Title: A Phase 2a, Multi-center, Double-blind, Placebo-controlled Study Evaluating ABI-H0731 as Adjunctive Therapy in Virally-suppressed Patients with Chronic Hepatitis B

NCT number: NCT03576066

Date: 09 Nov 2018

CLINICAL RESEARCH PROTOCOL

PROTOCOL TITLE: A Phase 2a, Multi-center, Double-blind, Placebo-controlled Study Evaluating ABI-H0731 as Adjunctive Therapy in Virally-suppressed Patients with Chronic Hepatitis B

STUDY NUMBER: ABI-H0731-201

DRUG: ABI-H0731

REFERENCE NUMBERS: US IND 136780

SPONSOR: Assembly Biosciences
[redacted]

PROTOCOL: Amendment 3, V4.0, 09 November 2018

Amendment 2, V3.0, 09 September 2018

Amendment 1, V2.0, 18 June 2018

Original, V1.0, 10 May 2018

CONFIDENTIAL

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase 2a, Multi-center, Double-blind, Placebo-controlled Study Evaluating ABI-H0731 as Adjunctive Therapy in Virally-Suppressed Patients with Chronic Hepatitis B

Study No: ABI-H0731-201

Protocol Date: 09 November 2018

This study protocol was subject to critical review and has been approved by the appropriate protocol review personnel of the Sponsor. The information contained in this protocol is consistent with:

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

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

Assembly Biosciences, Inc. Approvals	Approval Signature	Date
[redacted]	[redacted]	10NOV2018 10 Nov 2018

Summary of Changes Included in the Full Protocol Amendment of: ABI-H0731-201

A Phase 2a, Multi-center, Double-blind, Placebo-controlled Study Evaluating ABI-H0731 as Adjunctive Therapy in Virally-suppressed Patients with Chronic Hepatitis B

The amended Protocol is identified as: Amendment 3, Dated 09 November 2018

The primary purposes of this full version amendment are to:

1. Include change to Inclusion Criterion #7 which was implemented in a Clarification Letter #1, dated 14 September 2018.
2. Revise Inclusion Criterion #10 for HBeAg-positive subjects to allow for a lower HBsAg value of 400 IU/mL.
3. Modify the re-screening language in Section 5.5 (Screen Failures)
4. Clarify in Section 4.1 (Study Design) that safety data intervals are outlined in DMC charter.
5. Clarify a daily multivitamin is allowed in Section 5.4 (Lifestyle Considerations)
6. Administrative changes to protocol headers, Table 2 (Schedule of Assessments), Appendix II (Adverse Event Intensity Grading), and Appendix III (Cytochrome P450 2B6, 2C8, 2C9, and 2D6 Substrates) that have no effect on the way the study is to be conducted.

Additions to protocol text are indicated in **bold;** deletions are indicated by ~~strikethrough.~~ Unless otherwise stated, headers, section and page numbers reflect the current version of the protocol.

1. AMENDED INCLUSION CRITERION #7 AS PER CLARIFICATION LETTER #1

   - Added clarification to Inclusion Criterion #7

     7. Virologically suppressed (defined as HBV DNA ≤LOQ) for at least 6 months before screening on SOC NUC therapy

        a. Subjects with a low but quantifiable viral load (for example <60 IU/mL) within 6 months prior to screening which was shown to be an exception in a subject who has previously been well suppressed, may be eligible for study if the subject is virologically suppressed at screening

2. MODIFIED INCLUSION CRITERION # 10
   - The allowable HBsAg value for HBeAg-positive subjects has been lowered from 1000 IU/mL to 400 IU/mL. Clinically, there is no difference in risk factors or worse disease between subjects with HBsAg levels of 400 to 1000 IU/mL than subjects with HBsAg values greater than 1000 IU/mL. Additionally, the power to detect clinically meaningful declines of 0.5 log or more is retained. HBeAg-positive subjects who screen failed previously will be permitted to rescreen due to this criterion's revision.

     10. Hepatitis B surface antigen (HBsAg) levels:
         - HBeAg positive subjects must have >~~1000~~ **400** IU/mL HBsAg at screening;
         - HBeAg negative subjects must have >100 IU/mL HBsAg at screening

3. MODIFIED THE RESCREEN CRITERIA IN SECTION 5.5 (SCREEN FAILURES)
   - Revised to allow for medical monitor input

   Screen failures are defined as subjects who consent to participate in the clinical trial, but are not subsequently randomly assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of an abnormal screening laboratory value may be rescreened one time. **It will be at the discretion of the medical monitor on a case-by-case basis whether rescreening will be permitted under other circumstances.** ~~Rescreened subjects should be assigned the same subject number the initial screening.~~

4. CLARIFIED IN SECTION 4.1 (STUDY DESIGN) THAT SAFETY DATA REVIEW INTERVALS ARE SPECIFIED IN DMC CHARTER
   - Updated DMC text in section 4.1 Study Design to be consistent with Section 12.2 Data Monitoring Committee

   Safety will be monitored by a Data Monitoring Committee (DMC), including ~~a safety analysis after all subjects have completed Week 12 (or discontinued study without completing Week 12)~~ **laboratory data and adverse events, at intervals outlined in the DMC charter.**

5. CLARIFIED A DAILY MULTIVITAMIN IS ALLOWED IN SECTION 5.4 (LIFESTYLE CONSIDERTIONS)
   - Abstain from the use of herbal or other supplements **(a multivitamin is permitted)**

6. ADMINISTRATIVE CHANGES TO HEADERS, TABLE 2 SCHEDULE OF ASSESSMENTS, APPENDIX II ADVERSE EVENT INTENSITY GRADING, AND APPENDIX III CYTOCHROME P450 2B6, 2C8, 2C9 AND 2D6 SUBSTRATES
   - Modified protocol document headers to reflect Amendment 3 version date
   - Table 2 Schedule of Assessments: Updated Week 24 physical exam from symptom-directed to full physical exam.
   - Appendix II Adverse Event Intensity Grading: Corrected typos to Grade 4 high calcium and Grade 4 low sodium
   - Appendix III Cytochrome P450 2B6, 2C8, 2C9, and 2D6 Substrates: Updated for clarification

ABI-H0731-201

A Phase 2a, Multi-center, Double-blind, Placebo-controlled Study Evaluating ABI-H0731 as Adjunctive Therapy in Virally-suppressed Patients with Chronic Hepatitis B

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as described herein, in accordance with Good Clinical Practice (GCP) as set out in the current International Council for Harmonisation (ICH) guidelines (E6) and other applicable national or local requirements and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Assembly Biosciences or specified designees. I will discuss the material with them to ensure that they are fully informed about Assembly Biosciences and the study.

Principal Investigator Name (printed)	Signature
Date	Site Number

Please keep the original, signed copy of this Investigator signature page in your records and email a copy to your Clinical Research Associate.

1 SYNOPSIS

Protocol Number:	ABI-H0731-201
Title:	A Phase 2a, Multi-center, Double-blind, Placebo-controlled Study Evaluating ABI-H0731 as Adjunctive Therapy in Virally-suppressed Patients with Chronic Hepatitis B
Phase:	2a
Number of Subjects:	Approximately 70
Study Duration:	Approximately 2-3 months enrollment, 6 months treatment, and 3 months safety follow-up only for subjects who do not opt for the separate open-label, extension study
Rationale:	Chronic hepatitis B infection (CHB) is a major global cause of severe liver morbidity and liver-related mortality. ABI-H0731 is a direct-acting antiviral targeting the hepatitis B virus (HBV) core protein. It is anticipated that addition of ABI-H0731 to a standard of care (SOC) nucleos(t)ide analogue (NUC) therapy will be safe and potentially increase the functional cure rate for CHB patients. This study will explore the safety of this combination therapy and its efficacy on serum biomarkers of functional cure: quantitative and qualitative reduction in the viral antigens hepatitis B "e" antigen (HBeAg, in HBeAg positive subjects), hepatitis B surface antigen (HBsAg), and reduction in circulating HBV RNA.
Target Population:	Male or female subjects with CHB, age 18 to 70 years, with no evidence of cirrhosis or end-stage liver disease, on stable SOC NUC therapy whose viral load has been below the limit of quantitation (LOQ) for at least 6 months.
Test Product:	Active-treatment subjects will receive 300mg of ABI-H0731, administered orally, once daily, as three 100mg tablets in addition to their SOC NUC therapy (which must be either entecavir [ETV], tenofovir alafenamide fumarate [TAF], or tenofovir disoproxil fumarate [TDF]).
Reference Product:	Placebo subjects will receive placebo (matching placebo to ABI-H0731 100mg tablets), administered orally, once daily, as three tablets in addition to their SOC NUC therapy.
Study Design:	This is a Phase 2a, multi-center, randomized, double-blind, placebo-controlled study evaluating the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics of ABI-H0731 in combination with a SOC NUC in subjects with CHB virus infection who are virally-suppressed on SOC NUC therapy. Subjects will be randomized in a ratio of 3:2 (HBeAg Positive subjects: 27 subjects will receive ABI-H0731 + NUC: 18 subjects will receive matching placebo + NUC; HBeAg Negative subjects: 15 subjects will receive ABI-H0731 + NUC: 10 subjects will receive matching placebo + NUC) to receive investigational agent as add-on therapy to their current SOC NUC for up to 6 months. Efficacy, safety, and PK will be assessed during the 6-month

treatment period. At the end of the 6-month treatment period, subjects can opt to roll over to an optional, open-label, extension study of ABI-H0731 + SOC NUC (protocol ABI-H0731-211) or continue receiving their SOC NUC therapy and stop treatment with ABI-H0731/placebo. Subjects who opt not to roll over to the extension study must complete a 3-month, safety follow-up period after the 6-month treatment period.

Study Objectives:

Primary:

- To evaluate the potential for ABI-H0731 to increase clinical cure rates in CHB subjects whose viral replication is stably suppressed on a SOC NUC therapy, as measured by changes from Baseline in serum biomarkers (ie, HBsAg or HBeAg) of transcriptionally active covalently closed circular DNA (cccDNA)

Secondary:

- To evaluate the safety and tolerability of ABI-H0731 when added to SOC NUC therapy in subjects already virally suppressed on SOC therapy
- To confirm a lack of drug-drug interactions between SOC NUC and ABI-H0731

Exploratory:

- To evaluate the kinetics of and absolute changes from Baseline in biomarkers of transcriptionally active cccDNA (HBeAg and HBsAg)
- To evaluate the kinetics of and absolute changes from Baseline in circulating HBV RNA
- To assess the relationship between changes in exploratory viral biomarkers such as changes in viral RNA and hepatitis B core-related antigen (HBCrAg) with clinical outcomes
- To monitor for emergence of resistance, if any, for ABI-H0731 in combination with SOC NUC
- To explore the PK of ABI-H0731
- For subjects who provide an optional pharmacogenomic sample, to evaluate the potential contribution of host genomics to outcomes

Primary Endpoint:

The primary efficacy endpoint will be:

- Change in mean $\log_{10}$ serum viral antigen (HBsAg or HBeAg) from Baseline (Day 1) to Week 24 on ABI-H0731 + NUC as compared to placebo + NUC

Secondary Endpoints:

The secondary endpoints will be:

- Number of subjects with adverse events, premature discontinuations, abnormal safety laboratory results, electrocardiogram (ECG), or vital signs
- Subjects with abnormal alanine aminotransferase (ALT) at Baseline who have normal ALT at Week 24 on ABI-H0731 + NUC therapy as compared with placebo + NUC therapy
- Drug concentrations:

- Trough levels and (in subjects where optional samples are available) trough to peak ratios of ABI-H0731 on ABI-H0731 + NUC therapy
- Trough levels and (in subjects where optional samples are available) trough to peak ratios of NUC on ABI-H0731 + NUC therapy as compared with placebo + NUC therapy

Exploratory Endpoints:

Exploratory endpoints include:

- Quantitative changes in serum HBV RNA and HBCrAg levels on ABI-H0731 + NUC as compared with placebo + NUC, at each time point
- Subjects with loss (defined as below LOQ) or decline in HBsAg or HBeAg (<0.5 $\log_{10}$, ≥ 0.5 to 1.0 $\log_{10}$, or >1.0 $\log_{10}$ decrease in viral antigen) on ABI-H0731 + NUC as compared with placebo + NUC at end of treatment and end of follow-up
- Subjects with HBsAg seroconversion (loss of HBsAg and appearance of HBs antibody) or HBeAg seroconversion (loss of HBeAg and appearance of HBe antibody) on ABI-H0731 + NUC as compared with placebo + NUC
- Subjects with HBV DNA "detectable" at Baseline whose HBV DNA becomes "non-detectable" on ABI-H0731 + NUC as compared with placebo + NUC
- Emergence of resistant HBV variants, if any
- For subjects who do NOT rollover onto the optional extension study, ABI-H0731-211:
  - Subjects with suppression of detectable serum HBV RNA on treatment whose HBV RNA rebounds after discontinuing treatment with ABI-H0731 + SOC NUC as compared with placebo + SOC NUC
  - Subjects with changes from baseline in HBsAg or HBeAg whose viral antigen rebounds after discontinuing treatment with ABI-H0731 + SOC NUC as compared with placebo + SOC NUC
- Subjects with HBsAg or HBeAg loss at Week 24 that is maintained through end of follow-up (Week 36) after discontinuing treatment with ABI-H0731 + SOC NUC as compared with placebo + SOC NUC
- If differences are seen in outcomes/adverse events between racial or ethnic groups: Pharmacogenomics correlation with clinical outcomes subjects who provide optional informed consent

Statistical Methods:

As a proof-of-concept trial, statistical hypotheses to compare the treatment effects in this study will be explored descriptively, graphically and inferentially. Unless stated otherwise, the statistical null hypothesis for all assessments is that the effects of ABI-H0731 + SOC NUC and placebo + SOC NUC are not different. The alternative hypothesis is that effects of the two treatments are different.

A two-sample test of difference with a two-sided 0.05 significance level will be used to assess differences between the treatment groups in change in mean $\log_{10}$ serum antigen (HBsAg or HBeAg) from Baseline to Week 24.

Secondary and exploratory endpoints will be analyzed descriptively. All secondary and exploratory efficacy endpoints will be summarized.

For continuous variables, such as observed and change from Baseline HBsAg values at each timepoint, descriptive statistics will be used and will include the number, mean, standard deviation, median, minimum, maximum, and interquartile range and, where appropriate, a 95% confidence interval.

