CLINICAL RESEARCH PROTOCOL

PROTOCOL TITLE: A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled, Multiple Cohort Study Evaluating ABI-H2158-Containing Regimens in Chronic Hepatitis B Infection

STUDY NUMBER: ABI-H2158-201

DRUG: ABI-H2158

REFERENCE NUMBERS: [redacted]

SPONSOR: Assembly Biosciences
331 Oyster Point Boulevard, 4th Floor
South San Francisco, California 94080, USA
(833) 509-4583

PROTOCOL: Amendment 2, 14 December 2020

Amendment 1, 12 February 2020

ORIGINAL: 20 December 2019

CONFIDENTIALITY STATEMENT

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title:	A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled, Multiple Cohort Study Evaluating ABI-H2158-Containing Regimens in Chronic Hepatitis B Infection
Protocol Number:	ABI-H2158-201
Protocol Date:	Amendment 2, 14 December 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 (AEs), relating to treatment with the investigational product.

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

INVESTIGATOR STATEMENT

Protocol Title:	A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled, Multiple Cohort Study Evaluating ABI-H2158-Containing Regimens in Chronic Hepatitis B Infection
Protocol Number:	ABI-H2158-201
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I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as described herein, in accordance with Good Clinical Practice (GCP) as set out in the current International Council for Harmonisation (ICH) guidelines (E6) and other applicable national or local requirements and will make a reasonable effort to complete the study within the time designated.

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

Principal Investigator Signature:	
Print Name:	
Date:	

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

Protocol Amendment Summary of Changes Table

1 SYNOPSIS

Protocol Number:	ABI-H2158-201
Title:	A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled, Multiple Cohort Study Evaluating ABI-H2158-Containing Regimens in Chronic Hepatitis B Infection
Phase:	2a
Number of Subjects:	Approximately 80
Study Duration:	Up to 45 days for Screening, 72 weeks of treatment, and 24 weeks of follow-up
Rationale:	Chronic hepatitis B infection (CHB) is a major cause of liver-related morbidity and mortality worldwide. ABI-H2158 is a direct acting antiviral agent targeting the hepatitis B virus (HBV) core protein. It is anticipated that ABI-H2158 administered in combination with entecavir (ETV), a standard of care (SOC) nucleos(t)ide analogue (NrtI), will be safe, reduce viral nucleic acid (ie, HBV DNA and HBV pre-genomic [pg] RNA) to a greater extent than ETV alone, which will lead to subsequent reductions in viral antigens (ie, HBeAg, HBcrAg, and HBsAg) in subjects with CHB. This study will explore the safety of the ABI-H2158+ETV combination and its antiviral activity as measured by effects on serum HBV DNA, HBV pgRNA, and HBV antigens.
Target Population:	Male or female subjects with CHB, 18 to 65 years of age, inclusive, with no evidence of cirrhosis or end-stage liver disease. Cohort 1 will enroll treatment-naïve subjects with HBeAg positive CHB. Cohort 2 will enroll treatment-naïve subjects with HBeAg negative CHB.
Test Product:	Active treatment: ABI-H2158 300 mg administered orally, once daily, in addition to ETV
Reference Product:	Placebo (PBO) treatment: ABI-H2158 matching PBO administered orally, once daily, in addition to ETV
Study Design:	This is a Phase 2a, multicenter, randomized, single-blind (ie, investigational site and subjects are blinded), PBO-controlled study, evaluating the safety, antiviral activity, and pharmacokinetics (PK) of ABI-H2158 administered in combination with ETV in subjects with CHB. Multiple parallel cohorts will be enrolled in the study. In Cohort 1 approximately 40 treatment-naïve subjects with HBeAg- positive CHB will be randomized 3:1 to receive investigational agent (300 mg ABI-H2158 [n=30] or matching PBO [n=10]) in combination with ETV for 72 weeks. In Cohort 2 approximately 40 treatment-naïve subjects with HBeAg negative CHB will be randomized 3:1 to receive investigational agent (300 mg ABI-H2158 [n=30] or matching PBO [n=10]) in combination with ETV for 72 weeks. Treatment assignments for Cohort 1 will be stratified by the HBV DNA level measured at the Screening visit (ie, $\geq$8.0 $\log_{10}$ IU/mL versus <8.0 $\log_{10}$ IU/mL) and for Cohort 2, subjects will be stratified by the HBV DNA level measured at the Screening visit (ie, $\geq$6.0 $\log_{10}$ IU/mL versus <6.0 $\log_{10}$ IU/mL). Safety, antiviral activity, and PK will be assessed during treatment and the 24-week follow-up period. During the follow-up period all subjects will remain on ETV.

Objectives:

Primary Objectives:

- To evaluate the safety and tolerability of ABI-H2158 when administered in combination with ETV in subjects with CHB
- To evaluate the effect of ABI-H2158 in reducing HBV DNA in subjects with CHB

Secondary Objectives:

- To evaluate the PK of ABI-H2158 and ETV in subjects with CHB
- To evaluate the effect of ABI-H2158 in reducing HBV pgRNA levels in subjects with CHB
- To evaluate the effect of ABI-H2158 in reducing HBV antigens (ie, HBeAg, HBcrAg and HBsAg) in subjects with CHB
- To evaluate the effect of ABI-H2158 on normalization of alanine aminotransferase (ALT) in subjects with abnormal ALT
- To evaluate the emergence of resistance to ABI-H2158 when administered in combination with ETV

Exploratory Objectives:

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

Primary Endpoint:

Primary Endpoints:

- The proportion of subjects with adverse events (AEs), premature treatment discontinuation, and abnormal laboratory results
- The change in mean $\log_{10}$ HBV DNA from Baseline to Week 24 for ABI-H2158+ETV and PBO+ETV

Secondary Endpoints:

Secondary Endpoints:

- Analysis of ABI-H2158 and ETV drug concentrations:
  - Trough levels and trough to peak ratios of ABI-H2158 on ABI-H2158+ETV
  - Trough levels and trough to peak ratios of ETV on ABI-H2158+ETV and PBO+ETV
- The change in mean $\log_{10}$ HBV DNA for ABI-H2158+ETV and PBO+ETV at each timepoint
- The change in mean $\log_{10}$ HBV pgRNA from Baseline to Week 24 and at each timepoint for ABI-H2158+ETV and PBO+ETV
- The proportion of subjects with a reduction in HBV DNA below the assay lower limit of quantitation (LLOQ) for ABI-H2158+ETV and PBO+ETV at each timepoint
- The proportion of subjects with a reduction in HBV pgRNA below the assay LLOQ for ABI-H2158+ETV and PBO+ETV at each timepoint
- The change in serum viral antigens (ie, HBeAg, HBcrAg and HBsAg) on ABI-H2158+ETV and PBO+ETV at each timepoint
- The proportion of subjects with abnormal ALT at Baseline who have normal ALT at Week 24 and at each timepoint on ABI-H2158+ETV and PBO+ETV

- The incidence of HBV variants with reduced susceptibility to ABI-H2158

Exploratory Endpoints:

Exploratory Endpoints:

- The proportion of subjects with loss (defined as below LLOQ) or decline in HBsAg, HBcrAg, HBeAg or new biomarkers on ABI-H2158+ETV and PBO+ETV at each timepoint
- The proportion of subjects with HBsAg seroconversion (loss of HBsAg and appearance of HBsAb) or HBeAg seroconversion (loss of HBeAg and appearance of HBeAb) on ABI-H2158+ETV and PBO+ETV at each timepoint for applicable cohort
- The proportion of subjects whose HBV DNA is below the assay LLOQ and "target not detected" on ABI-H2158+ETV and PBO+ETV at each timepoint
- Pharmacogenomic correlations may be performed with clinical or virologic outcomes for subjects who provide an additional informed consent. Known gene variants and PK and/or safety of ABI-H2158 and its metabolites may be evaluated.

Statistical Methods:

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

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

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

Key Eligibility:

Inclusion Criteria

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

1. Willing and able to provide informed consent
2. Male or female between the ages 18 and 65 years (inclusive)
3. Female subjects must be non-pregnant and have a negative serum pregnancy test at Screening and a negative urine pregnancy test predose on Day 1
4. Chronic hepatitis B infection, defined as HBV infection for ≥6 months documented, for example, by at least two measurements of HBsAg positivity and/or detectable HBV DNA ≥6 months apart (inclusive of Screening). For subjects without clear documentation of CHB, anti-hepatitis B core antigen immunoglobulin M (IgM) antibody to the HBV core antigen (HBcAb) must be negative at Screening to exclude acute HBV infection
5. Body mass index (BMI) 18 to 36 kg/m^2 and a minimum body weight of 45 kg (inclusive)
6. HBV DNA $\geq 2 \times 10^5$ IU/mL for subjects who are treatment naïve HBeAg positive
7. HBV DNA $\geq 2 \times 10^3$ IU/mL for subjects who are treatment naïve HBeAg negative

8. HBsAg >1000 IU/mL at Screening for subjects who are treatment naïve HBeAg positive
9. Lack of cirrhosis or advanced liver disease as documented by the following:
    - Liver biopsy results of METAVIR F0-F2 (absence of bridging fibrosis or cirrhosis) within 1 year of Screening

      OR

    - Fasting FibroScan ≤8 kPa within 3 months of Screening (including Screening visit) or other Sponsor-approved hepatic imaging study (hepatic magnetic resonance elastography [MRE]) within 6 months of Screening indicating lack of cirrhosis or advanced liver disease (F0-F2 or equivalent)

    Subjects with a fasting FibroScan >8 kPa and ≤10 kPa are excluded from study participation unless a liver biopsy within the 1 year before Day 1 confirms the absence of bridging fibrosis and cirrhosis. Subjects with a FibroScan >10 kPa are excluded from study participation

    If results from both liver biopsy and FibroScan are available, then the result reporting the most advanced liver disease will be used to determine eligibility for the study
10. Agreement to comply with protocol-specified contraceptive requirements (Refer to Appendix 3)
11. Agreement to abstain 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 from screening until end of the study
12. In good general health, except for CHB
13. Have the ability to take oral medication and, in the opinion of the Investigator, be willing to adhere to study treatment.
14. Candidate for treatment with ETV and have no contraindications as described in the approved product labelling

Exclusion Criteria

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

1. Prior treatment for CHB; specifically
    a. lamivudine, telbivudine or adefovir (any duration)
    b. NrtI treatment for >4 weeks
    c. HBV core inhibitors (any duration)
    d. Previous treatment with an investigational agent for HBV infection
2. Co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis E virus (HEV), or hepatitis D virus (HDV)

3. Females who are lactating, or wish to become pregnant during the course of the study
4. History or evidence of advanced liver disease or hepatic decompensation (including jaundice, ascites, portal hypertension, gastrointestinal bleeding esophageal varices, hepatic encephalopathy,) at any time prior to, or at the time of Screening
5. History of persistent alcohol abuse (alcohol consumption exceeding 2 standard drinks per day on average [1 standard drink = 10 grams of alcohol]) or illicit drug abuse within 3 years before Screening
6. Clinically significant cardiac or pulmonary disease, chronic or recurrent renal or urinary tract disease, liver disease other than CHB, 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, ongoing infection or other medical conditions requiring frequent medical management or pharmacologic or surgical treatment that in the opinion of the Investigator or the Sponsor makes the subject unsuitable for study participation
7. History of hepatocellular carcinoma (HCC)
8. A history of malignancy other than HCC unless the subject's malignancy has been in complete remission off chemotherapy and without additional medical or surgical interventions during the 3 years before Screening
9. Poorly controlled or unstable hypertension; or sustained systolic blood pressure (BP) ≥160 mmHg or <90 mmHg, or diastolic BP >95 mmHg or <50 mmHg at Screening
10. History or presence of electrocardiogram (ECG) abnormalities deemed clinically significant including:
    a. Personal or family history of prolonged QT syndrome or family history of sudden death
    b. QTcF >450 msec (males) or >470 msec (females) or <300 msec at Screening or Day 1 visit
    c. ECG with QRS and/or T-wave judged to be unfavorable for a consistently accurate QT measurement as judged by the Investigator at Screening
    d. Evidence of atrial fibrillation, atrial flutter, complete bundle branch block, Wolff-Parkinson-White Syndrome, or cardiac pacemaker at Screening or Day 1 visit
11. History of hypersensitivity or idiosyncratic reaction to any components or excipients of the investigational drug or PBO formulation
12. History of any significant food or drug-related allergic reactions such as, anaphylaxis, Stevens-Johnson syndrome, or urticaria
13. The following exclusionary laboratory results at Screening:
    a. Platelet count <100,000/mm^3

b. Albumin < lower limit of normal (LLN)

c. Total bilirubin >1.2 × upper limit of normal (ULN) unless known Gilbert's syndrome; subjects with Gilbert's syndrome are eligible for study participation if the direct bilirubin is within the normal range

d. Direct bilirubin >1.2 × ULN

e. ALT >5 × ULN

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

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

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

i. Serum hemoglobin A1c (HbA1c) >6.5%

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

14. Subjects receiving prohibited concomitant medications, grapefruit (whole fruit and juice), herbal or over-the-counter medications (Section 6.4.1) within 7 days or 5 half-lives (if known), whichever is longer, prior to administration of the first dose of study drug and for the duration of the study period
15. Participation in another clinical trial of a drug or device whereby the last investigational drug/device administration is within 60 days or 5 half-lives prior to the first study drug administration, whichever is longer
16. Donated or lost >500 mL of blood within 2 months prior to Screening, or plasma donation within 7 days prior to Screening

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
AFP	alpha fetoprotein
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma-concentration curve
AUC_{0-24}	area under the plasma-concentration curve from time 0 to 24 hours postdose
AUC_{0-inf}	area under the plasma-concentration curve from time 0 extrapolated to infinity
BMI	body mass index
cccDNA	covalently closed circular DNA
CFR	Code of Federal Regulations
CHB	chronic hepatitis B infection
CI	core inhibitor
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{24hr}	trough plasma concentration
C_{max}	maximum plasma concentration
Cp	[HBV] core protein
CRO	Contract Research Organization
CSR	Clinical Study Report
CYP	cytochrome P450
DAIDS	Division of AIDS
DDI	drug-drug interaction
DRC	Data Review Committee
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
ETV	entecavir
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAV	hepatitis A virus
HbA1c	hemoglobin A1c
HBcAb	antibody to the HBV core antigen
HBcrAg	hepatitis B core-related antigen
HBeAb	HBeAg antibody
HBeAg	hepatitis B “e” antigen
HBsAb	HBsAg antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

Abbreviation	Definition
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse effect level
NrtI	nucleos(t)ide reverse transcriptase inhibitor of the HBV polymerase; also called nucleos(t)ide analogues or nucleos(t)ides
OC	oral contraceptive
pgRNA	[HBV] pre-genomic RNA
PHH	primary human hepatocytes
PK	pharmacokinetic(s)
PBO	placebo
QD	once daily
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
Sponsor	Assembly Biosciences
SVR	sustained virologic response
$t_{1/2}$	terminal elimination half-life
TEAE	treatment emergent adverse event
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
WHO	World Health Organization

2 INTRODUCTION

2.1 Background

Worldwide >240 million people are chronically infected with the hepatitis B virus (HBV), and chronic hepatitis B infection (CHB) is a major cause of severe liver morbidity and liver-related mortality (WHO 2019). An estimated 600,000 to 1 million people die each year due to cirrhosis and hepatocellular carcinoma (HCC), the end-stage complications of CHB (Colvin 2010, El-Serag 2012, EASL 2017, WHO 2019). The global prevalence of chronic HBV infection shows wide geographic variation, with a prevalence of more than 8% of people in highly endemic regions (eg, East Asia and equatorial Africa), 2% to 7% of people in moderately endemic regions (eg, the Middle East and the Indian subcontinent), and less than 2% in locales of low endemicity (eg, North America and Europe) (Schweitzer 2015, WHO 2015). Despite broad implementation of HBV vaccination programs, new cases of HBV infection are still common. The World Health Organization (WHO) estimates that there are over 4 million acute HBV infections worldwide each year (WHO 2015).

The clinical stages of HBV represent different risks for ongoing liver injury depending on the degree of HBV replication and individuals' concurrent immune responses to HBV infection (Yim 2006, Hoofnagle 2007, Lok 2009, Sorrell 2009, EASL 2012, Pungpapong 2013, Gish 2015). The standard virologic and serologic markers for HBV infection include HBV deoxyribonucleic acid (DNA), antibody to HBsAg (HBsAb), hepatitis B "e" antigen (HBeAg), antibody to HBeAg (HBeAb), and in almost all patients, antibody to the HBV core antigen (HBcAb). More recently, HBV pre-genomic RNA (pgRNA) and HBV core-related antigen (HBcrAg) have also been used as markers of infection. Historically, treatment goals include prevention of HBV-related liver injury through suppression of HBV DNA to low levels, achievement of HBeAg loss and seroconversion, and loss of HBsAg and seroconversion. A transition to an HBsAg negative, minimally replicative state is rare but usually durable and, if it precedes the development of cirrhosis and HCC, is associated with improved long-term clinical outcomes (EASL 2012). As such, HBsAg seroconversion is considered a "functional cure" and a potential endpoint for HBV therapy. However, as HBsAg is derived from both covalently closed circular DNA (cccDNA) as well as integrated HBV DNA, sustained undetectable HBV DNA without HBsAg loss after stopping treatment may be considered as an intermediate goal (Cornberg 2019).

