liver staging (Week 24 only)
- Measure body weight (Week 24 only)
- Vital signs (temperature, heart rate, respiration rate, and blood pressure; not at Week 6)
- Complete physical examination (excluding breast and genitalia, unless indicated; Week 24 only)
- Symptom-directed physical examination (not at Week 24)
- 12-lead ECG (Weeks 12 and 24 only)
- Review concomitant medications
- Review AEs
- Laboratory analyses (additional details are provided in the Laboratory Manual):
    - Safety labs: chemistry (not at Week 6), hematology (not at Week 6), coagulation (not at Week 2 or 6), TSH (only at Weeks 12 and 24), urinalysis (not at Week 2 or 6), urine pregnancy test (not at Week 6) (Appendix 2)
    - Virology: HBV DNA, HBV pgRNA, HBsAg (not at Week 2 or 6), HBeAg (not at Week 2 or 6), HBcrAg (not at Week 2 or 6), HBsAb and HBeAb (Weeks 12 and 24 only), sample for HBV sequencing and HBV nucleic acids (Appendix 2)

- PK samples: samples for 731, Peg-IFNα, and ETV between 30 min and 2 hours postdose at Weeks 2, 8, 12, and 24, and between 4 and 6 hours postdose at Weeks 16 and 20. Predose samples for 731, Peg-IFNα, and ETV will be collected at Week 4 and Week 24 only (Section 7.11)
- Review dosing diary and assess drug accountability
- Study drug dispensation (not at Weeks 2 and 6; Peg-IFNα will not be dispensed at Week 24)
- Study drug administration (731 and ETV in-clinic [except at Weeks 2 and 6]; Peg-IFNα may be administered at home)

7.6. Study Weeks 28 Through 48

The following assessments are performed at Study Weeks 28, 32, 36, 40, 44, and 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).

- Liver staging (Week 48 only)
- 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 (Week 48 only)
- Review concomitant medications
- Review AEs
- Laboratory analyses (additional details are provided in the Laboratory Manual):
    - Safety labs: chemistry, hematology, coagulation, urinalysis (Week 48 only), urine pregnancy test (Appendix 2)
    - Virology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb and HBeAb (Week 48 only), sample for HBV sequencing and HBV nucleic acids (Appendix 2)
- PK samples: samples for ETV may be collected predose at Week 44 (Section 7.11)
- Study drug administration (731 and ETV)
- Review dosing diary and assess drug accountability
- Study drug dispensation (only ETV will be dispensed at Week 48, not 731)

7.7. Study Weeks 52 Through 60 (Follow-up Assessments)

All subjects, including those who prematurely discontinue treatment or complete treatment per protocol will enter a 12-week follow-up period. Subjects will remain on ETV during the follow-up period. The following assessments are performed every 4 weeks unless otherwise indicated. A visit window of ±5 days is applied from Weeks 52 through 60.

- Measure body weight (Week 60 only)
- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated; Week 60 only)
- Symptom-directed physical examination (not at Week 60)
- 12-lead ECG (Week 60 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 (Appendix 2)
    - Virology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb and HBeAb (Week 60 only), sample for HBV sequencing and HBV nucleic acids (Appendix 2)
- Review dosing diary
- Assess drug accountability (final drug accountability performed at Week 60)
- Study drug dispensation (final study drug dispensation performed at Week 56)
- Study drug administration (ETV)

7.8. 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 (Appendix 2)

- Virology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, sample for HBV sequencing, and HBV nucleic acids (Appendix 2)
- PK samples: samples for 731 and Peg-IFNα (if appropriate), and ETV (Section 7.11)

Assessments performed should be documented in the subject's source documentation. Clinical laboratory assessments should be conducted through the central laboratory. The minimum assessments to be completed when managing ALT elevations at an Unscheduled Visit are noted in Section 9.4.

7.9. Premature Termination Visit

Should a subject prematurely discontinue treatment (Section 7.10.1) or discontinue from the study (Section 7.10), 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:

- 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
- Laboratory analyses (additional details are provided in the Laboratory Manual):
  - Safety labs: chemistry, hematology, coagulation, urinalysis, urine drug test, urine pregnancy test (Appendix 2)
  - Virology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb, and HBeAb, sample for HBV sequencing and HBV nucleic acids (Appendix 2)
  - PK samples: samples for 731and Peg-IFNα (if appropriate), and ETV (Section 7.11)
- Review dosing diary and assess drug accountability (if applicable)

7.10. 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, a Premature Termination Visit should be conducted (Section 7.9). If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such 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.

7.10.1. 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 731 or Peg-IFNα (if applicable). Entecavir may be continued at the discretion of the Investigator. Subjects who prematurely discontinue treatment (731 or Peg-IFNα as applicable) should immediately undergo the assessments listed for the Premature Termination Visit (Section 7.9) and then continue scheduled follow-up assessments (Section 7.7).

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 (731 or Peg-IFNα as applicable) will be discontinued in subjects with confirmed evidence of declining hepatic function during treatment, a Premature Termination Visit (Section 7.9) will be completed, and subjects will subsequently undergo the follow-up assessments described in Section 7.7. Entecavir may be continued at the discretion of the Investigator in accordance with local practice.

Any female subject with a negative urine pregnancy test at Baseline (Day 1) who is subsequently found to be positive on the Baseline (Day 1) serum pregnancy test should immediately discontinue treatment with 731 and Peg-IFNα, as applicable. At future visits, any positive urine pregnancy text will require confirmation by a serum pregnancy test. Female subjects with a positive serum pregnancy test should immediately discontinue treatment with 731 and Peg-IFNα, as applicable. In these instances, entecavir may be continued at the discretion of the Investigator in accordance with local practice and the approved ETV package insert. These subjects may be replaced at the discretion of the Sponsor.

7.10.2. 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 lost to follow-up.

7.11. Pharmacokinetic Assessments

During the study, predose plasma samples will be collected from all subjects to explore the PK profile of 731, Peg-IFNα, and ETV after combination treatment with or without Peg-IFNα in subjects with CHB. Additionally, postdose samples will be collected at the timepoints outlined in Table 1. Additional details regarding the collection, processing, storage, and shipment of PK samples is described in the Laboratory Manual. Plasma samples of Peg-IFNα and ETV will be collected and stored for future PK analyses if deemed necessary.

Table 1: Pharmacokinetic Sample Collection

Time period	Time relative to study drug administration [a]	Time relative to study drug administration [b]
Treatment	Predose [c]	Day 1, Weeks 4 and 24
	30 min to 2 hours postdose	Weeks 2, 8, 12, and 24
	2 to 4 hours postdose	Day 1
	4 to 6 hours postdose	Weeks 16 and 20
	Collect at same time with other central labs	At Unscheduled and Premature Termination Visits [d] and predose at the Week 44 visit

a. If the subject administers study drug at home, a pharmacokinetic sample should be collected during the 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 in the source documentation.
c. The predose sample may be collected up to 2 hours prior to study drug administration.
d. A pharmacokinetic sample should also be collected if an Unscheduled or Premature Termination Visit is performed.

