CLINICAL RESEARCH PROTOCOL

PROTOCOL TITLE:	A Multi-center, Open-label, Long-term Extension Study of ABI-H0731+Nucleos(t)ide as Finite Treatment for Chronic Hepatitis B Patients
STUDY NUMBER:	ABI-H0731-211
DRUG:	ABI-H0731
REFERENCE NUMBERS:	[redacted]
SPONSOR:	Assembly Biosciences 331 Oyster Point Blvd., Fourth Floor South San Francisco, CA 94080 USA (833) 509-4583
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CONFIDENTIAL

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Multi-center, Open-label, Long-term Extension Study of ABI-H0731+Nucleos(t)ide as Finite Treatment for Chronic Hepatitis B Patients

Study No: ABI-H0731-211

Protocol Date: Amendment 4, Version 5.0, 14 October 2020

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

- The current risk-benefit evaluation of the investigational product
- The ethical and scientific standards governing clinical research that are set out in the current International Council for Harmonisation (ICH) guideline (E6) on Good Clinical Practice (GCP), 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.

Name and Title	[redacted]
[redacted]	[redacted]

ABI-H0731-211

A MULTI-CENTER, OPEN-LABEL, LONG-TERM EXTENSION STUDY OF ABI-H0731+NUCLEOS(T)IDE AS FINITE TREATMENT FOR CHRONIC HEPATITIS B PATIENTS

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.

1.0 SYNOPSIS

Protocol Number:	ABI-H0731-211
Title:	A Multi-center, Open-label, Long-term Extension Study of ABI-H0731+Nucleos(t)ide as Finite Treatment for Chronic Hepatitis B Patients
Phase:	2a open-label extension
Number of Subjects:	Up to 100 anticipated
Rationale:	Chronic hepatitis B infection (CHB) is a major global cause of severe liver morbidity and liver-related mortality. ABI-H0731 (also known as vebicorvir) is a direct-acting antiviral targeting the hepatitis B virus (HBV) core protein. It is anticipated that the addition of ABI-H0731 to standard of care (SOC) nucleos(t)ide reverse transcriptase inhibitor (NrtI) therapy will be safe and result in an increase in the sustained viral response (SVR) rate for patients with CHB. ABI-H0731-211 is an open-label extension study that will assess the safety of extended treatment with ABI-H0731 (i.e., up to 148 weeks in ABI-H0731-211) when administered in combination with SOC NrtI in subjects previously participating in Studies ABI-H0731-201 and ABI-H0731-202. The study will also evaluate off-treatment virologic response rates following cessation of treatment in subjects meeting prespecified criteria. Additionally, the study will assess the effect of the combination regimen on serum biomarkers such as HBV deoxyribonucleic acid (DNA), quantitative and qualitative reduction in the viral antigens, hepatitis B "e" antigen (HBeAg), hepatitis B core-related antigen (HBcrAg) and hepatitis B surface antigen (HBsAg), as well as exploratory biomarkers such as reduction in circulating HBV pre-genomic RNA (pgRNA).
Target Population:	Male or female subjects with CHB who have completed 24 weeks of treatment in Study ABI-H0731-201 or ABI-H0731-202.
Duration of Participation:	Up to 148 weeks of treatment in ABI-H0731-211 (ie, cumulative duration of up to 172 weeks including treatment in ABI-H0731-201 or ABI-H0731-202). Following completion of treatment in ABI-H0731-211, subjects may be followed for up to 3 years.
Test Product:	ABI-H0731 300 mg, administered orally, once daily, as three 100 mg tablets in addition to SOC NrtI therapy.
Reference Product:	Not Applicable.
Study Design:	This is an open-label, multi-center, long-term extension study evaluating the safety and efficacy of ABI-H0731 in combination with a SOC NrtI in subjects with CHB who have completed 24 weeks of treatment in one of two parent studies, ABI-H0731-201 (Study 201) or ABI-H0731-202 (Study 202). In ABI-H0731-211 (Study 211), subjects may receive up to 148 weeks of treatment with ABI-H0731+NrtI. The actual duration of treatment received by each individual subject will be based on their HBV treatment history (ie, NrtI suppressed or treatment naïve) and HBeAg status (ie, HBeAg positive or HBeAg negative) at Baseline in the parent study, and the individual subject's virologic response in Study 211. Based on

assessment of these factors at specific study visits, each subject will be evaluated for virologic response and assigned to one of the following three treatment actions:

1) Discontinue both ABI-H0731+NrtI
2) Discontinue ABI-H0731 only and continue SOC NrtI alone
3) Continue both ABI-H0731+NrtI for up to 148 weeks

Table 1-1 summarizes the population subgroups, the study visits at which virologic response is assessed, the decision criteria applied and the subsequent treatment action.

Table 1-1 Decision Criteria and Treatment Actions

Parent Study	Treatment History†	HBeAg Status†	Study 211 Visit	Decision Criteria	Treatment Action
201	NrtI Suppressed	Negative	Week 52*	Both ABI-H0731+NrtI will be stopped in all subjects	Discontinue both ABI-H0731+NrtI. Enter long-term off-treatment follow-up for up to 3 years
201	NrtI Suppressed	Positive	Week 52*	If subject has total HBV nucleic acids (DNA+pgRNA) <20 IU/mL and HBeAg ≤5 IU/mL for ≥7 consecutive visits¥	Discontinue both ABI-H0731+NrtI. Enter long-term off-treatment follow-up for up to 3 years
				If subject does not have total HBV nucleic acids (DNA+pgRNA) <20 IU/mL and HBeAg ≤5 IU/mL for ≥7 consecutive visits¥	Discontinue ABI-H0731 only and continue SOC NrtI alone. Enter follow-up on SOC NrtI alone for 12 weeks
202	Treatment Naive	Positive	Week 52*	If subject has ≥2.5 $\log_{10}$ reduction in pgRNA from Baseline in the parent study or achieves pgRNA <LLOQ	Continue both ABI-H0731+NrtI for additional 96 weeks (ie, to Week 148)
				If subject has <2.5 $\log_{10}$ reduction in pgRNA from Baseline in the parent study or does not	Discontinue ABI-H0731 only and continue SOC NrtI alone. Enter follow-up on SOC NrtI alone for up to 12 weeks

				achieve pgRNA <LLOQ	
			Week 148	If subject has total HBV nucleic acids (DNA+pgRNA) <20 IU/mL and HBeAg ≤5 IU/mL for ≥7 consecutive visits[¥]	Discontinue both ABI-H0731+NrtI. Enter long-term off-treatment follow-up for up to 3 years
				If subject does not have total HBV nucleic acids (DNA+pgRNA) <20 IU/mL and HBeAg ≤5 IU/mL for ≥7 consecutive visits[¥]	Discontinue ABI-H0731 only and continue on SOC NrtI alone Enter follow-up on SOC NrtI alone for up to 12 weeks

†Treatment History and HBeAg-status at Baseline in the parent studies (Study 201 or Study 202)
[*]Subjects without virologic assessment at Week 52 will be evaluated at the next study visit.
[¥]Consecutive visits are determined from the last timepoint at which values are available for all parameters.

As described above, based on the respective treatment action, additional follow-up visits may be undertaken. These visits are briefly summarized below and described in further detail in later sections of the protocol.

3-Year Off-treatment Follow-up

All subjects who discontinue both ABI-H0731+NrtI will be followed for up to 3 years from the date of treatment discontinuation to assess the durability of virologic response. Subjects will have an Unscheduled Visit to notify them of the Treatment Action to be implemented, at which point, each individual subject's visit schedule is then reset after the Unscheduled Visit, and subjects will return to the clinic for follow-up every 4 weeks for visits at 4, 8, 12, 16, 20, and 24 weeks post-treatment discontinuation, then every 8 weeks for visits at 32, 40 and 48 weeks post-treatment discontinuation, and then every 12 weeks until completion of the 3-year follow-up. Additional unscheduled visits may be performed at the Investigator's discretion. Following completion of the visit 3 years after ABI-H0731+NrtI discontinuation, subjects will exit the study and be under the routine care of their physician.

12-Week Follow-up on NrtI Alone

All subjects who discontinue ABI-H0731 only and continue SOC NrtI alone will be followed for 12 weeks from the date of ABI-H0731 discontinuation. Subjects will have an Unscheduled Visit to notify them of the Treatment Action to be implemented, at which point, each individual subject's visit schedule is then reset after the Unscheduled Visit, and subjects will return to the clinic for follow-up visits at 4, 8, and 12 weeks after discontinuation of ABI-H0731. Additional unscheduled visits may be performed at the Investigator's discretion. Following completion of the follow-up visit 12 weeks after discontinuation of ABI-H0731, subjects will exit the study and be under the routine care of their physician.

Continuation of Treatment with ABI-H0731+NrtI

All subjects who continue ABI-H0731+NrtI beyond Week 52 will return to the clinic for visits every 4 weeks until Week 148. Subjects may be notified of their Treatment Action by phone and continue on their current study visit schedule. At Week 148, subjects will be evaluated for virologic response as described in the table above, and will either discontinue both ABI-H0731 and NrtI and be followed for up to 3 years (as described in Section 3-Year Off-treatment Follow-up above) or discontinue ABI-H0731 only and continue on SOC NrtI alone and be followed for 12 weeks (as described in Section 12-Week Follow-up on NrtI Alone above).

Criteria to Restart SOC NrtI Following Discontinuation of Both ABI-H0731 and NrtI

Subjects who discontinue both ABI-H0731+NrtI will be followed to assess the durability of virologic response. The Investigator will use clinical judgment as to when restarting SOC NrtI is indicated. However, SOC NrtI therapy will be reintroduced if any of the following criteria listed below are met.