For categorical variables, such as subjects with a 1 $\log_{10}$ drop in serum antigen (HBsAg or HBeAg) titers from Baseline and subjects with HBeAg (and HBsAg) loss and seroconversion, descriptive statistics will include number and percent who meet the endpoint criteria.

Kaplan-Meier methods will be used to evaluate time to event variables (eg, time to HBsAg levels less than LOQ), and the treatment groups will be compared using log-rank tests.

Cox proportional hazards regression models will be used to identify baseline factors associated with HBsAg loss rates, as defined in the statistical analysis plan.

Key Eligibility:

Inclusion Criteria

Subjects must meet inclusion criteria in order to be eligible for enrollment.

1. Male or female between ages 18 and 70 years (inclusive)
2. Female subjects must agree to use dual effective birth control methods for the duration of the study and follow-up or be surgically sterile for at least 6 months or at least 2 years post-menopausal, with serum follicle-stimulating hormone (FSH) levels consistent with a post-menopausal status. Effective birth control methods include male or female condom (may not be used together due to increased risk of breakage), vasectomy, intrauterine device (IUD) – inclusive of IUDs with hormonal components), diaphragm, or cervical cap. Systemic (oral/injectable) hormonal birth control are prohibited. Female subjects must have a negative serum pregnancy test at screening
3. All heterosexually active male subjects must agree to use dual effective birth control methods for the duration of the study and follow-up. Effective birth control methods include male or female condom (may not be used together due to increased risk of breakage), vasectomy, hormone-based contraception, IUD, diaphragm, or cervical cap
4. Body mass index (BMI) 18 to 36 kg/m^2 and a minimum body weight of 45 kg (inclusive)
5. Agreement to adhere to Lifestyle Considerations (including abstaining from alcohol abuse [defined as alcohol consumption exceeding 2 standard

drinks per day on average (1 standard drink = 10 grams of alcohol)] and the use of illicit substances, herbal or other substances, or unnecessary over-the-counter medications; see Protocol Section 5.4) throughout study duration

6. In good general health except for chronic HBV infection (defined as HBV infection for at least 6 months documented by – for example – history of two repeated HBsAg positivity and/or detectable viral load documented at least two times ≥6 months apart – inclusive of screening)

7. Virologically suppressed (defined as HBV DNA ≤LOQ) for at least 6 months before screening on SOC NUC therapy

   a. Subjects with a low but quantifiable viral load (for example <60 IU/mL)within 6 months prior to screening which was shown to be an exception in a subject who has previously been well suppressed, may be eligible for study if the subject is virologically suppressed at screening

8. Subjects will be stratified 9:5 HBeAg positive to HBeAg negative. Subjects in the HBeAg-positive cohort must be HBeAg positive at screening

9. HBsAg: HBeAg positive subjects must have >400 IU/mL HBsAg at screening; HBeAg negative subjects must have >100 IU/mL HBsAg at screening

10. Liver biopsy results of

    o Metavir F0-F2 (absence of bridging fibrosis or cirrhosis) within 1 year of screening

    OR

    o Fasting FibroScan ≤8 kPa within 3 months of screening (including screening visit) or other Sponsor-approved hepatic imaging study (hepatic magnetic resonance imaging [MRI], or hepatic ultrasound by a ultrasonographer with expertise in evaluation of liver fibrosis) within 6 months of screening indicating lack of cirrhosis or advanced liver disease (F0-F2 or equivalent).

    Subjects with an ambiguous non-invasive result, eg, a fasting FibroScan >8 kPa and ≤10 kPa are excluded unless a biopsy within the 12 months before first visit confirms the absence of bridging fibrosis and cirrhosis. Subjects with a FibroScan >10 kPa are excluded

11. Have the ability to take oral medication and be willing to adhere to the ABI-H0731-201 regimen in the opinion of the Investigator

12. Willing and able to provide informed consent

Exclusion Criteria

Subjects who meet the exclusion criteria will not be eligible for enrollment.

1. Co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis E virus (HEV), or hepatitis D virus (HDV)
2. History or evidence of hepatic decompensation (including gastrointestinal bleeding or esophageal varices) at any time prior to or at time of screening
3. Subject is febrile (temperature >37.5°C) at screening
4. Clinically significant cardiac or pulmonary disease, chronic or recurrent renal or urinary tract disease, liver disease other than HBV, endocrine disorder, autoimmune disorder, diabetes mellitus requiring treatment with insulin or hypoglycemic agents, neuromuscular, musculoskeletal, or mucocutaneous conditions requiring frequent treatment, seizure disorders requiring treatment, 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 the study
5. Previous treatment with an investigational agent for HBV other than ABI-H0731 in the last 6 months before screening
6. Previous treatment with an HBV capsid targeting agent other than ABI-H0731 at any time
7. Participation in another clinical trial of a drug or device whereby the last investigational drug/device administration is within 60 days or five half-lives prior to the first study drug administration, whichever is longer
8. History of persistent ethanol abuse (alcohol consumption exceeding 2 standard drinks per day on average [1 standard drink = 10 grams of alcohol]) or illicit drug abuse within 3 years before screening
9. Females who are lactating or pregnant or wish to become pregnant are excluded from the study
10. History of hepatocellular carcinoma (HCC)
11. A history of malignancy other than HCC unless the subject's malignancy has been in complete remission off chemotherapy and without additional medical or surgical interventions during the 3 years before screening
12. Exclusionary laboratory results
    a. Platelet count <100,000/mm^3
    b. Albumin <lower limit of normal (LLN)
    c. Total bilirubin >1.2×upper limit of normal (ULN) unless known Gilbert syndrome; subjects with Gilbert syndrome are eligible if direct bilirubin is within normal limits
    d. Direct bilirubin >1.2×ULN

e. ALT >5×ULN at screening

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

g. Prothrombin time: International Normalized Ratio (INR) >1.5×ULN

h. Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey 2009)

i. Serum hemoglobin A1c (HbA1c) >8%

j. Any other laboratory abnormality deemed clinically significant by the Sponsor or the Investigator

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AFP	alpha fetoprotein
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
CC_{50}	50% cytotoxic concentration
cccDNA	covalently closed circular DNA
CFR	Code of Federal Regulations
CHB	chronic hepatitis B infection
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	confidence interval
C_{max}	maximum plasma concentration
CNS	central nervous system
CpAM	core protein allosteric modifier
CRO	Clinical Research Organization (PRA Health Sciences)
CYP	cytochrome P450
DAA	direct acting antivirals
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
dsDNA	double-stranded DNA
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ETV	entecavir
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HAV	hepatitis A virus
HbA1c	hemoglobin A1c
HBCrAb	antibody to the HBV core protein
HBCrAg	hepatitis B core-related antigen
HBeAb	HBeAg antibody
HBeAg	hepatitis B “e” antigen
HBsAb	HBsAg antibody

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IgM	immunoglobulin M
INR	International Normalized Ratio
IRB	Institutional Review Board
ISG	IFN-stimulated gene
ITT	intent-to-treat
IUD	intrauterine device
LLN	lower limit of normal
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse effect level
NUC	nucleos(t)ide inhibitors of the HBV polymerase; also called nucleos(t)ide analogues or nucleos(t)ides
PBMC	peripheral blood mononuclear cell
pgRNA	pre-genomic RNA
PK	pharmacokinetic(s)
PK1	Pharmacokinetic Population 1
PK2	Pharmacokinetic Population 2
Pol/RT	polymerase/reverse transcriptase
PP	per-protocol
rcDNA	relaxed circular DNA
SAP	statistical analysis plan
SOC	standard of care
Sponsor	Assembly Biosciences
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
T_{max}	time to C_{max}

ULN	upper limit of normal
WHO	World Health Organization

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

Worldwide >240 million people are chronically infected with the hepatitis B virus (HBV), and chronic hepatitis B infection (CHB) is a major global cause of severe liver morbidity and liver-related mortality [WHO 2015]. Moreover, the burden of global mortality attributable to chronic viral hepatitis (B and C combined) has increased over the last two decades; it was the seventh leading cause of death worldwide in 2013, compared with the tenth in 1990 [Stanaway 2016]. Current therapies (comprising interferon [IFN] products and nucleos(t)ide inhibitors [NUCs] of the HBV polymerase) are highly effective at suppressing serum viremia but rarely lead to loss of viral antigenemia – a biomarker of persistent covalently closed circular DNA (cccDNA) activity. Additionally, in a surprising number of patients, ongoing low-level viremia remains detectable, as does cccDNA and intrahepatic viral intermediates [Boyd 2016; Marcellin 2014]. As a result of the persistence of active cccDNA, durable antiviral response is rare after cessation of treatment [Papatheodoris 2016]. New therapies are required which can increase clinical cures, either alone or in combination with existing standard of care (SOC) for CHB.

ABI-H0731 is a novel HBV core protein allosteric modifier (CpAM), or "Core Inhibitor" discovered by Assembly Biosciences ("the Sponsor"), and it is being developed as a potential therapeutic advance for CHB patients. ABI-H0731 inhibits HBV replication by interfering with essential functions of the HBV core protein, and it therefore inhibits HBV replication by different mechanisms than NUC analogues or IFN-α. In pre-clinical models, ABI-H0731 binds to the HBV core protein and induces altered, non-functional core protein assembly. Experience in patients with hepatitis C virus (HCV), another viral hepatitis, has shown that combination of multiple direct acting antivirals (DAAs) can increase rates of cures compared to monotherapy with a potent NUC inhibitor alone [Gane 2013]. Thus, inhibition of HBV core protein functions by ABI-H0731, when used in combination with currently approved HBV antivirals, may offer the potential to improve therapy for chronic HBV and provide patients with enhanced rates of durable clinical cures in a finite treatment period.

This Phase 2a study will be the first study to explore the potential to increase rates of clinical cure by addition of ABI-H0731 (a Core inhibitor) to SOC NUC therapy (entecavir [ETV], tenofovir alafenamide [TAF], or tenofovir disoproxil fumarate [TDF]) in patients who are chronically suppressed to the limit of quantitation (LOQ) on SOC NUC therapy alone, but who have ongoing expression of the viral antigens hepatitis B surface antigen (HBsAg) and hepatitis B "e" antigen (HBeAg) – biomarkers of active cccDNA transcription.

2.2 Background

2.2.1 Chronic Hepatitis B Virus

HBV remains a major public health burden. HBV contributes to as much as 30% of cases of cirrhosis and 45% of cases of hepatocellular carcinoma (HCC) [WHO 2015]. The standard serologic markers of HBV infection include: HBV DNA, HBsAg, antibody to HBsAg (HBsAb), HBeAg, antibody to HBeAg (HBeAb), and, in almost all patients, antibody to the HBV core

protein. Chronic HBV infection is clinically defined as the persistence of HBsAg in a subject for 6 to 12 months or more [Terrault 2018].

There are four 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 and Hnatyszyn 2005].

Despite broad implementation of HBV vaccination programs, new cases of HBV infection are still common. The World Health Organization (WHO) estimates that there are >4 million acute HBV infections worldwide each year [WHO 2015]. The global prevalence of chronic HBV infection shows wide geographic variation, with a prevalence of >8% people in highly endemic regions (eg, East Asia and equatorial Africa), 2% to 7% people in moderately endemic regions (eg, the Middle East and the Indian subcontinent), and <2% in locales of low endemicity (eg, North America and Europe) [Schweitzer et al 2015; WHO 2015].

Some HBV carriers will lose detectable serum HBsAg and HBV viremia will drop to non-detectable levels. Such a transition to an HBsAg-negative, minimally replicative state (termed "HBsAg seroconversion") is usually durable and, if it precedes the development of cirrhosis and HCC, is associated with improved long-term clinical outcomes [EASL 2012]. As such, HBsAg seroconversion is considered a "functional cure" and a potential endpoint for HBV therapy.

Currently there are two clinically accepted options for the treatment of CHB: IFNs and oral NUCs, which act as inhibitors of the viral polymerase. Of these, oral NUCs are much more broadly used, and have shown remarkable success in achieving maintained viral suppression in CHB patients, with associated decreases in long-term clinical complications [Lampertico and Liaw 2012]. Despite suppression of viremia for extended periods of time, however, HBsAg loss and/or seroconversion is rarely achieved in a practical timeframe with current therapies. HBsAg loss is achieved by <10% of CHB patients within 5 years after a year of treatment with IFN products and/or after 5 years of NUC antivirals, with slightly higher rates of HBsAg loss recently reported in combination studies of tenofovir disoproxil fumarate (TDF) together with pegylated IFN-alfa for one year [Marcellin 2014].

There is clearly a need for improved HBV therapies that are of finite duration and can produce a substantially higher rate of therapeutic responses that will be durable post-treatment. Specifically, improved rates of two types of durable outcomes are desirable for new HBV therapies: durable HBeAg loss/seroconversion (in HBeAg-positive patients), and HBsAg loss/seroconversion (in all patients), in addition to sustained off-treatment viral load suppression and normalization of transaminases. Such "clinical cures" are predicted to afford improved long-term patient outcomes, ie, reduced HBV-associated morbidity and mortality from end-stage liver disease and HCC.

2.2.2 Hepatitis B Virus Biology and Rationale for Hepatitis B Virus Core Protein Allosteric Modifiers (CpAMs)

2.2.2.1 Overview of Hepatitis B Virus Biology

HBV is a member of the *Hepadnaviridae* family. The HBV genome consists of a partially double-stranded DNA (dsDNA) (~3.2 kb) that is synthesized through reverse transcription of its pre-genomic RNA (pgRNA) precursor. The infectious HBV virion, called the Dane particle, comprises an enveloped nucleocapsid, which contains a single copy of the HBV genome as partially double-stranded, relaxed circular DNA (rcDNA) and viral reverse transcriptase, enclosed in a polymeric capsid, assembled from HBV core protein subunits. The life cycle of HBV can be conceptualized as occurring in several steps. Circulating HBV must enter cells. Following entry, virus must enter the nucleus where rcDNA is converted to a stable chromosome-like moiety (the cccDNA). The cccDNA functions as the template for full length pgRNA and the mRNAs for viral proteins. These proteins include polymerase/reverse transcriptase (Pol/RT), HBV X protein, core protein, and HBsAg. RNA produced from the cccDNA is transported from the nucleus into the hepatocyte cytoplasm, where it is bound by HBV polymerase and encapsidated by 120 viral core protein dimers. Within the capsid, pgRNA is reverse transcribed into viral dsDNA. This dsDNA filled particle can then either acquire an S antigen envelope and be secreted as new infectious virus or recycle rcDNA back to the nucleus where it can amplify the cccDNA pool. Details of the HBV replication cycle have recently been reviewed in detail by Seeger et al [Seeger 2013].