7.12. End of Study Definition

The study will be completed when the last subject completes the 12-week follow-up period, or is considered "lost to follow-up" (Section 7.10.2), whichever is later.

7.13. Resistance Monitoring

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, $\geq$1 $\log_{10}$ increase in on-treatment 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 in other treatment groups 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 AE. 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 (for all randomized subjects and excluding screen failures) will be entered in the electronic case report form (eCRF) 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.

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

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 (DAIDS) 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 drug (731, ETV, or Peg-IFNα) 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. Dose Modification due to Adverse Events

The dose of Peg-IFNα may be adjusted due to AEs. Where dose adjustment is required for moderate to severe adverse reactions (clinical and/or laboratory) initial dose reduction to 135 µg is generally adequate for patients. In some cases, dose reduction to 90 µg or 45 µg is necessary. Dose increases to or towards the original dose may be considered when the adverse reaction abates. Details of recommended dose reductions of Peg-IFNα are provided in the package insert for the commercially available product used in this study.

There is no dose modification allowed for 731 or ETV.

8.7. 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.

8.8. Pregnancy

8.8.1. Female subjects who become pregnant

Any female subject who becomes pregnant while participating in the study will discontinue the study drug(s) immediately (Section 7.10).

The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study, including the 12-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 Operations 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 ag e) 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.

8.8.2. 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 at least 1 dose of study drug (731, ETV, or Peg-IFNα).

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 Operations Manual for contact information for reporting a pregnancy.

9. SERIOUS ADVERSE EVENTS

9.1. Definition of Serious Adverse Event

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

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received 731
- 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 Operations 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.

It will be the responsibility of the individual Investigators to inform any local Independent Ethics Committees (IECs) of SAEs as required. Correspondence with the IEC(s) relating to the reporting of SAEs will be retained in the study file.

Serious adverse events will be recorded from the date informed consent is signed through the end of study (completion of follow-up period or if the subject is lost to follow-up).

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 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. At these visits, the following laboratory tests will be performed: ALT, aspartate aminotransferase (AST), total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum albumin, INR and creatine kinase. The Investigator will determine if other Unscheduled Visit

assessments (Section 7.8) should be performed. Additionally, the following guidance is provided for management of subjects with ALT elevations:

- ALT elevation without declining hepatic function
    - All subjects with an ALT elevation on treatment, defined as ALT >2 × Baseline or on-treatment nadir and ≥10 × ULN, should have the ALT findings confirmed within 3 days of receipt of the original results. All subjects should return for an Unscheduled Visit and complete all Unscheduled Visit procedures (Section 7.8).
    - If the ALT elevation is confirmed, then an additional Unscheduled Visit will be performed to further evaluate the subject. At this visit, the following tests will be performed: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum albumin, INR, creatine kinase, HBV DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is less than the lower limit of quantification (LLOQ)] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is <LLOQ]), HAV IgM, HCV RNA, HDV RNA, and HEV IgM. The Investigator will determine if other assessments specified in Section 7.8 should be performed.
        - If an intercurrent illness is determined to be causal, subjects with an ALT elevation without declining hepatic function and without contraindications may continue assigned treatment (ie, 731, ETV and Peg-IFNα as applicable) and the intercurrent illness should be treated as deemed medically appropriate by the Investigator.
        - In the absence of an intercurrent illness that is determined to be causal, subjects with an ALT elevation without declining hepatic function and without contraindications may continue assigned treatment (ie, 731, ETV and Peg-IFNα as applicable) under close observation.
    - If ALT is rising at the confirmatory visit, subjects should return for an Unscheduled Visit (Section 7.8) every 2 to 5 days until the ALT elevation has stabilized. At these visits only the following laboratory tests will be performed: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum albumin, INR, creatine kinase, HBV DNA, and quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is <LLOQ] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is <LLOQ]). The Investigator will determine if other assessments specified in Section 7.8 should be performed. 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 may continue on 731 and ETV as applicable and have the dose of Peg-IFNα adjusted, if applicable (Section 8.6). There are no dose adjustments for 731 or ETV.
        - Subjects with an ALT elevation without declining hepatic function and without contraindications should discontinue Peg-IFNα (if applicable) and 731 (if applicable) if the ALT remains persistently >2 × ULN elevated for

>8 weeks and there is no decline in viral parameters. Entecavir may be continued at the discretion of the Investigator in accordance with local practice. For information specific to dose modification or interruption, see Section 7.10.1 "Discontinuation from Treatment."

- Subjects with an ALT elevation >10 × ULN should consider dose interruption of Peg-IFNα (if applicable). After 8 weeks of interruption, if ALT has not returned to <2 × ULN, subject should discontinue Peg-IFNα (if applicable) and 731 (if applicable). If ALT returns to <2 × ULN, re-introduction of Peg-IFNα (if applicable) should be considered at the Investigator's discretion. Entecavir may be continued at the discretion of the Investigator in accordance with local practice.

- ALT elevation with declining hepatic function
  - Subjects with confirmed ALT elevation with evidence of declining hepatic function should discontinue Peg-IFNα (if applicable) and 731 (if applicable). Entecavir may be continued at the discretion of the Investigator in accordance with local practice. Elevation of ALT with declining hepatic function 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 (Section 7.8) every 2 to 5 days until the relevant laboratory values stabilize. Subjects whose hepatic function has stabilized should continue to be monitored weekly (or more frequently as deemed necessary by the Investigator) until the relevant laboratory values return to normal or Baseline.

All subjects with ALT elevation without or with declining hepatic function should continue to be followed on their regular study visit schedule, with the addition of Unscheduled Visits (Section 7.8) as described previously. If the ALT elevation has not substantially resolved by the last study follow-up visit, subjects should continue to return to clinic as deemed medically appropriate by the Investigator and in consultation with the Sponsor. 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.

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 description of analysis methods and detailed definitions for efficacy and safety endpoints will be provided in the statistical analysis plan (SAP), which will be finalized prior to database lock.

10.1. Determination of Sample Size

Approximately 60 eligible subjects with HBeAg positive CHB will be enrolled in the study. Subjects will be randomized to receive 1 of the following 3 treatments, 731+ETV, ETV+Peg IFNα, or 731+ETV+Peg IFNα in a 1:1:1 ratio.