Currently, there are 2 clinically accepted treatment options for CHB, interferon alfa (IFNα) and nucleos(t)ide (NrtI) reverse transcriptase inhibitors of the HBV polymerase. Of these agents, oral NrtIs are the more broadly used, and have demonstrated success in achieving and maintaining viral suppression in most patients (Lampertico 2012). However, there is a proportion of individuals who do not achieve complete viral suppression on current NrtI therapy to levels below quantitation on commercial assays, and there is evidence that those who are below quantitation still have infectious HBV (Agarwal 2018, Burdette 2019). Importantly, the level of HBV replication as measured by HBV DNA in those treated with and without virologic response has been predictive of progression of liver disease and risk of hepatocellular carcinoma (Papatheodoridis 2015, EASL 2017). Further, despite suppression of HBV DNA for extended periods of time, the template for ongoing viral replication, cccDNA, is not eliminated in most patients. As a result, off-treatment sustained virologic responses (SVRs) with currently approved agents are rare, necessitating long-term chronic suppressive treatment approaches. There is a need for improved, novel HBV therapies that further reduce HBV replication and produce a substantially higher rate of therapeutic responses that will be durable post-treatment, which are predicted to afford improved long-term patient outcomes, ie, reduction of HBV-associated hepatic inflammation leading to reduced morbidity and mortality from end-stage liver disease and HCC.

ABI-H2158 is a novel, second-generation HBV core inhibitor (CI) discovered by Assembly Biosciences, which is being developed as a potential therapeutic agent for the treatment of CHB. ABI-H2158 inhibits HBV replication by interfering with essential functions of the HBV core protein (Cp), and therefore inhibits HBV replication by different mechanisms than NrtIs or IFNα. Thus, inhibition of HBV Cp functions by ABI-H2158, when used in combination with currently approved HBV antivirals, or other investigational HBV therapies may offer the potential to improve therapy for chronic HBV infection and potentially provide patients with enhanced rates of SVR following a finite treatment period.

2.2 ABI-H2158

2.2.1 General Information

General information concerning ABI-H2158 is described in the Investigator's Brochure (IB).

2.2.2 Preclinical Pharmacology and Toxicology

Refer to the ABI-H2158 IB for a complete summary of the nonclinical and toxicology studies performed to date. In addition to those described in the IB, chronic toxicity studies have also been completed in rat and monkey for 6 and 9 months, respectively, of once-daily (QD) dosing. A detailed review of the findings from these two studies are provided in Sections 2.2.2.1 and 2.2.2.2 below.

2.2.2.1 Rat 6-Month Oral Toxicity Study with 21-Day Recovery

The objectives of this Good Laboratory Practice (GLP) study were to evaluate the toxicity and toxicokinetic profile of ABI-H2158 and its desmethyl metabolite, AB017213, following once daily oral gavage administration of ABI-H2158 to male and female Sprague-Dawley rats for 6 months, and to assess reversibility of any observed effects over a 21-day dose-free recovery period. Dose levels of ABI-H2158 were: 0 mg/kg/day (Group 1; vehicle control), 25 mg/kg/day (Group 2; Low), 75 mg/kg/day (Group 3; Mid) and 225 mg/kg/day (Group 4; High). The dosing volume was 7.5 mL/kg. Main study groups of animals contained 15/sex/group, and recovery groups (Low, Mid and High dose levels) contained 5/sex/group. Toxicokinetic groups consisted of 3/sex/group in the vehicle control and 9/sex/group in the drug treatment groups.

There were no ABI-H2158-related effects on clinical observations, body weight, food consumption, ophthalmology, coagulation, or urine parameters. Occasional, sporadic decreases of small magnitude in body weight gain were observed that were considered ABI-H2158-related and non-adverse.

ABI-H2158-related increases in serum glucose and serum alanine aminotransferase (ALT) levels were noted in both males and females on Days 44 and 46, respectively. The statistically significant increases in glucose were dose-dependent, present in both sexes and ranged from 11%-25% in the males and 10%-25% in the females. Statistically significantly elevated ALT levels were noted in both males (37%) and females (24%) dosed with 225 mg/kg. These changes were not considered adverse due to small magnitudes of change and lack of persistence over time.

ABI-H2158-related microscopic findings were observed in the liver. Centrilobular hepatocyte vacuolation was frequent in males, and uncommon in females. In males it was minimal to moderate, and occurred in all groups administered ABI-H2158, but in females it was minimal and was observed at ≥75 mg/kg. In males, incidence and severity were greater at ≥75 mg/kg as compared to 25 mg/kg. At

recovery termination, centrilobular hepatocyte vacuolation was still present, but was limited to males at ≥75 mg/kg and was less severe (few mild and no moderate instances), indicating reversibility.

ABI-H2158-related organ weight changes were observed for the kidneys and adrenals. Statistically significant increased absolute and relative kidney weights were observed for females administered 225 mg/kg ABI-H2158. Increased kidney weights correlated microscopically with vacuolation of medullary tubules (minimal to moderate). At completion of the recovery period vacuoles were not evident in the kidneys, indicating recovery. Statistically significant increased absolute and relative adrenal gland weights were observed for females administered 225 mg/kg ABI-H2158; however, there was not a microscopic correlate. These findings in kidneys, adrenals and livers were not considered adverse.

Oral administration of ABI-H2158 (25, 75 or 225 mg/kg/day) to male and female Sprague-Dawley rats for 182 days was well tolerated with no observed adverse effects. Therefore, the no-observed-adverse effect level (NOAEL) for male and female rats was considered to be 225 mg/kg/day, the highest dose administered in this study. The corresponding Day 182 maximum plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC) from time 0 to 24-hour postdose (AUC_{0-24}) exposures ranged from 95.4 (males) and 214 (females) µg/mL and 1,500 (males) and 2,800 (females) hr*µg/mL, respectively, which exceed the exposures obtained at the NOAEL dose in the 14-day rat study.

2.2.2.2 Cynomolgus Monkey 9-Month Oral Toxicity Study with 28-Day Recovery

The objectives of this GLP study were to evaluate the toxicity and toxicokinetic profile of ABI-H2158 and its desmethyl metabolite, AB017213, in male and female Cynomolgus monkeys after once daily oral gavage administration of ABI-H2158 for 9 months, and to assess reversibility of any effects over a 28-day dose-free period. Study animals (6/sex/group in Groups 1 and 4, and 4/sex/group in Groups 2 and 3) were assigned to four groups and treated with 0 mg/kg/day (Group 1; vehicle control), 20/15 mg/kg/day (Group 2), 60/30 mg/kg/day (Group 3) and 120 mg/kg/day (Group 4) of ABI-H2158. The dosing volume was 4 mL/kg. Two animals/sex/group from Groups 1 and 4 were used for assessment of reversibility. The initial dose levels administered to Groups 2 and 3 (20 and 60 mg/kg/day, respectively) were decreased to 15 and 30 mg/kg/day, respectively, on Day 21/19 (males/females) in order to increase the separation in exposure between these groups and the high dose group (120 mg/kg/day).

There was no ABI-H2158-related mortality or moribundity during this study. One Group 4 male was found dead on Day 192; the cause of death was pulmonary edema and inflammation in the lungs which was suggestive of aspiration pneumonia, likely related to the dosing procedure.

There were no ABI-H2158-related effects on food consumption, ophthalmology, electrocardiography, hematology, coagulation, urinalysis, or organ weights. There were no ABI-H2158-related macroscopic or microscopic findings.

Non-adverse ABI-H2158-related clinical abnormalities were limited to an increased incidence of non-severe hair loss for the Group 3 and 4 males when compared to the controls. Non-adverse ABI-H2158-related effects on body weight were limited to slightly lower mean body weights for the Group 3 and 4 females vs. controls at completion of dosing. At the initiation of the dosing period, mean body weights for the Group 3 and 4 females were 2 and 0.4%, respectively, lower than that of the controls, while at the end of the dosing period, they were both 10% lower than that of the controls.

Non-adverse ABI-H2158-related effects on serum chemistry parameters were limited to slightly lower serum lactate dehydrogenase (LDH) levels for the Group 2-4 males and females throughout the dosing period. Mean LDH values were comparable to control group values by the end of the recovery period. The LDH changes were not considered adverse due to the low magnitude, lack of microscopic correlates and reversibility.

Once daily oral (gavage) administration of ABI-H2158 to male and female Cynomolgus monkeys at dose levels of 0, 20/15, 60/30 or 120 mg/kg/day for 273 consecutive days was well tolerated. Non-adverse, ABI-H2158-related findings were limited to increased incidence of non-severe hair loss for the 60/30 and 120 mg/kg/day males, slightly lower body weights for the 60/30 and 120 mg/kg/day females vs controls, and lower serum lactate dehydrogenase levels for all ABI-H2158-treated male and female groups. Following daily oral doses for 9-months, the NOAEL for ABI-H2158 was considered to be 120 mg/kg/day for male and female Cynomolgus monkeys, a dose level yielding Day 273 mean plasma C_{max} of 14.4-19.8 µg/mL (average 17.1 µg/mL) and AUC_{0-24} of 182-223 hr*µg/mL (average of 203 hr*µg/mL). These exposures are approximately twice the average exposures at the NOAEL dose in the 14-day monkey study (C_{max} of 9.6 µg/mL and AUC_{0-24} of 86.6 hr*µg/mL), and approximately 20%-25% of the exposure levels that caused acute liver toxicity and morbidity at the 100 mg dose in the 14-day monkey study (C_{max} and AUC_{0-24} of 62.6 µg/mL and 1,035 hr*µg/mL).

2.2.3 Clinical Studies with ABI-H2158

Clinical experience with ABI-H2158 consists of 3 ongoing early-phase clinical studies: (1) a Phase 1a/1b dose-ranging study in healthy subjects and treatment-naïve subjects with CHB, ABI-H2158-101; (2) a relative bioavailability study in healthy subjects, ABI-H2158-102; (3) a drug-drug interaction (DDI) study in healthy subjects, ABI-H2158-103. Summary information on these studies is provided below with more complete and updated information described in the current version of the ABI-H2158 IB.

2.2.3.1 ABI-H2158-101

ABI-H2158-101 is an ongoing Phase 1a/b, randomized, single- and multiple-dose, dose escalation, partially -blinded, PBO-controlled study in healthy subjects and subjects with CHB. This study is the first-in-human and first-in-patient study of ABI-H2158 and is being conducted in 3 parts. Part 1 was designed to assess the dose-related safety, tolerability, and pharmacokinetic (PK) profile of ABI-H2158 and its metabolite following single ascending doses (SADs) in healthy subjects, and to assess the effect of food on ABI-H2158. Part 2 was designed to assess multiple-ascending dosing (MAD) in healthy subjects. Part 3 is designed to assess the antiviral activity of ABI-H2158 as monotherapy in subjects with CHB.

Part 1 and Part 2 of the study have been completed. In Part 1, there were 5 dose cohorts with 8 subjects each evaluating single oral doses of 5 mg to 500 mg of ABI-H2158. In each cohort, 6 subjects were randomized to receive ABI-H2158 and 2 were randomized to PBO. In Part 2, there was a single dose cohort which evaluated multiple doses of ABI-H2158 of 300 mg administered for 10 days. In this cohort, 6 subjects were randomized to receive ABI-H2158 and 2 subjects were randomized to PBO. A summary of the safety and PK data from Parts 1 and 2 is summarized below; refer to the ABI--H2158 IB for more details. Part 3 is currently ongoing. Each cohort includes 9 subjects: 7 subjects randomized to receive ABI-H2158 and 2 randomized to PBO. At this time, treatment has been completed in two cohorts, 100 mg once daily (QD; Cohort 1) and 300 mg QD (Cohort 2) administered for 14 days. Cohort 3

evaluating 500 mg QD is currently ongoing. Available safety, and antiviral activity data are summarized below.

2.2.3.1.1 Parts 1 and 2: Safety in Healthy Subjects

The final, unblinded safety data are available for Parts 1 and 2 in which 48 healthy subjects were enrolled, 36 of whom received ABI-2158 and 12 of whom received PBO. Across the groups, study drugs were generally well tolerated. No subjects discontinued treatment due to adverse events (AEs). Overall, 11% (4 of 36 subjects) who received ABI-H2158 and 17% (2 of 12 subjects) who received PBO experienced treatment-emergent AEs. All the AEs were Grade 1. The AE reported by more than 2 subjects who received ABI-H2158 was headache (3 subjects [8%] who received ABI-H2158 and 1 subject [8%] who received PBO). There have been no serious adverse events (SAEs) or deaths. Most laboratory abnormalities were Grade 1. No subjects experienced graded elevations in ALT. There have been no Grade 3 or 4 laboratory abnormalities.

2.2.3.1.2 Part 1: Single Dose Pharmacokinetics in Healthy Subjects

ABI-H2158 was rapidly absorbed with median time to maximum plasma concentration (T_{max}) ranging between 1 and 4 hours. The extent of exposure as measured by the AUC, as well as the trough plasma concentration (C24hr) increased proportionally with the dose. The Cmax, however, was slightly less than dose proportional. Summary PK parameters following single oral dose administration are summarized in Table 1. In general, the overall systemic exposure to ABI-H2158 was well-characterized with sampling time capturing more than 95% of the AUC at all dose levels except for the lowest dose, which was greater than 85%. The PK of ABI-H2158 appears to be linear with similar terminal elimination half-life (t1/2), CL/F, and Vz/F (data not shown) across dose levels, suggesting there are no saturable processes involved within this exposure range.

Five of the 6 subjects that received ABI-H2158 100 mg in the fasted cohort returned to receive ABI-H2158 100 mg in the fed state. ABI-H2158 was administered 30 minutes after the start of a high-fat breakfast in Period 2. No evidence of a significant food effect was seen on the PK profile of ABI-H2158 (Table 1).

Table 1: Summary of ABI-H2158 Pharmacokinetic Parameters Following Single Oral Doses

Parameters	5 mg fasting	25 mg fasting	100 mg fasting	100 mg fed	300 mg fasting	500 mg fasting
AUC_{0-24} (hr*µg/mL)	1.25 (32.7%)	5.80 (21.2%)	22.3 (31.8%)	25.2 (11.7%)	41.6 (35.5%)	85.9 (43.8%)
AUC_{0-inf} (hr* µg/mL)	1.51 (40.6%)	8.00 (30.3%)	31.8 (35.9%)	37.5 (20.9%)	65.0 (36.1%)	133 (57.7%)
C_{max} (µg/mL)	0.169 (29.6%)	0.544 (33.0%)	1.93 (31.7%)	2.01 (10.5%)	3.632 (29.4%)	6.48 (37.1%)
T_{max} (hr)	1 (0.5, 2)	1.5 (1, 3)	1 (1, 2)	2 (1, 4)	2.5 (1, 4)	4 (2, 5)
C_{24hr} (µg/mL)	0.0209 (47.7%)	0.114 (38.2%)	0.464 (45.1%)	0.542 (29.7%)	0.938 (37.9%)	2.09 (70.8%)
$t_{1/2}$ (hr)	9.8 (2.9)	12.9 (2.9)	14.4 (2.3)	16.1 (4.5)	20.7 (7.3)	16.0 (4.3)

AUC_{0-24}: Area under the plasma-concentration curve from time 0 to 24 hours postdose; C_{24hr}: trough plasma concentration; C_{max}: maximum plasma concentration; $t_{1/2}$: terminal elimination half-life; T_{max}: time to C_{max}

Geometric mean (Geometric CV%) are presented for AUCs, C_{max}, and C_{24hr}; Median (min, max) are presented for T_{max}; Mean (SD) are presented for $t_{1/2}$.

2.2.3.1.3 Part 2: Multiple Dose Pharmacokinetics in Healthy Subjects

The PK of ABI-H2158 on Day 1 was consistent with the PK observed in the SAD part of the study, at the same dose level. Accumulation ratios between 1.5 and 2 suggest an effective accumulation half-life ranging from 16 to 24 hours, in line with the observed $t_{1/2}$ in the SAD part of the study, suggesting that the PK of ABI-H2158 is not time dependent. The summary noncompartmental PK parameters obtained for ABI-H2158 in plasma are presented in Table 2.

Table 2: Summary of ABI-H2158 Pharmacokinetic Parameters Following Single and Multiple 300 mg Once-daily Oral Doses of ABI-H2158

Parameters	ABI-H2158		
	Day 1	Day 10	AR
$AUC_{0\text{-}24hr}$ (hr*µg/mL)	33.3 (83.4%)	55.1 (102%)	1.7 (0.6)
C_{max} (µg /mL)	2.84 (88.8%)	4.21 (92.0%)	1.5 (0.4)
T_{max} (hr)	2.5 (1, 4)	2 (2, 4)	-
C_{24hr} (µg/mL)	0.757 (90.5%)	1.38 (126%)	2.0 (0.9)
$t_{1/2}$ (hr)	14.3 (2.5)	18.4 (6.2)	-

AR: accumulation ratio Day 10/Day 1; $AUC_{0\text{-}24}$: Area under the plasma-concentration curve from time 0 to 24 hours postdose; $AUC_{0\text{-}inf}$: Area under the plasma-concentration curve from time 0 extrapolated to infinity; C_{24hr}: trough plasma concentration; C_{max}: maximum plasma concentration; $t_{1/2}$: terminal elimination half-life; T_{max}: time to C_{max}

Geometric mean and CV% are presented for AUCs, C_{max}, and C_{24hr}; Median (min, max) are presented for T_{max}; Mean (SD) are presented for $t_{1/2}$.

[a] Half-life was not determined since the terminal elimination phase was not sampled.

2.2.3.1.4 Part 3: Safety and Antiviral Activity in Subjects with CHB

Preliminary, unblinded safety data are available for Cohorts 1 and 2 in Part 3. In each cohort, 7 subjects were randomized to receive ABI-H2158 (100 mg in Cohort 1 and 300 mg in Cohort 2) and 2 were randomized to PBO. Across these cohorts the study drug has been generally well tolerated. No subjects have discontinued treatment due to AEs. Overall, 36% (5 of 14 subjects) who received ABI-H2158 and 50% (2 of 4 subjects) who received PBO have experienced treatment-emergent AEs (Table 3). All AEs have been Grade 1, except for one Grade 2 AE. The only AEs reported by more than 1 subject who received ABI-H2158 was headache (2 subjects). There have been no Grade 3 or 4 AEs, no SAEs, and no deaths.