2.2.2.2 Hepatitis B Virus Core (Capsid) Protein and Core Protein Functions

HBV core protein has several essential roles in the life cycle of HBV infection, including the formation of capsids. The appropriate kinetics of HBV core protein assembly is critical in enabling functional capsid formation and encapsidation of pgRNA. These steps are essential for the formation of new infectious virions. The HBV capsid is also essential for the process of nuclear import of the HBV rcDNA through a regulated interaction with nuclear pore proteins. In the nucleus, the rcDNA is converted to cccDNA. cccDNA is a long-lived circular, episomal DNA from which all HBV RNAs are derived. Core protein contributes to replenishing nuclear cccDNA pools by mediating nuclear import of genomic DNA from newly formed capsids in the cytoplasm of infected cells. Nuclear forms of HBV core protein can also affect the expression of viral and host genes and contribute to regulated splicing and nuclear export of HBV RNAs, and HBV CpAMs have been reported to be able to interfere with cccDNA function [Gruffaz 2013, Belloni 2013]. HBV core protein is therefore a critical component of the HBV life cycle. Additionally, some data suggest that HBV core protein induces an HBV-specific dysfunction of the innate immune response in HBV-infected hepatocytes [Gruffaz 2013], including a suppression of expression of IFN-stimulated genes (ISGs).

These findings suggest that allosteric modulation of core protein may allow targeting of multiple aspects of the viral life cycle: assembly into virion capsids, trafficking of HBV DNA into cell nuclei, cccDNA replenishment, and potentially interference with the innate immune response in infected cells.

2.2.2.3 Hepatitis B Virus Core Protein Allosteric Modifiers and ABI-H0731

2.2.2.3.1 *In Vitro* Activity of ABI-H0731

ABI-H0731 is a small molecule inhibitor of HBV replication that induces non-functional assembly of the HBV core protein and exhibits potent inhibition of HBV replication *in vitro* via a different mechanism than NUC or IFN-α therapy. ABI-H0731 binds to the HBV core protein and induces altered, non-functional core protein assembly *in vitro*. The antiviral activity of ABI-H0731 against HBV replication *in vitro* was evaluated using a standard HepAD38 cell line, which stably expresses infectious genotype D HBV. Analysis of intracellular HBV DNA showed a dose-dependent reduction of viral DNA in the presence of ABI-H0731. In an inducible cell line model of HBV, the mean 50% effective concentration (EC_{50}) for ABI-H0731 against HBV DNA replication was 173 nM, with no cellular toxicity observed at the highest concentration tested (50% cytotoxic concentration [CC_{50}] >10 μM). Similar or better antiviral activity (EC_{50} of 86-142 nM) was observed in HBV DNA transfection-based assays against representative HBV strains of genotypes A, B, C, and D. ABI-H0731 therefore showed broad inhibition across genotypes.

Specificity of ABI-H0731 for HBV was confirmed by the absence of antiviral activity when tested against other DNA and RNA viruses (HSV-1, HRV-16, and influenza A) at the highest concentrations tested (10 μM). ABI-H0731 was also evaluated for selectivity by determining the CC_{50} levels in seven human cell types/lines (Huh7, HepG2, HeLa H1A, HEK 293, NCI H226, and MOLT-4) and freshly isolated peripheral blood mononuclear cell (PBMC) cultures representing various human tissues following 4 days of incubation. ABI-H0731 showed no significant effects at a concentration of 3.3 μM (<7% reduction in cell viability) and up to 16% reduction in cell viability in some cell types/lines at 10 μM. These results demonstrate that ABI-H0731 is a highly selective and specific HBV inhibitor, consistent with specificity in targeting the HBV core protein target of ABI-H0731.

See the Investigator's Brochure (IB) for further information.

2.2.2.3.2 Combination Therapy

Combining drugs from different classes provides numerous advantages compared with monotherapy, including the potential for additive or synergistic antiviral effects and establishment of higher resistance barriers, reducing the likelihood of adverse mutations. Combination studies of ABI-H0731 with a representative NUC polymerase inhibitor, ETV (Baraclude®), showed additive to synergistic effects over a wide range of concentrations, with no evidence of antagonism, indicating that ABI-H0731 has the capacity to be successfully combined with NUCs in the treatment of HBV. Please see the IB for further information.

2.2.2.3.3 Study Drug Resistance

There are no established methods for the selection of drug resistance against HBV *in vitro* because there are no *in vitro* cell culture systems that allow multiple cycles of HBV replication. In the Phase 1b monotherapy study, ABI-H0731-101(b), CHB subjects treated with ABI-H0731 for 28 days were monitored closely for evidence of resistance emergence. To date, a single subject was

observed to enter study ABI-H0731-101(b) harboring a resistance variant at baseline (T109M). While this subject had a blunted response to therapy, they still exhibited a 1 $\log_{10}$ IU/mL decline in viral load over 28 days, suggesting that ABI-H0731 may achieve sufficient intrahepatic concentrations to inhibit replication of at least some naturally occurring resistant mutants. Importantly, the T109M mutant is not known to have a reduced susceptibility to SOC NUCs or pre-exist as a polymorphic substitution in HBV database sequences at any significant frequency. To date, no *de novo* mutations were noted to arise on treatment in any other subjects.

2.2.3 Summary of Nonclinical Pharmacology and Toxicology

The nonclinical pharmacokinetics (PK), absorption, distribution, metabolism, and excretion of ABI-H0731 were characterized *in vitro* and *in vivo* in mice, rats, dogs, rabbits, and monkeys. Results are summarized in the IB.

A standard battery of nonclinical safety studies, including safety pharmacology, genotoxicity, and *repeat* dose toxicity studies has been conducted. In safety pharmacology studies, there were no adverse central nervous system, cardiovascular, or respiratory system effects in rats or monkeys following single oral doses of ABI-H0731 up to 500 mg/kg. ABI-H0731 was not genotoxic in the *in vitro* bacterial or mammalian cell assays or in the *in vivo* rat micronucleus study.

In chronic toxicity studies, ABI-H0731 was well-tolerated at the highest tested dose levels of 250 mg/kg/day for 6 months in rats and 500 mg/kg/day for 9 months in monkeys, with no drug-attributed animal deaths and no patterns of adverse effects or changes in clinical pathology. There were no clear target organ findings in these studies. Histopathology observations in rats consisted of increased adrenal gland weight for males given ≥100 mg/kg/day and females given ≥200 mg/kg/day, with correlating microscopic findings of minimal or mild diffuse hypertrophy of the zona fasciculata and/or minimal to moderate multifocal cortical vacuolation in some animals given ≥100 mg/kg/day. These findings were considered non-adverse, based on the absence of any apparent detrimental effect on the overall health of the animals and the partial or complete reversibility of the effects during the 28-day recovery period. In monkeys, there were no measurable effects beyond normal morphologic variations. Therefore, the no-observed-adverse effect levels (NOAELs) are the highest doses tested, 250 mg/kg/day for 6 months in rats and 500 mg/kg/day for 9 months in monkeys. These dosing levels resulted in rat and monkey maximum plasma concentrations (C_{max}) levels of 10.0 µg/mL and 8.47 µg/mL, respectively, and area under the concentration-time curve from time 0 to 24 hours post-dose values of 147 hr*µg/mL and 122 hr*µg/mL, respectively. For more information, please refer to the IB.

2.2.4 Summary of Clinical Studies with ABI-H0731

Clinical experience with ABI-H0731 consists primarily of three early-phase clinical studies: (1) the recently completed Phase 1a/1b dose-ranging study in healthy volunteers and treatment-naïve CHB subjects, ABI-H0731-101; (2) an essentially identical sister Phase 1b study ABI-H0731-101(B) (in treatment-naïve subjects with CHB); and (3) the second recently completed Phase 1a study ABI-H0731-102. These studies are summarized briefly below. For more complete information, please refer to the IB.

2.2.4.1 Clinical Safety Data of ABI-H0731

Clinical experience with ABI-H0731 consists primarily of Phase 1 dose-ranging studies conducted to assess the safety, tolerability, PK, and initial efficacy of ABI-H0731 monotherapy:

- The first-in-human study Phase 1a conducted in healthy volunteers in New Zealand (ABI-H0731-101, Part 1). Intensive PK was assessed following single ascending doses (100, 300, 600, and 1,000 mg) under fasted (100 and 300 mg) and fed (300, 600, and 1,000 mg) conditions, as well as 800 mg once daily and 800 mg twice daily (under fed conditions) for 7 days. Overall, the results suggested that these single and multiple oral doses of ABI-H0731 were well-tolerated with dose-related increases in plasma exposures. During the off-treatment follow-up period, one patient in the 800 mg once daily cohort and two patients in the 800 mg twice daily cohort developed transient rashes that were considered mild (Grade 1).

- A Phase 1b study conducted at multiple sites in Australia, New Zealand, Hong Kong, England, South Korea, and Taiwan (ABI-H0731-101, Part 2, and ABI-H0731-101B) in which HBV patients received ABI-H0731 at doses of 100, 200, 300, or 400 mg once daily for 28 days. ABI-H0731 was well-tolerated in CHB patient cohorts at 100, 200, and 300 mg once daily through the 28-day dosing period and two weeks of follow-up (follow-up out to 4 weeks post-treatment is ongoing at the time of this IB update). One subject in the 300 mg cohort developed a transient localized (Grade 1) rash approximately two days following the end of therapy. The rash was considered unrelated to drug both by the Investigator and a consulting dermatologist. One of two patients dosed in the 400 mg once daily cohort developed a Grade 3 rash following 10 days of dosing. The rash was deemed related to study drug, and the subject was discontinued from treatment. The rash rapidly resolved off treatment with no other intervention required. Other than the individual patient with the Grade 3 rash, all other treatment-emergent adverse events were considered mild (Grade 1), and all Phase 1b subjects completed their study dosing and follow-up evaluations. There were no other premature treatment discontinuations, nor treatment dose modifications. There were no serious adverse events, or treatment emergent- laboratory abnormalities that were deemed drug related and clinically significant.

- A Phase 1a study conducted in healthy volunteers in the US to obtain additional safety and PK data for a longer dosing period (ABI-H0731-102). Three cohorts received ABI-H0731 at 100 mg, 200 mg or 300 mg once daily for 14 days. Treatment-emergent adverse events were infrequent (six in total), mild, and deemed unrelated to study drug. Laboratory abnormalities were generally minor, not related to dose, duration or target organ, and considered not clinically significant. PK data were consistent with the previous Phase 1a study.

For more complete information, please refer to the IB.

2.2.4.2 Preliminary Pharmacokinetic Data for ABI-H0731

PK parameters from studies ABI-H0731-101 and ABI-H0731-102 were calculated from plasma concentration over time, using WinNonlin™ software. In general, ABI-H0731 was rapidly and well absorbed following oral administration, with a median time to maximum plasma concentration (T_{max}) ranging from 3 to 4.5 hours. ABI-H0731 demonstrated increasing exposures

as doses increased, which were approximately dose proportional with modest variability through 600 mg, and it exhibited a terminal half-life of approximately 24 hours. Clinical activity was seen with the lowest doses explored (100 mg).

Based on the pre-dose trough assessments in ABI-H0731-101, ABI-H0731-101(B), and ABI-H0731-102 protocols, it appears that PK steady-state may be achieved by or prior to Day 8. Detailed information can be found in the IB.

2.3 Risk/Benefit Assessment

2.3.1 Known and Potential Risks

ABI-H0731 is a novel direct acting HBV inhibitor that will be among the first HBV CpAMs to be investigated in CHB patients for >28 days. At this stage of development, the risk considerations for ABI-H0731 are primarily based on the nonclinical and Phase 1 data summarized in the IB.

No evidence was found for genotoxicity or clastogenicity.

In the Good Laboratory Practices (GLP) chronic toxicology studies in rats and monkeys, ABI-H0731 was generally well-tolerated, with no animal deaths or severe in-life effects attributed to ABI-H0731 treatment at any exposure level (refer to the IB). There were no clear target organ findings in these studies, and the NOAELs were the highest doses tested, 250 mg/kg/day for 6 months in rats and 500 mg/kg/day for 9 months in monkeys. Specialized safety pharmacology studies were conducted to the same maximal dosing intensities as the 28-day GLP toxicology studies, 500 mg/kg/day in rats and 300 mg/kg/day in monkeys, with the results indicating no appreciable adverse effects on cardiac, respiratory, or central nervous system (CNS) functions at any ABI-H0731 dose level.

Human exposure data for ABI H0731 was obtained from the three Phase 1 clinical studies described above, in which a total of 84 healthy volunteers, and 38 CHB patients were treated with ABI-H0731 or matching placebo (refer to the IB). The single- and multiple-dose exposures were closely monitored with clinical and laboratory assessments at each study visit. ABI-H0731 was well-tolerated with no serious adverse events, no clinically significant vital sign or ECG changes, and no drug related clinically significant laboratory findings. One CHB patient was discontinued from treatment because of a Grade 3 rash, which resolved with no further intervention required other than drug discontinuation. Across all studies, with the possible exception of rash, no pattern of adverse events nor of laboratory abnormalities was seen with associated with either dose or duration of ABI-H0731 exposure suggesting any potential target organ pathology.

Refer to the IB for additional information.

2.3.2 Known and Potential Benefits

There is a need for improved HBV antiviral therapies that can offer a “clinical cure” for patients with CHB. Such therapy should produce durable post-treatment suppression of viral load and normalization of transaminases, and, ideally, a loss of detectable viral antigens in a higher

proportion of CHB patients than achieved with current therapies. The HBV core protein is involved in multiple aspects of the HBV life cycle. Therapy with CpAMs may disrupt multiple core protein functions (including cccDNA replenishment and possibly core-mediated interactions with HBV-specific immune responses) and thus is a highly attractive class of novel DAAs that may increase clinical cure rates for CHB.

In Phase 1a and 1b studies, ABI-H0731 has been able to achieve liver and blood levels sufficient to demonstrate significant antiviral activity. In the phase 1b studies, the resultant decrease in detectable HBV DNA and RNA in serum or plasma supports inhibition of RNA packaging and is consistent with the mechanism of action – inappropriate polymerization of HBV core protein. It is anticipated that this pleotropic mechanism of action may lead to more complete inhibition of the viral replicative cycle than inhibition of the viral polymerase alone, resulting in more rapid loss of active cccDNA and higher rates of clinical cures for CHB patients.