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

10.2. Analysis Populations

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

- Randomized Analysis Set: This analysis set includes all randomized subjects, classified according to the treatment group into which they were randomized regardless of the actual treatment received.
- Full Analysis Set: This analysis set includes all randomized subjects, classified according to the treatment group into which they were randomized regardless of the actual treatment received, who receive at least 1 dose of study drug. This is the main analysis population for the efficacy analysis.
- Safety Analysis Set: This analysis set includes all subjects, classified according to the actual treatment received regardless of random assignment, who receive at least 1 dose of study drug. This is the main analysis population for all safety analyses.
- Pharmacokinetic Evaluable Set: This analysis set consists of all subjects, classified according to the actual treatment received regardless of random assignment, who receive at least 1 dose of study drug. At least 1 PK blood sample following a dose of study drug (731) is required for inclusion in this analysis. This is the main analysis population for all PK analyses.

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

10.3.1. Disposition of the Study Subjects

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

10.3.2. Demographic and Baseline Characteristics

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

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 the Safety Analysis Set will also be described by treatment group.

10.3.4. Analysis of Efficacy Endpoints

The key efficacy endpoints include:

- Mean change in $\log_{10}$ HBV pgRNA from Baseline at each timepoint
- Mean change in $\log_{10}$ HBV DNA from Baseline 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 normal ALT at each timepoint
- The incidence of HBV variants with reduced susceptibility to 731

For the continuous variables, such as mean change from baseline, in addition to the descriptive statistics at each time point, they will be evaluated using a regression model with Baseline values and stratification as covariates.

The binary variables, such as the proportion of subjects with abnormal ALT at baseline who have normal ALT and incidence of HBV variants with reduced susceptibility will be evaluated pairwise among treatment groups using a Cochran-Mantel-Haenszel test accounting for stratification factors.

10.3.5. Pharmacokinetic Analysis

Drug concentrations of 731, Peg-IFNα, and ETV will be listed at end of study as follows:

- 731 on 731+ETV or on 731+ETV+Peg-IFNα therapy stratified by collection time window and collection day.
- Ad hoc analysis of ETV on 731+ETV therapy and ETV+Peg-IFNα therapy stratified by collection time window and study day.
- Ad hoc analysis of Peg-IFNα on 731+ETV+Peg-IFNα therapy stratified by collection time window and collection day.

Application to a population PK model may be applied, details of which will be provided in the pharmacometrics analysis plan.

10.3.6. Safety Analysis

All safety endpoints will be summarized using data from the Safety Analysis Set. Safety analyses will involve examination of the incidence, severity and type of TEAEs reported, changes from Baseline (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.

10.3.6.1. Treatment-emergent Adverse Events

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 TEAE categories:

- All AEs
- SAEs
- Drug-related AEs

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

All AEs will be recorded from the first dose of study drug (731, ETV, or Peg-IFNα) until the last study visit.

10.3.6.2. 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. 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.

10.3.6.3. 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. As an open-label study, the data will be reviewed periodically.

10.5. Independent Data Monitoring Committee

No Data Monitoring Committee is planned for this study.

10.6. Handling of Missing Data

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

10.7. Multiplicity Adjustment

No formal inference is planned in this study. Hence no multiplicity adjustment is required.

11. RESPONSIBILITIES

11.1. Investigator Responsibilities

11.1.1. Good Clinical Practice

This study will be conducted in compliance with Institutional Review Board (IRB)/IEC and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines (E6[R2]); Title 21 Part 56 of the United States (US) Code of Federal Regulations (CFR) relating to IRBs/IECs and GCP as described in the US Food and Drug Administration (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/Independent Ethics Committee

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 clinical study reports (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 2019; Battisti et al 2015).

12. REFERENCES

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13. APPENDICES

APPENDIX 1 SCHEDULE OF ASSESSMENTS TABLE

Period or Visit	**Screening**	**On Treatment**												**Follow-up**		**Premature Termination[3]**	**Unscheduled Visit [4]**
Study Day or Week	**Day -45 to Day -1**	**Day 1 [1]**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24 [2]**	**Wk 28 [2]**	**Wk 48**	**Wks 52, 56 [2]**	**Wk 60**		
Visit Window (days)		0	±1	±3	±3	±3	±3	±3	±3	±3	-3	±3	-3	±5	±5	NA	NA
Informed Consent(s)	X																
Demographics, medical history, and HBV history	X	X															
Liver staging [5]	X										X		X				
Height and weight [6]	X	X									X		X		X	X	
Vital signs	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Complete physical examination[7]	X	X									X [8]		X [8]		X [8]	X	
Symptom-directed physical [9]			X	X	X	X	X	X	X	X		X		X			X
12-lead ECG [10]	X	X						X [10]			X [10]		X [10]	.	X [10]	X	
Concomitant medications and AEs	X	X	X	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	X
Hematology	X	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	X
Serum AFP	X																
FSH (females only)	X																
TSH and T4 [11]	X							X [11]			X [11]						
Pregnancy Test [12]	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X			X		X	X	X	X	X		X	X	X	X	X
Urine drug test	X	X														X	X
HBV genotype	X [13]																

Period or Visit		Screening	On Treatment												Follow-up		Premature Termination[3]	Unscheduled Visit [4]
Study Day or Week		**Day -45 to Day -1**	**Day 1 [1]**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24 [2]**	**Wk 28 [2]**	**Wk 48**	**Wks 52, 56 [2]**	**Wk 60**		
Visit Window (days)			0	±1	±3	±3	±3	±3	±3	±3	±3	-3	±3	-3	±5	±5	NA	NA
HBV DNA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV pgRNA			X	X	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	X
HBcrAg			X			X		X	X	X	X	X	X	X	X	X	X	X
HBsAb, HBeAb		X	X						X			X		X		X	X	
Sample for HBV DNA sequencing and HBV nucleic acids [15]		X	X	X	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 [16]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug accountability				X	X	X	X	X	X	X	X	X [17]	X	X [17]	X [17]	X	X	
Study drug dispensation [17]			X			X		X	X	X	X	X	X	X	X [17]			
In-clinic dosing 731 [18]			X			X		X	X	X	X	X	X	X [19]				
In-clinic ETV dosing [18]			X			X		X	X	X	X	X	X	X	X	X [19]		
In-clinic Peg-IFNα dosing [18, 19]			X															
PK sample collection [20, 21]	731, Peg-IFNα		X		X	X		X	X	X	X	X					X	X
	ETV		X		X	X		X	X	X	X	X	X [21]				X	X
HBcAb (IgM) [22]		X																

Abbreviations: Ab = antibody; 731 = ABI-H0731; 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; IgM = immunoglobulin M; INR = international normalized ratio; IRT = Interactive Response Technology; NA = not applicable; PK = pharmacokinetic; pgRNA = pregenomic RNA; T4=thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; Wk(s) = week(s).