Table 3: Treatment-emergent Adverse Events in Subjects with Chronic Hepatitis B Infection (Cohorts 1 and 2, Part 3; preliminary)

System Order Class Preferred Term	Placebo (N=4) n (%)	ABI-H2158 100 mg (N=7) n (%)	ABI-H2158 300 mg (N=7) n (%)
Any adverse event	2 (50.0)	3 (42.9)	2 (28.6)
Metabolism and Nutrition Disorder Grade 2 Hypertriglyceridaemia	0	0	1 (14.3) 1 (14.3)
Nervous System Disorders Grade 1 Headache Grade 1 Dizziness	1 (25.0) 1 (25.0) 0	2 (28.6) 1 (14.3) 1 (14.3)	1 (14.3) 1 (14.3) 0
Gastrointestinal Disorders Grade 1 Abdominal Pain Upper	0	1 (14.3) 1 (14.3)	0

System Order Class **Preferred Term**	**Placebo** **(N=4)** **n (%)**	**ABI-H2158** **100 mg** **(N=7)** **n (%)**	**ABI-H2158** **300 mg** **(N=7)** **n (%)**
Skin and Subcutaneous Tissue Disorders Grade 1 Rash	0	1 (14.3) 1 (14.3)	0
General Disorders Grade 1 Fatigue	0	1 (14.3) 1 (14.3)	0
Investigations Grade 1 ALT Increase	1 (25.0) 1 (25.0)	0	0

ALT: alanine aminotransferase.

Twelve subjects (86%) who received ABI-H2158 and 3 subjects (75%) who received PBO have experienced graded laboratory abnormalities, most of which have been Grade 1 or 2 (Table 4). Four subjects (29%) who received ABI-H2158 and 1 subject (25%) who received PBO have experienced Grade 1 elevations in ALT; the ALT elevation observed by the subject who received PBO was reported as a Grade 1 AE considered possibly related to study drug by the Investigator. There was 1 Grade 3 elevated cholesterol experienced by a subject who received ABI-H2158, which was not reported as an AE. There have been no Grade 4 laboratory abnormalities.

Table 4: Treatment-emergent Laboratory Abnormalities by Grade in Subjects with CHB (Cohorts 1 and 2, Part 3; preliminary)

Laboratory Abnormality	Grade	Placebo (N=4) n (%)	ABI-H2158 100 mg (N=7) n (%)	ABI-H2158 300 mg (N=7) n (%)
Any	All	3 (75)	7 (100)	5 (71)
Elevated AST	1	1 (25)	2 (28.6)	1 (14.3)
Elevated ALT	1	1 (25)	2 (28.6)	2 (28.6)
Amylase	1	0	2 (28.6)	0
Cholesterol	1 2 3	1 (25) 0 0	0 0 1 (14.3)	1 (14.3) 2 (28.6) 0
Creatinine	1	1 (25)	0	0
Calcium	1	0	1 (14.3)	0
Uric acid	1	1 (25)	1 (14.3)	0
Glucose	1	0	1 (14.3)	0
Triglycerides	1 2	0 0	1 (14.3) 1 (14.3)	1 (14.3) 0

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Treatment-emergent laboratory abnormality is defined as worsened toxicity grade (DAIDS, July 2017, version 2.1) compared with Baseline.

Preliminary antiviral data are available for Cohorts 1 and 2. The ABI-H2158 100 mg QD dose demonstrated potent antiviral activity as reflected by mean 2.3 $\log_{10}$ and 2.1 $\log_{10}$ reductions in HBV DNA and HBV pgRNA, respectively, over the 14-day dosing interval. In Cohort 2 evaluating ABI-H2158 300 mg QD, the mean reductions in HBV DNA and HBV pgRNA were 2.5 $\log_{10}$ IU/mL and 2.12 $\log_{10}$ IU/mL over the 14-day dosing interval. At this time, a third dose group evaluating ABI-H2158 500 mg QD is currently ongoing.

2.2.3.2 ABI-H2158-102

ABI-H2158-102 is an ongoing Phase 1, randomized, open-label, 3-way crossover study, designed to evaluate the relative bioavailability of a new 100 mg ABI-H2158 tablet (Test) formulation relative to a prior 25 mg ABI-H2158 tablet (Reference) formulation, and to determine the effect of food on the PK of the ABI-H2158 100 mg film-coated tablets in healthy subjects. One cohort of 15 healthy subjects was randomly assigned in 3 groups of 5 subjects each to receive single doses of the Test and Reference tablet formulations under fasting conditions and Test tablet formulation under fed conditions during 3 sequential dosing periods. Each dose period was separated by a minimum 7-day washout period (inclusive). The Test formulation is intended for use in the current ABI-H2158-201 study in subjects with CHB.

Preliminary safety data are available, and the study drug has been generally well tolerated by the 15 subjects enrolled in the study. No subjects have discontinued treatment due to AEs. Overall, 27%

(4 of 15 subjects) enrolled have experienced treatment-emergent AEs, most of which were Grade 1 or Grade 2 and no AE was reported by more than 1 subject. One subject experienced elevated ALT and aspartate aminotransferase (AST) which were reported as Grade 1 AEs considered unlikely related to study drug by the Investigator. One subject experienced Grade 3 laboratory abnormalities of elevated triglycerides and elevated low-density lipoprotein which were reported as Grade 3 AEs and were considered unlikely related to study drug by the Investigator. No Grade 4 AEs or SAEs have been reported and no deaths have occurred. No other clinically significant laboratory abnormalities have been reported as AEs.

Interim PK estimates of AUC and C_{max} of ABI-H2158 were analyzed using analysis of variance with sequence, period, and treatment as fixed effects and subject within sequence as the random effect on naturally logarithmic-transformed values. Geometric least squares mean ratios of the 300 mg reference group (12 x 25 mg tablets) relative to the 300 mg test group (3 x 100 mg tablet) for C_{max} and AUC from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$) are 94.9 (100,600 and 106,000 ng/mL, respectively) and 80.4 (4720 and 5870 ng*hr/mL, respectively). Exposures after administration of the 300 mg test (3 x 100 mg tablets) in the fed state after a high-fat meal increased approximately 40% as measured by $AUC_{0\text{-}inf}$ (143,000 ng*hr/mL) and approximately 30% for C_{max} (6160 ng/mL).

2.2.3.3 ABI-H2158-103

ABI-H2158-103 is an ongoing Phase 1, single-center, open-label, fixed-sequence, drug-drug interaction study, split into 5 cohorts each planned to enroll 16 healthy subjects. The primary objective is to evaluate the effect of multiple-dose itraconazole (Cohort 1), rifampin (Cohort 2), and esomeprazole (Cohort 3) on the single-dose PK of ABI-H2158, and the effect of multiple-dose ABI-H2158 on the single-dose PK of midazolam (Cohort 4) and the multiple-dose PK of an oral contraceptive (OC) consisting of ethinyl estradiol and levonorgestrel (Cohort 5). Cohorts may be run consecutively or concurrently, with each subject only allowed to participate in one of the following cohorts:

- Cohort 1: Single oral doses of ABI-H2158 on Days 1 and 9; QD oral doses of itraconazole on Days 6 through 13
- Cohort 2: Single oral doses of ABI-H2158 on Days 1 and 12; QD oral doses of rifampin on Days 6 through 16
- Cohort 3: Single oral doses of ABI-H2158 on Days 1 and 11; QD oral doses of esomeprazole on Days 6 through 11
- Cohort 4: Single oral doses of midazolam on Days 1 and 11; QD oral doses of ABI-H2158 on Days 2 through 11
- Cohort 5/Cycle 1: QD oral doses of active OC (ethinyl estradiol/levonorgestrel) on Days 1 through 21 and PBO OC on Days 22 through 28
- Cohort 5/Cycle 2: QD oral doses of active OC (ethinyl estradiol/levonorgestrel) on Days 1 through 21, PBO OC on Days 22 through 26, and QD oral doses of ABI-H2158 on Days 11 through 24

In each cohort, serial PK blood samples will be collected before dosing and at specified timepoints after dosing as indicated in the PK sampling time schedules for each cohort.

Preliminary safety data are available, and the study drug has been generally well tolerated by the 77 subjects that have received study drug to date. No subjects have discontinued treatment due to AEs. Overall, 32% (25 of 77 subjects) enrolled have experienced treatment-emergent AEs, all of which were Grade 1 or 2. To date, the most frequently reported AEs were headache (6 subjects) and nausea (5 subjects). No Grade 3 or 4 AEs or SAEs have been reported and no deaths have occurred. No clinically significant laboratory abnormalities have been reported.

Coadministration of itraconazole (CYP3A inhibitor probe) and ABI-H2158 resulted in markedly increased ABI-H2158 exposure. Coadministration of rifampin (CYP3A, CYP2C19, CYP2C9, CYP2B6, CYP2C8 inducer and OATP inhibitor probe) and ABI-H2158 resulted in markedly decreased ABI-H2158 exposure. Coadministration of 300 mg ABI-H2158 with the proton pump inhibitor/stomach pH modifier (neutralizes stomach acidity), esomeprazole (40 mg), resulted in markedly decreased ABI-H2158 exposure.

Coadministration of 300 mg ABI-H2158 with midazolam (2 mg) (CYP3A substrate probe) resulted in mildly decreased midazolam exposure.

Coadministration of 300 mg ABI-H2158 with OC ethinyl estradiol 30 mcg/levonorgestrel 150 mcg (CYP3A4 substrate probe) resulted in minimally reduced ethinyl estradiol and levonorgestrel exposure.

2.3 Study Rationale

Current approved therapies are generally safe, well tolerated and effective at suppressing viral replication in most patients but do not eliminate viral replication and SVR is rare. Novel therapeutic modalities are required to improve chronic suppressive regimens and support finite duration therapy. The HBV Cp is involved in multiple steps in the HBV life cycle, including both viral replication and the establishment of new cccDNA (Levrero 2009, Belloni 2013). Inhibition of HBV Cp represents a novel therapeutic strategy for the treatment of CHB (Yang 2019). Interim analyses of Phase 2a studies, demonstrated subjects treated with the first-generation CI ABI-H0731 with a NrtI compared to those treated with NrtI alone achieved faster and deeper declines in HBV DNA and in HBV pgRNA, a surrogate marker of cccDNA. In these studies, the observed declines in HBV pgRNA correlated with reductions in HBeAg, HBcrAg, and HBsAg (Sulkowski 2019).

ABI-H2158 is a second-generation CI being developed by Assembly Biosciences. In vitro, ABI-H2158 has demonstrated potent antiviral activity as measured by inhibition of HBV DNA with a 50% effective concentration (EC_{50}) of 22 nM in HepAD38 cells and 41 nM in primary human hepatocytes (PHH). In the PHH infected cells, the EC_{50s} for inhibition of HBV pgRNA, HBeAg, and HBsAg production were 216 nM, 204 nM, and 160 nM, respectively. ABI-H2158 is currently being evaluated as monotherapy in a Phase 1b clinical study (ABI-H2158-101) in treatment-naïve subjects with HBeAg positive CHB (Section 2.2.3.1). In the initial dose group tested (100 mg ABI-H2158 QD), the mean declines in HBV DNA and HBV pgRNA from Baseline to Day 15 were 2.3 $\log_{10}$ IU/mL (range 1.7, -3.0) and 2.1 $\log_{10}$ IU/mL (range 1.5, -2.7), respectively. At the 300 mg QD dose level, the mean declines in HBV DNA and HBV pgRNA from Baseline to Day 15 were 2.5 $\log_{10}$ IU/mL (range 0.8, -3.3) and 2.12 $\log_{10}$ IU/mL (range 1.4, 2.6). At this time, a third dose group evaluating ABI-H2158 500 mg QD is currently ongoing.

Based on these data, the addition of ABI-H2158 to NrtI therapy may improve treatment responses compared with NrtI alone. It is anticipated that the addition of ABI-H2158 to entecavir (ETV) will be well tolerated and increase the rate and extent of decline in HBV DNA and HBV pgRNA. Furthermore,

ABI-H2158 may prevent the establishment of cccDNA more completely than ETV alone, resulting in a corresponding decline in HBV antigens reflective of cccDNA transcription (eg, HBeAg and HBcrAg). This study will explore the safety of the ABI-H2158+ETV combination in subjects with CHB and evaluate the antiviral activity as measured by the effects on HBV nucleic acids and HBV antigens.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

- To evaluate the safety and tolerability of ABI-H2158 when administered in combination with ETV in subjects with CHB
- To evaluate the effect of ABI-H2158 in reducing HBV DNA in subjects with CHB

3.1.2 Secondary Objectives

- To evaluate the PK of ABI-H2158 and ETV in subjects with CHB
- To evaluate the effect of ABI-H2158 in reducing HBV pgRNA levels in subjects with CHB
- To evaluate the effect of ABI-H2158 in reducing HBV antigens (ie, HBeAg, HBcrAg, and HBsAg) in subjects with CHB
- To evaluate the effect of ABI-H2158 on normalization of ALT in subjects with abnormal ALT
- To evaluate the emergence of resistance to ABI-H2158 when administered in combination with ETV

3.1.3 Exploratory Objectives

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

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoints are:

- The proportion of subjects with AEs, premature treatment discontinuation, and abnormal laboratory results
- The change in mean $\log_{10}$ HBV DNA from Baseline to Week 24 for ABI-H2158+ETV and PBO+ETV

3.2.2 Secondary Endpoints

The secondary endpoints are:

- Analysis of ABI-H2158 and ETV drug concentrations:
    - Trough levels and trough to peak ratios of ABI-H2158 on ABI-H2158+ETV
    - Trough levels and trough to peak ratios of ETV on ABI-H2158+ETV and PBO+ETV
- The change in mean $\log_{10}$ HBV DNA for ABI-H2158+ETV and PBO+ETV at each timepoint
- The change in mean $\log_{10}$ HBV pgRNA from Baseline to Week 24 and at each timepoint for ABI-H2158+ETV and PBO+ETV
- The proportion of subjects with a reduction in HBV DNA below the assay lower limit of quantitation (LLOQ) for ABI-H2158+ETV and PBO+ETV at each timepoint
- The proportion of subjects with a reduction in HBV pgRNA below the assay LLOQ for ABI-H2158+ETV and PBO+ETV at each timepoint
- The change in serum viral antigens (ie, HBeAg, HBcrAg, and HBsAg) on ABI-H2158+ETV and PBO+ETV at each timepoint
- The proportion of subjects with abnormal ALT at Baseline who have normal ALT at Week 24 and at each timepoint on ABI-H2158+ETV and PBO+ETV
- The incidence of HBV variants with reduced susceptibility to ABI-H2158

3.2.3 Exploratory Endpoints

Exploratory endpoints will include:

- The proportion subjects with loss (defined as below LLOQ) or decline in HBsAg, HBcrAg, HBeAg or new biomarkers on ABI-2158+ETV and PBO+ETV at each timepoint
- The proportion of subjects with HBsAg seroconversion (loss of HBsAg and appearance of HBsAb) or HBeAg seroconversion (loss of HBeAg and appearance of HBeAb) on ABI-H2158+ETV and PBO+ETV at each timepoint for applicable cohort
- The proportion of subjects whose HBV DNA is below the assay LLOQ and “target not detected” on ABI-H2158+ETV and PBO+ETV at each timepoint
- Pharmacogenomic correlations may be performed with clinical or virologic outcomes for subjects who provide an additional informed consent. Known gene variants and PK and/or safety of ABI-H2158 and its metabolites may be evaluated

4 STUDY PLAN

4.1 Study Design

This Phase 2a, multicenter, randomized, single-blind (ie, investigational site and subjects are blinded), PBO-controlled study will assess the safety, antiviral activity, and PK of ABI-H2158 administered QD in combination with ETV in subjects with CHB. It is planned that multiple parallel cohorts will be enrolled in the study.

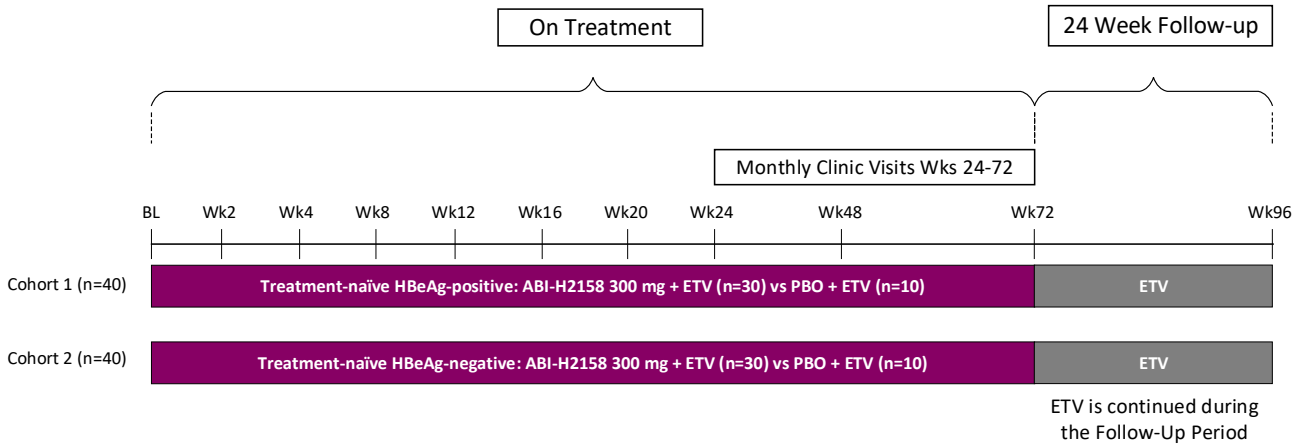
The first treatment cohort will evaluate ABI-H2158 300 mg in combination with ETV (n=30) compared to ETV alone (n=10) in treatment-naïve subjects with HBeAg positive CHB. The second treatment cohort will evaluate ABI-H2158 300 mg in combination with ETV (n=30) compared to ETV alone (n=10) in treatment-naïve subjects with HBeAg negative CHB. Additional cohorts may be added by future protocol amendment(s) based, in part, upon emergent safety, antiviral activity, and PK data from the ABI-H2158 regimens evaluated in the ongoing Phase 1b study ABI-H2158-101 (Section 2.2.3.1).