- Alanine aminotransferase (ALT) >10 × upper limit of normal (ULN)
- Direct bilirubin >2.0 × ULN
- International Normalized Ratio >1.5
- ALT >3 × ULN and HBV DNA >100,000 IU/mL
- ALT >ULN and HBV DNA >2,000 IU/mL on 3 consecutive visits at least one month apart
- Any clinical decompensation, regardless of HBV DNA level
- Physician or subject's decision

Should any of these criteria be met, then subjects may have an Unscheduled Visit to notify them to restart SOC NrtI. Subjects' visit schedules are then reset upon restarting SOC NrtI, and subjects who restart SOC NrtI will return for follow-up visits at 4, 8 and 12 weeks after starting SOC NrtI and will then complete participation in the study.

Study Objectives:

Primary Objective:

- To evaluate the potential for combination therapy with ABI-H0731+ NrtI to increase SVR rates in subjects who have CHB

Secondary Objectives:

- To evaluate the longer-term safety and tolerability of ABI-H0731 added to SOC NrtI therapy
- To evaluate improvement in transaminases in subjects on treatment and post-treatment

- To evaluate the durability of changes in viral antigen and viral DNA after discontinuation of combination therapy

Exploratory objectives:

- To evaluate the kinetics of and absolute changes from Baseline in biomarkers of transcriptionally active covalently closed circular DNA (cccDNA; HBeAg and HBsAg)
- To assess the relationship between exploratory viral biomarkers, such as changes in viral pgRNA and HBcrAg, and outcome
- To evaluate potential emergence of HBV resistance associated variants (RAVs), if any, to ABI-H0731 in combination with an SOC NrtI
- To evaluate the durability of virologic response between 24 weeks post-treatment discontinuation and 36 months post-treatment discontinuation
- For subjects who have provided an optional pharmacogenomic sample in parent studies (eg, ABI-H0731-201 or ABI-H0731-202), to evaluate the potential contribution of host genomics to outcomes
- To assess steady state plasma levels of ABI-H0731 and SOC NrtI for possible correlation with markers of safety and efficacy

Primary Endpoint:

The primary efficacy endpoint will be:

- Proportion of subjects with SVR at 24 weeks off treatment.

Secondary Endpoints:

Secondary endpoints include:

- Incidence of adverse events (AEs), premature discontinuations due to AE, abnormal safety laboratory results, electrocardiogram, or vital signs
- Incidence of subjects with abnormal ALT at Baseline who have normal ALT at end of treatment (EOT) and end of study.
- Incidence of subjects with suppression/loss of viral antigen/DNA on combination treatment whose viral antigens rebound off therapy

Exploratory Endpoints:

Exploratory endpoints include:

- Mean change from Baseline in $\log_{10}$ serum HBeAg
- Mean change from Baseline in $\log_{10}$ serum HBsAg
- Incidence of subjects with loss or change in $\log_{10}$ HBsAg or $\log_{10}$ HBeAg (<0.5, ≥ 0.5 to 1.0, or >1.0 in viral antigens) at EOT and end of follow-up

- Incidence of subjects with HBsAg seroconversion (loss of HBsAg and appearance of HBsAg antibody) or HBeAg seroconversion (loss of HBeAg and appearance of HBeAg antibody)
- Incidence of subjects with "detectable" HBV DNA by polymerase chain reaction at Baseline whose HBV DNA becomes "target not detected"
- Quantitative changes from Baselines in viral RNA on treatment and through end of follow-up
- Quantitative changes in serum HBcrAg levels on treatment and through end of follow-up
- Incidence of HBsAg or HBeAg seroreversion in subjects up to 3 years off therapy
- Incidence of subjects requiring retreatment following SVR through 3 years off therapy
- Incidence of subjects with emergence of HBV RAVs
- If differences are seen in outcomes/AEs between racial or ethnic groups: Pharmacogenomics correlation will be performed with clinical outcomes in subjects who have provided an optional informed consent and sample in Study ABI-H0731-201 or Study ABI-H0731-202
- Quantitative levels of ABI-H0731 and NrtI in plasma

Statistical Methods:

The primary objective will be evaluated based on the proportion of subjects who meet the definition of SVR at 24 weeks off treatment. The SVR rate and corresponding 95% confidence interval will be presented for the overall population while on combination therapy.

Secondary and exploratory endpoints will be analyzed descriptively. For continuous variables, such as change from Baseline in mean log10 serum HBeAg or HBsAg values at each timepoint, descriptive statistics will be used and will include the number, mean, standard deviation, median, minimum, and maximum and, where appropriate, a 95% CI.

For categorical variables, such as subjects with loss 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), summary statistics will include number and percent who meet the endpoint criteria.

Inclusion Criteria:

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

1. Willing and able to provide informed consent.
2. Previously enrolled in a study of ABI-H0731 and completed the treatment period, with demonstrated compliance in the opinion of the Investigator.

3. Female subjects must agree to use an effective birth control method for the duration of the study and follow-up, or be surgically sterile for at least 6 months, or at least 2 years postmenopausal with serum follicle-stimulating hormone levels consistent with a postmenopausal 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), diaphragm, or cervical cap. Female subjects of childbearing potential must have a negative pregnancy test.
4. All heterosexually active male subjects must agree to use an effective birth control method 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 (only female partner of a male subject), IUD, diaphragm, or cervical cap.
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 g 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.
7. Have the ability to take oral medication and be willing to adhere to the ABI-H0731-211 regimen in the opinion of the Investigator.

Exclusion Criteria:

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

1. Must not have had evidence of RAVs or lack of compliance on a previous study of ABI-H0731.
2. Must not have had a treatment-emergent AE or laboratory abnormalities deemed clinically significant and possibly or probably related to drug while on a previous study of ABI-H0731, that in the opinion of the Investigator or the Sponsor makes the subject unsuitable for this study.
3. Current 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.
4. Females who are lactating or pregnant or wish to become pregnant within the duration of the ABI-H0731-211 study.

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LIST OF ABBREVIATIONS AND TERMS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
cccDNA	covalently closed circular DNA
CFR	Code of Federal Regulations
CHB	chronic hepatitis B infection
CI	confidence interval
CpAM	core protein allosteric modifier
CRO	Clinical Research Organization (PRA Health Sciences)
CSR	Clinical Study Report
CYP	cytochrome P450
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
dsDNA	double-stranded DNA
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
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
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E 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
IUD	intrauterine device
LTFU	Long-term Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
NrtI	Nucleos(t)ide reverse transcriptase inhibitor
OLE	open-label extension
pgRNA	pre-genomic RNA
PK	pharmacokinetic
PP	per-protocol
RAV	HBV resistance associated variant
rcDNA	relaxed circular DNA
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	standard of care
SVR	sustained viral response
ULN	upper limit of normal
WHO	World Health Organization

2.0 INTRODUCTION AND RATIONALE

2.1 Study Rationale

Worldwide more than 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 2 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 reverse transcriptase inhibitors [NrtIs] 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 [Papatheodoridis 2016]. New therapies are required which can increase sustained off-treatment viral response, either alone or in combination with existing standard of care (SOC) for CHB.

ABI-H0731 (also known as vebicorvir) is a novel HBV core protein inhibitor (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 NrtI analogues or IFN-α. In pre-clinical models, ABI-H0731 binds to the HBV core protein and induces altered, nonfunctional core protein assembly. 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 "sustained viral response" (SVR) – defined as sustained off-treatment loss or suppression of viral antigens, and lack of DNA rebound, after a finite treatment period.

This study will assess the safety of extended treatment with ABI-H0731 (i.e., up to 148 weeks in ABI-H0731-211) when administered in combination therapy with a SOC NrtI in subjects previously participating in Studies ABI-H0731-201 and ABI-H0731-202. The study will also evaluate off-treatment virologic response rates following cessation of treatment in subjects meeting prespecified criteria.

Additionally, the study will assess the effect of the combination regimen on serum biomarkers such as HBV deoxyribonucleic acid (DNA), quantitative and qualitative reduction in the viral antigens hepatitis B "e" antigen (HBeAg), hepatitis B core-related antigen (HBcrAg) and hepatitis B surface antigen (HBsAg), as well as exploratory biomarkers such as reduction in circulating HBV pre-genomic RNA (pgRNA).

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, hepatitis B surface antigen (HBsAg), antibody to HBsAg (HBsAb), hepatitis B "e" antigen (HBeAg), antibody to HBeAg (HBeAb), and, in almost all patients, antibody to the HBV core protein. 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 4 major HBV genotypes (A, B, C, and D). Genotype A is regarded as pandemic and is predominantly found in North America, Northern/Western Europe, and Central Africa. HBV genotype B is most common in Asia including China, Vietnam, Japan, Taiwan, and Indonesia. Genotype C is predominant in East Asia and Oceania. Genotype D (also pandemic) is most highly prevalent in North America, Asia (including India), the Mediterranean, India, and the Middle East [Guettouche 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% of people in highly endemic regions (eg, East Asia and equatorial Africa), 2% to 7% of people in moderately endemic regions (eg, the Middle East and the Indian subcontinent), and <2% of people in locales of low endemicity (eg, North America and Europe) [Schweitzer 2015; WHO 2015].

Some HBV carriers will lose detectable serum HBsAg and HBV viremia will drop to nondetectable 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 2 clinically accepted options for the treatment of CHB: IFNs and oral NrtIs, which act as inhibitors of the viral polymerase. Of these, oral NrtIs 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 NrtI antivirals, with slightly higher rates of HBsAg loss recently reported in combination studies of tenofovir disoproxil fumarate together with pegylated IFN-α 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 sustained post-treatment. Specifically, improved rates of 2 types of outcomes are desirable for new HBV therapies: durable viral antigen loss/seroconversion (HBeAg in HBeAg-positive patients and HBsAg loss/seroconversion in all patients), in addition to sustained off-treatment viral load suppression. Such "SVRs" are predicted to afford improved long-term patient outcomes, (ie, reduced HBV-associated morbidity and mortality from virus induced inflammation resulting in end-stage liver disease and HCC).