This study will specifically evaluate a 6-month course of therapy that may provide a lasting therapeutic benefit. Subjects who complete this study will be offered the opportunity to enroll in an open-label extension study of ABI-H0731. In the extension study, all subjects will receive up to 12 months active treatment.

2.3.3 Assessment of Potential Risks and Benefits

In this study, chronically HBV-infected adults who have previously been found to be viremic but are currently suppressed to the limits of quantitation on an approved SOC NUC therapy for HBV will be enrolled. These subjects are expected to have normal alanine aminotransferase (ALT) and have reduced, if any, liver inflammation. They will, however, have detectable circulating biomarkers of ongoing active cccDNA transcription – HBsAg, HBeAg (in HBeAg positive subjects), hepatitis B core-related antigen (HBCrAg), and encapsidated viral RNA. The 24-week treatment period in this Phase 2a trial is expected to be sufficient to assess the safety and tolerability of ABI-H0731 + SOC NUC therapy as well as the potential for increased rates of clinical cure via increased loss of active cccDNA as compared to subjects on SOC NUC therapy alone.

As compared to monotherapy with a NUC, addition of ABI-H0731 is expected to result in more complete suppression of cccDNA metabolism and pleotropic effects on the viral core protein, potentially resulting in accelerated loss of cccDNA. ABI-H0731 is thus anticipated to demonstrate clinical antiviral effects not seen with NUC monotherapy (eg, serum HBV RNA, HBsAg, and HBeAg reductions). The degree of reduction or duration of effect with 24 weeks of therapy, however, may be insufficient to establish any lasting clinical benefit for any of the subjects enrolled. The predictable benefits of this study are thus primarily the clinical care provided as a part of this clinical study, with the potential for additional benefits if ABI-H0731 does increase rates of cccDNA loss.

The nonclinical profile and Phase 1a and Phase 1b clinical data for ABI-H0731 predicts adequate safety margins for assessing ABI-H0731 dosing in CHB subjects at the 300-mg dose in this protocol, with a likelihood for demonstrable antiviral efficacy for ABI-H0731 on biomarkers of active cccDNA transcription (HBeAg, HBsAg) in the proposed Phase 2a evaluation. The kinetics

of viral antigen declines observed in this study will help define the length of treatment required for more definitive “HBV cure studies” to follow. These considerations support the advancement of ABI-H0731 into Phase 2a clinical investigation.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

- To evaluate the potential for ABI-H0731 to increase clinical cure rates in CHB subjects whose viral replication is stably suppressed on SOC NUC therapy, as measured by changes from Baseline in serum biomarkers (i.e., HBsAg or HBeAg) of transcriptionally active cccDNA

3.1.2 Secondary Objectives

- To evaluate the safety and tolerability of ABI-H0731 when added to SOC NUC therapy in subjects already virally suppressed on SOC therapy
- To confirm a lack of drug-drug interaction between SOC NUC therapies and ABI-H0731

3.1.3 Exploratory Objectives

- To evaluate the kinetics of and absolute changes from Baseline in biomarkers of transcriptionally active cccDNA (HBeAg and HBsAg)
- To evaluate the kinetics of and absolute changes from Baseline in circulating HBV RNA
- To assess the relationship between changes in exploratory viral biomarkers such as changes in viral RNA and HBCrAg with clinical outcomes
- To monitor for emergence of resistance, if any, for ABI-H0731 in combination with SOC NUC
- To explore the PK of ABI-H0731
- For subjects who provide an optional pharmacogenomic sample, to evaluate the potential contribution of host genomics to outcomes

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary efficacy endpoint will be:

- Change in mean $\log_{10}$ serum viral antigen (HBsAg or HBeAg) from Baseline (Day 1) to Week 24 on ABI-H0731 + NUC as compared to placebo + NUC

3.2.2 Secondary Endpoints

The secondary endpoints will be:

- Number of subjects with adverse events, premature discontinuations, abnormal safety laboratory results, electrocardiogram (ECG), or vital signs
- Subjects with abnormal ALT at Baseline who have normal ALT at Week 24 on ABI-H0731 + NUC therapy as compared with placebo + NUC therapy
- Drug concentrations:
    - Trough levels and (in subjects where optional samples are available) trough to peak ratios of ABI-H0731 on ABI-H0731 + NUC therapy
    - Trough levels and (in subjects where optional samples are available) trough to peak ratios of NUC on ABI-H0731 + NUC therapy as compared with placebo + NUC therapy

3.2.3 Exploratory Endpoint

Exploratory endpoints include:

- Quantitative changes in serum HBV RNA and HBCrAg levels on ABI-H0731 + NUC as compared with placebo + NUC, at each time point
- Subjects with loss (defined as below LOQ) or decline in HBsAg or HBeAg (<0.5 $\log_{10}$, ≥ 0.5 to 1.0 $\log_{10}$, or >1.0 $\log_{10}$ decrease in viral antigen) on ABI-H0731 + NUC as compared with placebo + NUC at end of treatment and end of follow-up
- Subjects with HBsAg seroconversion (loss of HBsAg and appearance of HBs antibody) or HBeAg seroconversion (loss of HBeAg and appearance of HBe antibody) on ABI-H0731 + NUC as compared with placebo + NUC
- Subjects with HBV DNA “detectable” at Baseline whose HBV DNA becomes “non-detectable” on ABI-H0731 + NUC as compared with placebo + NUC
- Emergence of resistant HBV variants, if any
- For subjects who do NOT rollover onto the optional extension study, ABI-H0731-211:
    - Subjects with suppression of detectable serum HBV RNA on treatment whose HBV RNA rebounds after discontinuing treatment with ABI-H0731 + SOC NUC as compared with placebo + SOC NUC

- Subjects with changes in HBsAg or HBeAg whose viral antigen rebounds after discontinuing treatment with ABI-H0731 + SOC NUC as compared with placebo + SOC NUC

- Subjects with HBsAg or HBeAg loss at Week 24 that is maintained through end of follow-up (Week 36) after discontinuing treatment with ABI-H0731 + SOC NUC as compared with placebo + SOC NUC

- If differences are seen in outcomes/adverse events between racial or ethnic groups: Pharmacogenomics correlation with clinical outcomes subjects who provide optional informed consent

4 STUDY PLAN

4.1 Study Design

This Phase 2a, multi-center, randomized, double-blind, placebo-controlled study will assess the safety, efficacy, PK, and pharmacodynamics of 300 mg ABI-H0731 daily in combination with SOC NUC therapy in subjects with CHB who are already virally suppressed on SOC NUC therapy at entry to study. Subjects will be stratified 9:5 (HBeAg positive:HBeAg negative) and randomized 3:2 to receive investigational agent as add-on therapy to their current SOC NUC therapy for up to 6 months (HBeAg positive subjects: 27 subjects will receive ABI-H0731 + NUC therapy: 18 subjects will receive matching placebo + NUC therapy; HBeAg negative subjects: 15 subjects will receive ABI-H0731 + NUC therapy: 10 subjects will receive matching placebo + NUC therapy). NUC treatment will continue uninterrupted for the duration of the study as well as during follow-up.

Table 1 Subject Allocation by HBeAg status

	Total	Patients receiving ABI-H0731	Patients receiving placebo
HBeAg positive	45	27	18
HBeAg negative	25	15	10

Safety will be monitored by a Data Monitoring Committee (DMC), including laboratory data and adverse events, at intervals outlined in the DMC Charter. There will be an assessment of PK data after all subjects have completed Week 4 (or discontinued study without completing Week 4) to confirm a lack of an important impact of ABI-H0731 on the steady-state PK of SOC NUC therapy.

At the end of the treatment period in this study, subjects will either continue their SOC NUC therapy and stop treatment with ABI-H0731/placebo, or they may elect to roll over onto the optional, open-label, extension study ABI-H0731-211.

- Subjects who do not roll into optional open-label study ABI-H0731-211 will continue on SOC NUC therapy alone and be monitored for an additional 12 weeks to determine if any changes in either viral antigens or viral RNA which may have been noted on treatment will persist through end of follow-up.

- Subjects who do elect to roll over to the optional, open-label, extension study of ABI-H0731 + SOC NUC (protocol ABI-H0731-211) will continue on open-label combination therapy as per that study. The objective of the extension study, ABI-H0731-211, will be to evaluate the safety and potential for benefits of up to one additional year of therapy with ABI-H0731. Subjects will be required to sign a separate informed consent form for the ABI-H0731-211 study.

4.2 Scientific Rationale

It is anticipated that the addition of ABI-H0731, a DAA targeting the HBV core protein, to SOC NUC therapy will be safe and may potentially result in an increase in the functional cure rate for subjects with CHB by preventing the establishment and possible maintenance of cccDNA more completely than SOC NUC therapy alone. Loss of cccDNA is expected to result in a decrease in serum viral RNA as well as serum viral antigens which reflect the activity of cccDNA (eg, HBsAg and HBeAg). This study will explore both the safety of combination therapy in subjects whose viral load has already been suppressed to the LOQ on a SOC NUC, as well as reduction in circulating viral RNA and potential serum biomarkers of functional cures: quantitative and qualitative reduction in the viral antigens HBeAg (in HBeAg positive subjects) and HBsAg.

4.3 Dose Justification

In the Phase 1 clinical studies, ABI-H0731 was well-tolerated in healthy subjects at single doses of up to 1000 mg daily, at twice daily doses of 800 mg for 7 days, and at single daily doses of up to 300 mg for 14 days. All treatment-emergent adverse events (TEAE) were considered mild (Grade 1) and reversible. In subjects with CHB, ABI-H0731 was well-tolerated at doses of up to 300 mg daily for 28 days. One subject with CHB developed a Grade 3 rash after approximately 10 days of repeated doses of 400 mg daily, the rash resolved off treatment with no intervention other than dose discontinuation required.

Preliminary data indicated that there is a dose-dependent decrease in viral load at doses of 100 mg, 200 mg, and 300 mg daily in subjects with CHB. It is expected that 300 mg daily will be safe and provide sufficient exposure to ABI-H0731 to produce the desired antiviral effect in CHB subjects in this study, and within the dose range that was well-tolerated in previously treated healthy subjects and subjects with CHB.

4.4 Study Drug Resistance Monitoring

There are no established methods for the selection of drug resistance against HBV *in vitro* because there are no *in vitro* cell culture systems that allow multiple cycles of HBV replication. In this study, all subjects who enter study are expected to have a Baseline viral load below LOQ. As such, no sequencing of the Cp region is possible. As all subjects will remain on their SOC NUC therapy throughout the study including the follow-up period, the potential for emergence of resistance to combination therapy is minimal. However, all subjects will have viral load monitored throughout the study, and any subject who develops persistent (i.e., 2 consecutive visits) HBV DNA viremia on study to a quantifiable level sufficient for DNA sequencing, will have the RT and Cp regions sequenced and evaluated for potential resistance mutations.

4.5 End of Study Definition

The study will be completed when the last subject completes the 12-week post-treatment follow-up period or when the last subject transitions to protocol ABI-H0731-211 (or when the last subject discontinues the study before completing the follow-up period or transitioning to the extension study), whichever is later.

4.6 Management of Toxicities

4.6.1 Subjects with Alanine Aminotransferase Elevations

Subjects experiencing ALT elevations ≥2 × Baseline or on-treatment nadir and >2×upper limit of normal (ULN) during study treatment or during post-treatment follow-up will be closely monitored. The following guidance is offered for management of study subjects with ALT elevations or biochemical evidence of declining hepatic function:

- ALT flare on treatment
    - All subjects with an ALT flare 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 undergo a symptom-directed physical examination, review of concomitant medications (including herbal medications or supplements), and the following laboratory tests: ALT, aspartate aminotransferase (AST), total bilirubin, International Normalized Ratio (INR), and serum albumin. If the ALT flare is confirmed, HBV DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]), hepatitis A virus (HAV) immunoglobulin M (IgM), HCV RNA, hepatitis D virus (HDV) RNA, and hepatitis E virus (HEV) IgM should also be drawn.
        - If an intercurrent cause is determined to be causal, the intercurrent cause should be treated as deemed medically appropriate by the treating physician.
        - In the absence of evidence of declining hepatic function, and in the absence of contraindications, subjects with an ALT flare may continue on study under close observation.
            - If ALT is rising at the confirmatory visit, subjects should return for an unscheduled visit every 2-5 days until the ALT elevation has stabilized. 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 ALT “flares” or ALT elevations without declining hepatic function or contraindications should stop study drug if the ALT remains persistently elevated for > two weeks in the absence of decreasing HBV DNA (if detectable), and/or HBV RNA, and/or viral antigen (HBeAg or HBsAg).

- Declining hepatic function during treatment

- Subjects with confirmed biochemical evidence of declining hepatic function, should be discontinued from study treatment. 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
    - An albumin decline ≥0.5 g/dL OR INR >2×Baseline OR
    - Symptoms of liver inflammation (fatigue, weakness, lack of appetite, nausea, vomiting, jaundice or discolored feces)
- Subjects with evidence of declining hepatic function should return for an unscheduled visit every 2-5 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 treating physician) until the relevant laboratory values return to normal or baseline.

- Post-treatment ALT "flare" or ALT elevation with declining hepatic function
  - For subjects who elect not to enroll in the open-label, extension study ABI-H0731-211, risk of post-treatment flare is mitigated by advising subject to continue with their previous SOC NUC therapy for CHB. Any subject with a post-treatment ALT elevation meeting the ALT "flare" definition or a lesser post-treatment ALT elevation with biochemical evidence of declining hepatic function (described above), while on treatment with a regulatory-approved HBV antiviral agent should return for an unscheduled visit every 2-5 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 treating physician) until the relevant laboratory values return to normal or baseline. Subsequently, subjects should continue to be followed on their regular study visit schedule, with the addition of any unscheduled visits the Principal Investigator believes are merited for the safety and well-being of the subject.

All subjects with declining hepatic function or ALT flare (on or off treatment) should continue to be followed on their regular study visit schedule, with the addition of unscheduled visits as described above. If the post-treatment ALT flare has not substantially resolved by the last study follow-up visit, subjects should continue to return to clinic as deemed medically appropriate by the Principal Investigator, in consultation with the Sponsor, and the unscheduled visit module in the case report form should be utilized as needed to gather additional clinical and laboratory data until the ALT flare is documented to be either resolved or resolving (defined as consistent ALT declines of 10% or more or normalization of ALT) on at least two successive visits.