[1] The assessments that need to be performed prior to the first dose of study drugs on Day 1 are listed in Section 7.3.
[2] Study visits occur every 4 weeks between Weeks 24 and 60.
[3] Subjects who discontinue treatment before Week 24 (731 or Peg-IFNα) or Week 48 (731) should immediately undergo the assessments listed for the Premature Termination Visit and then continue the scheduled follow-up assessments. ETV administration may be continued at the discretion of the Investigator.
[4] Any subjects with alanine aminotransferase (ALT) elevation should return to the clinic for an Unscheduled Visit. The minimum assessments to be completed when managing ALT elevations are noted in Section 9.4.
[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 by liver biopsy (within 1 year of Screening), by fasting FibroScan (within 3 months of Screening) or other Sponsor-approved hepatic imaging method within 6 months of Screening, and again at Weeks 24 and 48.
[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 Screening, Day 1, and Weeks 24, 48, and 60.
[9] Symptom-directed physical exam is performed only at the visits when a complete physical exam is not performed.
[10] Any clinically significant ECG result or change from Baseline (Day 1) should be confirmed, and if confirmed, should be recorded as an AE. A 12-lead ECG will be performed at Weeks 12, 24, 48, and 60.
[11] T4 and TSH are measured only at Screening. TSH is measured at Weeks 12 and 24 (only for Peg-IFNα-containing treatment groups).
[12] A serum pregnancy test is required at Screening. On Day 1 both urine and serum tests 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). All post-Day 1 pregnancy tests may be performed on urine. If the result from a urine pregnancy test is positive, then a serum pregnancy test should be performed.
[13] HBV genotype results should be received prior to Day 1 as this is required for treatment stratification.
[14] If quantitative HBsAg and/or HBeAg is less than the lower limit of quantification (LLOQ) at any visit subsequent to Screening, reflex qualitative HBsAg and/or HBeAg testing will be done. If HBsAg and/or HBeAg are <LLOQ at any visit, reflex qualitative HBsAb and/or HBeAb testing will be done to assess for seroconversion.
[15] HBV DNA sequencing will not be performed routinely at Screening and subsequent study visits. Samples will be collected, stored, and analyzed only in the event of an observed viral breakthrough or blunted response. If HBV DNA sequencing is not required, then these samples may be used for additional HBV DNA or HBV pgRNA testing as required.
[16] A dosing diary is provided to all subjects on Day 1. At subsequent in-clinic visits, the diary is reviewed and a new diary card is provided. At Week 60, only review of dosing diary is performed.
[17] Final study drug dispensation of Peg-IFNα will occur at Week 20, 731 at Week 44, and ETV at Week 56. Final study drug accountability of Peg-IFNα is performed at Week 24, 731 at Week 48, and ETV at Week 60.
[18] 731 and ETV administration are in-clinic at the study visits and self-administered once daily at home on all other days. Day 1 Peg-IFNα administration is in-clinic for injection training purposes; subsequently, subjects will administer Peg-IFNα once weekly at home.
[19] Dosing with Peg-IFNα (if applicable) will stop at Week 24. Dosing with 731 (if applicable) will stop at Week 48. Dosing with ETV will continue until Week 60.
[20] If the subject inadvertently administers study drug prior to collection, a PK sample should still be drawn. Refer to Section 7.11.
[21] Predose PK samples for 731, ETV, and Peg-IFNα on Day 1 and Weeks 4 and 24. Postdose PK samples for 731, ETV, and Peg-IFNα may be collected from 2 to 4 hours postdose on Day 1, and between 30 min and 2 hours after in-clinic study drug administration at Weeks 2, 8, 12, and 24. Postdose samples at Weeks 16 and 20 may be collected between 4 and 6 hours after in-clinic study drug administration. Predose samples for ETV may be collected at Week 44.
[22] HBcAb IgM testing may be performed for some subjects at Screening, see Inclusion Criterion #5, Section 5.2.

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 2.

Table 2: 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, creatine kinase, and INR; Refer to Section 9.4 for virology and serology
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 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, barbiturates, benzodiazepines, cocaine metabolite, ethanol, opiates, and phencyclidine
Antibodies	HBcAb IgM (see Inclusion Criterion #5, Section 5.2), 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; 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 731 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 ensure 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 (to be performed in the event of observing a viral breakthrough or blunted response) and HBV pgRNA testing will be shipped frozen to 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.

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

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 U-wave 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 (July 2017).

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)* *≥18 years of age*	140 to <160 mmHg systolic OR 90 to <100 mmHg diastolic	≥160 to <180 mmHg systolic OR ≥100 to <110 mmHg diastolic	≥180 mmHg systolic OR ≥110 mmHg diastolic	Life-threatening consequences in a 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 *Report only one* *≥16 years of age*	PR interval 0.21 to <0.25 seconds	PR interval ≥0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds	Complete AV block
Prolonged QTc Interval [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: AV = atrioventricular; 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 *≥1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over Baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over Baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (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* *≥18 years of age*	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

Abbreviation: 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 *≥12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR Non-serviceable hearing (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: dB = decibel; kHz = kilohertz; 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] *>5 to 19 years of age*	WHO BMI z-score <-1 to -2	WHO BMI z-score <-2 to -3	WHO BMI z-score <-3	WHO BMI z-score <-3 with life-threatening consequences
Unintentional Weight Loss *(excludes postpartum weight loss)*	NA	5 to <9% loss in body weight from Baseline	≥9 to <20% loss in body weight from Baseline	≥20% loss in body weight from Baseline OR Aggressive intervention indicated (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 for subjects >5 to 19 years of age may be accessed at the following URL: http://www.who.int/growthref/who2007_bmi_for_age/en/.

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

Abbreviation: 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 × ULN	2.5 to <5.0 × ULN	5.0 to <10.0 × ULN	≥10.0 × 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 × ULN	2.5 to <5.0 × ULN	5.0 to <10.0 × ULN	≥10.0 × 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 × ULN	2.5 to <5.0 × ULN	5.0 to <10.0 × ULN	≥10.0 × 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× U LN	>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 [l,m] or eGFR, Low *Report only one*	NA	<90 to 60 mL/min or mL/min/1.73 m^2 OR 10 to <30% decrease from 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 *≥18 years of age*	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	NA
LDL, Fasting, High *≥18 years of age*	130 to <160 *3.37 to <4.12*	160 to <190 *4.12 to <4.90*	≥190 *≥4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to <1,000 *>5.7 to 11.4*	>1,000 *>11.4*
Magnesium [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; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; 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 adverse event 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*) [p] *≥13 years of age; male only*	10.0 to 10.9 *6.19 to 6.76*	9.0 to <10.0 *5.57 to <6.19*	7.0 to <9.0 *4.34 to <5.57*	<7.0 *<4.34*
Hemoglobin [p], Low (g/dL; *mmol/L*) [p] *≥13 years of age; female only*	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
INR, High (not on anticoagulation therapy)	1.1 to <1.5 × 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*

Abbreviations: HIV = human immunodeficiency virus; INR = international normalized ratio; LLN = lower limit of normal; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell; ULN = upper limit of normal.