2.2.2 Hepatitis B Virus Biology and Rationale for Hepatitis B Virus Core Inhibitors

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, 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 core 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 core protein allosteric modifiers (CpAMs) - or "core inhibitors" - 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.

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 Inhibitors and ABI-H0731

Please refer to the Investigator's Brochure (IB) for additional information describing:

- *in vitro* activity of ABI-H0731
- combination therapy
- study drug resistance
- nonclinical pharmacokinetics
- nonclinical pharmacology and toxicology
- clinical experience

2.3 Summary of Additional Clinical Data with ABI-H0731

2.3.1 Phase 2a Studies

Study ABI-H0731-211 is an open-label extension (OLE) of Phase 2a double-blinded, placebo-controlled proof-of-concept studies (ABI-H0731-201 and ABI-H0731-202). No new on-treatment safety signals have been identified during the course of these studies following 2 independent pre-scheduled Data Monitoring Committee reviews. Refer to the IB for additional details.

2.3.2 Recently Completed Clinical Pharmacology Studies

2.3.2.1 Drug-Drug Interaction (DDI) Study

Clinical Study ABI-H0731-103 was conducted with sensitive index substrates of cytochrome P450 (CYP) 3A4, 2B6, 2C8, 2C9, 2C19, and 2D6 to test the inhibition potential of ABI-H0731 300 mg. This study also investigated the effect of ABI-H0731 300 mg on the induction of CYP2B6 and CYP3A4. ABI-H0731-103 was conducted in a total of 58 healthy volunteers. Results from this clinical study indicate that ABI-H0731, when given along with a cocktail of index substrates, is not an inhibitor of CYP2C19 or CYP2D6. In addition, ABI-H0731 is not an inhibitor of CYP2C8, CYP3A4, or CYP2B6. ABI-H0731 is a weak inhibitor of CYP2C9, increasing the concentration of the index substrate tolbutamide by ~30%. ABI-H0731 300 mg is not an inducer of CYP2B6. Midazolam levels were reduced by approximately 30% after 7 days of daily administration and remained at the same lower level after 14 days of administration of ABI-H0731 300 mg. The CYP3A4 mediated metabolite of midazolam, 1-hydroxymidazolam, was not increased on either Day 7 or 15. These results suggest ABI-H0731 is not an inducer of CYP3A4; however, the mechanism of midazolam exposure reduction remains unclear.

2.4 Overall Risk/Benefit Assessment

ABI-H0731 is a novel, potent, direct-acting, once daily, HBV core inhibitor that is among the first HBV core inhibitors to be investigated in CHB patients for more than 28 days. The combination of ABI-H0731 with a SOC NrtI has the potential to be a once-daily regimen for the treatment of HBV infection. This extension study will enroll chronically HBV-infected subjects who have completed Study ABI-H0731-201 or Study ABI-H0731-202. This study will specifically evaluate

whether extending a course of combination therapy (ABI-H0731+ SOC NrtI) for at least 52 weeks may provide a lasting therapeutic benefit.

As compared with monotherapy, the potential benefits of an ABI-H0731 + SOC NrtI combination for the treatment of HBV include:

- A potential novel therapeutic option for those with ongoing low-level viremia on existing SOC NrtI
- Greater on-treatment antiviral efficacy (more rapid and greater extent of suppression of HBV replication with resultant reduction of viral replication induced inflammation) compared to current SOC alone
- Greater inhibition of cccDNA establishment - and thus greater loss of cccDNA - as compared to current SOC alone
- Potential for finite therapy as compared to SOC NrtIs which are often lifelong therapies.

The safety database currently includes approximately 250 healthy subjects and CHB subjects who have been administered ABI-H0731. No new clinical safety issues specifically related to ABI-H0731 have been identified to date beyond those described in the IB.

Based on the available data from completed Phase 1 studies and preliminary data from the Phase 2 studies, ABI-H0731-201 and ABI-H0731-202, ABI-H0731+NrtI combination treatment is generally well-tolerated, and there is no expectation of significant overlapping or new, unexpected toxicities upon continued administration of ABI-H0731 together with SOC NrtI therapies.

During the conduct of this OLE study, the Sponsor will perform ongoing safety data reviews of the clinical and laboratory assessments at each study visit. To provide consistency for the intensity assessments of clinical adverse events (AEs) and lab abnormalities for the interim safety reviews and for the eventual study report, any observed AEs and laboratory abnormalities during this study will be graded according to the table in APPENDIX II , "Toxicity Grading of Clinical Adverse Events and Laboratory Abnormalities," which has been adapted by the Sponsor from the July 2017 (Version 2.1) Division of AIDS (DAIDS)/NIAID grading table. Additional specific guidance has been provided for evaluation of potential hepatic or dermatologic abnormalities (Section 4.7.1 and Section 4.7.3) should they arise.

In summary, there is no approved all-oral, direct-acting antiviral therapy for HBV-infected patients that provides a high rate of off-treatment cure. As compared to monotherapy with a NrtI, it is anticipated that addition of ABI-H0731 to SOC NrtI therapy may result in more complete suppression of cccDNA metabolism and pleotropic effects on the viral core protein, potentially resulting in accelerated loss of cccDNA. It is thus anticipated that over the course of therapy in this study, ABI-H0731+NrtI may demonstrate greater clinical antiviral effects than seen with NrtI monotherapy alone (eg, serum HBV DNA, HBV pgRNA, HBsAg, and HBeAg reductions). However, it is unknown whether the degree of reduction or duration of effect of ABI-H0731+NrtI therapy will be sufficient to establish any lasting clinical benefit for any of the subjects enrolled.

The predictable benefits of this study are thus limited to 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. If high rates of "SVR" can be obtained with a finite regimen for HBV, then the anticipated reduction in burden of disease would offer a favorable risk-benefit determination for treatment-experienced individuals with chronic HBV infection, and would potentially support further registrational clinical studies for ABI-H0731.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

- To evaluate the potential for combination therapy with ABI-H0731+ NrtI to increase SVR rates in subjects who have CHB

3.1.2 Secondary Objectives

- To evaluate the longer-term safety and tolerability of ABI-H0731 added to SOC NrtI therapy
- To evaluate improvement in transaminases in subjects on treatment and post-treatment
- To evaluate the durability of changes in viral antigen and viral DNA after discontinuation of combination therapy

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 assess the relationship between exploratory viral biomarkers, such as changes in viral pgRNA and hepatitis B core-related antigen (HBcrAg), and outcome
- To evaluate potential emergence of HBV resistance associated variants (RAVs), if any, to ABI-H0731 in combination with an SOC NrtI
- To evaluate the durability of virologic response between 24 weeks post-treatment discontinuation and 36 months post-treatment discontinuation
- For subjects who have provided an optional pharmacogenomic sample in parent studies (eg, ABI-H0731-201 or ABI-H0731-202), to evaluate the potential contribution of host genomics to outcomes
- To assess steady state plasma levels of ABI-H0731 and SOC NrtI for possible correlation with markers of safety and efficacy

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary efficacy endpoint will be:

- Proportion of subjects with SVR at 24 weeks off treatment.

3.2.2 Secondary Endpoints

The secondary endpoints include:

- Incidence of AEs, premature discontinuations due to AEs, abnormal safety laboratory results, electrocardiogram, or vital signs
- Incidence of subjects with abnormal ALT at Baseline who have normal ALT at end of treatment (EOT) and end of study (EOS)
- Incidence of subjects with suppression/loss of viral antigen/DNA on combination treatment whose viral antigens rebound off therapy

3.2.3 Exploratory Endpoints

Exploratory endpoints include:

- Mean change from Baseline in $\log_{10}$ serum HBeAg
- Mean change from Baseline in $\log_{10}$ serum HBsAg
- Incidence of subjects with loss or change in $\log_{10}$ HBsAg or $\log_{10}$ HBeAg (<0.5, ≥ 0.5 to 1.0, or >1.0 in viral antigens) at EOT and end of follow-up
- Incidence of subjects with HBsAg seroconversion (loss of HBsAg and appearance of HBsAg antibody) or HBeAg seroconversion (loss of HBeAg and appearance of HBeAg antibody)
- Incidence of subjects with "detectable" HBV DNA by polymerase chain reaction at Baseline whose HBV DNA becomes "target not detected"
- Quantitative changes from Baselines in viral RNA on treatment and through end of follow-up
- Quantitative changes in serum HBcrAg levels on treatment and through end of follow-up
- Incidence of HBsAg or HBeAg seroreversion in subjects up to 3 years off therapy
- Incidence of subjects requiring retreatment following SVR through 3 years off therapy
- Incidence of subjects with emergence of HBV RAVs
- If differences are seen in outcomes/AEs between racial or ethnic groups: Pharmacogenomics correlation will be performed with clinical outcomes in subjects who have provided an optional informed consent and sample in Study ABI-H0731-201 or Study ABI-H0731-202