In Cohort 1, subjects will be randomized in a 3:1 ratio to receive 300 mg ABI-H2158+ETV (n=30) or matching PBO+ETV (n=10) for 72 weeks (Figure 1). Treatment assignments will be stratified by the HBV DNA level measured at the Screening visit (ie, $\geq$8.0 $\log_{10}$ IU/mL versus <8.0 $\log_{10}$ IU/mL). After completing treatment at Week 72, or following premature treatment discontinuation, all subjects will enter a 24-week follow-up period. During the follow-up period all subjects will remain on ETV and undergo the follow-up assessments described in Section 7.5. After completing the 24-week follow-up period, all subjects will resume management by their treating physician in accordance with local standard of care.

In Cohort 2, subjects will be randomized in a 3:1 ratio to receive 300 mg ABI-H2158+ETV (n=30) or matching PBO+ETV (n=10) for 72 weeks (Figure 1). Treatment assignments will be stratified by the HBV DNA level measured at the Screening visit (ie, $\geq$6.0 $\log_{10}$ IU/mL versus <6.0 $\log_{10}$ IU/mL). After completing treatment at Week 72, or following premature treatment discontinuation, all subjects will enter a 24-week follow-up period. During the follow-up period all subjects will remain on ETV and undergo the follow-up assessments described in Section 7.5. After completing the 24-week follow-up period, all subjects will resume management by their treating physician in accordance with local standard of care.

Additional cohort may be added to this study by future protocol amendment(s) in order to evaluate other doses of ABI-H2158, other ABI-H2158-containing regimens, and/or other subgroups of patients with CHB.

Figure 1: Study Overview



PBO: placebo; ETV: entecavir; HBeAg: hepatitis B "e" antigen; NrtI: nucleos(t)ide reverse transcriptase inhibitor of the hepatitis B virus polymerase.

The schedule of study procedures is described in Section 7 and presented in tabular form in Appendix 1. In addition to the routine medical oversight of the study, safety will also be closely monitored by an internal Data Review Committee (DRC). The team membership, roles and responsibilities and the frequency of analyses will be specified within the DRC Charter.

An assessment of PK data will be performed after all subjects in each cohort have completed their Week 4 study visit (or discontinued study without completing Week 4) in order to confirm the absence of important drug interactions between ABI-H2158 and ETV at steady state. A detailed review of the planned PK analyses in this study is provided in Section 7.8.8.

4.2 Dose Justification

In the ongoing Phase 1a/b clinical study ABI-H2158-101 (Section 2.2.3.1), single ABI-H2158 doses of 5 mg, 25 mg, 100 mg, and 300 mg QD were administered to healthy subjects (6 active, 2 PBO per dose level). Following completion of the SAD assessment, ABI-H2158 was subsequently administered as 300 mg QD to healthy subjects for 10 days (6 active, 2 PBO). Finally, in treatment-naïve subjects with HBeAg positive CHB, ABI-H2158 100 mg and 300 mg (7 active, 2 PBO per dose level) was administered once daily for 14 days. No safety signals have been observed in a cumulative data analysis. All dose levels were well tolerated and no subject prematurely discontinued treatment due to AEs. There were no Grade 3 or 4 AEs or SAEs. Treatment-emergent AEs did not increase in frequency or severity with either dose or duration. All treatment-emergent laboratory abnormalities were Grade 1 or Grade 2. Preliminary data indicates that there is a dose-dependent decrease in HBV DNA at doses of 100 mg and 300 mg daily in subjects with CHB (Section 2.3). The results of the following doses of ABI-H2158 (500 mg QD and 300 mg BID) for 14 days is described in the current version of the ABI-H2158 IB.

Interim analysis indicates exposures in the 100 mg and 300 mg CHB patient cohorts are similar to exposures in healthy volunteers. Mean Day 14 C_{max} values in the 100 mg and 300 mg CHB cohorts are 3390 and 8400 ng/mL, respectively, and mean Day 14 AUC_{0-24} are 46,100 and 112,000 ng*hr/mL, respectively.

It is anticipated that the 300 mg QD regimen will be safe and provide sufficient ABI-H2158 exposure to evaluate the antiviral effect in CHB subjects in this study, and within the dose range that has been well tolerated in healthy volunteers and subjects with CHB to date.

4.3 Study Treatment

This study is designed to evaluate the safety, PK, and antiviral activity of various ABI-H2158-containing regimens in subjects with CHB. These regimens will be evaluated in multiple treatment cohorts. Cohort 1 will enroll treatment-naïve subjects with HBeAg positive CHB and Cohort 2 will enroll treatment-naïve subjects with HBeAg negative CHB.

The study treatment (ABI-H2158 or PBO) will be administered in combination with a standard-of-care known effective therapy (ETV). All subjects will receive ABI-H2158 or matching PBO as three 100 mg tablets QD. ETV will be administered as a single 0.5 mg tablet QD. ABI-H2158, matching PBO, and ETV will be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal) at approximately the same time each day. Further information is provided in the ETV package insert. On study visit days, ABI-H2158 or PBO will be administered in the clinic; subjects will self-administer assigned treatment on all other days. On study visit days which include PK collection (Section 7), subjects will administer ABI-H2158 or PBO and ETV in the clinic except for Week 16 and Week 20. Study personnel will document the time of study drug administration in the subject's medical record. Subjects will be required to record the dates and times of each dose of study drug (ie, ABI-H2158 or PBO and ETV) they self-administer in the dosing diary provided to them at the Day 1 visit.

4.4 Duration of Treatment

All subjects will receive their randomized treatment assignment in a blinded manner for up to 72 weeks. After completing treatment at Week 72, or following premature treatment discontinuation, all subjects will enter a 24-week follow-up period. During the follow-up period all subjects will remain on ETV and undergo the follow-up assessments described in Section 7.5. After completing the 24-week follow-up period, all subjects will resume management by their treating physician in accordance with local standard of care.

5 POPULATION

5.1 Number of Subjects

A total of approximately 80 subjects (40 subjects per Cohorts 1 and 2) are planned.

5.2 Inclusion Criteria

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

1. Willing and able to provide informed consent
2. Male or female between the ages 18 and 65 years (inclusive)
3. Female subjects must be non-pregnant and have a negative serum pregnancy test at Screening and a negative urine pregnancy test predose on Day 1
4. Chronic HBV infection, defined as HBV infection for ≥6 months documented, for example, by at least two measurements of HBsAg positivity and/or detectable HBV DNA ≥6 months apart (inclusive of Screening). For subjects without clear documentation of CHB, anti-hepatitis B core antigen immunoglobulin M (IgM) antibody to the HBV core antigen (HBcAb) must be negative at Screening to exclude acute HBV infection
5. Body mass index (BMI) 18 to 36 kg/m^2 and a minimum body weight of 45 kg (inclusive)
6. HBV DNA ≥2 × 10^5 IU/mL for subjects who are treatment naïve HBeAg positive
7. HBV DNA ≥2 x 10^3 IU/mL for subjects who are treatment naïve HBeAg negative
8. HBsAg >1000 IU/mL at Screening for subjects who are treatment naïve HBeAg positive
9. Lack of cirrhosis or advanced liver disease as documented by the following:

    - Liver biopsy results of METAVIR F0-F2 (absence of bridging fibrosis or cirrhosis) within 1 year of Screening

      OR

    - Fasting FibroScan ≤8 kPa within 3 months of Screening (including Screening visit) or other Sponsor-approved hepatic imaging study (hepatic magnetic resonance elastography [MRE]) within 6 months of Screening indicating lack of cirrhosis or advanced liver disease (F0-F2 or equivalent)

    Subjects with a fasting FibroScan >8 kPa and ≤10 kPa are excluded from study participation unless a liver biopsy within the 1 year before Day 1 confirms the absence of bridging fibrosis and cirrhosis. Subjects with a FibroScan >10 kPa are excluded from study participation

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

10. Agreement to comply with protocol-specified contraceptive requirements (Refer to Appendix 3)
11. Agreement to abstain 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 from screening until end of the study
12. In good general health, except for CHB
13. Have the ability to take oral medication and, in the opinion of the Investigator, be willing to adhere to study treatment
14. Candidate for treatment with ETV and have no contraindications as described in the approved product labelling

5.3 Exclusion Criteria

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

1. Prior treatment for CHB; specifically
    a. lamivudine, telbivudine or adefovir (any duration)
    b. NrtI treatment for >4 weeks
    c. HBV core inhibitors (any duration)
    d. Previous treatment with an investigational agent for HBV infection
2. Co-infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis E virus (HEV), or hepatitis D virus (HDV)
3. Females who are lactating, or wish to become pregnant during the course of the study
4. History or evidence of advanced liver disease or hepatic decompensation (including jaundice, ascites, portal hypertension, gastrointestinal bleeding, esophageal varices, hepatic encephalopathy) at any time prior to, or at the time of Screening
5. History of persistent alcohol abuse (alcohol consumption exceeding 2 standard drinks per day on average [1 standard drink = 10 grams of alcohol]) or illicit drug abuse within 3 years of Screening
6. Clinically significant cardiac or pulmonary disease, chronic or recurrent renal or urinary tract disease, liver disease other than CHB, 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, ongoing infection or other medical conditions requiring frequent medical management or pharmacologic or surgical treatment that in the opinion of the Investigator or the Sponsor makes the subject unsuitable for study participation
7. History of HCC

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

9. Poorly controlled or unstable hypertension; or sustained systolic blood pressure (BP) ≥160 mmHg or <90 mmHg, or diastolic BP >95 mmHg or <50 mmHg at Screening

10. History or presence of electrocardiogram (ECG) abnormalities deemed clinically significant including:

    a. Personal or family history of prolonged QT syndrome or family history of sudden death

    b. QTcF >450 msec (males) or >470 msec (females) or <300 msec at Screening or Day 1 visit

    c. ECG with QRS and/or T-wave judged to be unfavorable for a consistently accurate QT measurement as judged by the Investigator at Screening

    d. Evidence of atrial fibrillation, atrial flutter, complete bundle branch block, Wolff-Parkinson-White Syndrome, or cardiac pacemaker at Screening or Day 1 visit

11. History of hypersensitivity or idiosyncratic reaction to any components or excipients of the investigational drug or PBO formulation

12. History of any significant food or drug-related reactions such as anaphylaxis, Stevens-Johnson syndrome, or urticaria

13. The following exclusionary laboratory results at Screening:

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

    b. Albumin < lower limit of normal (LLN)

    c. Total bilirubin >1.2 × upper limit of normal (ULN) unless known Gilbert's syndrome; subjects with Gilbert's syndrome are eligible for study participation if the direct bilirubin is within the normal range

    d. Direct bilirubin >1.2 × ULN

    e. ALT >5 × ULN

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

    g. International normalized ratio (INR) >1.5 × ULN

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

    i. Serum hemoglobin A1c (HbA1c) >6.5%

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

14. Subjects receiving prohibited concomitant medications, grapefruit (whole fruit and juice), herbal or over-the-counter medications (Section 6.4.1) within 7 days or 5 half-lives (if known), whichever is longer, prior to administration of the first dose of study drug and for the duration of the study period

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

16. Donated or lost >500 mL of blood within 2 months prior to Screening, or plasma donation within 7 days prior to Screening

5.4 Lifestyle Consideration

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 prohibited concomitant medication, grapefruit (whole fruit and juice), and over-the-counter concomitant medications (Section 6.4.1)
- Use dual effective birth control methods as outlined in Appendix 3.

5.5 Strategies for Retention and Safety

To reduce immediate risk to study subjects and minimize potential exposure to COVID-19, study visits may be conducted by a home health care provider in the home or agreed location 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 health care 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-19 restrictions. Blood and urine sampling for telemedicine visits may be drawn by a home health care provider.

6 INVESTIGATIONAL MEDICAL PRODUCTS

6.1 Randomization, Blinding and Treatment Codes

6.1.1 Randomization

Within each treatment cohort, randomization of eligible subjects to their respective treatment assignments will be performed centrally using an Interactive Response Technology (IRT) system. Following successful completion of Screening assessments and confirmation of subject eligibility, site personnel will enter the subject specific information in the IRT system and following acceptable completion of the procedure will receive a subject number and treatment assignment. For both Cohorts1 and 2, the IRT system will assign eligible subjects in a 3:1 ratio to receive 300 mg ABI-H2158+ETV (n=30) or matching PBO+ETV (n=10). Individual subject treatment assignments will be stratified according to the HBV DNA level measured at the Screening visit (ie, HBeAg positive ≥8.0 $\log_{10}$ IU/mL versus <8.0 $\log_{10}$ IU/mL, and HBeAg negative ≥6.0 $\log_{10}$ IU/mL versus <6.0 $\log_{10}$ IU/mL). Additional information on the use of the IRT is provided in the IRT user manual.

6.1.2 Blinding

Study subjects, Investigators and other site personnel administering the study drug, performing the clinical assessments and handling data on the study subjects, will be blinded to individual subject treatments assignments (ie, ABI-H2158+ETV therapy or PBO+ETV therapy) throughout the duration of the study. Since decreases in HBV pgRNA may unblind site personnel, HBV pgRNA results will not be provided to sites until study completion.

A limited internal Sponsor team will be unblinded to individual subjects' treatment assignments throughout the study to ensure timely analysis of any emergent safety/tolerability issues, and completion of the prespecified safety data reviews that will be performed by the Data Review Committee (DRC) (see Section 10.6). The unblinded individuals will be identified in the DRC Charter along with their specific roles and responsibilities. All other Sponsor personnel will remain blinded until completion of the study. The contract research organization's (CRO's) Medical Monitor may be unblinded to individual subjects' treatment assignments where required for assessment of emergent safety/tolerability issues.

6.1.2.1 Unblinding in Emergency Situations

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

The request for unblinding should include the protocol number, site number, subject identifier (eg, subject number), treating Investigator's contact info, a detailed reason for the unblinding, and date the

information is needed. All key correspondence between the requestor and Sponsor or CRO Medical Monitor should be saved in the Trial Master File (TMF).

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

6.2 Description and Handling of ABI-H2158 and Matching Placebo

6.2.1 Formulation

The ABI-H2158 drug product is a tablet formulation containing ABI-H2158 free base and standard pharmaceutical excipients including hypromellose, sodium lauryl sulfate, croscarmellose sodium, microcrystalline cellulose, lactose monohydrate, magnesium stearate, and Opadry film coating. ABI-H2158 100 mg tablets are manufactured according to Good Manufacturing Practice (GMP). Matching PBO tablets containing microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry film coating, are also manufactured according to GMP.

6.2.2 Packaging and Labeling

ABI-H2158 tablets and matching PBO tablets are packaged in high density polyethylene bottles fitted with child-resistant screw caps, induction sealed and shipped to sites under ambient conditions.

Study drug will be labelled in accordance with US FDA requirements and EU GMP Annex 13, Investigational Medicinal Products. Additional local labelling requirements in countries of study conduct will be incorporated in the study drug label(s).

6.2.3 Storage and Handling

Bottled drug product at the study sites should be stored at controlled room temperature (15°C to 30°C [59°F to 89°F]) in a secure, locked location at the sites, accessible only to designated study personnel.

6.3 Description and Handling of Entecavir

All subjects participating in this study will initiate and continue oral administration of 0.5 mg ETV tablets, QD, for the duration of the study. ETV tablets will either be provided by Assembly Biosciences or sourced locally by the site. Provision of ETV for the purposes of the study will be discussed and agreed with each investigational site prior to study conduct. Details describing the packaging, labelling, storage, and handling of ETV are described in the package insert.

6.4 Prior and Concomitant Medications

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins, medications, vaccinations, herbal preparations and supplements that is administered to a study subject during the conduct of the clinical trial. For randomized subjects, concomitant medications are discouraged, unless they are prescribed by the Investigator for treatment of an emergent medical event

occurring during the course of the study. No concomitant procedures will be performed during the study unless approved by the Investigator.

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

6.4.1 Prohibited Concomitant Therapy

As the potential for DDIs between ABI-H2158 and other compounds has not yet been fully evaluated, consumption of grapefruit (whole fruit and juice) is prohibited. Medications with narrow therapeutic indices should be avoided. In particular, medications metabolized by cytochrome P450 (CYP) isoenzymes 3A4, 2C8, and 2C19 should be avoided (see Appendix 4). Proton pump inhibitors, H-2 receptor blockers, antacids, or herbal medications intended to change stomach pH should not be taken with ABI-H2158. In addition, inducers and inhibitors of CYP3A4 should be avoided.

Provisions regarding concomitant medications described in the ETV product labeling must also be followed during the study.

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

6.5 Drug Accountability

Regulatory requirements stipulate accounting of all investigational drug received by the study site. Records of drug disposition must include the date received by the site, date administered, quantity administered, and the subject to whom study drug was administered. The Investigator is responsible for the accountability of all study drug at their site. This includes all used and unused study drug containers and unused study drug (ie, ABI-H2158, matching PBO, and ETV).

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 site and the location of study drug records at the site is appropriate.