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 731 have not been conducted in animals, therefore effects of 731 on pregnancy are unknown. Contraceptive requirements for female subjects of childbearing potential are required as described below. Contraceptive requirements for ETV and Peg-IFNα are described in the respective package inserts.

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

Note that the drug-drug interaction of 731 and systemic (oral/injectable/implantable) hormonal birth control has not been assessed; therefore, systemic hormonal birth control is not considered an effective birth control method for female subjects for the purposes of this study.

Female subjects of childbearing potential (defined above) must agree to use dual effective birth control methods for the duration of the study including the follow-up period. 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. 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 including the follow-up period. In this case, effective birth control methods include systemic (oral/injectable/implantable) 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 should be avoided when taking 731:

CYP3A4 Inhibitors	
HIV antivirals	indinavir, nelfinavir, ritonavir, saquinavir
Other	clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, idelalisib, ribociclib, telithromycin, aprepitant, erythromycin, fluconazole, grapefruit, 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 and are prohibited or should be avoided when taking 731:

CYP2C9 Substrates	
Narrow therapeutic index substrates that are prohibited while taking 731	Warfarin, phenytoin
Substrates that should be avoided while taking 731	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 731:

CYP3A4 Inducers	
Inducers that should be avoided while taking 731	Barbiturates, brigatinib, carbamazepine, efavirenz, enzalutamide, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, st. john's wort, troglitazone

Abbreviations: 731 = ABI-H0731; CYP = cytochrome P450.
Source: The Flockhart Table. http://medicine.iupui.edu/clinpharm/ddis/main-table# (Accessed 6 March 2020).

Note: Refer to Exclusion Criterion #1, Section 5.3 of the protocol for prohibited medications. Additionally, the list of medications included in this appendix is not exhaustive. The Investigator should evaluate the mechanism of other concomitant medications to determine if they should be allowed in the study.

The details of prohibited concomitant medications and medications with a potential for drug-drug interactions with ETV and Peg-IFNα are described in the respective package inserts.

Study Title: A Randomized Phase 2a, Multicenter, Open-label Study Evaluating ABI-H0731-Containing Regimens in Patients with Chronic Hepatitis B

NCT Number: 04781647

Date of Document: 09 January 2023

STATISTICAL ANALYSIS PLAN

Sponsor:	Assembly Biosciences, Inc 331 Oyster Point Blvd South San Francisco, CA 94030
Protocol Number:	ABI-H0731-203
Protocol Title:	A Randomized Phase 2a, Multicenter, Open-Label Study Evaluating ABI-H0731-Containing Regimens in Patients with Chronic Hepatitis B
Product:	ABI-H0731
Protocol Version (Date):	Amendment 3.0 (29 July 2021)
Indication:	Chronic Hepatitis B Virus Infection
Analysis Type:	Final Analysis for Synoptic CSR
Analysis Plan Version (Date):	Version 2.0 (09 January 2023)
Analysis Plan Author:	[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN APPROVAL FORM

Protocol Title:	A Randomized Phase 2a, Multicenter, Open-Label Study Evaluating ABI-H0731-Containing Regimens in Patients with Chronic Hepatitis B
Protocol Number:	ABI-H0731-203
SAP Version (Date):	Version 2.0 (09 January 2023)

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

Name and Title	**Approval Signature/Date**
[redacted] Assembly Biosciences	See e-signature page
[redacted] Assembly Biosciences	See e-signature page
[redacted] Assembly Biosciences	See e-signature page

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

AASLD	american association for the study of liver diseases
AE	adverse event

ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BLOQ	below the limit of quantitation
BMI	body mass index
cHBV	chronic hepatitis B virus infection
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
DRC	data review committee
ECG	electrocardiogram
eCRF	case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
ET	early termination
ETV	entecavir
FAS	full analysis set
GT	genotype
Hb	hemoglobin
HBcrAb	antibody to the HBV core-related antigen
HBcrAg	hepatitis B core-related antigen
HBeAb	HBeAg antibody
HBeAg	hepatitis B “e” antigen
HBsAb	HBsAg antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HLGT	high-level group term
HLT	high-level term
ID	identification
IFNα	interferon alpha
INR	international normalized ratio
IPD	important protocol deviation(s)
IRT	interactive response technology
LLOQ	lower limit of quantitation
LLT	lower-level term
LOD	limit of detection
LOQ	limit of quantitation

MedDRA	medical dictionary for regulatory activities
MMRM	mixed model for repeated measures
NrtI	Nucleos(t)ide reverse transcriptase inhibitor
PD	protocol deviation(s)
Peg	pegylated
pgRNA	pregenomic ribonucleic acid
PK	pharmacokinetics
PT	preferred term
Q1, Q3	first quartile, third quartile
QD	once daily
RAV	resistance associated variants
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
VBR	vebicorvir
WHO	world health organization

1. INTRODUCTION

Study ABI-H0731-203 is a randomized Phase 2a, multicenter, open-label study evaluating vebicorvir (VBR; formerly ABI-H0731) -containing regimens in subjects with chronic hepatitis B virus (HBV) infection (cHBV). The target population is male or female subjects, 18 to 65 years of age, inclusive, treatment naïve with hepatitis B virus "e" antigen (HBeAg) positive cHBV and no evidence of cirrhosis or end-stage liver disease.

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study ABI-H0731-203. This SAP is based on the study protocol amendment 3, dated 29 July 2021 and the electronic case report form (eCRF). In July 2022, Assembly made the decision to terminate this study and discontinue the development of VBR after review of interim data suggested that none of the study drug regimens were likely to lead to functional cure. Subsequently, participants in Study ABI-H0731-203 ended study treatment and entered in follow-up period with entecvir (ETV) for 12 weeks.. . Therefore, only key safety and efficacy endpoints will be performed for this study. The SAP will be finalized before database lock. Any changes made after the finalization of the SAP will be documented in the Synoptic CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of VBR) when administered in combination with entecavir (ETV) with or without pegylated interferon alpha (Peg-IFNα) in subjects with cHBV

The secondary objectives of this study are as follows:

- To evaluate the effect of VBR when administered in combination with ETV with or without Peg-IFNα in reducing HBV pgRNA levels in subjects with cHBV
- To evaluate the effect of VBR when administered in combination with ETV with or without Peg-IFNα in reducing HBV deoxyribonucleic acid (DNA) levels in subjects with cHBV
- To evaluate the effect of VBR when administered in combination with ETV with or without Peg-IFNα in reducing HBV antigens (ie, HBeAg, hepatitis B core-related antigen [HBcrAg], and hepatitis B surface antigen [HBsAg]) in subjects with cHBV
- To evaluate the effect of VBR when administered in combination with ETV with or without Peg-IFNα on normalization of alanine aminotransferase (ALT)
- To evaluate the pharmacokinetics (PK) of VBR and future PK evaluation of Peg-IFNα and ETV in subjects with cHBV
- To evaluate the emergence of resistance to VBR when administered with ETV with or without Peg-IFNα