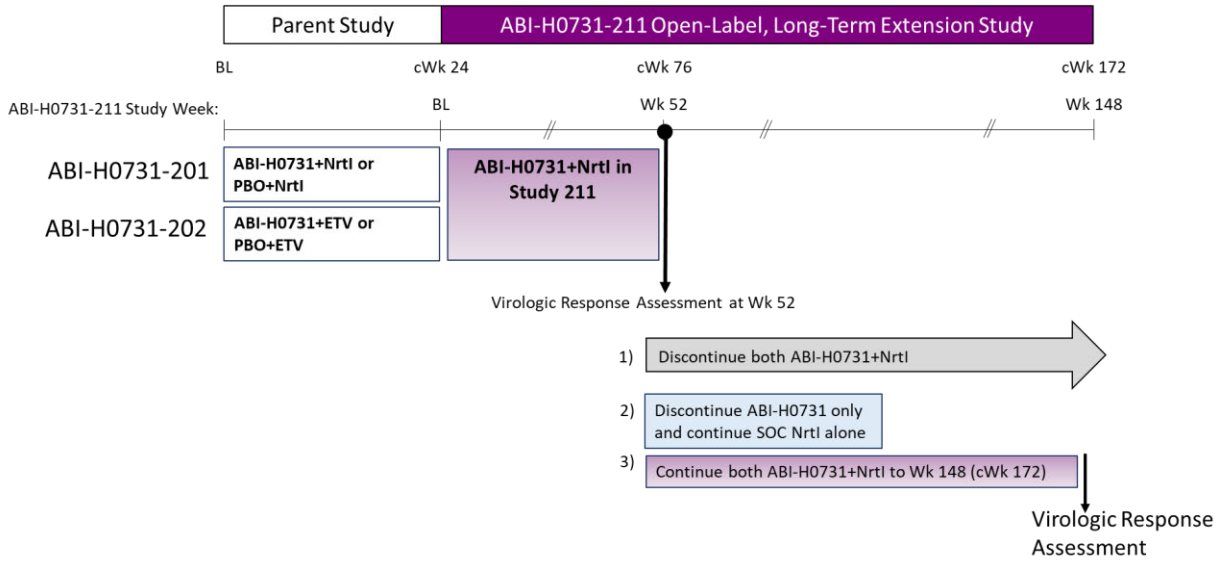
- Quantitative levels of ABI-H0731 and NrtI in plasma

4.0 STUDY PLAN

4.1 Study Design

This is an open-label, multi-center, long-term extension study evaluating the safety and efficacy of ABI-H0731 in combination with a SOC NrtI in CHB subjects who have completed 24 weeks of treatment in either of the parent Studies ABI-H0731-201 (Study 201) or ABI-H0731-202 (Study 202). Figure 4-1 presents an overview of the study design.

Figure 4-1 ABI-H0731-211 Study Overview



cWk = cumulative treatment week includes duration on the parent study (ie, ABI-H0731-201 or ABI-H0731-202) plus treatment duration on ABI-H0731-211
BL = baseline; NrtI = nucleos(t)ide reverse transcriptase inhibitor; PBO = placebo; SOC = standard of care; Wk = week

To participate in ABI-H0731-211 (Study 211), in addition to completing 24 weeks of treatment in ABI-H0731-201 or ABI-H0731-202, subjects must also meet the eligibility criteria described in Section 5.2 and Section 5.3.

In ABI-H0731-211, subjects may receive up to 148 weeks of treatment with ABI-H0731+NrtI. The actual duration of treatment received by each individual subject will be based on their HBV treatment history (ie, NrtI suppressed or treatment naïve) and HBeAg status (ie, HBeAg positive or HBeAg negative) at Baseline in the parent study, and the individual subject's virologic response in ABI-H0731-211. Based on assessment of these factors at specific study visits, each subject will be evaluated for virologic response and assigned one of the following three treatment actions:

1) Discontinue both ABI-H0731+NrtI

2) Discontinue ABI-H0731 only and continue SOC NrtI alone

3) Continue both ABI-H0731+NrtI for up to 148 weeks

Table 4-1 below summarizes, the population subgroups, the study visits at which virologic response is assessed, the decision criteria applied and the subsequent treatment action.

Table 4-1 Decision Criteria and Treatment Actions

Parent Study	Treatment History†	HBeAg Status†	Study 211 Visit	Decision Criteria	Treatment Action
201	NrtI Suppressed	Negative	Week 52*	Both ABI-H0731+NrtI will be stopped in all subjects	Discontinue both ABI-H0731+NrtI. Enter long-term off-treatment follow-up for up to 3 years
201	NrtI Suppressed	Positive	Week 52*	If subject has total HBV nucleic acids (DNA+pgRNA) <20 IU/mL **and** HBeAg ≤5 IU/mL for ≥7 consecutive visits¥	Discontinue both ABI-H0731+NrtI. Enter long-term off-treatment follow-up for up to 3 years
				If subject does not have total HBV nucleic acids (DNA+pgRNA) <20 IU/mL **and** HBeAg ≤5 IU/mL for ≥7 consecutive visits¥	Discontinue ABI-H0731 only and continue SOC NrtI alone. Enter follow-up on SOC NrtI alone for 12 weeks
202	Treatment Naive	Positive	Week 52*	If subject has ≥2.5 $\log_{10}$ reduction in pgRNA from Baseline in the parent study or achieves pgRNA <LLOQ	Continue both ABI-H0731+NrtI for additional 96 weeks (ie, to Week 148)
				If subject has <2.5 $\log_{10}$ reduction in pgRNA from Baseline in the parent study or does not achieve pgRNA <LLOQ	Discontinue ABI-H0731 only and continue SOC NrtI alone. Enter follow-up on SOC NrtI alone for up to 12 weeks
			Week 148	If subject has total HBV nucleic acids (DNA+pgRNA) <20 IU/mL **and** HBeAg ≤5 IU/mL for ≥7 consecutive visits¥	Discontinue both ABI-H0731+NrtI. Enter long-term off-treatment follow-up for up to 3 years
				If subject does not have total HBV nucleic acids (DNA+pgRNA) <20 IU/mL **and** HBeAg ≤5 IU/mL for ≥7 consecutive visits¥	Discontinue ABI-H0731 only and continue on SOC NrtI alone. Enter follow-up on SOC NrtI alone for up to 12 weeks

†Treatment History and HBeAg-status at Baseline in the parent studies (Study 201 or Study 202)
*Subjects without virologic assessment at Week 52 will be evaluated at the next study visit.
¥Consecutive visits are determined from the last timepoint at which values are available for all parameters.

As described in Table 4-1, based on the respective treatment action, additional follow-up visits may be undertaken. These visits are briefly summarized below with further details provided in Table 4-2, Table 4-3, and Table 4-4.

4.1.1 3-Year Off-treatment Follow-up

All subjects who discontinue both ABI-H0731+NrtI will be followed for up to 3 years from the date of treatment discontinuation to assess the durability of virologic response. Subjects will have an Unscheduled Visit to notify them of the Treatment Action to be implemented, at which point, each individual subject's visit schedule is then reset after the Unscheduled Visit, and subjects will return to the clinic for follow-up every 4 weeks for visits at 4, 8, 12, 16, 20, and 24 weeks post-treatment discontinuation, then every 8 weeks for visits at 32, 40 and 48 weeks post-treatment discontinuation, and then every 12 weeks until completion of the 3-year follow-up (Table 4-3). Additional unscheduled visits may be performed at the Investigator's discretion. Following completion of the visit 3 years after ABI-H0731+NrtI discontinuation, subjects will exit the study and be under the routine care of their physician.

4.1.2 12-Week Follow-up on NrtI Alone

All subjects who discontinue ABI-H0731 only and continue SOC NrtI alone will be followed for 12 weeks from the date of ABI-H0731 discontinuation. Subjects will have an Unscheduled Visit to notify them of the Treatment Action to be implemented, at which point, each individual subject's visit schedule is then reset after the Unscheduled Visit, and subjects will return to the clinic for follow-up visits at 4, 8, and 12 weeks after discontinuation of ABI-H0731. Additional unscheduled visits may be performed at the Investigator's discretion. Following completion of the follow-up visit 12 weeks after discontinuation of ABI H0731, subjects will exit the study and be under the routine care of their physician.

4.1.3 Continuation of Treatment with ABI-H0731+NrtI

All subjects who continue ABI-H0731+NrtI beyond Week 52 will return to the clinic for visits every 4 weeks until Week 148. Subjects may be notified of their Treatment Action by phone and continue on their current study visit schedule. At Week 148, subjects will be evaluated for virologic response as described in Table 4-1, and will either discontinue both ABI H0731 and NrtI and be followed for up to 3 years (as described in Section 4.1.1) or discontinue ABI-H0731 only and continue on SOC NrtI alone and be followed for 12 weeks (as described in Section 4.1.2).

4.1.4 Criteria to Restart SOC NrtI Following Discontinuation of Both ABI-H0731 and NrtI

Subjects who discontinue both ABI-H0731+NrtI will be followed to assess the durability of virologic response. The Investigator will use clinical judgment as to when restarting SOC NrtI is indicated. However, SOC NrtI therapy will be reintroduced if any of the following criteria listed below are met.

- Alanine aminotransferase (ALT) >10 × upper limit of normal (ULN)
- Direct bilirubin >2.0 × ULN

- International Normalized Ratio >1.5
- ALT >3 × ULN and HBV DNA >100,000 IU/mL
- ALT >ULN and HBV DNA >2,000 IU/mL on 3 consecutive visits at least one month apart
- Any clinical decompensation, regardless of HBV DNA level
- Physician or subject's decision

Should any of these criteria be met, then subjects may have an Unscheduled Visit to notify them to restart SOC NrtI. Subjects' visit schedules are then reset upon restarting SOC NrtI, and subjects will return for follow-up visits at 4, 8, and 12 weeks after restarting SOC NrtI and will then complete participation in the study (Table 4-4).

4.2 Scientific Rationale

There is a significant unmet medical need for HBV therapies that can provide durable clinical responses off therapy. The HBV core protein is a pleotropic molecule involved in multiple parts of the HBV life cycle. Non-clinical and clinical work has shown that core inhibitors are potent DAAs which can prevent establishment of cccDNA and have the potential to be additive to or synergistic with SOC NrtIs in the inhibition of viral replication. This study will explore the long-term safety of the ABI-H0731+NrtI combination in subjects completing participation in the ABI-H0731-201 and ABI-H0731-202 Phase 2 studies. Additionally, the study will evaluate the effect of the combination regimen on serum biomarkers of functional cures, specifically, serum HBV DNA, quantitative and qualitative reduction in the viral antigens HBeAg, HBcrAg, HBsAg, and reduction in circulating HBV pgRNA. As compared to monotherapy with a NrtI, the ABI-H0731+NrtI combination 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 thus may demonstrate greater clinical antiviral effects not seen with NrtI monotherapy (eg, serum HBV DNA, RNA, HBsAg, and HBeAg reductions), and potentially higher rates of off-treatment SVRs.