Each time designated site personnel dispense study drug for a subject, he or she is to record the date dispensed, the quantity of study drug dispensed, and his or her initials. Study site personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused study drug. The site monitor will review the study drug accountability records during monitoring visits. The site pharmacist or designated staff member will keep accurate records of drug dispensation routinely during the study. Study drug dispensation is planned for Day 1 and at designated scheduled visits thereafter during the treatment period. ETV dispensation is also planned for designated scheduled visits during the follow-up period (Section 7; Appendix 1).

6.6 Study Drug Compliance

To monitor study drug compliance and to facilitate drug accountability at the study site, subjects will be required to record each dose of ABI-H2158 or PBO and ETV they take in a dosing diary provided to them at the Day 1 visit. Subjects will also be asked to return used bottles and any unused study drug at study visits for accountability and compliance assessment. Returned ABI-H2158 or PBO and ETV will be counted and reconciled against the diary entries by study site personnel preferably in the presence of the subject. Subjects who forget to return study drugs at a given visit will be asked to return them at the next study visit.

6.7 Return or Disposal of Study Drug

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

7 STUDY ASSESSMENTS AND PROCEDURES

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

7.1 Subject Enrollment and Treatment Assignment

Following provision of informed consent and completion of all Screening and Day 1 assessments, if a subject meets all protocol eligibility requirements the Investigator or designee will then randomize the subject using the IRT system described in Section 6.1.1. Protocol waivers will not be granted.

7.1.1 Screen Failures

Screen failures are defined as subjects who sign consent, are assigned a subject number, and are screened but subsequently never randomized to study treatment. Minimal information to be retained on all screen failures includes demography, screen failure details, eligibility criteria, and any SAE information.

Individuals who do not meet the protocol eligibility criteria for participation in this study (screen failure) may not be rescreened, however, a single retest for a laboratory parameter(s) is permitted if there is considered to be a specific issue related to the collection, shipping, processing or analysis of a sample (eg, receipt of a hemolyzed sample at the testing laboratory, or samples received by the testing laboratory outside of the acceptable temperature range).

Subjects who previously screen failed due to Inclusion Criteria 7 (HBeAg ≥500 IU/mL at Screening) under Protocol Amendment 1 may be rescreened for the study. The subject will be assigned a new subject number and will be required to be re-consented.

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

It is recommended, though not mandated, that invasive procedures, such as a liver biopsy (if required) are not conducted until it has been determined that the subject is broadly eligible for study participation. The following Screening assessments must be completed within 45 days of the scheduled Day 1 visit. Subjects who meet all study eligibility requirements but are not able to complete the Day 1 visit within the prespecified 45-day window, may be rescreened for the study.

- Obtain written informed consent
- Record demographics and medical history, including HBV history
- Liver staging (as required per inclusion criteria; ie, fasting FibroScan or liver biopsy)
- Measure height and body weight
- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated)
- 12-lead ECG
- Review of concomitant medications

- Review of AEs occurring after provision of informed consent
- Laboratory analyses (additional details are provided in the Laboratory Manual):
    - Safety Labs: Chemistry, hematology, coagulation, serum AFP, urinalysis, urine drug test, follicle-stimulating hormone (FSH) (all females regardless of fertility status), serum pregnancy test
    - Virology/Immunology: HBV DNA, HBsAg, HBeAg, HBsAb, HBeAb, sample for HBV sequencing and HBV nucleic acids, HIV Ab, HCV Ab, HDV Ab, hepatitis A virus (HAV) (IgM), HEV (IgM), HBcAb (for subjects without clear documentation of CHB)

7.3 Day 1

The following assessments must be completed at Day 1 prior to dosing:

- Update medical history, including HBV history
- Measure body weight
- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated)
- 12-lead ECG
- Review concomitant medications
- Confirm subject eligibility
- Complete randomization (IRT)
- Review AEs
- Laboratory analyses (additional details are provided in the Laboratory Manual):
    - Safety Labs: Chemistry, hematology, coagulation, urinalysis, urine drug test, serum and urine pregnancy test
    - Virology/Immunology: HBV genotype, HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb, HBeAb, sample for HBV sequencing and HBV nucleic acids
    - Pharmacogenomic Sample: Optional and only collected in subjects who provide additional informed consent
    - PK Samples: Predose samples for ABI-H2158 or PBO and ETV. Postdose samples for ABI-H2158 and ETV between 2 to and 4 hours following study drug administration. See Section 7.8.8 for additional information.

- Study drug dispensation
- Study drug administration (ABI-H2158 or PBO and ETV) during clinic visit. Provide dosing diary to the subject and record first dose administration

7.4 Study Weeks 2 Through 72

The following assessments are performed at Study Weeks 2, 4, 8, 12, 16, 20, 24 and then every 4 weeks thereafter through Week 72 (inclusive) unless otherwise indicated. A visit window of ±3 days is applied to each visit through Week 24 and ±5 days from Weeks 28 through 72:

- Measure body weight (Weeks 24, 48, and 72 only)
- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Complete physical examination (excluding breast and genitalia, unless indicated; Weeks 24, 48 and 72 only)
- Symptom-directed physical examination (Not at Weeks 24, 48 or 72)
- 12-lead ECG (Weeks 12, 24, 36, 48, 60 and 72 only)
- Review concomitant medications
- Review AEs
- Review dosing diary
- Assess drug accountability (not at Week 2)
- Study drug dispensation (not at Week 2; through Week 68 only for ABI-H2158 or PBO; and through Week 72 for ETV)
- Study drug administration (ABI-H2158 or PBO and ETV) during clinic visit (Weeks 2, 4, 8, 12, 24, 28, 48 and 72 only)
- Laboratory analyses (additional details are provided in the Laboratory Manual):
    - Safety Labs: Chemistry, hematology, coagulation (not at Week 2), urinalysis (not at week 2), and urine pregnancy test (if positive on dipstick, serum pregnancy test should be performed).
    - Virology/Immunology: HBV DNA, HBV pgRNA, HBsAg (not at Week 2), HBeAg (not at Week 2), HBcrAg (not at Week 2), HBsAb and HBeAb (Weeks 12, 24, 36, 48, 60, and 72 only), sample for HBV sequencing and HBV nucleic acids
    - PK Samples: Predose samples for ABI-H2158 or PBO and ETV on Weeks 4, 48, and 72 only. Samples for ABI-H2158 or PBO and ETV 30 min to 2 hours postdose on Weeks 2, 8, 12, 24, and 28. Samples for ABI-H2158 or PBO and ETV 4 to 6 hours postdose on Weeks 16 and 20 only). See Section 7.8.8, Table 6 for additional information.

7.5 Follow-up Assessments

All subjects who complete treatment per protocol or prematurely discontinue treatment will enter a 24-week follow-up period during which they will have the following assessments performed at 4, 8, 12, and 24 weeks (±5 days) after the last dose of ABI-H2158 or PBO unless otherwise stated:

- Measure body weight (24 Weeks post only)
- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Complete physical examination (24 Weeks post only)
- Symptom-directed physical examination (not at 24 Weeks post)
- 12-lead ECG (24 Weeks post only)
- Review concomitant medications
- Review AEs
- Assess drug accountability (for ETV)
- Study drug dispensation (for ETV, 4 Weeks post and 12 Weeks post only)
- Laboratory analyses (additional details are provided in the Laboratory Manual):
    - Safety Labs: Chemistry, hematology, coagulation, urinalysis (4 Weeks post, 12 Weeks post, and 24 Weeks post only), and urine pregnancy test (if positive on dipstick, serum pregnancy test should be performed [4 Weeks post only]).
    - Virology/Immunology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb and HBeAb (24 Weeks post only) sample for HBV sequencing and HBV nucleic acids
    - PK Sample: Sample for ETV can be collected at the same time with other labs (4 Weeks post only)

7.6 Unscheduled Visit

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

- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Symptom-directed physical examination
- Review concomitant medications

- Review AEs
- Laboratory analyses (additional details are provided in the Laboratory Manual):
  - Safety Labs: Chemistry, hematology, coagulation, urinalysis, urine drug test, and urine pregnancy test (if positive on dipstick, serum pregnancy test should be performed).
  - Virology/Immunology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, sample for HBV sequencing and HBV nucleic acids
  - PK Samples: Samples for ABI-H2158 or PBO and ETV can be collected at the same time with other labs. See Section 7.8.8 for additional information on PK sampling.

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

7.7 Premature Termination Visit

Should a subject prematurely discontinue treatment (Section 7.9.1) or discontinue from the study (Section 7.9.2), a Premature Termination visit should be scheduled. While the Investigator may include additional assessments and evaluations determined by the status of the individual subject, at the minimum, the following assessments should be performed as soon as feasibly possible:

- Vital signs (temperature, heart rate, respiration rate and blood pressure)
- Complete physical examination (excluding breast and genitalia unless indicated)
- 12-lead ECG
- Review concomitant medications
- Review AEs
- Review dosing diary and assess drug accountability (if applicable)
- Laboratory analyses (additional details are provided in the Laboratory Manual):
  - Safety Labs: Chemistry, hematology, coagulation, urinalysis, urine drug test, and urine pregnancy test (if positive on dipstick, serum pregnancy test should be performed).
  - Virology/Immunology: HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, HBsAb and HBeAb, sample for HBV sequencing and HBV nucleic acids
  - PK Samples: Samples can be collected at the same time with other labs. See Section 7.8.8 for additional information.

7.8 Study Assessments

This section describes evaluations and procedures to be performed and items to be recorded or available on source documents. Data from some required evaluations may not be required to be recorded on case report forms (e.g. laboratory results). For further details, refer to Appendix 1.

7.8.1 Demographics, Medical and HBV History

Demographic characteristics including age, race, and ethnicity will be recorded. The Investigator or designee will collect a complete medical, surgical, and HBV history at Screening. Any changes to medical, surgical, and HBV history since Screening will also be recorded for the duration of the study.

Height (cm) and body weight (kg) without shoes will be measured and BMI will be calculated using the height obtained at Screening. The subject's BMI will be calculated using metric units and rounded to the nearest whole number according to the following formula: BMI = weight (kg)/(height [m])^2.

7.8.2 Liver Staging

Liver staging is to be performed to determine lack of cirrhosis or advanced liver disease as required by inclusion criteria (see Section 5.2). The methods for noninvasive, simple, and painless procedures are (1) Fibroscan (if available) or (2) Magnetic Resonance elastography (MRE). The Medical Monitor may be contacted for questions concerning liver staging.

7.8.3 Physical Examination

Complete physical examinations will be performed by the Investigator or qualified Sub-Investigator at the protocol designated timepoints. The complete physical examination will consist of the following body systems: head, eyes, ears, nose, and throat; cardiovascular; respiratory; gastrointestinal; dermatologic; musculoskeletal; nervous; extremities; and lymph nodes. Additional body systems may be evaluated at the Investigator's discretion. Examination of the breast and genitalia are not required unless clinically indicated.

Additional symptom-directed physical examinations will be performed at the protocol designated timepoints. Additional symptom-directed of complete physical examinations made be performed at the Investigator's discretion throughout the course of the study. If the subject reports feeling unwell or has ongoing AEs, the Investigator or qualified Sub-Investigator will examine the appropriate body system(s).

7.8.4 Electrocardiograms

A standard 12-lead ECG will be obtained as specified in the Schedule of Assessments (Appendix 1). Prior to the conduct of the12-lead ECG, subjects should rest in a supine position for 10 mins. ECGs should be conducted in accordance with local practice and equipment. The ECG assessment will include interpretation of the tracings (eg, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T-wave, and Uwave abnormalities). The Investigator or a physician Sub-Investigator is responsible for reviewing and overreading the ECG interpretation, for assessing whether the ECG machine interpretation findings are accurate, appropriate,

normal or abnormal, and for providing corrected interpretations as appropriate. In addition, any abnormal ECGs will be assessed for clinical significance.

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

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

7.8.5 Vital Signs

Vital signs will include temperature, heart rate, respiration rate, and blood pressure at timepoints specified in the Schedule of Assessments in Appendix 1.

7.8.6 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the designated Central laboratories at the timepoints indicated in the Schedule of Assessments table in Appendix 1. Should any laboratory parameter require urgent testing to support immediate medical care of a subject, samples should be collected for both local and central laboratory assessment. The local result may be used to manage the emergent medical situation, however only the results from the central laboratory will be reported in the study database for analysis purposes.

The specific components of the clinical laboratory tests are listed below in Table 5.

Table 5: Clinical Laboratory Tests

Panel	Tests
Clinical Chemistry	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
In case of ALT Elevation	ALT, AST, total bilirubin, serum albumin, creatine kinase, and INR
Hematology	Complete blood counts: hemoglobin, hematocrit, RBC indices (MCV, MCHC), reticulocyte counts, leukocyte counts (total and differential), and platelet counts

Panel	Tests
Coagulation	Prothrombin time/INR and aPTT
Urinalysis	pH, specific gravity, protein, glucose, ketones, and occult blood
Other	AFP, HbA1c, and FSH (ALL Females regardless of fertility status)
Pregnancy tests	For females only; a serum pregnancy test must be performed at Screening. On Day 1, urine and serum pregnancy test should be performed predose. Subject may begin treatment based on urine results. Any subject negative by urine subsequently found to be positive on serum should immediately discontinue treatment. All post-Day 1 pregnancy tests may be conducted by urine dipstick. If positive on dipstick, reflex to serum. A positive result disqualifies the subject for study treatment.
Urine drug Screening	Amphetamine/methamphetamine, barbiturates, benzodiazepines, cocaine metabolite, ethanol, opiates, phencyclidine, and propoxyphene.
Antibodies	HCV, HDV, HAV IgM, HEV IgM, and HIV

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

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

7.8.7 **HBV Virology**

To provide an assessment of the antiviral efficacy of ABI-H2158 in subjects with CHB, this study will evaluate treatment effects on the following parameters:

- HBV genotyping
- HBV DNA
- HBV pgRNA
- HBsAg
- HBeAg
- HBcrAg
- HBsAb
- HBeAb
- HBcAb
- HBV sequence analysis for assessment of resistance

To ensure standardization of the virologic methodologies utilized in this study, HBV DNA-related, HBV antigen-related and HBV antibody-related virologic assessments will be conducted at a central reference laboratory. Subject serum samples for resistance-related sequencing and HBV pgRNA testing will be shipped frozen to the Sponsor or a designated third-party laboratory for testing. The HBV virology tests will be performed at the timepoints indicated in the Schedule of Assessments table in Appendix 1. HBV pgRNA results could unblind individual subject's treatment assignments and therefore will not be

reported to investigative sites or other blinded personnel until completion of the study, the database has been locked and the study has been unblinded.

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

7.8.8 Pharmacokinetic Assessments

During the study, predose plasma samples will be collected from all subjects to explore the PK profile of ABI-H2158 and ETV following combination treatment in subjects with CHB. Additionally, postdose samples will be collected. The timing of PK sample collection is outlined in Table 6. Additional details regarding the collection, processing, storage, and shipment of PK samples are described in the Laboratory Manual.

Table 6: Pharmacokinetic Sample Collection

Time Period	Time Relative to Study Drug Administration [a,]	Study Visit
Treatment	Predose	Day 1, Weeks 4, 48, and 72
	30 min to 2 hours postdose	Weeks 2, 8, 12, 24, and 28
	2 to 4 hours postdose	Day 1
	4 to 6 hours postdose	Weeks 16 and 20
Follow-up	Collect at same time with other central labs	At Unscheduled and Premature Termination Visits and the Week 4 Post Treatment Follow-up visit

[a] Sample collection times are targeted times. Samples collected outside of these targeted times will not be considered protocol deviations. The actual sample collection date/time should be accurately recorded on source documentation. If the subject administers study drug at home, a pharmacokinetic sample should be collected during the visit with documentation of date and time of the dose in the subject's source documents.

7.9 Discontinuation

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. At the time of discontinuing from the study, if possible, a Premature Termination visit should be conducted (Section 7.7). If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.9.1 Discontinuation From Treatment

If an individual subject is not satisfactorily tolerating study drug treatment due to AEs in the judgment of the Investigator, then – in consultation with the Sponsor - the subject may discontinue treatment with ABI-H2158 or PBO. ETV may be continued at the discretion of the Investigator. A subject also has the

right to discontinue treatment with AHI-H2158 or PBO due to his/her wish. Discontinuation from treatment does not mean discontinuation from the study. Subjects who prematurely discontinue treatment should immediately undergo the assessments listed for the Premature Termination visit (Section 7.7) and then continue scheduled follow-up assessments.

If a subject is determined to have developed substitutions in HBV Cp gene sequences associated with viral resistance or blunted treatment response (Section 7.11), then they will discontinue treatment with ABI-H2158 or PBO. ETV may be continued at the discretion of the Investigator. Subjects who prematurely discontinue treatment should immediately undergo the assessments listed for the Premature Termination visit (Section 7.7) and then continue scheduled follow-up assessments.

In this study, subjects will be closely monitored for any evidence of worsening hepatic function. Procedures to be followed for these subjects are described in Section 9.4. Study treatment will be discontinued in subjects with confirmed evidence of declining hepatic function during treatment, a Premature Termination visit (Section 7.7) will be completed and subjects will subsequently undergo the follow-up assessments described in Section 7.5.

Any subjects negative by urine pregnancy test at Baseline (Day 1) who are subsequently found to be positive on serum pregnancy test should immediately discontinue treatment with ABI-H2158 or PBO. ETV may be continued if indicated based on Investigator judgment in accordance with local practice and the approved ETV package insert. These subjects may be replaced at the discretion of the Sponsor.