1.2. Study Design

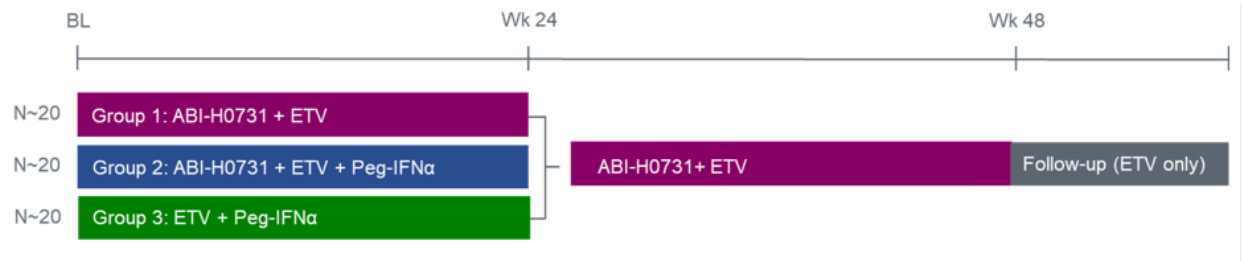
This study will assess the safety, antiviral activity, and PK of VBR administered in combination with ETV with or without Peg-IFNα in treatment-naïve, HBeAg positive Chinese subjects with cHBV. The study will be conducted at approximately 5 to 10 study sites in China.

Approximately 60 eligible subjects with HBeAg positive cHBV will be randomly assigned in a 1:1:1 ratio to the treatment groups shown in the study overview presented in Figure 1-1 Study Overview.

Treatment with VBR and/or ETV will be administered orally, once daily; treatment with Peg-IFNα will be administered subcutaneously, once weekly. Group 1 will receive VBR+ETV for 24 weeks, Group 2 will receive VBR+ETV+Peg-IFNα for 24 weeks and Group 3 will receive ETV+Peg-IFNα for 24 weeks. All subjects will receive VBR+ETV from Week 24 through Week 48 and then ETV alone from Week 48 through Week 60 during the 12-week follow-up period.

Treatment assignments will be stratified by the HBV genotype (GT;ie, GT A or B vs GT C or D, vs other GTs) and baseline ALT (ie, ALT <5 × upper limit of normal [ULN] vs ALT ≥5 × ULN) during the Screening visits.

Figure 1-1 Study Overview



Abbreviations: BL = Baseline; ETV = entecavir; Peg-IFNα = pegylated-interferon alpha; Wk = week.

Note: ABI-H0731 is the former designation for VBR.

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

1.3. Sample Size and Power

Approximately 60 eligible male or female subjects between the ages of 18 and 65 years with HBeAg positive cHBV will be enrolled in the study. Subjects will be randomized to receive 1 of the following 3 treatments, VBR+ETV, ETV+Peg-IFNα, or VBR+ETV+Peg-IFNα in a 1:1:1 ratio.

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. The IRT system will assign eligible subjects in a 1:1:1 ratio to receive either VBR+ETV, VBR+ ETV+Peg-IFNα or ETV+Peg-IFNα for 24 weeks. Treatment assignments will be stratified by the HBV GT (ie, GT A or B vs GT C or D, vs other GTs) and baseline ALT (ie, ALT <5 × ULN vs ≥5 × ULN) collected at Screening. Additional information on the use of the IRT is provided in the IRT User Manual.

1.4.2. Blinding

Not applicable as this is an open-label study.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

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

2.2. Final Analysis

As of 25 July 2022, the study was terminated early. The final analysis to support a 'Synoptic Clinical Study Report' will be performed after all subjects have discontinued or completed the 12-week follow-up visits, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

No formal inference is planned in this study. Hence no multiplicity adjustment is required.

3.1. Analysis Sets

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

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

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

3.1.3. Safety Analysis Set

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

3.2. Subject Grouping

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

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via an IRT system in a 1:1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables during the Screening visits:

- HBV GT (ie, GT A or B vs GT C or D, vs other GTs)
- Baseline ALT (ie, ALT <5 × upper limit of normal ULN vs ALT ≥5 × ULN)

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

3.4. Data Handling Conventions and Transformations

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

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

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

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

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

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

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

3.5. Missing Data and Outliers

3.5.1. Missing Data

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

For missing last dose date of study drug, imputation rules are described in Section 4.2.1. The handling of missing efficacy data is described in Section 6.1.2. The handling of missing or incomplete dates for adverse event (AE) onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

3.5.2. Outliers

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

3.6. Analysis Visit Windows

3.6.1. Definition of Study Drug

In this study, study drugs are defined as VBR, ETV, and Peg-IFNα.

3.6.2. Definition of Study Phase

The following phases will be defined: Randomized Treatment Phase and Overall Treatment Phase are on treatment; and the Follow-up Phase is off treatment.

- Randomized Treatment Phase: from first dose date through Week 24 visit (or premature termination visit if before Week 24)
- Overall Treatment Phase: from first dose date through Week 48 visit (or premature termination visit if before Week 48)
- Follow-up Phase: after Week 48 visit (or premature termination visit) through end of study

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

3.6.3. Definition of Study Day

The first dose date of VBR when administered in combination with ETV with or without Peg-IFNα will be calculated where applicable. Study Day 1 is defined as the first dose date of study drug, which is the earliest/minimum of the first dose dates of VBR, ETV, and Peg-IFNα in a treatment group. If the first dose date is missing, the date of randomization will be used.

The last dose date of VBR, ETV, and of Peg-IFNα will be calculated where applicable. For the Randomized Treatment Phase, the last dose date of study drug VBR will be the Week 24 visit date or the end date on study drug administration CRF if a subject discontinued study drug prior to Week 24 visit. For study drug ETV, the last dose date will be obtained from End of Treatment-ETV eCRF. For study drug Peg-IFNα, the last dose date will be obtained from End of Treatment-Peg-IFNα eCRF. For the Overall Treatment Phase, the last dose date for each drug will be the end date on the respective End of Treatment eCRF pages. The last dose date of study drug will be defined as the latest/maximum of the last dose dates of VBR, ETV, and Peg-IFNα in a treatment group.

For the on-treatment phases, Study Day will be calculated from Study Day 1 and derived as follows:

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

For the Follow-up Phase, the follow-up Study Day 1 is defined as the day after Week 48 visit or Premature Termination visit. The follow-up study day will be derived as Assessment Date – follow-up Study Day 1 +1.