If 2 or more subjects meet these LFT flare management criteria, the US FDA and other relevant regulatory agencies will be notified.

It is important to note that ALT elevations early on in treatment tend to resolve with continued treatment and are more common in patients with greater early antiviral efficacy responses, e.g.

rapid serum HBV DNA reductions that may be associated with higher rates of HBeAg or HBsAg clearance. In contrast, ALT flares occurring following immunosuppression or cessation of treatment with a NUC can be severe and can be associated with biochemical signs of hepatic insufficiency [Chang and Liaw 2014, EASL 2012, Perrillo 2009, Perrillo, 2001]. Therefore, subjects on study will not be discontinued from treatment unless they meet discontinuation criteria listed above (see Section 4.6.1). For subjects remaining on the study, it is anticipated that the close laboratory and clinical monitoring, as well as the provision for all subjects to continue on SOC NUC therapy during the treatment period of this study is appropriate to minimize excess risk for study participants.

4.6.2 Subjects with Rash

In the event of any rash, subjects should return to clinic for evaluation for an unscheduled visit (Day 0 of rash). Digital photographs of the rash should be taken, and blood samples should be taken and evaluated at the site's local laboratory as well as the central laboratory. Laboratory tests should include: erythrocyte sedimentation rate, complete blood count (with differential), creatinine, ALT, AST, and total bilirubin. Local laboratory reports and digital photographs will be de-identified, collected by the site monitor, and securely stored by the Sponsor.

If the rash diagnosis is uncertain, or if a rash is Grade 2, a referral to a dermatologist should be made and a skin biopsy should be conducted if recommended by the dermatologist. For a rash that is Grade 3 or higher, a referral to a dermatologist should be made and a skin biopsy should be requested of the dermatologist. All dermatologist reports and skin biopsy results will be included in the source and electronic case report form (eCRF). A copy of the dermatologist report will be de-identified and collected by the monitor on behalf of the Sponsor.

If the rash is considered by the Investigator to be likely related to a non-study exposure (drug, food, or concomitant illness), then subjects should be treated symptomatically and as deemed appropriate by the Investigator (or consulting dermatologist) until the rash has resolved. Additional unscheduled visits should be performed during the study at the Investigator's prerogative until resolution of the rash. Digital photographs of lesions should be obtained at each visit to document any change in condition. If required for patient management, local and central laboratory samples should also be drawn at additional unscheduled visits. Any local laboratory test results and digital photographs will be de-identified, collected by the site monitor, and securely provided to PRA Health Sciences ("the Clinical Research Organization [CRO]") for provision to the Sponsor.

If rash is considered possibly or probably related to study drug, then:

- For Grade 1 rashes, subjects can continue to take study drug at the Investigator's discretion
- For Grade 2 rashes, subjects may continue to take study drug in consultation with Sponsor and at the Investigator's discretion. If the rash progresses or worsens, subjects must discontinue study drug. Subjects should be advised to contact the study site staff immediately if the rash worsens, if systemic signs develop, or if mucosal lesions develop

- For Grade 3 and higher rashes, study drug will be discontinued, and the subjects will continue on study as described below

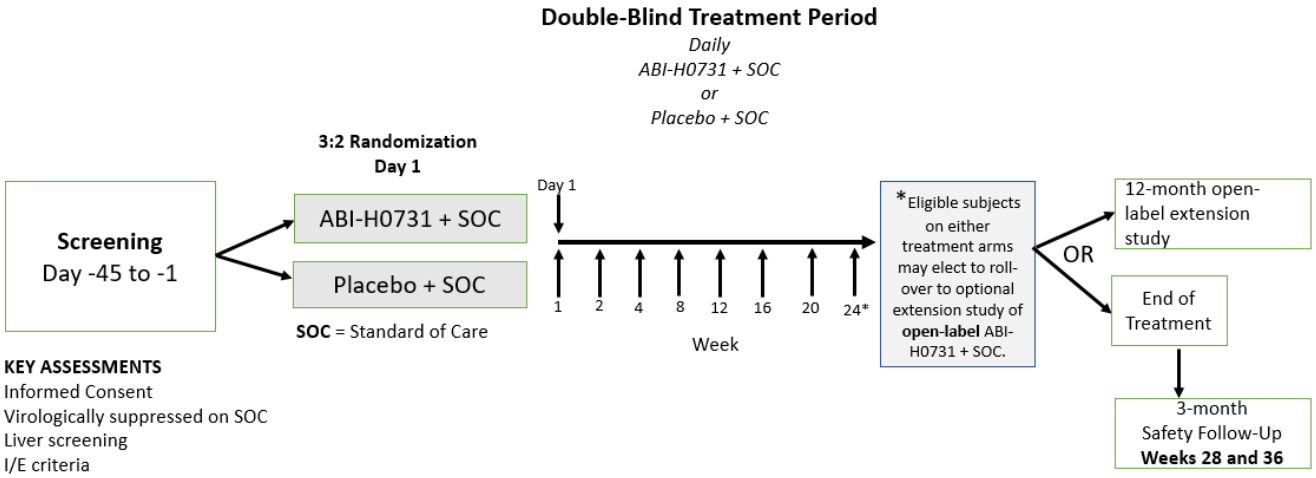
Subjects with rashes should continue to be followed on their study visit schedule even if treatment is discontinued, with additional unscheduled visits as deemed medically appropriate by the Investigator.

If the rash has not substantially resolved by the last study visit, subjects should return for an unscheduled visit at least every other week or as deemed medically appropriate by the Investigator. Unscheduled visits should continue until the rash has resolved or declined to Grade 1 or less for two successive visits.

4.7 Study Schematic

The study schematic is presented in Figure 1.

Figure 1 Study Schematic



I/E = inclusion/exclusion

4.8 Schedule of Assessments

The Schedule of Assessments is presented in Table 2.

Table 2 Schedule of Assessments

Period or Visit	Screening	On Treatment								Follow-Up [a]		Premature Termination [b]	Unscheduled [c]
Study Day or Week	Day (-45) to Day (-1)	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24 [a]	Week 28	Week 36	Varies	Varies
Visit Window (days)		0	+/- 2	+/- 2	+/- 3	+/- 3	+/- 3	+/- 3	- 3	+/- 3	+/- 3	N/A	N/A
Informed Consent(s) [d]	X								X [j]				
Demographic data	X												
Medical history	X												
Medication history	X												
Liver screening [e]	X												
Full physical examination	X								X		X	X	
12 Lead ECG	X	X				X			X		X	X	if indicated
Height and weight	X	X		X					X		X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications / Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Confirm eligibility		X											
Randomization (IRT)		X											
Symptom directed physical exam		X	X	X	X	X	X	X		X			X
Paper diary		X	X	X	X	X	X	X	X	X			
Study drug accountability			X	X	X	X	X	X	X	X		if applicable	
Study drug dispensation		X	X	X	X	X	X	X	X				
In-clinic dosing: study drug		X	X	X	X	X	X	X	X				
Dosing: SOC NUC [k]		X[k]	X[k]	X[k]	X	X	X	X	X	X			
Digital photography [c]													if indicated
Virology/Immunology													
HBV genotype	X												
HBV DNA viral load	X	X	X	X	X	X	X	X	X	X	X	X	X
Quant HBsAg, quant HBeAg [f]	X	X		X	X	X	X	X	X	X	X	X	X
HBsAb, HBeAb	X	X				X			X		X	X	
HBV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2 Schedule of Assessments (continued)

Period or Visit		Screening	On Treatment								Follow-Up [a]		Premature Termination [b]	Unscheduled [c]
Study Day or Week		Day (-45) to Day (-1)	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24 [a]	Week 28	Week 36	Varies	Varies
HIV Ab		X												
HCV Ab; HDV Ab; HAV (IgM); HEV (IgM)		X												X[c]
Laboratory Assessment														
Chemistry[b]		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
Coagulation		X	X		X	X	X	X	X	X	X	X	X	X
Serum AFP		X												
FSH (females only)		X												
Urinalysis		X	X		X	X	X	X	X	X	X	X	X	X
Urine drug test		X	X										X	X
Pregnancy Test [g]		X	X	X	X	X	X	X	X	X	X		X	X
PK Sample Collection														
Pre-dose [h]	ABI-H0731		X	X	X		X			X	X		X	X
	Nucleos(t)ide analogue		X	X	X		X			X	X		X	X
Optional post-dose [i] 4 (±2) hours after ABI-H0731 and NUC administration			X	X	X									
Exploratory														
Optional PG sample [c]			X											
Core protein (HBCrAg)			X	X	X	X	X	X	X	X	X	X	X	X
Viral nucleic acid			X	X	X	X	X	X	X	X	X	X	X	X

a Subjects who elect NOT to enter rollover study ABI-H0731-211 at Week 24 will enter into the 12-week follow-up period (inclusive of Weeks 28 and 36).

b Subjects who discontinue treatment before Week 24 should immediately undergo the assessments listed for the Premature Termination visit and then continue scheduled assessments, except that these subjects need only two further PK collections (at the Premature Termination visit and the next scheduled time point). Subjects who discontinue study assessments before completing the 12-week follow-up period should undergo the assessments listed for the Premature Termination visit.

c Any subjects with rash or ALT flare (defined in Section 4.6) should return to the clinic for an unscheduled visit as soon as possible, ideally within 3 days.
Unscheduled visit for ALT flare: All subjects should have the laboratory findings confirmed within 3 days of receipt of the original results. All subjects should undergo a symptom directed physical examination and the following laboratory tests: ALT, AST, total bilirubin, INR, and serum albumin. If the ALT flare is confirmed, perform the following tests: HBV

DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative], HAV IgM, HCV RNA, HDV RNA, and HEV IgM

Unscheduled visit for rash: Digital photographs of the rash should be taken and blood samples should be taken (for erythrocyte sedimentation rate, complete blood count [with differential], creatinine, ALT, AST, and total bilirubin). If the rash diagnosis is uncertain, or if a rash is Grade 2, a referral to a dermatologist should be made and a biopsy should be conducted if recommended by the dermatologist. For a rash that is Grade 3 or higher, a referral to a dermatologist should be made and a biopsy should be requested of the dermatologist. All dermatologist reports and biopsy results will be included in the source and eCRF. Digital photographs of the rash should be obtained at each visit to document any change in condition. Unscheduled visits should continue until the rash has resolved or declined to Grade 1 or less for two successive visits.

d Study specific including optional PG consent. PG sample collection requires documentation of completed PG consent.

e Liver evaluation to be done by any protocol approved method (Biopsy, fasting FibroScan, MRI, liver ultrasound), unless a liver biopsy demonstrating lack of cirrhosis or bridging fibrosis has been conducted in the last 6 months.

f If quant HBsAg or HBeAg are negative at any visit subsequent to Screening, reflex to qualitative.

g A serum pregnancy test is required at screening, and on Day 1 both urine and serum should be performed (subjects may begin treatment based on urine results; any subjects negative by urine subsequently found to be positive on serum should immediately discontinue treatment and may be replaced). All post-Day 1 pregnancy tests may be conducted by urine dipstick. If positive on dipstick, please reflex to serum.

h If the subject inadvertently administers study drug prior to collection, a PK sample should still be drawn. Refer to the protocol PK Assessments Section 8.3.

i Optional post-dose PK samples for ABI-H0731 and NUC targeted collection is 4 (±2) hours after in-clinic study drug + NUC administration at Day 1 and either Week 2 or Week 4.

j Subjects who elect to roll over onto the open-label extension study will be required to sign a separate consent at Week 24.

k It is recommended that subjects take SOC NUC in-clinic on Day 1, Week 2 and Week 4, if subjects opt to provide the optional post-dose PK samples.

Ab=antibody; AFP=alfa fetoprotein; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; eCRF=electronic case report form; FSH=follicle-stimulating hormone; HAV=hepatitis A virus; HBCrAg =hepatitis B core-related antigen; HBeAb=HBeAg antibody; HBeAg=hepatitis B “e” antigen; HBsAb=HBsAg antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDV=hepatitis D virus; HEV=hepatitis E virus; HIV=human immunodeficiency virus; IgM=immunoglobulin M; MRI=magnetic resonance imaging; N/A=not applicable; PG=pharmacogenomic; PK=pharmacokinetic; Quant=quantitative; ULN =upper limit of normal.

5 POPULATION

5.1 Number of Subjects

Globally, approximately 70 male or female subjects with CHB, between the ages of 18 and 70, with no evidence of cirrhosis or end-stage liver disease, and on stable SOC NUC therapy, whose HBV DNA viral load has been below the LOQ for at least 6 months, will be randomized.

5.2 Inclusion Criteria

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

1. Male or female between ages 18 and 70 years (inclusive)

2. Female subjects must agree to use dual effective birth control methods for the duration of the study and follow-up or be surgically sterile for at least 6 months or at least 2 years post-menopausal, with serum follicle-stimulating hormone (FSH) levels consistent with a post-menopausal status. Effective birth control methods include male or female condom (may not be used together due to increased risk of breakage), vasectomy, intrauterine device (IUD – inclusive of IUDs with hormonal components), diaphragm, or cervical cap. Systemic (oral/injectable) hormonal birth control are prohibited. Female subjects must have a negative serum pregnancy test at screening

3. All heterosexually active male subjects must agree to use dual effective birth control methods for the duration of the study and follow-up. Effective birth control methods include male or female condom (may not be used together due to increased risk of breakage), vasectomy, hormone-based contraception, IUD, diaphragm, or cervical cap

4. Body mass index (BMI) 18 to 36 kg/m^2 and a minimum body weight of 45 kg (inclusive)

5. Agreement to adhere to Lifestyle Considerations (including abstaining from alcohol abuse [defined as alcohol consumption exceeding 2 standard drinks per day on average (1 standard drink = 10 grams of alcohol)] and the use of illicit substances, herbal or other substances, or unnecessary over-the-counter medications; see Section 5.4) throughout study duration

6. In good general health except for chronic HBV infection (defined as HBV infection for at least 6 months documented by – for example – history of two repeated HBsAg positivity and/or detectable viral loads documented at least two times ≥6 months apart – inclusive of screening),

7. Virologically suppressed (defined as HBV DNA ≤LOQ) for at least 6 months before screening on NUC therapy

    a. Subjects with a low but quantifiable viral load (for example <60 IU/mL) within 6 months prior to screening which was shown to be an exception in a subject who has previously been well suppressed, may be eligible for study if the subject is virologically suppressed at screening

8. Subjects will be stratified 9:5 (HBeAg Positive:HBeAg negative). HBeAg-positive cohort must be HBeAg positive at screening

9. Hepatitis B surface antigen (HBsAg) levels:

    - HBeAg positive subjects must have >400 IU/mL HBsAg at screening;
    - HBeAg negative subjects must have >100 IU/mL HBsAg at screening

10. Liver biopsy results of

    o Metavir F0-F2 (absence of bridging fibrosis or cirrhosis) within 1 year of screening

    OR

    o Fasting FibroScan ≤8 kPa within 3 months of screening (including screening visit) or other Sponsor-approved hepatic imaging study (hepatic magnetic resonance imaging [MRI], or hepatic ultrasound by an ultrasonographer with expertise in evaluation of liver fibrosis) within 6 months of screening indicating lack of cirrhosis or advanced liver disease (F0-F2 or equivalent).