7.9.2 Discontinuation From Study

Discontinuation from study (ie, withdrawal of consent) means that the subject does not wish to receive further protocol-required treatments or undergo protocol-required procedures, and the subject does not wish to, or is unable to continue further study participation. Subjects who discontinue from the study during follow-up should undergo the assessments listed for the Premature Termination visit (Section 7.7). Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent.

7.9.3 Subjects Lost to Follow-up

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

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

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

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

7.10 End of Study Definition

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

7.11 Resistance Monitoring

To assess potential HBV Cp gene sequences associated with viral resistance or blunted treatment response, serum samples from subjects at each visit will be collected (Section 7). Samples from those subjects with evidence of nonresponse to treatment, such as viral breakthrough (ie, $\geq$1 $\log_{10}$ increase in on-treatment HBV DNA from on-treatment nadir) or if there is no apparent and consistent decline in HBV nucleic acids throughout the study, will be selected for HBV Cp gene sequencing, with sequence comparisons to baseline sequences, as well as comparisons to Cp gene sequences from subjects who received PBO and HBV database sequences.

7.12 Use of Subject Samples for Exploratory Objectives Research

With the subject's approval and as approved by local IRBs/IECs and Country Regulatory Agencies, biological samples collected to assess the relationship between new and known viral biomarkers and virologic and/ or clinical outcomes, will be stored by the Sponsor or their designee. Apart from the analysis described in exploratory objectives (Sections 3.1.3 and 3.2.3), these samples could be used to research CHB, its complications, and other conditions for which individuals with CHB are at increased risk, and to improve treatment. The Sponsor will also have a code-link that will allow linking the biological specimens with the phenotypic data from each subject, maintaining the blinding of the identity of the subject.

8 ADVERSE EVENTS

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

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

8.1 Documenting Adverse Events

Adverse events will be monitored throughout the entire study. Investigators will ask the subject at each visit if they have experienced any untoward effects since the last study visit. All AEs will be entered in the electronic case report forms (eCRFs) provided: a description of the event, severity, time of occurrence, duration, any action (eg, treatment and follow-up tests), and the outcome should be provided along with the Investigator's assessment of the relationship to the study treatment.

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

8.2 Assessment of Intensity

The severity of each AE and laboratory abnormality is to be assessed by the Investigator according to the modified Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric AEs (Appendix 2), which grades the severity of clinical AEs and laboratory abnormalities in a 4-category system.

For AEs not included in Appendix 2, 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 and functional activities with intervention or hospitalization indicated (Of note, the term "severe" does not necessarily equate to "serious")
- **Life-Threatening (Grade 4):** Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

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

8.3 Assessment of Causality

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

- **Not related**: An AE with sufficient evidence to accept that there was no causal relationship to administration of study drug (eg, no temporal relationship because the study drug was administered after the onset of the event, an investigation showed that study drug was not administered, another cause was proven).

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

8.4 Expectedness

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

8.5 Abnormal Laboratory Test Values

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

8.6 Adverse Event Follow-up

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

8.7 Pregnancy

8.7.1 Female subjects who become pregnant

Any female subject who becomes pregnant while participating in the study including the 24-week follow-up period will discontinue the study drug(s) immediately. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate for 6 to 8 weeks after birth. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

The Investigator must inform the Sponsor of the pregnancy. The initial information will be recorded on the Pregnancy Reporting form and submitted to the CRO Pharmacovigilance group within 24 hours of learning of a subject's pregnancy.

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

Any post-study pregnancy related SAE considered reasonably related to the study drug(s) by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

8.7.2 Male subjects with partners who become pregnant

If a female partner of a male subject participating in this study becomes pregnant, the Investigator will ask the pregnant female partner to consent to be followed through to the end of her pregnancy and the neonate for 6 to 8 weeks after birth. This applies only to male subjects who receive the study drug.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the Pregnancy Reporting form and submit it to the CRO Pharmacovigilance group within 24 hours of learning of the partner's pregnancy. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks after birth. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

9 SERIOUS ADVERSE EVENTS

9.1 Definition of Serious Adverse Event

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

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received ABI-H2158
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    - Development of drug dependency or drug abuse

Definition of Terms

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

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

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

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

9.2 Reporting Serious Adverse Events

All SAEs must be reported within 24 hours of learning about the event using the SAE Report form to the CRO Pharmacovigilance group. 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 investigators to inform any local IRBs/IECs of SAEs as required. Correspondence with the IRB(s)/IEC(s) relating to the reporting of SAEs will be retained in the study file.

9.3 Overdose

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

9.4 Management of ALT Elevations

All subjects participating in the study will be closely monitored for ALT elevations and/or signs of potential decline in hepatic function (see Figure 2). Subjects experiencing ALT elevations ≥2 × Baseline (Day 1) or on-treatment nadir and >2 × ULN during study treatment or during post-treatment follow-up should be closely monitored with regular Unscheduled Visits every 1-2 weeks at the discretion of the Investigator. At these visits, the following laboratory tests will be performed: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum albumin, INR and creatine kinase. The Investigator will determine if other Unscheduled Visit assessments should be performed. Additionally, the following guidance is provided for management of subjects with ALT elevations:

- ALT Elevation without Declining Hepatic Function
    - All subjects with an ALT elevation on treatment, defined as ALT >2 × Baseline or on-treatment nadir and ≥10 × ULN, should have the ALT findings confirmed within 3 days of receipt of the original results. All subjects should return for an Unscheduled Visit (Section 7.6).
    - If the ALT elevation is confirmed, then an additional Unscheduled Visit will be performed to further evaluate the subject. At this visit, the following laboratory tests will be performed: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum

albumin, INR, creatine kinase, HBV DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative]), HAV IgM, HCV RNA, HDV RNA, and HEV IgM. The Investigator will determine if other Unscheduled Visit assessments should be performed.

- If an intercurrent cause is determined to be causal, subjects with an ALT elevation without declining hepatic function and without contraindications may continue treatment and the intercurrent illness should be treated as deemed medically appropriate by the Investigator.
- Subjects with an ALT elevation without declining hepatic function and without contraindications may continue treatment with study drug under close observation.
  - If ALT is rising at the confirmatory visit, subjects should return for an Unscheduled Visit every 2 to 5 days until the ALT elevation has stabilized. At these visits, the following laboratory tests will be performed: ALT, AST, total bilirubin (if total bilirubin is elevated, reflex to direct bilirubin), serum albumin, INR, creatine kinase, HBV DNA, quantitative HBV serologies (HBeAg [reflex to qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex to qualitative HBsAg if quantitative HBsAg is negative]). The Investigator will determine if other Unscheduled Visit assessments should be performed. Subjects whose ALT has stabilized should continue to be monitored weekly (or more frequently, as deemed necessary by the treating physician) until ALT values return to normal or Baseline levels.

- ALT Elevation with Declining Hepatic Function
  - Subjects with confirmed ALT elevation with evidence of declining hepatic function should be discontinued from study treatment. This is defined as:
    - ALT elevation ≥2 × Baseline (Day 1) or nadir and >2 × ULN AND
      - Direct bilirubin increase to ≥2 × Baseline (Day 1) and ≥2 × ULN OR
      - Albumin decline ≥0.5 g/dL OR INR >2 × Baseline (Day 1) OR
      - Symptoms of liver inflammation (eg, fatigue, weakness, lack of appetite, nausea, vomiting, jaundice or discolored feces)
  - Subjects with evidence of declining hepatic function should return for an Unscheduled Visit every 2 to 5 days until the relevant laboratory values stabilize. Subjects whose hepatic function has stabilized should continue to be monitored weekly (or more frequently as deemed necessary by the Investigator) until the relevant laboratory values return to normal or Baseline (Day 1).

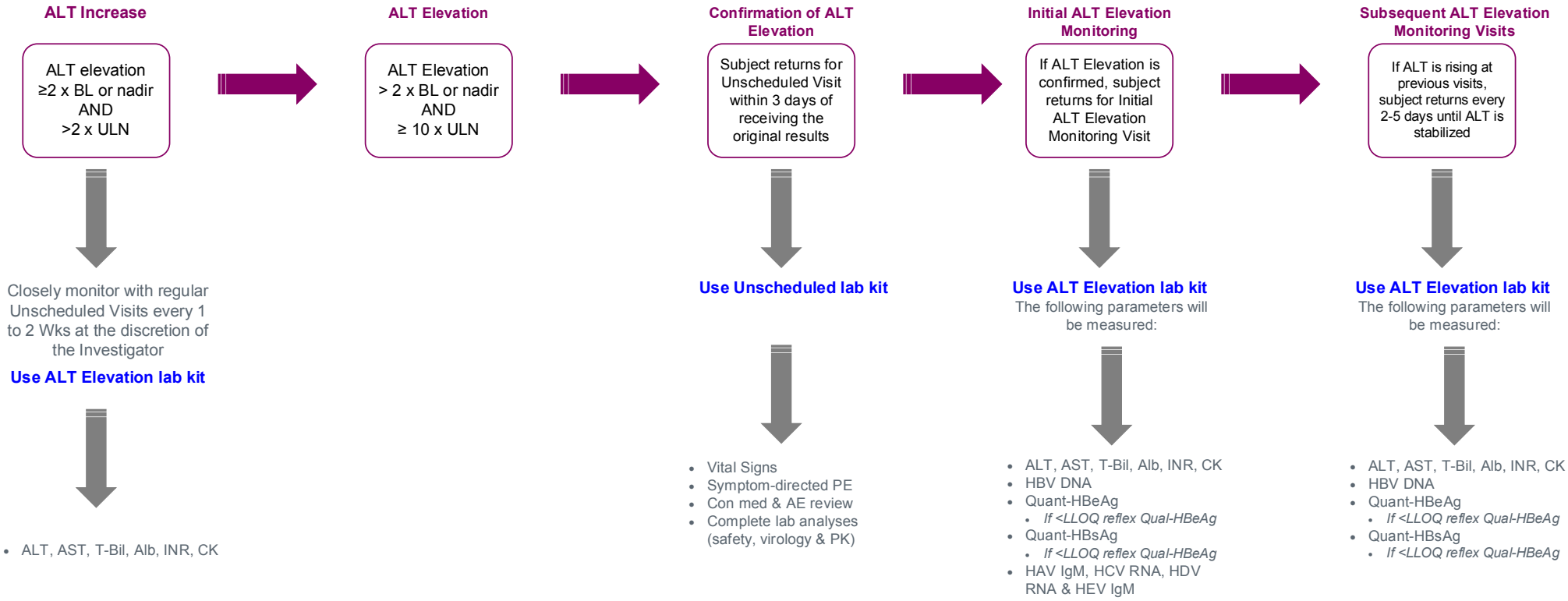
All subjects with ALT elevation with or without declining hepatic function should continue to be followed on their regular study visit schedule, with the addition of Unscheduled Visits as described above. If the post-treatment ALT elevation has not substantially resolved by the last study follow-up visit, subjects should continue to return to clinic as deemed medically appropriate by the Investigator, in consultation with the Sponsor. The Unscheduled Visit module in the case report form should be utilized as needed to gather additional clinical and laboratory data until the ALT elevation is documented to be

either resolved or resolving (defined as consistent ALT declines of 10% or more or normalization of ALT) on at least 2 successive visits.

If 2 or more subjects meet these ALT elevation management criteria, the US FDA and other relevant regulatory agencies will be notified, and subsequent steps will be determined after consultation with these agencies.

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

Figure 2: Management of ALT Elevation



10 STATISTICAL CONSIDERATIONS

10.1 General Considerations

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

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

10.2 Sample Size Determination

Forty treatment-naïve subjects with HBeAg positive CHB will be enrolled in Cohort 1 and 40 treatment-naïve subjects with HBeAg negative CHB will be enrolled in Cohort 2. Subjects will be randomized to receive either placebo or 300 mg ABI-H2158 in a 1:3 ratio. That is, in Cohort 1 and in Cohort 2, 10 subjects will be randomized to treatment with placebo, and 30 subjects will be randomized to treatment with ABI-H2158. This sample size is not based on statistical considerations but is adequate for a proof-of-concept study.

10.3 Analysis Populations

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

- Randomized Analysis Set: It includes all randomized subjects, classified according to the treatment group into which they were randomized regardless of the actual treatment received.

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

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

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

10.4 Planned Analysis and Reports

10.4.1 Analysis of Primary Endpoint(s)

The primary endpoint is the change in mean $\log_{10}$ HBV DNA from Baseline to Week 24 for ABI-H2158+ETV compared to PBO+ETV. The primary comparison will be made using an analysis of covariance (ANCOVA) model, including baseline value, the stratification factors and treatment group. The estimated least square means of treatment effects and estimated difference in treatment effects between treatment groups will be presented along with the 95% confidence intervals and p-values.

10.4.2 Analysis of Secondary and Exploratory Endpoints

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

For continuous variables, such as observed and change from Baseline HBV DNA values at each timepoint, descriptive statistics will be used, and will include the number, mean, standard deviation, median, minimum, maximum, and, where appropriate, a 95% confidence interval. Missing data methods and imputation rules will be defined in the SAP. Additional sensitivity analysis may also be performed and will be described in the study SAP.

For categorical variables, such as subjects with a reduction in HBV DNA below LLOQ, descriptive statistics will include number and percent who meet the endpoint criterion.

10.4.3 Analysis of Pharmacokinetic Endpoints

The following will be analyzed descriptively after all subjects in each cohort have completed their Week 4 study visit (interim) and end of study (final):

Trough levels and trough to peak ratios of ABI-H2158 on ABI-H2158+ETV therapy

Trough levels and trough to peak ratios of ETV on ABI-H2158+ETV therapy as compared with PBO+ETV therapy

After all subjects have completed Week 4 (or discontinued before completing Week 4), PK data will be reviewed by an unblinded pharmacology reviewer to ensure ETV steady state PK levels are not being affected by combination treatment with ABI-H2158. Similarly, the potential impact of ETV on the steady state PK levels of ABI-H2158 will be assessed. All PK timepoints will be included in the final analysis.

10.4.4 Analysis of Safety Endpoints

The safety parameters to be assessed are described in Section 7.8 Displays for safety results will utilize descriptive statistics. No formal hypothesis testing of safety data is planned.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Incidence of each body system and preferred term will be tabulated for each treatment group. Treatment-emergent adverse events (TEAE) are defined as those reported on or after the first dose of study drug through 28 days from the last dose of study drug. Summaries will include all TEAEs, TEAEs

considered related to study treatment by investigators, Graded TEAEs, and SAEs. All AEs, emergent or non-emergent, will be listed by subject. Any TEAEs leading to premature discontinuation from the study intervention and serious TEAEs will be presented by 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.

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

10.5 Interim Analysis

This study will be conducted in a single-blind manner. A DRC as described in Section 10.6 will be assembled with an unblinded Sponsor team to perform regular review of safety and antiviral activity data. The DRC will also review the interim PK analysis described in Section 10.4.3. Details concerning these analyses will be documented in the SAP and the DRC charter.

10.6 Data Review Committee (DRC)

To assess the safety and/or efficacy of ABI-H2158 for planning and development of this compound, an Assembly internal unblinded team independent of the blinded study team will be assembled as a DRC. This committee will consist of at least one representative from Clinical Research, Biostatistics, and may include other personnel as necessary. The Medical Monitor and clinical research staff directly interacting with the study center will not be unblinded to the subject treatment assignment. The Assembly internal unblinded team will be granted access to unblinded clinical data at the individual subject or group summary level including treatment assignments to closely monitor study progress and drug safety.

The membership, conduct, and meeting schedule of the DRC Charter as specified in Assembly SOPs.

11 RESPONSIBILITIES

11.1 Investigator Responsibilities

11.1.1 Good Clinical Practice

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

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

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

11.1.3 Informed Consent

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

The Sponsor or its designee will provide a sample ICF. The final, version dated, ICF must be agreed to by the Sponsor 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 and by the person who conducted the informed consent discussion. In the case where the subject is unable to read, an impartial witness must be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The original, signed ICF will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed ICF.

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

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

11.1.4 Confidentiality

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

Identification of subjects and eCRFs shall be by identification codes and not by their name (e.g. subject number). The Investigator should keep a subject enrollment log showing codes, names, and addresses. The Investigator must maintain documents not for submission to the Sponsor or designees (eg, subject's written consent forms) in strict confidence.

If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

11.1.5 Study Files and Retention of Records

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

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

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

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

11.1.6 Audits and Inspections

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

Government regulatory authorities may also inspect the site during or after the study. The Investigator or designee should contact the Sponsor and/or the CRO, immediately if this occurs. The site must

cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

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

11.1.7 Protocol Compliance

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

11.2 Sponsor Responsibilities

11.2.1 Protocol Amendments and Modifications

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

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

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

11.2.2 Data Management

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

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

11.2.3 Study Report and Publications

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

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

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

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

12 REFERENCES

Agarwal K, Brunetto M, Seto WK, et al (2018) 96weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 68(4):672-681.

Battisti WP, Wager E, Baltzer L, et al (2015) Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3. Ann Intern Med 163(6):461-464.

Belloni L, Li L, Palumbo G, et al (2013) HAPs hepatitis B virus (HBV) capsid inhibitors block core protein interaction with the viral minichromosome and host cell genes adn affect cccDNA transcription and stability: 138. Hepatology 58:277A.

Burdette D, Cathcart A, Shauf A, et al (2019) PS-150-Evidence for the presence of infectious virus in the serum from chronic hepatitis B patients suppressed on nucleos (t)ide therapy with detectable but not quantifiable HBV DNA. Journal of Hepatology 70(1):e95.

Colvin H, Mitchell AE (2010). Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. Washington, D.C., The National Academies Press.

Cornberg M, Lok AS, Terrault NA, et al (2019) Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference. Hepatology.

EASL (2012) Clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 57(1):167-185.

EASL (2017) Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of Hepatology 67(2):370-398.

El-Serag HB (2012) Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 142(6):1264-1273 e1261.