4.3 Dose Justification

The ABI-H0731 dose selected for continued evaluation in this study is 300 mg PO QD. 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 AEs 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.

ABI-H0731 monotherapy in CHB subjects resulted in dose-dependent decreases in viral load at doses of 100, 200, and 300 mg daily in subjects with CHB. It is anticipated that 300 mg daily will

be well-tolerated and provides sufficient ABI-H0731 exposure to produce the desired antiviral effect in CHB subjects in this study.

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 the study are expected to have a Baseline viral load near or below the lower limit of quantification. As such, no sequencing of the Cp region may be possible. As all subjects will remain on their SOC NrtI therapy with demonstrated high barriers to resistance throughout this OLE study, the potential for emergence of RAVs to combination therapy is considered minimal. However, all subjects will have samples collected for viral load monitoring throughout the study.

To assess potential HBV core gene sequences associated with viral resistance or blunted treatment response, serum samples from subjects with evidence of nonresponse to treatment, including on-treatment viral DNA rebound (≥1 $\log_{10}$ HBV DNA rebound from on-treatment nadir) or viral load plateauing (≥2 consecutive samples with viral load remaining within 0.5 $\log_{10}$ of nadir) will be selected for HBV core gene sequencing, with sequence comparisons to Baseline sequences, as well as comparisons to core gene sequences from placebo recipients and HBV database sequences.

Subjects with persistent viral rebound found to have developed resistance to treatment, or in whom no resistance is found and are identified as significantly noncompliant, or who have <0.5 HBV DNA $\log_{10}$ reduction from Baseline for ≥3 consecutive visits at least 4 weeks apart will be discontinued from ABI-H0731 treatment.

4.5 HCC Surveillance

All subjects entering Study ABI-H0731-211 will undergo regular HCC surveillance per SOC for the duration of time they are on study. HCC surveillance will consist of an abdominal ultrasound, unless another modality is specifically clinically indicated and discussed with the Sponsor. Subjects who enter long-term follow-up (off treatment), will continue to have HCC surveillance conducted approximately every 6 months for the duration of study.

4.6 End of Study (EOS) Definition

The study will be completed when the last subject completes the last post-treatment follow-up visit (see Section 4.8, Schedule of Assessments) or when the last subject discontinues the study before completing the last follow-up visit.

4.7 Management of Toxicities

4.7.1 General Stopping Rules

Any individual subject who meets either of the criteria below will be requested to stop treatment with study drug, in consultation with the Sponsor:

- Any serious adverse events (SAE) deemed at least possibly related to the study drug

- Any Grade 3 or 4 AE deemed related to the study drug

4.7.2 Subjects with Alanine Aminotransferase (ALT) Elevations

All subjects participating in the study will be closely monitored for ALT elevations and/or signs of potential decline in hepatic function. Subjects experiencing ALT elevations ≥2 × Baseline or on-treatment nadir and >2 × ULN during study treatment or during post-treatment follow-up will be closely monitored with regular Unscheduled visits every 1 to 2 weeks at the discretion of the Investigator. If analysis of blood samples collected at these visits cannot be performed at the central laboratory, then a local laboratory may be used. In which case, local laboratory reports will be de-identified, collected by the Site Monitor, securely stored by the Sponsor and will not entered in the study database. The following guidance is offered for management of study subjects with ALT elevations or biochemical evidence of declining hepatic function.

- **ALT Flare:**
    - An ALT flare is defined as:
        - ALT >2 × Baseline and ≥10 × ULN, or
        - ALT >2 × on-treatment nadir and ≥10 × ULN
    - Subjects with an ALT flare should have the ALT findings confirmed within 3 days of receipt of the original results. All such 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 (if total bilirubin is elevated, reflex to direct bilirubin), International Normalized Ratio (INR), serum albumin, and creatine kinase. 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), hepatitis C virus (HCV) RNA, hepatitis D virus (HDV) RNA, and hepatitis E virus (HEV) IgM should also be drawn.
        - If an intercurrent illness is determined to be causal, subjects with an ALT elevation without declining hepatic function and without contraindications may continue treatment and the intercurrent illness should be treated as deemed medically appropriate by the Investigator.
        - 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 to 5 days until the ALT elevation has stabilized. At these visits, subjects will undergo a symptom-directed physical examination, review of concomitant medications (including herbal

medications or supplements) and the following laboratory tests should be performed: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), INR, serum albumin, creatine kinase, HBV DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]). Subjects whose ALT has stabilized should continue to be monitored weekly (or more frequently as deemed necessary by the Investigator) until ALT values return to normal or Baseline levels.

- In the absence of declining hepatic function or contraindications, extension of the monitoring period to 4 weeks is considered clinically appropriate to safely monitor subjects during the period of increased ALT.

- **Declining hepatic function during treatment**

  - Subjects with confirmed ALT elevation and biochemical evidence of declining hepatic function should be discontinued from study treatment, 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 to 5 days until the relevant laboratory values stabilize. Subjects whose hepatic function has stabilized should continue to be monitored weekly (or more frequently as deemed necessary by the Investigator) until the relevant laboratory values return to normal or Baseline.

- **Post-treatment ALT "flare" or ALT elevation with declining hepatic function**

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

  All subjects with 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 Investigator, in consultation with the Sponsor, until the ALT flare is documented to be either resolved or stabilized/resolving (defined as consistent ALT declines of 10% or more or normalization of ALT) on at least 2 successive visits.

If 2 or more subjects meet these flare management criteria, the US Food and Drug Administration (FDA) and other relevant regulatory agencies will be notified, and subsequent steps will be determined after consultation with these agencies.

4.7.3 Subjects with Rash

In the event of any rash, subjects should return to clinic for evaluation for an unscheduled visit (Day 1 of rash). Digital photographs of the rash should be taken, and blood samples should be collected for central laboratory evaluation. At the Investigator's discretion, a site's local laboratory may be used in addition to the central laboratory, but such laboratory data will not be entered into the study database. 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 documents. A copy of the dermatologist report will be de-identified and collected by the Site 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 discretion 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, copied 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, with additional unscheduled visits as deemed medically appropriate by the Investigator. Subjects who discontinue treatment should be followed on the appropriate follow-up schedule after treatment is discontinued.

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 2 successive visits.

4.8 Schedule of Assessments

Table 4-2 Schedule of Assessments: On-treatment (ABI-H0731+NrtI) through Week 100

Period or Visit	Open-Label Combination Treatment																										Premature Termination	Unscheduled[a]
Study Day or Week	Day 1[b]	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52[c]	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Varies	Varies
Visit Window (Days)	0	±2	±2	±3	±3	±3	±3	±3	(- 5)	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	N/A	N/A
Informed consent(s)[d]	X																												
Assessment of response[e]															X														
Full physical examination	X							X							X						X						X	X	
12-lead ECG	X				X				X						X						X						X	X	If indicated
Weight	X								X	X											X	X							
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[l] review, adverse events review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm eligibility	X																												
Symptom-directed physical exam		X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X			X
Dermatologic assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If applicable	
Study drug dispensation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		
Digital photography[a]																													If indicated
HCC surveillance[g]		X						X						X						X					X			
Laboratory Studies																													
HBV DNA viral load, HBV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg,[h] HBeAg[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAb[h], HBeAb[h]	X				X			X			X			X			X			X			X			X		X	
HCVAb; HDVAb; HAV(IgM); HEV(IgM)																													If indicated
Exploratory biomarkers: core protein (HBCrAg) and viral nucleic acid[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, hematology, coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X		X				X			X			X			X			X			X			X	X	X
Urine drug test																												X	If indicated
Pregnancy test (WOCP only)[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If indicated
PK sample[n]														X															

Table 4-2 (Continued) Schedule of Assessments: On-treatment (ABI-H0731+NrtI) Week 104 to Week 148

Period or Visit	Open-Label Combination Treatment											
Study Day or Week	**Week 104**	**Week 108**	**Week 112**	**Week 116**	**Week 120**	**Week 124**	**Week 128**	**Week 132**	**Week 136**	**Week 140**	**Week 144**	**Week 148**
Visit Window (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Assessment of response[e]												X
Full physical examination						X						X
12-lead ECG						X						X
Weight						X						X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[l] review, adverse events review	X	X	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical exam	X	X	X	X	X		X	X	X	X	X	
Dermatologic assessment	X	X	X	X	X	X	X	X	X	X	X	X
Study drug accountability	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation	X	X	X	X	X	X	X	X	X	X	X	X
HCC surveillance[g]					X						X	
Laboratory Studies												
HBV DNA viral load, HBV RNA	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg[h], HBeAg[h]	X	X	X	X	X	X	X	X	X	X	X	X
HBsAb[h], HBeAb[h]		X			X			X			X	
Exploratory biomarkers: core protein (HBCrAg) and viral nucleic acid[i]	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, hematology, coagulation	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis			X			X			X			X
Pregnancy test (WOCP only)[j]	X	X	X	X	X	X	X	X	X	X	X	X

Table 4-3 Schedule of Assessments: Long-term Off-treatment Follow-up for Subjects Who Discontinue Both ABI-H0731+NrtI