3.6.4. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. In general, the baseline value will be the last nonmissing value on or prior to the first dose date of study drug. The on-treatment phases include Randomized Treatment Phase and Overall Treatment Phase. For the Randomized Treatment Phase, the data will be summarized up to the Week 24 visit or premature termination visit. For the Overall Treatment Phase, the data will be summarized up to the Week 48 visit or premature termination visit. For the Follow-up Phase, the data will be summarized from follow-up Study Day 1 through the end of study, where Follow-Up Baseline data is from Week 48 visit or premature termination visit.

The analysis windows for the on-treatment HBV DNA and HBV pgRNA assessments are provided in Table 3-1.

Table 3-1 On-Treatment Analysis Visit Windows for HBV DNA and pgRNA

Nominal Visit	On-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	(none)	1
Week 1	7	2	10
Week 2	14	11	21
Week 4	28	22	35

Nominal Visit	On-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Week 6	42	36	49
Week 8	56	50	70
Week 12	84	71	98
Week 16	112	99	126
Week 20	140	127	154
Week 24	168	155	182
Week 28	196	183	210
Week 32	224	211	238
Week 36	252	239	266
Week 40	280	267	294
Week 44	308	295	322
Week 48	336	323	≥336

The analysis windows for the on-treatment assessments of vital signs, chemistry, and hemotology are provided in Table 3-2.

Table 3-2 On-Treatment Analysis Visit Windows for Vital Signs, Chemistry, and Hematology

Nominal Visit	On-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	(none)	1
Week 2	14	2	21
Week 4	28	22	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	99	126
Week 20	140	127	154
Week 24	168	155	182
Week 28	196	183	210
Week 32	224	211	238
Week 36	252	239	266
Week 40	280	267	294

Nominal Visit	On-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Week 44	308	295	322
Week 48	336	323	≥336

The analysis windows for the on-treatment HBsAg, HBeAg, HBcrAg, and coagulation assessments are provided in Table 3-3.

Table 3-3 On-Treatment Analysis Visit Windows for HBsAg, HBeAg, HBcrAg, and Coagulation

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

The analysis windows for the on-treatment urinalysis assessments are provided in Table 3-4.

Table 3-4 On-Treatment Analysis Visit Windows for Urinalysis

Nominal Visit	On-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	(none)	1
Week 4	28	2	42
Week 8	56	43	70

Nominal Visit	On-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Week 12	84	71	98
Week 16	112	99	126
Week 20	140	127	154
Week 24	168	155	252
Week 48	336	253	≥336

The analysis windows for on-treatment electrocardiograms (ECG) measurements are provided in Table 3-5.

Table 3-5 On-Treatment Analysis Visit Windows for ECG

Nominal Visit	On-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	(none)	1
Week 12	84	2	126
Week 24	168	127	252
Week 48	336	253	≥336

The analysis windows for Follow-up Phase study assessments of efficacy (except HBsAb and HBeAb), vital signs, and laboratory assessments (chemistry, hematology, coagulation and urinalysis) are provided in Table 3-6.

Table 3-6 Follow-Up Analysis Visit Windows for Efficacy, Vital Signs, and Laboratory Assessments

Nominal Visit	Off-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
FU-Baseline	-1	(none)	-1
FU-Week 4	28	1	42
FU-Week 8	56	43	70
FU-Week 12	84	71	≥126

The analysis windows for Follow-Up Phase ECG is provided in.

Table 3-7 Follow-Up Analysis Visit Windows for ECG

Nominal Visit	Off-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
FU-Baseline	-1	(none)	-1
FU-Week 12	84	1	≥126

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

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

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

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

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

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

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

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

- Continuing study drug VBR
- Completed study drug VBR
- Did not complete study drug VBR and reasons for study drug discontinuation
- Continuing study drug ETV
- Completed study drug ETV
- Did not complete study drug ETV and reasons for study drug discontinuation
- Continuing study drug Peg-IFNα
- Completed study drug Peg-IFNα
- Did not complete study drug Peg-IFNα and reasons for study drug discontinuation

- Continuing study
- Completed study
- Did not complete the study and reasons for study discontinuation

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

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

- Reasons for premature study drug or study discontinuation
- Dispensed bottle number and lot number for VBR, lot number for Peg-IFNα and ETV

4.2. Extent of Study Drug Exposure and Compliance

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

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to each study drug through Week 24 will be defined as the last dose date at Week 24 minus the first dose date plus 1 for VBR and for ETV, plus 7 for Peg-IFNα , regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). Duration (weeks) = Duration (days) /7. Total duration of exposure to VBR through Week 48 will also be summarized and defined as the last dose date of VBR minus the first dose date plus 1 for VBR, similar calculation will be performed for total duration of ETV exposure. The last dose date of individual study drug is defined in Section 3.6.3. If the last study drug dose date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used for subjects included in the final analyses or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis.

The total duration of exposure to study drug will be summarized using descriptive statistics. Summaries will be provided by treatment group in each on-treatment phase for the Safety Analysis Set. For the Randomized Treatment Phase, the expected total duration of Randomized Treatment Phase for all subjects is 24 weeks. The distribution of subjects by the total number of weeks on therapy (ie, ≤4 weeks, >4-8 weeks, >8-12 weeks, >12-16 weeks, >16-20 weeks, >20-24 weeks, and ≥24 weeks) will be presented. After completion of the randomized treatment, all subjects will receive VBR+ETV for an additional 24 weeks. For the Overall Treatment Phase, the duration of exposure to VBR and ETV will be summarized. The expected total duration of

Overall Treatment Phase for all subjects is 48 weeks. The distribution of subjects by the total number of weeks on therapy (ie, ≤12 weeks, >12-24 weeks, >24 -<48 weeks, and ≥48 weeks) will be presented.

4.2.2. Study Drug Compliance

Compliance will be calculated for study drugs VBR, ETV and Peg-IFNα.

The total number of tablets (VBR and ETV) and injections (Peg-IFNα) administered will be summarized by treatment phases using descriptive statistics.

The presumed total number of tablets (VBR and ETV) administered to a subject will be determined by the data collected on the Drug Accountability- ABI-H0731 and ETV CRFs respectively using the following formula:

$$\text{Total Number of Tablets Administered} =$$

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

The presumed total number of injections (Peg-IFNα) administered to a subject will be determined by the data collected on the Drug Accountability- Peg-IFNα CRF using the following formula:

$$\text{Total Number of Doses Administered} =$$

$$\left(\sum \text{No. of Syringes Dispensed}\right) - \left(\sum \text{No. of Syringes Returned}\right)$$

4.2.2.1. On-Treatment Compliance

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

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

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

Per protocol, each subject completing treatment and receiving VBR is expected to take three 100 mg tablets of VBR daily during the Randomized Treatment Phase (ie, a total of 504 tablets is expected in a 24-week period) and during the Overall Treatment Phase (ie, a total of 1008 tablets are expected in a 48-week period). Each subject completing treatment and receiving ETV is expected to take a single oral 0.5 mg tablet once daily during the Randomized Treatment Phase (ie, a total of 168 tablets is expected in a 24-week period), during the Overall Treatment Phase

(ie, a total of 336 tablets are expected in a 48-week period). Each subject completing treatment and receiving Peg-IFNα is expected to have a total of 24 syringes of Peg-IFNα administered.