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

Hoofnagle JH, Doo E, Liang TJ, et al (2007) Management of hepatitis B: summary of a clinical research workshop. Hepatology 45(4):1056-1075.

ICMJE (2019) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. International committee of medical journal editors. from http://www.icmje.org/icmje-recommendations.pdf.

Lampertico P and Liaw YF (2012) New perspectives in the therapy of chronic hepatitis B. Gut 61 Suppl 1:i18-24.

Levey AS, Stevens LA, Schmid CH, et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150(9):604-612.

Levrero M, Pollicino T, Petersen J, et al (2009) Control of cccDNA function in hepatitis B virus infection. J Hepatol 51(3):581-592.

Lok AS and McMahon BJ (2009) Chronic hepatitis B: update 2009. Hepatology 50(3):661-662.

Papatheodoridis GV, Chan HL, Hansen BE, et al (2015) Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. J Hepatol 62(4):956-967.

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

Schweitzer A, Horn J, Mikolajczyk RT, et al (2015) Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 386(10003):1546-1555.

Sorrell MF, Belongia EA, Costa J, et al (2009) National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. Ann Intern Med 150(2):104-110.

Sulkowski M, Agarwal K, Fung SK, et al (2019) Continued therapy with ABI-H0731+NrtI results in sequential reduction/loss of HBV DNA, HBV RNA, HBeAg, HBcrAg and HBsAg in HBeAg positive patients The liver Meeting 2019, Boston, MA, AASLD from https://www.aasld.org/sites/default/files/2019-10/2019-TLM-LateBreakingAbstracts-v2.pdf

WHO (2015) Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Retrieved 14 Dec 2020 from https://www.who.int/hepatitis/publications/hepatitis-b-guidelines/en/.

WHO (2019) Hepatitis B Fact Sheet. Retrieved October 10, 2019 from http://www.who.int/mediacentre/factsheets/fs204/en/.

Yang L, Liu F, Tong X, et al (2019) Treatment of Chronic Hepatitis B Virus Infection Using Small Molecule Modulators of Nucleocapsid Assembly: Recent Advances and Perspectives. ACS Infect Dis 5(5):713-724.

Yim HJ and Lok AS (2006) Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology 43(2 Suppl 1):S173-181.

13 APPENDICES

14 APPENDIX 1: SCHEDULE OF ASSESSMENTS TABLE

Period or Visit	Screening	On Treatment																		
Study Day or Week	**Day -45 to Day -1**	**Day 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**
Visit Window (days)		0	±3	±3	±3	±3	±3	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Informed Consent(s) [a]	X																				
Demographics and height	X																				
Medical and HBV history	X	X																			
Liver staging [b]	X																				
Complete physical exam [c]	X	X							X						X						X
Symptom-directed physical exam			X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	
12-lead ECG [d]	X	X				X			X			X			X			X			X
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
Concomitant medications and adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirm subject eligibility		X																			
Complete randomization (IRT)		X																			
Dosing diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug accountability [e]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensation [e]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
In-clinic ABI-H2158/PBO dosing		X	X	X	X	X			X	X					X						X
In-clinic ETV dosing		X	X	X	X	X			X	X					X						X
HBV genotype		X																			
HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg, HBeAg [f]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBcrAg		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period or Visit	**Screening**	**On Treatment**																		
Study Day or Week	**Day -45 to Day -1**	**Day 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**
Visit Window (days)		0	±3	±3	±3	±3	±3	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
HBsAb, HBeAb	X	X				X			X			X			X			X			X
HBV pgRNA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sample for HBV DNA sequencing and HBV nucleic acids	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Ab, HCV Ab, HDV Ab, HAV (IgM), HEV (IgM), HBcAb [g]	X																				
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum AFP	X																				
FSH (all females regardless of fertility status)	X																				
Urinalysis	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug test	X	X																			
Pregnancy test [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sample Collection																					
Predose [i]		X		X											X						X
Postdose: **30 min to 2 hours**			X		X	X			X	X											
Postdose: **2 to 4 hours**		X																			
Postdose: **4 to 6 hours**							X	X													
Pharmacogenomic sample		X																			

Period or Visit	Follow-Up				ALT Elevation[k]	Premature Termination [j]	Unscheduled [k]
Study Day or Week	4 Wks Post	8 Wks Post	12 Wks Post	24 Wks Post			
Visit Window (days)	±5	±5	±5	±5	NA	NA	NA
Complete physical exam [c]				X		X	
Symptom-directed physical exam	X	X	X				X
12-lead ECG [d]				X		X	
Weight				X			
Vital signs	X	X	X	X		X	X
Concomitant medications and adverse events	X	X	X	X		X	X
Dosing diary						X	
Study drug accountability [e]	X	X	X	X		X	
Study drug dispensation [e]	X		X				
HBV DNA	X	X	X	X	X	X	X
HBsAg, HBeAg [f]	X	X	X	X	X	X	X
HBcrAg	X	X	X	X		X	X
HBsAb, HBeAb				X		X	
HBV pgRNA	X	X	X	X		X	X
Sample for HBV DNA sequencing and HBV nucleic acids	X	X	X	X		X	X
ALT, AST, total bilirubin, serum albumin, creatine kinase, & INR					X		
HAV (IgM), HCV RNA, HDV RNA, HEV (IgM)					X		
Chemistry	X	X	X	X		X	X
Hematology	X	X	X	X		X	X
Coagulation	X	X	X	X		X	X
Urinalysis	X		X	X		X	X
Urine drug test						X	X
Pregnancy test [h]	X					X	X
PK sample collection	X					X	X

PBO: placebo; ECG: electrocardiogram; ETV: entecavir; FSH: follicle-stimulating hormone; HAV: hepatitis A virus; HBcAb: antibody to the HBV core antigen; HBcrAg: hepatitis B core-related antigen; HBeAb: HBeAg antibody; HBeAg: hepatitis B "e" antigen; HBsAb: HBsAg antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus; HEV: hepatitis E virus; HIV: human immunodeficiency virus; IgM: immunoglobulin M; IRT: Interactive Response Technology; NA: not applicable; PK: pharmacokinetic.

[a] In addition to the study specific Main Informed Consent Form, a separate consent is required for optional pharmacogenomic sampling.

[b] Liver staging is to be performed to determine lack of cirrhosis or advanced liver disease as required by inclusion criteria.

[c] Examination of the breasts and genitalia are not required unless indicated.

[d] During the study, any clinically significant ECG result should be confirmed, and if confirmed, should be recorded as an AE.

[e] Study drug dispensation from Week 72 onwards and drug accountability from 4 weeks post treatment onwards only applies to ETV therapy; ETV will be continued throughout the 24-week follow-up period.

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

[g] HBcAb is performed if the subject has no clear documentation of CHB per Inclusion Criteria #4.

[h] A serum pregnancy test is required at Screening. On Day 1, urine and serum pregnancy test should be performed predose. Subjects may begin treatment based on urine results; any subjects negative by urine subsequently found to be positive on serum should immediately discontinue treatment and may be replaced. All post-Day 1 pregnancy tests may be conducted by urine dipstick. If positive on dipstick, reflex to serum.

[i] If the subject inadvertently administers study drug prior to collection, a PK sample should still be drawn. Refer to Section 7.8.8.

[j] Subjects who discontinue treatment before Week 72 should immediately undergo the assessments listed for the Premature Termination visit and then continue the scheduled follow-up assessments.

[k] Any subjects with ALT elevation (defined as ALT ≥2 × Baseline and ≥10 × ULN) should return to the clinic for an Unscheduled Visit (see Section 9.4):

15 APPENDIX 2: TOXICITY GRADING SCALE FOR ADVERSE EVENTS AND LABORATORY ABNORMALITIES

Adapted from the US National Institutes of Health (Division of AIDS) Table for Grading Severity of Adult Adverse Experiences (Corrected Version 2.1 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 subject not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (eg, hypoxemia) OR Intervention indicated (eg, oxygen)	Life-threatening consequences OR Urgent intervention indicated (eg, vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of □ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated

Cardiovascular				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Prolonged PR Interval or AV Block	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged 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*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (eg, pulmonary embolism, thrombus)

1 As per Bazett's formula.

Dermatologic				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Alopecia (scalp only)	Detectable by study subject, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (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	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus [3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions **OR** Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Stevens-Johnson syndrome **OR** Toxic epidermal necrolysis

3 For pruritus associated with injections or infusions, see the Site Reactions to Injections and Infusions section.

Endocrine and Metabolic				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life- Threatening**
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study subject, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (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 subject, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study subject, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

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

Gastrointestinal				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (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	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over Baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over Baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (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	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Perforation *(colon or rectum)*	NA	NA	Intervention indicated	Life-threatening consequences

Gastrointestinal				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & 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	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)

Musculoskeletal				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia [6]				
≥30 years of age	BMD t-score -2.5 to -1	NA	NA	NA
<30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis [6] *≥30 years of age*	NA	BMD t-score <-2.5	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
<30 years of age	NA	BMD z-score <-2	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

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

Neurologic				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (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
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***	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (eg, severity or focality)	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)

Neurologic				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Syncope	Near syncope without loss of consciousness (eg, presyncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

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

7 Definition: A pregnancy loss occurring at <20 weeks gestational age.

Psychiatric				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70 to <80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to <70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to <50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow <25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to <95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilator support indicated (eg, CPAP, BPAP, intubation)

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

Systemic				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome [8]	Mild signs and symptoms AND Therapy (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 (non-axillary temperatures only)	38.0 to <38.6°C or 100.4 to <101.5°F	≥38.6 to <39.3°C or ≥101.5 to <102.7°F	≥39.3 to <40.0°C or ≥102.7 to <104.0°F	≥40.0°C or ≥104.0°F
Pain [9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness [10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (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)*	NA	5 to <9% loss in body weight from Baseline	≥9 to <20% loss in body weight from Baseline	≥20% loss in body weight from Baseline OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)

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 subjects >5 to 19 years of age

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

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
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

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

Laboratory Values*: Chemistries				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Acidosis	NA	pH≤7.3 to <LLN	pH<7.3 without life- threatening consequences	pH<7.3 with life- threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN 30 to < LLN	≥ 2.0 to < 3.0 ≥ 20 to < 30	< 2.0 < 20	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to □ 7.5	pH > 7.5 without life- threatening consequences	pH > 7.5 with life- threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin ***Direct Bilirubin, High***	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life- threatening consequences (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*	≥3.5 *≥3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	>ULN to <6.0 *>ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 *≥1.8*
Calcium, Low (mg/dL; *mmol/L*)	7.8 to <8.4 *1.95 to <2.10*	7.0 to <7.8 *1.75 to <1.95*	6.1 to <7.0 *1.53 to <1.75*	<6.1 *<1.53*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 *<LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 *<0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to <6×ULN	6 to <10×ULN	10 to <20×ULN	≥20×ULN
Creatinine, High **Report only one*	1.1 to 1.3×ULN	>1.3 to 1.8×ULN OR Increase to 1.3 to <1.5×subject's baseline	>1.8 to <3.5×ULN OR Increase to 1.5 to <2.0×subject's baseline	≥3.5×ULN OR Increase of ≥2.0×subject's baseline

Laboratory Values*: Chemistries				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Creatinine Clearance[13] **or eGFR, Low** **Report only one*	NA	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to <30% decrease from subject's baseline	<60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to <50% decrease from subject's baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from subject's baseline or dialysis needed

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

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*

Laboratory Values*: Chemistries				
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×subject's baseline	>1.8 to <3.5×ULN OR Increase to 1.5 to <2.0×subject's baseline	≥3.5×ULN OR Increase of ≥2.0×subject's baseline
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 subject's baseline	<60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to <50% decrease from subject's baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from subject's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to <6.95*	>125 to 250 *6.95 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Nonfasting, High	116 to 160 *6.44 to <8.89*	>160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*)	55 to 64 *3.05 to <3.55*	40 to <55 *2.22 to <3.05*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
Lactate, High	ULN to <2.0×ULN without acidosis	≥2.0×ULN without acidosis	Increased lactate with pH <7.3 without life- threatening consequences	Increased lactate with pH <7.3 with life- threatening consequences
Lipase, High	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High***	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	NA
LDL, Fasting, High	130 to <160 *3.37 to <4.12*	160 to <190 *4.12 to <4.90*	≥190 *≥4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to <1,000 *>5.7 to 11.4*	>1,000 *>11.4*
Magnesium[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*

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

*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/1.73m^2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.
14 To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Laboratory Values: Hematology

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *(not HIV infected)*	300 to <400 *300 to <400*	200 to <300 *200 to <300*	100 to <200 *100 to <200*	<100 <100
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *(not HIV infected)*	600 to <650 *0.600×10^9 to <0.650×10^9*	500 to <600 *0.500×10^9 to <0.600×10^9*	350 to <500 *0.350×10^9 to <0.500×10^9*	<350 *<0.350×10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)	800 to 1,000 *0.800×10^9 to 1.000×10^9*	600 to 799 *0.600×10^9 to 0.799×10^9*	400 to 599 *0.400×10^9 to 0.599×10^9*	<400 *<0.400×10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00×LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75×LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50×LLN	<50 *<0.50* OR <0.25×LLN OR Associated with gross bleeding
Hemoglobin [15], Low (g/dL; *mmol/L*) [16] *Male only*	10.0 to 10.9 *6.19 to 6.76*	9.0 to <10.0 *5.57 to <6.19*	7.0 to <9.0 *4.34 to <5.57*	<7.0 *<4.34*
Hemoglobin [15], Low (g/dL; *mmol/L*) [16] *female only*	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
INR, High (not on anticoagulation therapy)	1.1 to <1.5×ULN	1.5 to <2.0×ULN	2.0 to <3.0×ULN	≥3.0×ULN
Methemoglobin (% hemoglobin)	5.0 to <10.0%	10.0 to <15.0%	15.0 to <20.0%	≥20.0%
PTT, High (not on anticoagulation therapy)	1.1 to <1.66×ULN	1.66 to <2.33×ULN	2.33 to <3.00×ULN	≥3.00×ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <125,000 *100.000×10^9 to <125.000×10^9*	50,000 to <100,000 *50.000×10^9 to <100.000×10^9*	25,000 to <50,000 *25.000×10^9 to <50.000×10^9*	<25,000 *<25.000×10^9*
PT, High (not on anticoagulation therapy)	1.1 to <1.25×ULN	1.25 to <1.50×ULN	1.50 to <3.00×ULN	≥3.00×ULN
WBC, Decreased (cells/mm^3; *cells/L*)	2,000 to 2,499 *2.000×10^9 to 2.499×10^9*	1,500 to 1,999 *1.500×10^9 to 1.999×10^9*	1,000 to 1,499 *1.000×10^9 to 1.499×10^9*	<1,000 *<1.000×10^9*

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

Laboratory Values: Urinalysis				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤250 mg	2+ or >250 to ≤500 mg	>2+ or >500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥10 RBCs per high power field	Gross, with or without clots OR with RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

16 APPENDIX 3: PREGNANCY PRECAUTIONS AND THE DEFINITION OF CHILDBEARING POTENTIAL AND CONTRACEPTIVE REQUIREMENTS

Pregnancy Precautions

Embryofetal development studies with ABI-H2158 have not been conducted in animals, and so the effects of ABI-H2158 on pregnancy are unknown. Contraceptive requirements for female subjects of childbearing potential are required as described below.

Definition of Female Subjects of Childbearing Potential

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

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

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

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

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

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

Contraceptive Requirements

The DDI study with ABI-H2158 and OC that contains levonorgestrel and ethinyl estradiol concluded that oral contraceptives may be used as one of the dual effective birth control methods. Female subjects of childbearing potential (defined above) must agree to use dual effective birth control methods for the duration of the study and follow-up. Effective birth control methods include male or female condom (may not be used together due to increased risk of breakage), vasectomy, tubal sterilization, intrauterine device (IUD), diaphragm, oral contraceptives or cervical cap. Female subjects must have a negative serum pregnancy test at Screening and a negative urine pregnancy test prior to receiving the first dose of study drug at Day 1.

All male subjects must agree to use dual effective birth control methods with their female partners if they are of childbearing potential for the duration of the study and follow-up. In this case, effective birth control methods include systemic (oral/injectable) hormonal birth control, male or female condom (may not be used together due to increased risk of breakage), vasectomy, tubal sterilization, IUD, diaphragm, or cervical cap.