Period or Visit	**Post-treatment Follow-up[k]: 3-Year Follow-Up**									
Study Week/Month	**4 Wk FU**	**8 Wk FU**	**12 Wk FU**	**16 Wk FU**	**20 Wk FU**	**24 Wk FU**	**32 Wk FU**	**40 Wk FU**	**48 Wk FU**	**Q3 Months** (Months 15-36)
Visit Window (Weeks)	±1	±1	±1	±1	±1	±1	±1	±1	±1	±3
Full physical examination	X									
12-lead ECG	X									
Weight	X									
Vital signs	X									
Concomitant medications[l] / adverse events	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical exam		X	X	X	X	X	X	X	X	X
HCC surveillance[g]					X			X		Q6 Months
Laboratory studies										
HBV DNA viral load, HBV RNA	X	X	X	X	X	X	X	X	X	X
HBsAg[h], HBeAg[h]	X	X	X	X	X	X	X	X	X	X
HBsAb[h], HBeAb[h]			X			X		X		Q3 Months
Exploratory biomarkers: core protein (HBcrAg) / viral nucleic acid[i]	X	X	X	X	X	X	X	X	X	X
Chemistry, hematology, coagulation	X									
Liver panel		X	X	X	X	X	X	X	X	X
Urinalysis	X									
Pregnancy test (WOCP only)[j]	X									

Table 4-4 Schedule of Assessments: Follow-up for Subjects Who 1) Prematurely Discontinue the Study, 2) Stop ABI-H0731 only and Continue NrtI alone, or 3) Start SOC NrtI after Discontinuation of both ABI-H0731+NrtI

Period or Visit	**Post-treatment: 12-Week Follow-Up**		
Study Day or Week	**Follow-up 1[m]**	**Follow-up 2[m]**	**Follow-up 3[m] / EOS**
Visit Window (Days)	±7	±7	±7
Full physical examination	X		
12-lead ECG	X		
Weight	X		
Vital signs	X		
Concomitant medications[l] / adverse events	X	X	X
Symptom-directed physical exam		X	X
Laboratory studies			
HBV DNA viral load, HBV RNA	X	X	X
HBsAg[h], HBeAg[h]	X	X	X
HBsAb[h], HBeAb[h]			X
Exploratory biomarkers: core protein (HBcrAg) / viral nucleic acid[i]	X	X	X
Chemistry, hematology, coagulation	X		
Liver panel		X	X
Urinalysis	X		
Pregnancy test (WOCP only)[j]	X		

Schedule of Assessments Footnotes and Acronyms – Applies to All Tables

a Any subjects with rash or ALT flare (defined in Sections 4.7.1 and 4.7.2) should return to the clinic for an unscheduled visit as soon as possible, ideally within 3 days for assessments described in Section 4.7.2.
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 documents. 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 2 successive visits.

b OLE Day 1 is the final in-clinic treatment visit of the parent study.

c Timepoints of assessment of SVR.

d Written informed consent must be obtained prior to enrolling in OLE study and receiving open-label study drug. This can be done up to and including OLE Day 1 (the last on-treatment visit of the parent study). Subjects who complete the parent study's treatment period will be eligible to enter the OLE study.

e The criteria for evaluating each subject's virologic response and the corresponding course of action for each individual subject are listed in Table 4-1.

f Study drug is dispensed only for subjects who continue ABI-H0731+NrtI treatment. If the subject continues taking SOC NrtI, then NrtI should continue to be dispensed as normal. If the subject discontinues ABI-H0731+NrtI, then no study drug should be dispensed to the subject.

g The HCC surveillance window is ±4 weeks from the scheduled visit, or approximately every 6 months for the duration of the study. Refer to Section 4.5 for additional details.

h If quantitative HBeAg and/or HBsAg is <LLOQ at any visit, reflex qualitative HBeAg and/or HBsAg testing will be done. If HBeAg and/or HBsAg are <LLOQ at any visit, reflex qualitative HBeAb and/or HBsAb testing will be done to assess for seroconversion.

i HBV resistance testing, using exploratory research samples (i.e., viral nucleic acid), will be performed on subjects whose on-treatment HBV DNA viral load increases by $\geq$1 $\log_{10}$ IU/mL from on-treatment nadir. Resistance testing may also be performed on subjects who do not respond to treatment (≥2 consecutive samples with viral load remaining within 0.5 $\log_{10}$ of nadir).

j WOCP: women of child-bearing potential only.

k Subjects with a post-treatment ALT elevation >2x ULN or HBV DNA >2000 IU/mL will be asked to return to clinic every 2 weeks for an unscheduled visit to monitor liver function and viral load until subject's lab values resolve or the subject requires restart of NrtI therapy. Refer to Section 4.1.4 for criteria to restart NrtI after discontinuing ABI-H0731+NrtI.

l 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), with the exception of concomitant medications used for treatment of HBV in subjects who are restarted on HBV therapy, which should be collected through end of follow-up.

m The Follow-up 1, 2, and 3 Visits will occur 4, 8, and 12 weeks (respectively) after the subject discontinues ABI-H0731 and continues NrtI, or re-starts SOC NrtI, or prematurely terminates from the study. Additional Follow-up (Unscheduled) visits may occur as clinically indicated, eg, AE/AESI, ALT flare (see Section 4.7.2).

n A trough PK sample is to be taken prior to ABI-H0731 administration at Week 48 ± 8 weeks.

Abbreviations: AE=adverse event; AESI=adverse event of special interest; ALT=alanine aminotransferase; AST=aspartate aminotransferase; d=days; ECG=electrocardiogram; eCRF=electronic case report form; EOS=end of study; 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; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; HDV=hepatitis D virus; HEV=hepatitis E virus; IgM=immunoglobulin M; INR=International Normalized Ratio; LTFU=Long-term Follow-up; N/A=not applicable; NrtI= nucleos(t)ide inhibitors of the HBV polymerase; OLE=open-label extension; PK=pharmacokinetic; Q3=every 3 months; Q6=every 6 months; SOC=standard of care; SVR=sustained viral response; Wk=week; WOCP=women of childbearing potential.

5.0 POPULATION

5.1 Number of Subjects

Globally, it is anticipated that less than 100 male or female subjects with CHB, who completed 24 weeks of treatment in ABI-H0731-201 or ABI-H0731-202 will be enrolled.

5.2 Inclusion Criteria

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

1. Willing and able to provide informed consent.

2. Previously enrolled on a study of ABI-H0731 and completed the treatment period, with demonstrated compliance in the opinion of the Investigator.

3. Female subjects must agree to use an effective birth control method for the duration of the study and follow-up, or be surgically sterile for at least 6 months, or at least 2 years postmenopausal with serum follicle-stimulating hormone levels consistent with a postmenopausal 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), diaphragm, or cervical cap. Female subjects of childbearing potential must have a negative pregnancy test.

4. All heterosexually active male subjects must agree to use an effective birth control method 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 (only female partner of a male subject), IUD, diaphragm, or cervical cap.

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.

7. Have the ability to take oral medication and be willing to adhere to the ABI-H0731-211 regimen in the opinion of the Investigator.

5.3 Exclusion Criteria

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

1. Must not have had evidence of RAVs or lack of compliance on a previous study of ABI-H0731.

2. Must not have had a treatment-emergent AE or laboratory abnormalities deemed clinically significant and possibly or probably related to drug while on a previous study of ABI-H0731, that in the opinion of the Investigator or the Sponsor makes the subject unsuitable for this study.

3. Current 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.

4. Females who are lactating or pregnant or wish to become pregnant within the duration of the ABI-H0731-211 study.

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 other supplements

- 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 Strategies for Recruitment and Retention

Subjects will be enrolled globally from ongoing studies of ABI-H0731.

Subjects will be enrolled by their treating physician while in process of completing a parent study. No subjects who are not already participating in a study of ABI-H0731 will be allowed to enroll in the study.

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

6.0 STUDY DRUG

6.1 Description

ABI-H0731 active pharmaceutical ingredient is a white to off-white crystalline powder manufactured under current Good Manufacturing Practices (GMP) via standard synthetic chemistry methods.

6.1.1 Formulation

[redacted]

6.1.2 Storage

[redacted]

6.2 Packaging and Shipment

[redacted]

6.3 Dose and Administration

6.3.1 Dosing in the Study

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

Subjects will self-administer study drug during this study. If possible, study personnel will document time of study drug and SOC NrtI administration in subject's medical record.

Refer to the Site Operations Manual for detailed instructions on managing missed or incorrect doses. In general, if a subject remembers within 8 hours of having missed their scheduled dose, they should take that day's dose. Subjects who miss a dose should not "catch up" and take twice the dose on the following day. If a subject reports having missed 2 or more consecutive doses, or multiple missed single doses, then the Medical Monitor should be contacted before taking any further action. These missed doses should be recorded in the source documents. If a subject demonstrates continued noncompliance with study drug dosing, despite educational efforts, the Investigator should contact the Medical Monitor to discuss discontinuation of the subject from the study.

6.4 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 and bottles 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 tablets and bottles. The Site 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 treatment period.

6.5 Compliance

To monitor compliance, tablet counts will be conducted on returned bottles. 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.

At every study visit, the Investigator should reinforce to his/her subject(s) the importance of consistently maintaining compliance with the study drug regimen (ABI-H0731+NrtI). Subjects should be reminded of the importance of taking both drugs daily as prescribed. The treatment only works as a combination and missing one or both of the study drugs is a study deviation that should be avoided.

6.6 Concomitant Therapy

ABI-H0731 300 mg is a weak inhibitor of CYP2C9. ABI-H0731 300 mg has been shown to decrease the concentration of midazolam by ~30% after daily administration for 7 days. The mechanism of midazolam decrease doesn't appear to be CYP3A4 mediated induction, however, the mechanism remains unknown.