    Subjects with an ambiguous non-invasive result, eg, fasting FibroScan >8 kPa and ≤10 kPa are excluded unless a biopsy within the 12 months before first visit confirms the absence of bridging fibrosis and cirrhosis. Subjects with a FibroScan >10 kPa are excluded

11. Have the ability to take oral medication and be willing to adhere to the study regimen in the opinion of the Investigator

12. Willing and able to provide informed consent

5.3 Exclusion Criteria

Subjects who meet ANY of the following exclusion criteria will not be eligible for enrollment:

1. Co-infection with human immunodeficiency virus (HIV), HCV, HEV, or HDV

2. History or evidence of hepatic decompensation (including gastrointestinal bleeding or esophageal varices) at any time prior to or at time of screening

3. Subject is febrile (temperature >37.5°C) at screening

4. Clinically significant cardiac or pulmonary disease, chronic or recurrent renal or urinary tract disease, liver disease other than HBV, endocrine disorder, autoimmune disorder, diabetes mellitus requiring treatment with insulin or hypoglycemic agents, neuromuscular, musculoskeletal, or mucocutaneous conditions requiring frequent treatment, seizure disorders requiring treatment, 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 the study

5. Previous treatment with an investigational agent for HBV other than ABI-H0731 in the last 6 months before screening

6. Previous treatment with an HBV capsid targeting agent other than ABI-H0731 at any time

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

8. History of persistent ethanol abuse (alcohol consumption exceeding 2 standard drinks per day on average [1 standard drink = 10 grams of alcohol]) or illicit drug abuse within 3 years before screening

9. Females who are lactating or pregnant or wish to become pregnant are excluded from the study

10. History of HCC

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

12. Exclusionary laboratory results
    a. Platelet count <100,000/mm^3
    b. Albumin <lower limit of normal (LLN)
    c. Total bilirubin >1.2×ULN of unless known Gilbert syndrome; subjects with Gilbert syndrome are eligible if direct bilirubin is within normal limits
    d. Direct bilirubin >1.2×ULN
    e. ALT >5×ULN at screening
    f. Serum alpha fetoprotein (AFP) ≥100 ng/mL. If AFP at Screening is >ULN but <100 ng/mL, subject is eligible if a hepatic imaging study prior to the initiation of study drug reveals no lesions suspicious of possible HCC
    g. Prothrombin time: INR >1.5×ULN
    h. Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey 2009)
    i. Serum hemoglobin A1c (HbA1c) >8%
    j. Any other laboratory abnormality deemed clinically significant by the Sponsor or the Investigator

5.4 Lifestyle Considerations

During this study, subjects are asked to:

- Abstain from abuse of alcohol (defined as alcohol consumption exceeding 2 standard drinks per day on average [1 standard drink = 10 grams of alcohol]) and from any use of illicit substances for the duration of the study
- Abstain from the use of herbal or supplements (other than over the counter multivitamins)
- Abstain from use of over-the-counter concomitant medications unless they are medically indicated for the health and well-being of the subject in the opinion of the Investigator

5.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial, but are not subsequently randomly assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of an abnormal screening laboratory value may be rescreened one time. It will be at the discretion of the medical monitor on a case-by-case basis whether rescreening will be permitted under other circumstances.

5.6 Strategies for Recruitment and Retention

Approximately 70 subjects will be enrolled globally.

Outpatient subjects will be enrolled by their treating physician or referred to an enrolling Investigator by their treating physician. Subject recruitment will be performed by the study sites in accordance with local standards and regulations and will be detailed in a separate plan.

Subjects who complete the treatment phase of the study will be eligible to receive continued treatment in an extension protocol. Subjects randomized to active drug and subjects randomized to placebo will all receive active treatment in an open-label fashion in the extension study.

6 STUDY DRUG

6.1 Description

ABI-H0731 active pharmaceutical ingredient (API) is manufactured under current Good Manufacturing Practices (GMP) via standard synthetic chemistry methods.

Drug Substance

Code name	ABI-H0731
US Adopted Name	Not yet assigned
International Nonproprietary Name	Not yet assigned
Relative molecular mass	467.44 amu

Physicochemical Properties

Appearance	White to off-white powder
Physical form	Crystalline
Melting point	301°C

Solubility

0.1 N HCl (pH 1.1)	4 μg/mL
FaSSIF (pH 6.5)	35 μg/mL
Acetone	17 mg/mL
Dimethyl acetamide	>625 mg/mL
Ethanol	Insoluble

FaSSIF=fasted state simulated intestinal fluid; HCl = hydrochloride

6.2 Formulation

The drug product is a tablet containing ABI-H0731 in a solid dispersion produced by spray drying a solution of ABI-H0731 with an inert polymer. This spray-dried dispersion has been mixed with standard pharmaceutical excipients, such as microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate, and compressed into a tablet containing approximately 100 mg ABI-H0731, manufactured according to GMP. Matching placebo tablets contain the same excipients and are also manufactured according to GMP.

6.3 Storage

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

6.4 Packaging and Shipment

ABI-H0731 tablets and placebo tablets are packaged in high density polyethylene bottles fitted with child-resistant screw caps containing a desiccant (silica gel) and stored at controlled room temperature.

6.5 Dose and Administration

6.5.1 Dosing in the Study

All subjects will take study drug (ABI-H0731 or matching placebo) as three 100-mg tablets once daily, after a meal, at approximately the same time each day. SOC NUC should be taken as per package insert.

On study treatment visit days, study drug will be administered in the clinic; subjects will self-administer study drug on all other treatment days. Subjects will be required to record the dates and times of each dose they self-administer in a patient diary. If possible, study personnel will document time of study drug and SOC NUC administration in subject's medical record.

Refer to the Site Operations Manual for detailed instructions on managing missed or incorrect doses.

6.5.2 Preparation

Not applicable.

6.5.3 Blinding

Study subjects and site personnel administering the study drug and performing the clinical assessments on the subjects, will be blinded to individual subjects' treatments assignments (ABI-H0731 + NUC therapy or placebo + NUC therapy). The DMC, as well as select individuals at the Sponsor and the CRO will not be blinded to subjects' treatment assignments to facilitate randomization, prompt analysis of any arising safety/tolerance issues, and the DMC safety data review. As this is an exploratory Phase 2a study, certain individuals may also be unblinded to the efficacy results before the final analysis.

6.6 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 used and unused study drug containers and unused study drug.

The 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 CRO will confirm if the method

of recording study drug accountability by the clinical site and the location of study drug records at the site is appropriate.

Each time study personnel dispense study drug for a subject, he or she is to record the date dispensed, the number of tablets or vials 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 containers. The clinical monitor will review 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 each scheduled visit thereafter during the dosing period.

6.7 Compliance

To monitor compliance and to facilitate drug accountability at the study site, subjects will be required to record each dose they take in a diary. Subjects will also be asked to return used bottles and any unused study drug at study visits. Subjects who forget to return bottles will be asked to return them at the next study visit.

6.8 Concomitant Therapy

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins, over-the-counter medications, and supplements. For all randomized subjects, all concomitant medications are discouraged, and any concomitant medications must be recorded in the designated eCRF from the date informed consent is obtained to 30 days following the last dose of all study drug(s).

All subjects on this study will continue to take their SOC NUC therapy for the duration of the study. Subjects will provide a log of their ongoing SOC NUC therapy together with that of ABI-H0731/placebo at each clinic visit.

6.8.1 Prohibited Concomitant Therapy

As the potential for drug-drug interactions between ABI-H0731 and other compounds has not yet been fully evaluated, consumption of grapefruit/grapefruit juice is forbidden. Systemic (oral, injectable or implanted) hormonal birth control is not permitted as an acceptable means of birth control for female subjects of child bearing potential. Additional prescription medication use is discouraged, unless required for an emergent medical need occurring during the course of the study. To the extent possible, medications with narrow therapeutic indices should be avoided. In particular, medications metabolized by cytochrome P450 (CYP) isoenzymes 2B6, 2C8, 2C9, or 2D6 should be avoided (see APPENDIX III). Concomitant prescription medications, over-the-counter medications, and supplements will be reported in the eCRF.

6.8.2 Other Medications and Treatments

Within the suggested guidelines above, subjects may receive any other medication or treatment that is deemed medically necessary by the treating physician. All medication and treatments should

be recorded in the eCRF, including name of the medication or treatment, the start and stop dates, and the indication.

7 STUDY CONDUCT

7.1 Study Procedures by Time Point

Refer to the Schedule of Assessments (Table 2).

7.2 Discontinuation

7.2.1 Discontinuation from Treatment

If an individual subject is not satisfactorily tolerating study drug treatment in the judgment of the clinical investigator, then -in consultation with the sponsor- that participant may be discontinued from treatment. Discontinuation from treatment does not mean discontinuation from the study. Subjects who discontinue treatment before Week 24 should immediately undergo the assessments listed for the Premature Termination visit (Table 2) and then continue scheduled assessments, except that these subjects need only two further PK collections (at the Premature Termination and the next scheduled time point). If a clinically significant finding is identified (including, but not limited to changes from Baseline) after enrollment, the Investigator or qualified designee will determine if any change in subject management is needed. Any new clinically relevant finding will be reported as an adverse event.

In this study, subjects will be closely monitored for any evidence of worsening hepatic function or evidence of dermatologic adverse events. Subjects with post-Baseline ALT elevations of 2-fold or higher will be closely monitored. Study treatment will be discontinued in subjects with confirmed evidence of declining hepatic function during treatment (Section 4.6.1).

Specific guidance on management and the data to be collected at the time of study intervention discontinuation are described below.

Any subjects negative by urine pregnancy test on Day 1 who are subsequently found to be positive on serum pregnancy test should immediately discontinue treatment and may be replaced.

7.2.2 Discontinuation from Study

Discontinuation from study (withdrawal of consent) means that the subject does not wish to receive further protocol-required therapies or undergo protocol-required procedures, and the subject does not wish to or is unable to continue further study participation. Subjects who discontinue during follow-up should undergo the assessments listed for the Premature Termination visit unless they withdraw consent to do so. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The Investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8 DESCRIPTION OF STUDY PROCEDURES

8.1 Efficacy Assessments

To provide an assessment of the antiviral efficacy of ABI-H0731 in NUC-suppressed HBV subjects, this study will evaluate treatment-related changes in serum HBsAg, serum HBeAg, HBCrAg, and serum HBV RNA levels. Additionally, in CHB subjects where HBV DNA is detectable in serum, an evaluation will be made to determine if HBV has become undetectable.

To assure standardization of the virologic methods in this study, HBV DNA-related and HBV antigen-related virologic assessments will be conducted at a central reference laboratory. Subject serum samples for resistance-related sequencing and HBV RNA testing will be shipped frozen to the Sponsor or a designated third-party laboratory for testing.

8.1.1 Primary Efficacy Assessment

The primary endpoint is viral antigen decline (serum HBsAg or HBeAg). Samples for quantitative HBsAg and HBeAg levels will be collected at screening, Day 1, and Weeks 4, 8, 12, 16, 20, and 24 (or at the time of discontinuation). Follow-up samples will be collected Weeks 28 and 36 for subjects who do not continue treatment in the extension protocol. Subjects who enter the continuation protocol will have samples collected according to the extension protocol.

8.1.2 Secondary and Exploratory Efficacy Assessments

Blood samples for the assessment of secondary and exploratory efficacy endpoints will be collected as described below. For all analytes, the follow-up samples will only be collected for subjects who do not continue treatment in the extension protocol. Subjects will have the following samples collected according to the Schedule of Assessments (Table 2):

- Quantitative/qualitative HBsAg and HBeAg levels
- HBsAb and HBeAb
- HBV DNA
- HBV RNA
- HBCrAg (HBV Core related Antigen)
- Samples for exploratory viral research

HBV resistance testing, using exploratory research samples, will only be performed on subjects whose HBV DNA viral load becomes persistently (≥ 2 consecutive visits) detectable at a sufficient viral quantity for sequence analysis.

8.1.3 Additional Efficacy Assessments and Pharmacogenomic Assessments

Pharmacogenomic samples will be collected at Day 1 for subjects who consent to this procedure. These samples may be saved for future research.

8.2 Safety Assessments

For adverse events, see Section 9.

For serious adverse events, see Section 10.

8.2.1 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the timepoints indicated in the Schedule of Assessments (Table 2). The clinical laboratory assessments are listed in Table 3.

Table 3 Clinical Laboratory Tests

Panel	Tests
Clinical chemistries	Blood glucose levels, serum or plasma electrolytes (sodium, potassium, chloride, bicarbonate), calcium, blood urea nitrogen, creatinine, 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 ALT flares	ALT, AST, total bilirubin, serum albumin, and INR
Hematology	Complete blood counts: hemoglobin, hematocrit, RBC indices (MCV, MCHC), reticulocyte counts, leukocyte counts (total and differential), and platelet counts
Coagulation	Prothrombin time/INR and aPTT
Urinalysis	pH, specific gravity, protein, glucose, ketones, and occult blood
Rash Panel	Erythrocyte sedimentation rate, complete blood count (with differential), creatinine, ALT, AST, and total bilirubin.
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 Day 1; urine pregnancy test may be performed at all subsequent visits. A positive result disqualifies the subject for study treatment
Urine drug screening	Amphetamine/methamphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine metabolite, ecstasy, ethanol, opiates, phencyclidine, and propoxyphene. Note: If cannabinoids are not illegal in the subject's local, cannabinoids are not exclusionary
Antibodies	HCV, HDV, HAV IgM, HEV IgM, and HIV

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

a Perform fractionated bilirubin, if total bilirubin >ULN.