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

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

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

4.3. Protocol Deviations

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

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

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

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (i.e., age, age group [<50/ ≥ 50 years], sex, race, and ethnicity), baseline characteristics (body weight [in kg], height [in m], body mass index [BMI; in kg/m2]) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set.

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

5.2. Baseline Disease Characteristics

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

- Years positive for HBV
- HBV Genotype
- Baseline HBV DNA (log_{10} IU/mL)
- Baseline HBV pgRNA (log_{10} U/mL)
- Baseline HBeAg (log_{10} IU/mL)
- Baseline HBcrAg (log_{10} kU/mL)
- Baseline HBsAg (log_{10} IU/mL)
- Baseline HBeAg antibody (HBeAb)
- Baseline HBsAg antibody (HBsAb)
- Baseline antibody to the HBV core-related antigen (HBcrAb)
- Baseline ALT (U/L)
- Baseline ALT group (>ULN [Covance], >ULN [American Association for the Study of Liver Diseases (AASLD)])

- Baseline ALT group (<5 × ULN, ≥5 × ULN)
- Liver biopsy staging
- Fibroscan result
- Metavir Fibrosis Stage

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

5.3. Medical History

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

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

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

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

6. EFFICACY ANALYSES

The primary analysis set for efficacy analyses will be the FAS, defined in Section 3.1.2. All the efficacy analyses will be performed for each cohort separately.

6.1. Efficacy Endpoints

6.1.1. Definition of Primary Efficacy Endpoints

The efficacy endpoints include the following:

- Mean change in $\log_{10}$ HBV DNA from Baseline at each timepoint
- Mean change in $\log_{10}$ HBV pgRNA from Baseline at each timepoint
- Mean change in $\log_{10}$ serum viral antigens (ie HBcrAg, HBeAg, and HBsAg) from Baseline at each timepoint

6.1.2. Primary Analysis for Primary Efficacy Endpoints

The observed and mean change in $\log_{10}$ HBV DNA, HBV pgRNA, HBcrAg, HBeAg and HBsAg from Baseline will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group.

The comparison in change from baseline between treatment groups will be performed using the analysis of covariance (ANCOVA) model, including baseline value, the stratification factors, and treatment group as covariates. The estimated least square means of treatment effects and estimated difference in treatment effects between treatment groups will be presented along with the 95% CIs and p-values. The analysis will be based on observed data only. No imputation will be done for missing data.

6.2. Changes From Protocol-Specified Efficacy Analyses

Since the study is terminated early, the efficacy analyses for the key secondary and other secondary endpoints specified in the protocol will not be performed.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Relationship to Study Treatment" based on his/her clinical assessment. Events for which the investigator did not record relationship to an applicable study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs with an onset date/time equal to or after the date/time of first dose of study drug and no later than 28 days after the last dose date of any study drug.

7.1.5.2. Incomplete Dates

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

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

- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 28 days after the date of the last dose of any study drug

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

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set for the Randomized Treatment Phase (up to the last dose at Week 24) and the Overall Treatment Phase (up to the last dose of any study drug plus 28 days).

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

- TEAEs

- TEAEs by severity grade

- TEAEs related to VBR

- TEAEs related to ETV

- TEAEs related to Peg-IFNα

- TE SAEs

- TE SAEs related to VBR

- TE SAEs related to ETV

- TE SAEs related to Peg-IFNα

- TEAEs leading to VBR discontinuation

- TEAEs leading to ETV discontinuation

- TEAEs leading to Peg-IFNα discontinuation

- TEAEs leading to study discontinuation
- COVID-19 specific TEAEs
- COVID-19 specific TE SAEs

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

For the Follow-up Phase, a summary table will also be provided for all the AEs that occurred after the last dose of any study drug + 28 days through the end of study by the above category and by PT.

A data listing containing all AEs will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods based on the Safety Analysis Set. The lab values that are below LLOQ or above the upper LOQ will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.4.

7.2.1. Graded Laboratory Values

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

7.2.1.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from Baseline at any postbaseline time point, up to and including the date of last dose of any study drug plus 28 days for the Overall Treatment Phase. For the Randomized Treatment Phase, the treatment-emergent laboratory abnormalities will be summarized up to the last dose at Week 24.

If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.1.2. Summaries of Laboratory Abnormalities

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

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 28 days after last dose date for the Overall Treatment Phase and up to Week 24 dose date for the Randomized Treatment Phase.

The maximum postbaseline grade observed up to 28 days after last dose date or the Week 24 dose date will be tabulated for each laboratory test, and percentages will be based on the number of subjects with a postbaseline evaluation of the specific laboratory test. The laboratory abnormalities during the Follow-up Phase will also be summarized.

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

7.2.2. ALT Elevation

7.2.2.1. ALT Elevation without Declining Hepatic Function

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

7.2.2.2. ALT Elevation with Declining Hepatic Function

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

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

7.3. Vital Signs

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

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

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

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.3.

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

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary (WHODrug Global 1Sep2020).

7.4.1. Prior Medications

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

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

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

- A medication with a start date prior to the first dose date of study drug will be included in the prior medication summary regardless of when the stop date is.
- If a partial start date is entered, the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dose date.

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

Summaries will be based on the Safety Analysis Set.

7.4.2. Concomitant Medications

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

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

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

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

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

A medication with a stop date prior to the date of first dose date of study drug or a start date after the last dose date of study drug will be excluded from the summary.

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

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

7.5. Electrocardiogram Results

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

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

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

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

7.6. Other Safety Measures

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

8. REFERENCES

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

9. SOFTWARE

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

10. DOCUMENT HISTORY

Version	Date (DD MMM YYYY)	Summary of Changes
1.0	05 JAN 2023	Original
2.0	09 JAN 2023	Added changes to imputation rules

11. APPENDICES

None.

Signature Page for VV-TMF-57431 v2.0

Reason for signing: Approved	[redacted] Date of signature: 09-Jan-2023 22:46:13 GMT+0000

Reason for signing: Approved	[redacted] Date of signature: 09-Jan-2023 22:48:33 GMT+0000

Reason for signing: Approved	[redacted] Date of signature: 09-Jan-2023 22:52:45 GMT+0000

Signature Page for VV-TMF-57431 v2.0