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins over-the-counter medications, and supplements. Concomitant medications are discouraged. 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. To the extent possible, medications with narrow therapeutic indices should be avoided. Since ABI-H0731 is a weak inhibitor of CYP2C9, concomitant use with warfarin and other CYP2C9 substrates should be avoided. Concomitant prescription medications, over-the-counter medications, and supplements will be reported in the eCRF from the date informed consent is obtained to 30 days

following the last dose of all study drug(s), with the exception of medications used to manage HBV in subjects who restarted on HBV therapy. Medications for management of HBV, including NrtI therapy, should be captured until the last follow-up visit.

6.6.1 Prohibited Concomitant Therapy

As the potential for DDIs between ABI-H0731 and other compounds has not yet been fully evaluated, 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.

6.6.2 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.

7.0 STUDY CONDUCT

7.1 Study Procedures by Time Point

Refer to the Schedule of Assessments in Section 4.8.

7.1.1 Premature Discontinuation from Treatment

If an individual subject is not satisfactorily tolerating study drug treatment in the judgment of the Investigator, then, in consultation with the Sponsor, that subject may be discontinued from treatment. Subjects may also be discontinued from treatment if they are significantly noncompliant with study drug, develop resistance to treatment, or show evidence of virologic nonresponse to the treatment (refer to Section 4.4).

Discontinuation from treatment does not mean discontinuation from the study. Subjects who discontinue treatment prematurely, should immediately undergo the assessments listed for the Premature Termination Visit (Table 4-4) and then continue with scheduled follow-up assessments as per Premature Termination Visits (Visit Numbers F-U 1, F-U 2, and F-U 3) listed in Table 4-4. 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 adverse finding will be reported as an AE.

In this study, subjects will be closely monitored for any evidence of worsening hepatic function or evidence of dermatologic AEs. See Section 4.7.1 for specific management of confirmed toxicities that may require early discontinuation. Specific guidance on management and the data to be collected at the time of study intervention discontinuation are described below.

7.1.2 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.

8.0 DESCRIPTION OF STUDY PROCEDURES

8.1 Efficacy Assessments

To provide an assessment of the rate of SVR and other evidence of the effect of ABI-H0731, this study will evaluate treatment-related changes in serum HBsAg, serum HBeAg, and serum ALT levels. Additionally, antibodies to HBeAg and HBsAg, HBV DNA, pgRNA, HBcrAg, and the genetic assessment of HBV variants may be assessed.

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 pgRNA 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 the proportion of subjects with SVR at 24 weeks off treatment. Samples will be collected as outlined in Section 4.8.

8.1.2 Secondary and Exploratory Efficacy Assessments

Blood samples for the assessment of secondary and exploratory efficacy endpoints will be collected as described in Section 4.8. Subjects will have the following samples collected:

- Quantitative/qualitative HBsAg and HBeAg levels (qualitative to be performed if quantitative Ag is below the limit of quantification
- HBsAb and HBeAb
- HBV DNA
- HBV pgRNA
- HBcrAg
- Samples for exploratory viral research
- Pharmacokinetic (PK) sample for ABI-H0731 and SOC NrtI

HBV resistance testing, using exploratory research samples, will be performed on subjects whose on-treatment HBV DNA increases by≥1 $\log_{10}$ IU/ml from on-treatment nadir. Resistance testing may also be performed on subjects who do not respond to treatment (<0.5 $\log_{10}$ HBV DNA for ≥3 consecutive study visits at least 4 weeks apart).

8.2 Safety Assessments

For AEs, see Section 9.0.

For SAEs, see Section10.0.

8.2.1 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the timepoints indicated in the Schedule of Assessments (Refer to Section 4.8) The clinical laboratory assessments are listed in Table 8-1.

Table 8-1 Clinical Laboratory Tests

Panel	Tests
Clinical chemistries	Blood glucose levels, serum or plasma electrolytes (sodium, potassium, chloride, bicarbonate), calcium, creatine kinase, 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
Liver panel	ALT, AST, total bilirubin, (reflex direct and indirect bilirubin if Total bilirubin is abnormal), serum albumin, INR, creatine kinase
Hematology	Complete blood counts: hemoglobin, hematocrit, red blood cell 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
Pregnancy tests	Females of child-bearing potential only; urine pregnancy test (if positive, confirmatory blood test is required). A positive result disqualifies the subject for study treatment
Urine drug	Amphetamine/methamphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine metabolite, ecstasy, ethanol, opiates, phencyclidine, and propoxyphene. Note: If cannabinoids are not illegal in the subject's locale, cannabinoids are not exclusionary
Antibodies	HCVAb, HDVAb, HAV IgM, HEV IgM

Abbreviations: ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; GGT=gamma-glutamyl transpeptidase; HAV=hepatitis A virus; HCV=hepatitis C virus; HDV=hepatitis D virus; HEV=hepatitis E virus; IgM=immunoglobulin M; INR=International Normalized Ratio; LDH=lactate dehydrogenase; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; 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 of this OLE study should be recorded as an AE (Section 9.0).

8.2.2 Other Safety Assessments

Other safety assessments include the following:

- Vital Signs
- 12-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 AE (Section 9.0)

- Concomitant medications, including supplements and over-the-counter medications, will be recorded

8.3 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 review of data.

9.0 ADVERSE EVENTS

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

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

9.1 Documenting Adverse Events

AEs/SAEs will be monitored throughout the entire study. Investigators will ask the subject at each visit if they have experienced any untoward effects since the last study visit. All AEs will be 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.

With the exception of "liver flares" or toxicity associated with potential viral rebound, AEs will be recorded from the time written informed consent is signed until 4 weeks following cessation of the last dose of treatment with the study drug (ABI-H0731). Any "flare" or viral rebound related toxicity should be recorded as an AE until the end of follow-up. For SAE documentation see Section 10.2.

9.2 Assessment of Intensity

The severity of each AE and laboratory abnormality is to be assessed by the Investigator according to the DAIDS Toxicity Grading of Laboratory Abnormalities and Clinical Adverse Events(APPENDIX II), which grades the severity of clinical AEs and laboratory abnormalities in a four-category system.

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

9.3 Assessment of Causality

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. Each AE must be recorded in the source 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 AE 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 AE, 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 AE 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 AE 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 (de-challenge) was clinically reasonable.

9.4 Expectedness

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

9.5 Adverse Events of Special Interest

AEs 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 AEs 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 AE 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 AE or SAE 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 AEs and SAEs 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. Subjects who have an ongoing AE or SAE at the end of the trial will be followed until resolution or stabilization of the AE or SAE.

9.8 Pregnancy

Pregnancy in itself is not regarded as an AE 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 SAEs** (Section 10.2). Female subjects should report any pregnancies that occur during the study treatment period and up to 4 weeks after the last dose of study drug.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to the CRO.

Pregnancies among female partners of male subjects that occur during the study treatment period and up to 4 weeks after the last dose of study drug will also be reported and be requested for consent to be followed for outcome.

10.0 SERIOUS ADVERSE EVENT

10.1 Definition of Serious Adverse Event

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

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

Definition of Terms

Life-threatening: An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything, untoward is reported during the procedure, that occurrence must be reported as an AE, either “serious” or “nonserious” according to the usual criteria.

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

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

10.2 Reporting Serious Adverse Events

SAEs will be recorded from the time written informed consent is signed until the last study visit. All SAEs 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 [redacted]:

North America:
[redacted]

Europe/Asia/Pacific:
[redacted]

The initial report should be promptly followed by detailed, written reports, which will include copies of relevant hospital case reports, autopsy reports, and other documents when requested and applicable. This additional information will be requested, if necessary, by the responsible monitor within 5 days of receipt of the alert report. This is to ensure that the initial reporting of SAEs is made to 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 SAEs as required. It will be the responsibility of the individual Investigator(s) to inform any local IRBs/IECs of SAEs as required. Correspondence with the IRB(s)/IEC(s) relating to the reporting of SAEs will be retained in the study file.

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 AE unless it results in untoward medical effects. Any AE associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills the criteria of an SAE, then the event should be reported to the Sponsor or CRO within 24 hours after the site learns of the event.

11.0 STATISTICS

11.1 Statistical Hypotheses

Efficacy and safety data will be presented descriptively. No formal hypotheses will be tested although inferential statistics such as p-values and confidence intervals may be used descriptively to assess magnitude of effect.

11.2 Sample Size

It is anticipated that approximately 100 subjects will enroll in this trial and receive study medication. The sample size for this study is not based on statistical considerations and will be determined by optional enrollment from other ABI-H0731 studies. All subjects who complete a prior study of ABI-H0731 and have not discontinued treatment (such as subjects in Study ABI-H0731-201, Study ABI-H0731-202) will have the opportunity to enroll in this study. All subjects will receive open-label ABI-H0731 and continue their same SOC NrtI that was administered in the prior study.

11.3 Analysis Populations

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

- Full Analysis Set (FAS) Population: The FAS population will be defined as all subjects who received any amount of study medication and who had at least one post-dose assessment for the endpoint of interest.

- Per-Protocol Population: The PP population will include subjects who are at least 80% compliant with scheduled study drug dosing, and who have no major protocol violations.

- Safety Population: The safety population will include all subjects who received at least one dose of study drug.

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

- Pharmacokinetic Population 2 (PK2): The PK2 population will include all subjects in the safety population who have SOC NrtI 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 and efficacy analyses is given below. An 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 or safety observations in this study (eg, pre-treatment ALT level, HBsAg level, HBeAg level, ethnicity, gender). These and other subgroup analyses will be further defined in the SAP.

11.4.2 Efficacy Endpoints

Unless otherwise is stated, the evaluation of all efficacy endpoints will be based on the FAS population.

11.4.2.1 Primary Endpoint

The primary efficacy endpoint is the proportion of subjects who meet the definition of "SVR" at 24 weeks off treatment. The SVR rate will be computed as the number of subjects who achieved SVR divided by the total number of subjects in the FAS eligible to stop treatment. The SVR rate and corresponding 95% confidence interval (CI) will be presented.