During the study, any clinically significant laboratory abnormality or clinically significant change from Baseline should be recorded as an adverse event (Section 9).

8.2.2 Other Safety Assessments

Other safety assessments include the following:

- Vital signs.
- Twelve-lead ECG. During the study, any clinically significant ECG result or change from Baseline should be confirmed, and if confirmed, should be recorded as an adverse event (Section 9).
- Concomitant medications, including supplements and over-the-counter medications, will be recorded.

8.3 Pharmacokinetic Assessments

Pre-dose samples will be collected to determine trough concentrations of ABI-H0731 and the SOC NUC therapy. Post-dose samples for both ABI-H0731 and SOC NUC will be collected from subjects willing and able to provide the sample 4 ± 2 hours after in-clinic dosing. Sample timing is outlined in Table 4.

Table 4 Pharmacokinetic Sample Collection

Time Period	Timepoint [a]	Time Relative to Study Drug Administration [b]
Double-Blind Treatment	Study Day 1 pre-dose	Before
	Study Weeks 2, 4, 12, 24 pre-dose	Before
	OPTIONAL [c] Day 1, Week 2, and/or Week 4, post-dose (see laboratory manual)	4 (±2) hours post-dose
Follow-Up	Study Week 28 pre-dose	Collect at same time with other central labs

a A PK sample should be collected if an unscheduled or premature termination visit is performed.
b Sample collection times are targeted times. Samples collected outside of these targeted times will not be considered protocol deviations as long as the actual collection time of the sample is accurately recorded on source documentation and the case report form.
c If a subject can only provide optional samples on Weeks 2 or 4, those may be collected from subjects that were not able to provide optional PK samples on Day 1.

8.4 Other Assessments

Other assessments include the following:

- Liver assessment at screening: To be eligible, subjects must have liver biopsy results of

- Metavir F0-F2 (absence of bridging fibrosis or cirrhosis) within 1 year of screening

  OR

- Fasting FibroScan <8 kPa within 3 months of screening (including screening visit) or other approved hepatic imaging study (hepatic MRI, or hepatic ultrasound by an ultrasonographer with expertise in evaluation of liver fibrosis) within 6 months of screening indicating lack of cirrhosis or advanced liver disease (F0-F2 or equivalent). FibroScan should be conducted after an overnight fast.

  Subjects with an ambiguous non-invasive result, eg, a FibroScan >8 kPa and ≤10 kPa are excluded unless a biopsy within the 12 months before first visit confirms the absence of bridging fibrosis and cirrhosis. Subjects with a FibroScan >10 kPa are excluded.

- Demography, medical history, and full physical examination will be performed at screening.

8.5 Protocol Deviations

Any deviations from the protocol will be identified by the site monitor, medical monitor, site staff, or statistician, based on the protocol and criteria defined in the Medical Monitoring Plan. Identified deviations will be confirmed and documented by the site monitor. Prior to database lock, protocol deviations will be reviewed and a list of important protocol deviations, and subjects who will be excluded from the per-protocol (PP) dataset will be determined based on blinded review of data.

9 ADVERSE EVENTS

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

An adverse event, 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 Informed Consent Form (ICF) for participation is considered an adverse event. This includes any side effect, injury, toxicity, or sensitivity reaction.

9.1 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 adverse events will be recorded on the eCRFs provided: a description of the event, severity, time of occurrence, duration, any action (eg, treatment and follow-up tests), and the outcome should be provided along with the Investigator's assessment of the relationship to the study treatment.

Adverse events will be recorded from the time written informed consent is signed until completion of the Week 36 follow-up visit or until 30 days following cessation of the last dose of treatment with the study drug for subjects who discontinue from follow-up.

9.2 Assessment of Intensity

The severity of each adverse event 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 Adverse Events (APPENDIX II), which grades the severity of clinical adverse events and laboratory abnormalities in a four-category system.

For adverse events not included in APPENDIX II, the following guidelines will be used to describe severity:

- **Mild (Grade 1):** Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
- **Moderate (Grade 2):** Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
- **Severe (Grade 3):** Severe symptoms causing inability to perform usual social & 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 adverse event or laboratory abnormality that is life-threatening as it exists constitutes a serious adverse event.

9.3 Assessment of Causality

All adverse events must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. Each adverse event must be recorded in the source and eCRF, 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 adverse event with sufficient evidence to accept that there was no causal relationship to administration of study medication (eg, no temporal relationship because the study medication was administered after the onset of the event, an investigation showed that study medication was not administered, another cause was proven).
- **Unlikely related**: An adverse event, including a clinical laboratory test abnormality, with a temporal relationship to administration of study medication that made a causal relationship improbable and in which other drugs, events, or underlying disease provided plausible explanations.

- **Possibly related**: An adverse event with a reasonable time sequence to administration of study medication but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may have been lacking or unclear.

- **Related**: An adverse event occurred in a plausible time relationship to administration of study medication and that could not be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) was clinically reasonable.

9.4 Expectedness

An adverse event 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 adverse event is expected or unexpected.

9.5 Adverse Events of Special Interest

Adverse events of Special Interest include rash and ALT flare and should be reported using the Adverse Events form of the eCRF. There are no expedited reporting requirements for adverse events of Special Interest (other than those that meet other reporting requirements).

9.6 Clinical Laboratory Changes

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 adverse event and followed up until it returns to the normal range and/or an adequate explanation of the abnormality is found.

9.7 Adverse Event Follow-up

After the initial adverse event or serious adverse event report, the Investigator will follow-up proactively on each subject and provide further information to the CRO on the subject's condition. During the study, all adverse events or serious adverse events should be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve due to the subject's underlying disease, or the subject is lost to follow-up.

9.8 Pregnancy

Pregnancy in itself is not regarded as an adverse event unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. **All pregnancies must be reported using the Pregnancy Report Form within 24 hours of learning of the pregnancy following the same procedures as for reporting serious adverse events (see Section 10.2).**

All reports of congenital abnormalities/birth defects are serious adverse events. Spontaneous miscarriages should also be reported and handled as serious adverse events. Elective abortions

without complications should not be handled as adverse events. All outcomes of pregnancy must be reported to the CRO.

Pregnancies among female partners of male subjects will also be reported and followed for outcome.

10 SERIOUS ADVERSE EVENT

10.1 Definition of Serious Adverse Event

A serious adverse event is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received ABI-H0731
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse event 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 adverse event 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: adverse events requiring hospitalization should be considered serious adverse events. Hospitalization for elective surgery or routine clinical procedures that are not the result of adverse event (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered adverse events or serious adverse events. If anything untoward is reported during the procedure, that occurrence must be reported as an adverse event, 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 adverse event should be considered serious.

Disability/incapacitating: An adverse event 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.

10.2 Reporting Serious Adverse Events

All serious adverse events must be reported within 24 hours of learning about the event. This can be done by emailing or faxing a completed Safety Report Form or by direct telephone communication to the numbers below. A Safety Report Form must follow all telephone reports within 24 hours.

Fax, phone, or email SAE information to the CRO:

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 serious adverse events is made to the Health 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 Health Authorities will be the responsibility of the Sponsor and the CRO.

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

10.3 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. An overdose is not in and of itself considered to be an adverse event unless it results in untoward medical effects. Any adverse event

associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills the criteria of a serious adverse event, then the event should be reported to the Sponsor or CRO within 24 hours after the site learns of the event.

11 STATISTICS

11.1 Statistical Hypotheses

As a proof-of-concept trial, statistical hypotheses to compare the treatment effects in this study will be explored descriptively, graphically and inferentially. Unless stated otherwise, the statistical null hypothesis for all assessments is that the effects of ABI-H0731 + SOC NUC and placebo + SOC NUC are not different. The alternative hypothesis is that effects of the two treatments are different.

11.2 Sample Size

The primary objective of the study will be measured by changes from Baseline in serum biomarkers (ie, HBsAg or HBeAg). As the results for this study will be used to collect information for future studies, both biomarkers will be reviewed independently with no control of the type I error (α) level.

Subjects will be stratified 9:5 (HBeAg positive:HBeAg Negative). HBeAg positive subjects and HBeAg negative subjects will be evaluated both together and independently. With a sample size of 45 HBeAg positive subjects, randomized in a 3:2 ratio (27 active:18 placebo), a 2-sample t-test with a 2-sided α=0.05 significance level has 89.5% power to detect a difference of at least 0.5 $\log_{10}$ (IU/mL) in the mean change from Baseline in serum HBsAg or HBeAg at Week 24. A similar test has 80% power to detect power to detect a treatment difference of at least 0.6 $\log_{10}$ (IU/mL) in the change from Baseline in serum HBsAg at Week 24 in HBeAg Negative Subjects. An equal standard deviation of 0.5 is assumed for both treatment group (Table 5 and Table 6).

Table 5 Power Calculations under Various Mean Differences in the Change from Baseline in HBsAg (or HBeAg) levels at Week 24 between Treatment Groups

	Power for N=45 HBeAg Positive subjects (27 ABI-H0731: 18 Placebo)			
Estimated mean difference at Week 24 between placebo + NUC and ABI-H0731 + NUC groups Change from Baseline HBsAg (or HBeAg) levels	**SD = 0.25**	**SD = 0.30**	**SD = 0.50**	**SD = 0.60**
0.25 $\log_{10}$ IU/mL	0.895	0.763	0.362	0.268
0.30 $\log_{10}$ IU/mL	0.971	0.895	0.487	0.362
0.40 $\log_{10}$ IU/mL	0.999	0.990	0.729	0.572
0.50 $\log_{10}$ IU/mL	>0.999	>0.999	0.895	0.763
0.60 $\log_{10}$ IU/mL	>0.999	>0.999	0.971	0.895

Calculated using SAS, based on a two-sided, two-sample t-test for mean differences, and alpha=0.05.
HBeAg=hepatitis B "e" antigen; HBsAg=hepatitis B surface antigen; NUC=nucleos(t)ide analogue; SD=standard deviation

Table 6 Power Calculations under Various Mean Differences in the Change from Baseline in HBsAg levels at Week 24 between Treatment Groups

	Power for N= 25 HBeAg Negative subjects (15 ABI-H0731: 10 Placebo)			
Estimated mean difference at Week 24 between placebo + NUC and ABI-H0731 + NUC groups Change from Baseline HBsAg levels	**SD = 0.25**	**SD = 0.30**	**SD = 0.50**	**SD = 0.60**
0.25 $\log_{10}$ IU/mL	0.650	0.498	0.217	0.165
0.30 $\log_{10}$ IU/mL	0.804	0.650	0.291	0.217
0.40 $\log_{10}$ IU/mL	0.963	0.878	0.467	0.347
0.50 $\log_{10}$ IU/mL	0.997	0.974	0.650	0.498
0.60 $\log_{10}$ IU/mL	>0.999	0.997	0.804	0.650

Calculated using SAS, based on a two-sided, two-sample t-test for mean differences, and alpha=0.05.
HBeAg=hepatitis B "e" antigen; HBsAg=hepatitis B surface antigen; NUC=nucleos(t)ide analogue; SD=standard deviation

11.3 Analysis Populations

The following populations for analysis will be used in this study:

- Intent-to-treat (ITT) Population: The ITT population will be defined as all randomized subjects. Subjects in this population will be analyzed according to their randomized treatment assignment, regardless of the actual treatment received.

- Per-Protocol (PP) Population: The PP population will include subjects who are at least 80% compliant with scheduled study drug dosing in the 24-week treatment period, and who have no major protocol violations.

- Safety Population: The safety population will include all randomized subjects who received at least one dose of study drug. Subjects in this population will be analyzed according to the actual treatment received.

- Pharmacokinetic (PK1) Population 1: The PK1 population will include all subjects in the safety population who have ABI-H0731 PK data assessments available.

- Pharmacokinetic (PK2) Population 2: The PK2 population will include all subjects in the safety population who have SOC NUC PK data assessments available.

Additional populations may be defined in the statistical analysis plan (SAP).

11.4 Statistical Methods

11.4.1 General Considerations

Information regarding the safety, PK, and efficacy analyses is given below. A SAP containing the detailed planned statistical methods will be finalized prior to locking of the study database for the analyses, and it will form the basis for the programming of the displays and analyses of the final study data. The plan will define populations to be used for each analysis endpoint, outline all data handling conventions including missing data methods, and specify statistical methodology to be used for analysis of safety and efficacy.

Subgroup analyses will be conducted to assess virologic efficacy endpoints in subjects infected with different HBV genotypes and for subject subgroups with different baseline characteristics which could potentially influence the efficacy, safety, or PK observations in this study (eg, pre-treatment ALT level, HBsAg level, HBeAg level, ethnicity, gender, etc.). These and other subgroup analyses will be further defined in the SAP.

11.4.2 Primary Endpoint(s)

The primary efficacy parameter is the change in mean $\log_{10}$ serum HBsAg or HBeAg from Baseline to Week 24. A two-sample test of difference with a two-sided 0.05 significance level will be used to assess differences between the treatment groups.

11.4.3 Secondary and Exploratory Endpoint(s)

Secondary and exploratory endpoints will be analyzed descriptively. All secondary and exploratory efficacy endpoints will be summarized (Section 3.2.2 and Section 3.2.3).

For continuous variables, such as observed and change from Baseline HBsAg values at each timepoint, descriptive statistics will be used, and will include the number, mean, standard deviation, median, minimum, maximum, and interquartile range and, where appropriate, a 95% CI. Missing

data methods and imputation rules will be defined in the SAP. Additional sensitivity analysis may also be performed and will be described in the study SAP.

For categorical variables, such as subjects with a 1 $\log_{10}$ drop in serum HBsAg or HBeAg titers from Baseline and subjects with HBeAg (and HBsAg) loss and seroconversion, descriptive statistics will include number and percent who meet the endpoint criteria.

Kaplan-Meier methods will be used to evaluate time to event variables (eg, time to HBsAg loss), and the treatment groups will be compared using log-rank tests.

Cox proportional hazards regression models will be used to identify baseline factors associated with HBsAg loss rates, as defined in the SAP.

Descriptive p-values may be defined in the SAP.