11.4.2.2 Secondary and Exploratory Endpoints

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

For continuous variables, such as change from Baseline in $\log_{10}$ serum HBeAg and HBsAg values at each timepoint, descriptive statistics will be used and will include the number, mean, standard deviation, median, minimum, and maximum and, where appropriate, a 95% CI.

For categorical variables, such as subjects with 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), summary statistics will include number and percent who meet the endpoint criteria.

Trough PK levels of ABI-H0731 and trough PK levels of NrtI will be analyzed descriptively.

11.4.3 Analysis of Safety

The safety parameters to be assessed are described in Section 8.2, Section 9.0, and Section 10.0. Displays for safety results will utilize descriptive statistics. No formal hypothesis testing of safety data is planned.

AEs summaries will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) body system and preferred term, for each treatment group. Summaries will include all AEs, AEs considered possibly or probably related to treatment, Grade ≥3 (or severe) AEs, and SAEs. All AEs will be listed by subject. Any AEs leading to premature discontinuation from the study intervention and serious treatment-emergent AEs 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 study treatment will be summarized descriptively and will include data from the double-blinded parent studies in order to evaluate the effects of total time on combination therapy with efficacy endpoints. Compliance on study treatment from the time of study enrollment in the long-term extension study 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.

Exposure to treatment will be summarized descriptively by treatment group.

Any changes in physical examination findings noted after Day 1 of the OLE study will be summarized in tabular form, by treatment group.

11.5 Interim Analysis

Data will be monitored in an ongoing, unblinded fashion in this open-label study. Descriptive statistics and graphical displays may be provided at various times during the study to ensure patient safety and acceptable risk-benefit. No formal hypothesis testing will be done. As such, no type I error rate is specified for this study and no adjustment will be made to any type I error rate to account for multiple comparisons, endpoints or subgroups.

11.6 Final Study Report

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

12.0 ETHICS AND RESPONSIBILITIES

12.1 Good Clinical Practice

This study will be conducted in compliance with IRB/IEC and current ICH and GCP (E6) Guidelines; Title 21 Part 56 of the US Code of Federal Regulations (CFR) relating to IRBs/IECs and GCP as described in the US FDA CFR (21 CFR § 50, 56, 312); applicable ICH 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 and Ongoing Safety Reviews

No data monitoring committee is planned. The Sponsor will oversee safety in this open-label study. Individual AEs and aggregated safety will be reviewed in ongoing fashion for this open-label study to assess safety of the study medications. No formal stopping rules are provided for the trial; however, the Sponsor reserves the right to terminate the study at any time if potential safety or futility concerns arise during the study.

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 to the IRB/IEC. 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, subject 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.

13.0 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 AEs 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 its designee 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 their designee 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 their designee 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 Site 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.

14.0 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 business 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.

15.0 STUDY REPORT AND PUBLICATIONS

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

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

16.0 STUDY DISCONTINUATION

Both the Sponsor and the Investigator reserve the right to terminate the study overall and at any 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.

17.0 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 the subject's enrollment 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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19.0 APPENDICES

19.1 APPENDIX I – Names of Study Personnel

Sponsor:	Assembly Biosciences 331 Oyster Point Blvd., Fourth Floor South San Francisco, CA 94080 USA Phone: +1-833-509-4583
Sponsor Medical Monitor:	[redacted]
Sponsor Clinical Research Lead:	[redacted]
CRO Medical Monitors:	[redacted]

19.2 APPENDIX II – Adverse Event Intensity Grading

The severity of each AE and laboratory abnormality is to be assessed by the Investigator according to the table below.

TOXICITY GRADING OF LABORATORY ABNORMALITIES AND CLINICAL ADVERSE EVENTS. PUBLISH DATE: JULY 2017 (Version 2.1, corrected version)

Adapted from the US National Institutes of Health (Division of AIDS) Table for Grading Severity of Adult Adverse Experiences (July 2017).

MAJOR CLINICAL CONDITIONS

Cardiovascular

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)*	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 (eg, malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	N/A	N/A	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (eg, hypoxemia) OR Intervention indicated (eg, oxygen)	Life-threatening consequences OR Urgent intervention indicated (eg, vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	N/A	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
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[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 (eg, Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	N/A	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (eg, pulmonary embolism, thrombus)

Abbreviations: ECG=electrocardiogram; IV=intravenous; N/A=not applicable; RBC=red blood cell.
[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	N/A	N/A
Bruising	Localized to one area	Localized to more than one area	Generalized	N/A
Cellulitis	N/A	Non-parenteral treatment indicated (eg, oral antibiotics, antifungals, antivirals)	IV treatment indicated (eg, IV antibiotics, antifungals, antivirals)	Life-threatening consequences (eg, sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	N/A	N/A
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	N/A	N/A
Petechiae	Localized to one area	Localized to more than one area	Generalized	N/A
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	N/A
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

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
				OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

Abbreviations: IV=intravenous; N/A=not applicable.
[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 (eg, ketoacidosis, hyperosmolar nonketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	N/A
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 (eg, 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 (eg, 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	N/A

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
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	N/A

Abbreviations: N/A=not applicable.
[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 (eg, tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (eg, diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	N/A
Cholecystitis	N/A	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis, perforation)
Constipation	N/A	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over Baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over Baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Dysphagia or Odynophagia *Report only 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

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 (eg, 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 (eg, aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (<24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR Rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	N/A	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Perforation *(colon or rectum)*	N/A	N/A	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 (eg, perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	N/A	N/A
Vomiting	Transient or intermittent AND	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR	Life-threatening consequences (eg, hypotensive shock)

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
	No or minimal interference with oral intake		Aggressive rehydration indicated (eg, IV fluids)	

Abbreviations: IV=intravenous; N/A=not applicable.

Musculoskeletal

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Arthralgia	Joint pain causing no or minimal interference with usual social & 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	N/A	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	N/A	N/A	N/A
<30 years of age	BMD z-score -2 to -1	N/A	N/A	N/A
Osteoporosis [6] *≥30 years of age*	N/A	BMD t-score <2.5	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
<30 years of age	N/A	BMD z-score <2	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

Abbreviations: BMD=bone mineral density; N/A=not applicable.

[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	N/A	N/A	Transient ischemic attack	Cerebral vascular accident (eg, stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & 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

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

Abbreviations: CNS=central nervous system; N/A=not applicable.

Pregnancy, Puerperium, and Perinatal

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Stillbirth (report using mother's participant ID) *Report only one*	N/A	N/A	Fetal death occurring at ≥20 weeks gestation	N/A
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	N/A

Abbreviations: ID=identification; N/A=not applicable.
[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	N/A
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

Abbreviation: N/A=not applicable.

Respiratory

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70 to <80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to <70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & 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 (eg, CPAP, BPAP, intubation)

Abbreviations: BPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure.

Sensory

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Hearing Loss	N/A	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR Non-serviceable hearing (ie, >50 dB audiogram and <50% speech discrimination)
Tinnitus	Symptoms causing no or minimal interference with usual social & 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	N/A
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)

Abbreviation: N/A=not applicable.

Systemic

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	N/A
Cytokine Release Syndrome [8]	Mild signs and symptoms AND Therapy (ie, antibody infusion) interruption not indicated	Therapy (ie, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (eg, requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & 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 (nonaxillary 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

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (eg, antihistamines)	Severe signs and symptoms AND Higher-level intervention indicated (eg, steroids or IV fluids)	Life-threatening consequences (eg, requiring pressor or ventilator support)
Underweight[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)*	N/A	5 to <9% loss in body weight from Baseline	≥9 to <20% loss in body weight from Baseline	≥20% loss in body weight from Baseline OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)

Abbreviations: BMI=body mass index; IV=intravenous; N/A=not applicable; WHO=World Health Organization

[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	N/A	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Abbreviation: N/A=not applicable.

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 (eg, 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

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
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	N/A

Abbreviation: N/A=not applicable.
[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 (eg, signs and symptoms of liver failure)
Total Bilirubin, High	1.1 to <1.6×ULN	1.6 to <2.6×ULN	2.6 to <5.0×ULN	≥5.0 × ULN
Calcium, High (mg/dL; *mmol/L*)	10.6 to <11.5 *2.65 to <2.88*	11.5 to <12.5 *2.88 to <3.13*	12.5 to <13.5 *3.13 to <3.38*	≥13.5 *≥3.38*

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
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 × participants Baseline
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

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
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*	≤120 *≤120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to <10.0 *0.45 to <0.59*	10.0 to <12.0 *0.59 to <0.71*	12.0 to <15.0 *0.71 to <0.89*	≥15.0 *≥0.89*

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CKD=chronic kidney disease; DAIDS=Division of AIDS; eGFR=estimated glomerular filtration rate; LLN=lower limit of normal; MDRD=modification of diet in renal disease; N/A=not applicable; SGOT=serum glutamic-oxaloacetic transaminase; ULN= upper limit of normal.

*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 (ie, Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73 m^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*
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*

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life- Threatening
PT, High (not on anticoagulation therapy)	1.1 to <1.25×ULN	1.25 to <1.50×ULN	1.50 to <3.00×ULN	≥3.00 × ULN
WBC, Decreased (cells/mm^3; *cells/L*)	2,000 to 2,499 *2.000×10^9 to 2.499×10^9*	1,500 to 1,999 *1.500×10^9 to 1.999×10^9*	1,000 to 1,499 *1.000×10^9 to 1.499×10^9*	<1,000 *<1.000×10^9*

Abbreviations: ANC=absolute neutrophil count; HIV=human immunodeficiency virus; LLN=lower limit of normal; PT=prothrombin time; PTT=partial thromboplastin time; ULN=upper limit of normal; WBC=white blood cell.

[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 (ie, 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	N/A
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Abbreviations: N/A=not applicable; RBC=red blood cell.