11.4.4 Pharmacokinetic Endpoints and Analyses

The following will be analyzed descriptively:

- Trough levels and (for subjects who provide optional post dose samples) trough to peak ratios of ABI-H0731 on ABI-H0731 + SOC NUC therapy

- Trough levels and (for subjects who provide optional post dose samples) trough to peak ratios of NUC on ABI-H0731 + SOC NUC therapy as compared with placebo + SOC NUC therapy

After all subjects have completed Week 4 (or discontinued before completing Week 4), PK data will be reviewed by an unblinded pharmacology reviewer to ensure NUC steady-state PK levels are not being affected by combination treatment with ABI-H0731. All PK time points will be included in the final analysis.

11.4.5 Analysis of Safety

The safety parameters to be assessed are described in Section 8.2, Section 9, and Section 10. Displays for safety results will utilize descriptive statistics. No formal hypothesis testing of safety data is planned; however, exploratory p-values to assess any potential treatment-related differences in the incidence of clinical adverse events, laboratory abnormalities, and treatment-emergent abnormal ECGs may be defined in the SAP.

Adverse events summaries will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) body system and preferred term, for each treatment group. Summaries will include all adverse events, adverse events considered possibly or probably related to treatment, Grade ≥3 (or severe) adverse events, and serious adverse events. All adverse events will be listed by subject. Any adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent adverse events will be presented as a separate table or a listing.

Clinical laboratory results will be summarized descriptively by treatment group including values, changes from Baseline, and incidence of laboratory abnormalities. Laboratory results will be listed for each subject.

Exposure to treatment will be summarized descriptively, and compliance on treatments for both active and placebo (matching ABI-H0731 100-mg tablets) will be evaluated.

Vital signs data reported at each visit will be displayed by treatment, using descriptive statistics for observed and change from Baseline values.

Any post-screening changes in physical examination findings will be summarized in tabular form, by treatment group.

11.4.6 Demographic and Baseline Characteristics

Other variables, including subject disposition and demographic and baseline characteristics will be summarized descriptively by treatment group. The demographics and baseline characteristics include age (in years, at time of signing informed consent), race, ethnicity, height, weight, BMI, HBV genotype, pre-treatment ALT levels, and prior SOC NUC therapy.

11.5 Interim Analysis

No formal interim analyses will be conducted to modify or stop the study. As such, there is no adjustment to the type I error rate for this trial. As this is an early development trial, patient safety is of primary importance. Data summaries will be provided to a DMC to evaluate safety and to an unblinded Pharmacologist to evaluate study drug exposure levels and potential drug-drug interactions. See Section 12.2 for the DMC evaluation and Section 11.4.4 for the Week 4 PK analysis.

11.6 Exploratory Analyses

Multiple exploratory endpoints may be assessed in this study. NUCs of the HBV Pol/RT inhibit HBV DNA synthesis from encapsidated pre-genomic HBV RNA, resulting in reductions in serum HBV DNA levels. In NUC-treated subjects, while circulating HBV DNA declines due to inhibition of HBV Pol/RT activity, encapsidated HBV RNA remains detectable in circulating virus particles. This is not seen with CpAMs such as ABI-H0731 because the mechanisms of action by which viral load is reduced with ABI-H0731 differs from that of NUCs. As an HBV CpAM, ABI-H0731 specifically induces accelerated mis-assembly of HBV core protein into oligomers, with reduced incorporation of pre-genomic HBV RNA into functional nucleocapsids. In contrast to HBV NUC therapies, ABI-H0731 treatment may reduce circulating levels of HBV RNA [Wang 2016]. By altering the encapsidation and tertiary structure of HBV capsid, ABI-H0731 may potentially reduce circulating HBCrAg. When NUCs are used in conjunction with a CpAM, inhibition of multiple aspects of the viral life cycle may also lead to accelerated loss of viral cccDNA.

Analysis of changes in serum HBV antigen kinetics, viral RNA, and HBCrAg levels in this study may thus provide additional assessments of antiviral efficacy and unique mechanisms of ABI-H0731 in HBV subjects.

Data collected for this study will be analyzed and stored by the CRO. After the study is completed, the de-identified, archived data will be stored by the Sponsor or their designee.

With the participant's approval and as approved by local IRBs/IECs, de-identified biological samples will be stored by the Sponsor or their designee. These samples could be used to research CHB, its complications and other conditions for which individuals with CHB are at increased risk, and to improve treatment. The Sponsor will also have a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

12 ETHICS AND RESPONSIBILITIES

12.1 Good Clinical Practice

This study will be conducted in compliance with IRB/IEC and current International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines (E6); Title 21 Part 56 of the US Code of Federal Regulations (CFR) relating to IRBs/IECs and GCP as described in the US FDA CFR (21 CFR § 50, 56, 312); applicable ICH regulations 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.

12.2 Data Monitoring Committee

A DMC external to the Sponsor and the CRO will be formed with members consisting of individuals chosen for their expertise in treatment of HBV. Members of the DMC will include, at a minimum, physicians external to the Sponsor and the CRO and appropriate statistical representation. The primary role of this independent DMC will be to monitor safety data.

The DMC will review unblinded safety data at specified intervals, including the Week 12 safety data (clinical adverse events and laboratory abnormalities), as outlined in the DMC charter.

In addition, an ad hoc meeting of the DMC may be called at any time by the DMC Chairperson or Sponsor if there is an imminent participant safety issue or a significant safety concern to review safety and any other aspect of the studies. Significant safety events may include, but are not limited to:

- A death or life-threatening condition sustained by a participant, regardless of causality
- An unexpected serious safety issue newly identified during the development program that could expose participants to unnecessary risks
- Any other concern regarding participant safety raised by any DMC member, investigator, or the Sponsor

The DMC will communicate major safety concerns and recommendations regarding study modification or termination to the Sponsor's senior management at any time during the conduct of the study.

Records of all DMC decisions will be archived by the CRO. Selected Sponsor or CRO staff may serve as liaisons with the external DMC, but will not be voting members, and will not be unblinded to the results. Details regarding the DMC will be provided in the DMC charter.

12.3 Institutional Review Board/Independent Ethics Committee

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

12.4 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 consent form must be personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed ICF.

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

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

12.5 Records Management

12.5.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and recorded data from automated instruments.

All source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons. The original signed informed consent for each subject shall be filed with records kept by the Investigator and a copy shall be given to the subject.

12.5.2 Study Files and Record Retention

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.

12.6 Conflicts of Interest

Any conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

13 DATA MANAGEMENT, AUDITING, AND MONITORING

13.1 Data Management

An eCRF will be used for the current study, and a data management plan will be prepared by the CRO. The data will be collected via electronic data capture (EDC) using the eCRFs. The site will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The CRO will be responsible for the data management of this trial, including quality checking of the data.

The data management methodology will be consistent with the CRO's standard operating procedures and applicable regulatory guidelines. The data management plan will specify methods to ensure the accuracy and quality of the study data.

Previous and concomitant medications will be coded using the latest available WHO Drug Reference Dictionary. Coexistent diseases and adverse events will be coded using MedDRA.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between the Sponsor (or designee) and the CRO project team.

13.2 Auditing

The Sponsor or 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 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.

13.3 Monitoring

The Sponsor or CRO will assign site monitors to conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to allow personnel authorized by the Sponsor or the CRO direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Whenever a subject name is revealed on a document that is to be collected for the Sponsor, the name must be blacked out permanently by the site personnel, leaving the initials visible (or other appropriate de-identifying information), and annotated with the subject number as identification.

14 AMENDMENTS

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, then the currently approved written ICF will require similar modification. In such cases, the amended ICF will be required for subjects to sign prior to continued participation into the study.

15 STUDY REPORT AND PUBLICATIONS

The Sponsor or its designee is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of the Sponsor is discussed in the Investigator's Clinical Research Agreement.

16 STUDY DISCONTINUATION

Both the Sponsor and the Investigator reserve the right to terminate the study at the Investigator’s site at any time. Should this be necessary, the Sponsor or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Investigator will inform the IRB/IEC of the same. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects’ interests.

17 CONFIDENTIALITY

All information generated in this study is considered highly 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 initials and screening and treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

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19 APPENDICES

19.1 APPENDIX I – Names of Study Personnel

Sponsor: [redacted]

CRO Medical Monitor: [redacted]

19.2 APPENDIX II – Adverse Event Intensity Grading

TOXICITY GRADING OF LABORATORY ABNORMALITIES AND CLINICAL ADVERSE EVENTS. PUBLISH DATE: JULY 2017

Adapted from the U.S. National Institutes of Health (Division of AIDS) Table for Grading Severity of Adult Adverse Experiences (2017). Parameters within the table that have been modified for this study are designated by an asterisk (*).

MAJOR CLINICAL CONDITIONS

Cardiovascular

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist 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 QTc Interval[1]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

1 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 participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus [3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions **OR** Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Stevens-Johnson syndrome **OR** Toxic epidermal necrolysis

3 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 (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

4 Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
5 Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

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 (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., 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 & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake

Gastrointestinal

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (<24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation *(colon or rectum)*	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

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 & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia [6] *≥30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
<30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis [6] *≥30 years of age*	NA	BMD t-score <-2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
<30 years of age	NA	BMD z-score <-2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

6 BMD t and z scores can be found in: Kanis JA on behalf of the WHO Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

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 (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & 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 & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Neurologic

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure***	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., presyncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to <37 weeks gestational age	Live birth at 28 to <34 weeks gestational age	Live birth at 24 to <28 weeks gestational age	Live birth at <24 weeks gestational age
Spontaneous Abortion or Miscarriage [7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

7 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 & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

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 & functional activities	Forced expiratory volume in 1 second or peak flow 25 to <50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow <25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to <95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Hearing Loss	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical 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 & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

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 & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome [8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to <38.6°C or 100.4 to <101.5°F	≥38.6 to <39.3°C or ≥ 101.5 to <102.7°F	≥39.3 to <40.0°C or ≥ 102.7 to <104.0°F	≥40.0° C or ≥104.0° F
Pain [9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness [10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight [11]	WHO BMI z-score <-1 to -2	WHO BMI z-score <-2 to -3	WHO BMI z-score <-3	WHO BMI z-score <-3 with life-threatening consequences
Unintentional Weight Loss *(excludes postpartum weight loss)*	NA	5 to <9% loss in body weight from baseline	≥9 to <20% loss in body weight from baseline	≥20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

8 Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
9 For pain associated with injections or infusions, see the Site Reactions to Injections and Infusions section.
10 Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

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

Urinary

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

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

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

Laboratory Values*: Chemistries

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Acidosis	NA	pH≤7.3 to <LLN	pH<7.3 without life-threatening consequences	pH<7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN 30 to < LLN	≥ 2.0 to < 3.0 ≥ 20 to < 30	< 2.0 < 20	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0 × ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin ***Direct Bilirubin, High***	NA	NA	> ULN with other signs and symptoms of hepatotoxicity	> ULN with life-threatening consequences (e.g., 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 **Report only one*	1.1 to 1.3×ULN	>1.3 to 1.8×ULN OR Increase to 1.3 to <1.5×participant's baseline	>1.8 to <3.5×ULN OR Increase to 1.5 to <2.0×participant's baseline	≥3.5 × ULN OR Increase of ≥2.0 × participant's baseline

Laboratory Values*: Chemistries

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Creatinine Clearance [13] or eGFR, Low **Report only one*	NA	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to <30% decrease from participant's baseline	<60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to <50% decrease from participant's baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to <6.95*	>125 to 250 *6.95 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Nonfasting, High	116 to 160 *6.44 to <8.89*	>160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*)	55 to 64 *3.05 to <3.55*	40 to <55 *2.22 to <3.05*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
Lactate, High	ULN to <2.0×ULN without acidosis	≥2.0×ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
Lipase, High	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0 × ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High***	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	NA
LDL, Fasting, High	130 to <160 *3.37 to <4.12*	160 to <190 *4.12 to <4.90*	≥190 *≥4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to <1,000 *>5.7 to 11.4*	>1,000 *>11.4*
Magnesium [14], 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*	<121 *<121*
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*

*Reminder: Choose the method that selects for the higher grade.
*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.
13 Use the applicable formula (i.e., 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.
14 To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

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 [15], Low (g/dL; *mmol/L*) [16] *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 [15], Low (g/dL; *mmol/L*) [16] *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*

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

16 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.

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

19.3 APPENDIX III – Cytochrome P450 2B6, 2C8, 2C9, and 2D6 Substrates

The following drugs are known substrates of CYP 2B6, 2C8, 2C9, and 2D6 and should only be used with caution while receiving ABI-H0731. Drugs with a low therapeutic index should be avoided.

- 2B6: Artemisinin, bupropion, cyclophosphamide, efavirenz, ifosphamide, ketamine, meperidine, methadone, nevirapine, propafol

- 2C8: Amodiaquine, cerivastatin, paclitaxel, repaglinide, sorafenib, torsemide

- 2C9: *NSAIDs:* Diclofenac, ibuprofen, lornoxicam, meloxicam, S-naproxen→Nor, piroxicam, suprofen
  Oral Hypoglycemic Agents: Tolbutamide, glipizide
  Angiotensin II Blockers: Losartan, Irbesartan
  Sulfonylureas: Glyburide, glibenclamide, glipizide, glimepiride, tolbutamide
  Other: Amitriptyline, celecoxib, fluoxetine, fluvastatin, glyburide, nateglinide, phenytoin-4-OH2, rosiglitazone, tamoxifen

- 2D6: Tamoxifen
  Beta Blockers: Carvedilol, S-metoprolol, propafenone, timolol
  Antidepressants: Amitriptyline, clomipramine, desipramine, fluoxetine, imipramine, paroxetine, venlafaxine
  Antipsychotics: Haloperidol, perphenazine, risperidone→9-OH, thioridazine, zuclopenthixol
  Other: Alprenolol, amphetamine, aripiprazole, atomoxetine, bufuralol, chlorpheniramine, chlorpromazine, clonidine, codeine (→O-desMe), debrisoquine, dexfenfluramine, dextromethorphan, donepezil, duloxetine, encainide, flecainide, fluvoxamine, lidocaine, metoclopramide, methoxyamphetamine, mexiletine, minaprine, nebivolol, nortriptyline, ondansetron, oxycodone, perhexiline, phenacetin, phenformin, promethazine, propafenone, propranolol, risperidone, sparteine, tramadol

Source: The Flockhart Table. http://medicine.iupui.edu/clinpharm/ddis/main-table# [Accessed 26 Apr 2018]