17 APPENDIX 4: CYTOCHROME P450 3A4 INHIBITORS AND CYP3A4, 2C8, AND 2C19 SUBSTRATES, PROTON PUMP INHIBITORS, H-2 RECEPTOR BLOCKERS, AND ANTACIDS

The following drugs are known inhibitors of CYP3A4 and stomach pH modifying agents and should be avoided when taking ABI-H2158:

CYP3A4 Inhibitors	
HIV antivirals	indinavir; nelfinavir; ritonavir, saquinavir
Other	clarithromycin; itraconazole; ketoconazole; nefazodone; saquinavir; idelalisib, ribociclib, telithromycin; aprepitant; erythromycin; fluconazole; grapefruit (whole fruit and juice); netupitant/palonosetrone, verapamil; diltiazem; voriconazole cimetidine; amiodarone; NOT azithromycin; chloramphenicol; boceprevir; ciprofloxacin; delaviridine; diethyl-dithiocarbamate; fluvoxamine; gestodene; imatinib; mibefradil; mifepristone; norfloxacin; norfluoxetine; starfruit; telaprevir; voriconazole
Stomach pH Modifying Agents	
Proton pump inhibitors	esomeprazole; lansoprazole; omeprazole; pantoprazole
H-2 receptor blockers	cimetidine, famotidine, nizatidine, ranitidine
Other	Aluminum hydroxide, magnesium carbonate, magnesium hydroxide, sodium bicarbonate, calcium carbonate

The following drugs are known substrates of CYP3A4, 2C19, and 2C8 and should be avoided when taking ABI-H2158:

CYP3A4 Substrates	
Macrolide antibiotics	clarithromycin; erythromycin; NOT azithromycin; telithromycin
Anti-arrhythmics	quinidine→3-OH
Benzodiazepines	alprazolam; diazepam→3OH; midazolam; triazolam
Immune modulators	cyclosporine; tacrolimus (FK506)
HIV antivirals	indinavir; nelfinavir; ritonavir; saquinavir
Prokinetic	cisapride
Antihistamines	astemizole; chlorpheniramine; terfenadine
Calcium channel blockers	amlodipine; diltiazem; felodipine; lercanidipine; nifedipine; nisoldipine; nitrendipine; verapamil
HMG CoA reductase inhibitors	atorvastatin; cerivastatin; lovastatin; NOT pravastatin; NOT rosuvastatin; simvastatin
Steroid 6beta-OH	estradiol; hydrocortisone; progesterone; testosterone
Miscellaneous	alfentanil; aprepitant; aripiprazole; boceprevir; buspirone; carbamazepine; cafergot; caffeine→TMU; cilostazol; cocaine; codeine-N-demethylation; dapsone; dexamethasone; dextromethorphan; docetaxel; domperidone; eplerenone; fentanyl; finasteride; gleevec; haloperidol; irinotecan; LAAM; lidocaine; methadone; nateglinide; nevirapine; ondansetron; pimozide; propranolol; quetiapine; quinine; risperidone; romidepsin; salmeterol; sildenafil; sirolimus; sorafenib; sunitinib; tamoxifen; taxol; telaprevir; terfenadine; torisel; trazodone; vemurafenib; vincristine; zaleplon; ziprasidone; zolpidem

CYP2C19 Substrates	
Proton pump inhibitors	esomeprazole; lansoprazole; omeprazole; pantoprazole
Anti-epileptics	diazepam→Nor; phenytoin(O); S-mephenytoin; phenobarbitone; amitriptyline; carisoprodol; citalopram; chloramphenicol; clomipramine; clopidogrel; cyclophosphamide; hexobarbital; imipramine N-DeME; indomethacin; labetalol; R-mephobarbital; moclobemide; nelfinavir; nilutamide; primidone; progesterone; proguanil; propranolol; teniposide; R-warfarin→8-OH; voriconazole
CYP2C8 Substrates	
	Amodiaquine, cerivastatin, paclitaxel, repaglinide, selexipag, sorafenib, torsemide

The following drugs are known inducers of CYP3A4 and should be avoided when taking ABI-H2158:

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

Source: The Flockhart Table. http://medicine.iupui.edu/clinpharm/ddis/main-table# (Accessed 16 Dec 2019).

STATISTICAL ANALYSIS PLAN

Sponsor:	Assembly Biosciences, Inc 331 Oyster Point Blvd South San Francisco, CA 94030
Protocol Number:	ABI-H2158-201
Protocol Title:	A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled, Multiple Cohort Study Evaluating ABI-H2158-Containing Regimens in Chronic Hepatitis B Infection
Product:	ABI-H2158
Protocol Version (Date):	Amendment 2 (14 December 2020) Amendment 2/ GBR-2 (17 December 2020) Amendment 2/KOR-1 (05 February 2021)
Indication:	Chronic Hepatitis B Virus Infection
Analysis Type:	Final Analysis For Synoptic CSR
Analysis Plan Version (Date):	Version 1.0 (25 January 2022)
Analysis Plan Author:	[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN APPROVAL FORM

Protocol Title: A Phase 2a, Multicenter, Single-Blind, Placebo-Controlled, Multiple Cohort Study Evaluating ABI-H2158-Containing Regimens in Chronic Hepatitis B Infection

Protocol Number: ABI-H2158-201

SAP Version (Date): Version 1.0 (25 January 2022)

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

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

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LIST OF ABBREVIATIONS

AASLD	american association for the study of liver diseases
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BLOQ	below the limit of quantitation
BMI	body mass index
cHBV	chronic hepatitis B virus infection
CI	confidence interval
CSR	clinical study report
DAIDS	Division of AIDS
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
DRC	data review committee
ECG	electrocardiogram
eCRF	case report form
EDC	electronic data capture
ET	early termination
ETV	entecavir
FAS	full analysis set
Hb	hemoglobin
HBcrAb	antibody to the HBV core-related antigen
HBcrAg	hepatitis B core-related antigen
HBeAb	HBeAg antibody
HBeAg	hepatitis B “e” antigen
HBsAb	HBsAg antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HLGT	high-level group term
HLT	high-level term
ID	identification
IPD	important protocol deviation(s)
IRT	interactive response technology
LLOQ	lower limit of quantitation
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	medical dictionary for regulatory activities
PBO	placebo

PD	protocol deviation(s)
pgRNA	pregenomic RNA
PT	preferred term
PK	pharmacokinetics
Q1, Q3	first quartile, third quartile
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal

1. INTRODUCTION

Study ABI-H2158-201 is a Phase 2a, multicenter, randomized, single-blind, placebo (PBO)-controlled, multiple cohort study evaluating ABI-H2158-containing regimens in chronic hepatitis B virus (HBV) infection (cHBV). The target population is male or female subjects with cHBV, 18 to 65 years of age, inclusive, with no evidence of cirrhosis or end-stage liver disease. Cohort 1 will enroll treatment-naïve subjects with hepatitis B virus "e" antigen (HBeAg) positive cHBV. Cohort 2 will enroll treatment-naïve subjects with HBeAg negative cHBV.

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study ABI-H2158-201. This SAP is based on the Study Protocol Amendment 2, dated 14 December 2020; UK country-specific protocol amendment, dated 17 December 2020; Korea-country specific protocol amendment, dated 05 February 2021; ABI-H2158-201 Protocol Clarification Letter for Amendment 2; dated 14 Dec 2020, 07 September 2021; and the electronic case report form (eCRF). On 01 September 2021, Assembly made the decision to discontinue the development of ABI-H2158 following the observation of elevated alanine aminotransferase (ALT) levels consistent with drug-induced liver injury (DILI) in study ABI-H2158-201. Therefore, only key safety and efficacy endpoints will be performed. The SAP will be finalized before final database lock. Any changes made after the finalization of the SAP will be documented in the Synoptic CSR.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of ABI-H2158 when administered in combination with entecavir (ETV) in subjects with cHBV
- To evaluate the effect of ABI-H2158 in reducing HBV DNA in subjects with cHBV

The secondary objectives of this study are as follows:

- To evaluate the pharmacokinetics (PK) of ABI-H2158 and ETV in subjects with cHBV
- To evaluate the effect of ABI-H2158 in reducing HBV pregenomic RNA (pgRNA) levels in subjects with cHBV
- To evaluate the effect of ABI-H2158 in reducing HBV antigens (ie, HBeAg, hepatitis B core-related antigen [HBcrAg] and hepatitis B surface antigen [HBsAg]) in subjects with cHBV
- To evaluate the effect of ABI-H2158 on normalization of ALT in subjects with abnormal ALT
- To evaluate the emergence of resistance to ABI-H2158 when administered in combination with ETV

The exploratory objectives of this study are as follows:

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

1.2. Study Design

This study will assess the safety, antiviral activity, and pharmacokinetics (PK) of ABI-H2158 administered once daily (QD) in combination with ETV in subjects with cHBV. Multiple parallel cohorts will be enrolled in the study.

In Cohort 1, approximately 40 treatment-naïve subjects with HBeAg positive cHBV will be randomized in a 3:1 ratio to receive 300 mg ABI-H2158+ETV (n=30) or matching PBO+ETV (n=10) for 72 weeks (Figure 1-1). In Cohort 2, approximately 40 treatment-naïve subjects with HBeAg negative cHBV will be randomized in a 3:1 ratio to receive 300 mg ABI-H2158+ETV (n=30) or matching PBO+ETV (n=10) for 72 weeks (Figure 1-1). Treatment assignments for Cohort 1 will be stratified by the HBV DNA level measured at the Screening visit (ie, $\geq$8.0 $\log_{10}$ IU/mL versus <8.0 $\log_{10}$ IU/mL) and for Cohort 2 will be stratified by the HBV DNA level measured at the Screening visit (ie, $\geq$6.0 $\log_{10}$ IU/mL versus <6.0 $\log_{10}$ IU/mL).

After completing treatment at Week 72, or following premature treatment discontinuation, all subjects will enter a 24 week follow-up period. During the follow-up period all subjects will remain on ETV and undergo the follow-up assessments. After completing the 24-week follow-up period, all subjects will resume management by their treating physician in accordance with local standard of care.

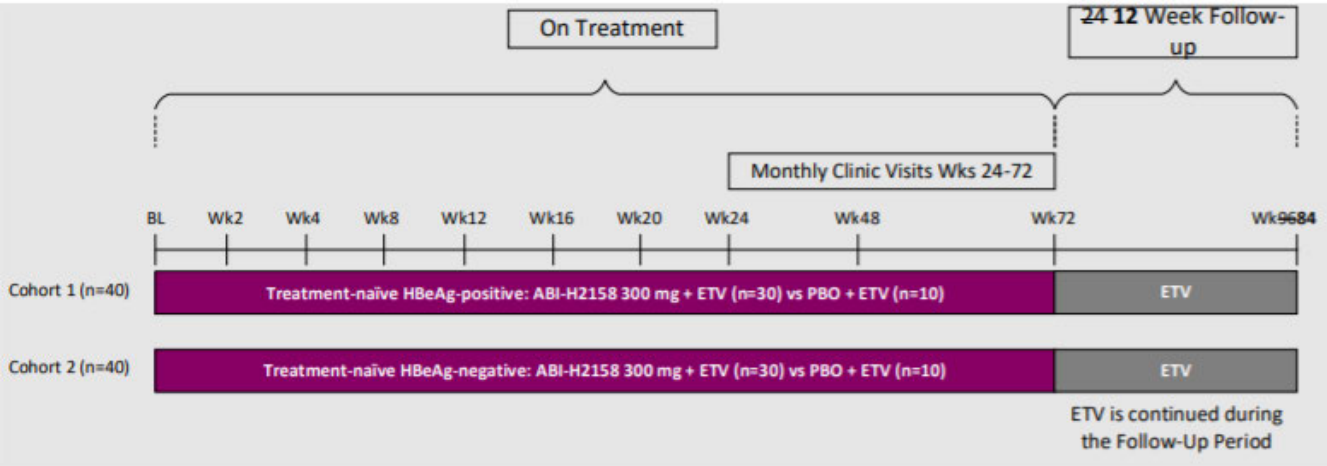
The schedule of assessments is presented in Protocol Appendix 1.

An assessment of PK data will also be performed after all subjects have completed study Week 4 (or discontinued study without completing Week 4) in order to confirm the absence of important drug interactions between ABI-H2158 and ETV at steady state.

Following the early termination of Study ABI-H2158-201, in accordance with the ABI-H2158-201 Protocol Clarification Letter for Amendment 2 dated 14 Dec 2020, 07 September 2021, subjects were instructed to complete the follow-up assessments through 12 weeks after the last dose of study medication.

Throughout the 12-week follow-up period, all subjects should continue treatment with ETV.

Figure 1-1. Study Overview



Abbreviations: PBO: placebo; ETV: entecavir; HBeAg: hepatitis B "e" antigen.

1.3. Sample Size and Power

It is planned that approximately 80 subjects (40 subjects per Cohort 1 and Cohort 2) will be enrolled in this study. Subjects will be randomized to receive either 300 mg ABI-H2158 or PBO or in a 3:1 ratio. That is, 30 subjects randomized to treatment with ABI-H2158 per Cohort 1 and Cohort 2 and 10 subjects will be randomized to treatment with PBO per Cohort 1 and 2. This sample size is not based on statistical considerations but is considered adequate for a proof-of-concept study.

1.4. Methods of Assigning Subjects to Treatment

1.4.1. Randomization

Within each treatment cohort, randomization of eligible subjects to their respective treatment assignments will be performed centrally using an Interactive Response Technology (IRT) system. Following successful completion of Screening assessments and confirmation of subject eligibility, site personnel will enter the subject specific information in the IRT system and following acceptable completion of the procedure will receive a subject identification number and treatment assignment. Additional information on the use of the IRT is provided in the IRT User Manual.

In Cohort 1, the IRT system will assign treatment-naïve subjects with HBeAg positive cHBV subjects in a 3:1 ratio to receive either 300 mg ABI-H2158+ETV (n=30) versus matching PBO+ETV (n=10). Individual subject treatment assignments will be stratified according to the HBV DNA level measured at the Screening visit (ie, $\geq$8.0 $\log_{10}$ IU/mL versus <8.0 $\log_{10}$ IU/mL).

In Cohort 2, the IRT system will assign treatment-naïve subjects with HBeAg negative cHBV subjects in a 3:1 ratio to receive either 300 mg ABI-H2158+ETV (n=30) versus matching

PBO+ETV (n=10). Individual subject treatment assignments will be stratified according to the HBV DNA level measured at the Screening visit (ie, ≥6.0 $\log_{10}$ IU/mL versus <6.0 $\log_{10}$ IU/mL).

1.4.2. Blinding

This is a single-blind study. Subjects, Investigators and other site personnel administering study drug, performing the clinical assessments, and handling data on the study subjects, will be blinded to individual subject treatments assignments (ie, ABI-H2158+ETV or PBO+ETV) throughout the duration of the study. The CRO and Sponsor study team responsible for study execution will also remain blinded to mitigate any potential operational bias. A DRC, comprising a limited number of internal Sponsor members who are independent of the study team, will be unblinded to individual subjects' treatment assignments for the prespecified safety data reviews (see Section 2.1).

2. TYPE OF PLANNED ANALYSIS

2.1. DRC Interim Analyses

An internal DRC will perform regular unblinded reviews of safety data to ensure timely analysis of any emergent safety/tolerability issues, and completion of the prespecified safety data reviews. As this is an exploratory Phase 2a study, the DRC will also assess the unblinded HBV virology parameter (HBeAg, HBsAg, HBcrAg, HBV DNA and HBV pgRNA) results at prespecified timepoints before the final analysis to make strategic decisions relating to drug development. The aggregated virology data may be released for external communication.

The initial DRC review will be conducted after approximately 25% of planned enrolled subjects in Cohort 1 have completed at least 4 weeks of treatment. Additional meetings will be scheduled approximately every month. In addition to regular review of safety and virology data, the DRC will also review the interim PK analysis when all randomized subjects in each cohort or approximately 2-5 subjects from South Korean sites, have completed Week 4 assessments or discontinued before completing Week 4.

The DRC will comprise Sponsor's representatives from Clinical Research and Biometrics. Other functional area members may be included as necessary. The DRC's role and responsibilities and the scope of the analysis will provided in a charter, which will define the DRC membership, meeting logistics, and meeting frequency. The DRC members will not be directly involved in the study conduct and will not have interactions with the study sites. The unblinded study results they may review and the meeting minutes, along with any decisions or recommendations made, will be archived in a secure location. All other Sponsor personnel will remain blinded until completion of the study.

The study remains blinded following the study termination. The DRC meetings are held to review and monitor the safety data after study drug discontinuation before the study unblinding.

2.2. Final Analysis

As of 01 September 2021, the study is early terminated. The final analysis to support a 'Synoptic Clinical Study Report' will be performed after all subjects have discontinued or completed the 12-week follow-up visits, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

Given that the study is early terminated, no formal statistical testing will be performed.

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

3.1. Analysis Sets

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

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

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

3.1.3. Safety Analysis Set

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

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set and FAS, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, subjects will be grouped according to the actual treatment received. The actual

treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via IRT in a 3:1 ratio to receive either 300 mg ABI-H2158+ETV (n=30) versus matching PBO+ETV (n=10) using a stratified randomization schedule. Stratification will be based on the HBV DNA level measured at the Screening visit as follows:

- For Cohort 1, HBV DNA level measured at the Screening visit, ≥8.0 $\log_{10}$ IU/mL versus <8.0 $\log_{10}$ IU/mL.
- For Cohort 2, HBV DNA level measured at the Screening visit, ≥6.0 $\log_{10}$ IU/mL versus <6.0 $\log_{10}$ IU/mL.

If there are discrepancies in stratification factor values between the IRT and the clinical database, the values recorded in the clinical database will be used for analyses.

3.4. Data Handling Conventions and Transformations

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

In general, laboratory data that are continuous in nature but are less than the lower limit of quantitation (LLOQ) or above the upper limit of quantitation (LOQ) will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is <20, a value of 19 will be assigned).

- A value that is 1 unit less than the LLOQ will be used to calculate descriptive statistics if the datum is reported in the form of "<x" (where x is considered the LOQ). For example, if the values are reported as <50 and <5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as <1 or <0.1, etc. For values reported as <1 or <0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of ">x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.
- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤x" or "≥x" (where x is considered the LOQ).

For selected analyses, virology efficacy data will be transformed to the logarithmic (base 10) scale ($\log_{10}$ IU/mL).

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

3.5. Missing Data and Outliers

3.5.1. Missing Data

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

For missing last dose date of study drug, imputation rules are described in Section 4.2.1. The handling of missing efficacy data is described in Section 6. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2.

3.5.2. Outliers

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

3.6. Analysis Visit Windows

3.6.1. Definition of Study Day

In this study, study drug is defined as ABI-H2158 (or matching PBO) and ETV.

The first dose date of ABI-H2158/PBO and of ETV will be calculated. Study Day 1 is defined as the first dose date of study drug, which is the minimum of the first dose dates of ABI-H2158 /PBO and ETV in a treatment group. If the first dose date is missing, the date of randomization will be used.

The last dose date of ABI-H2158/PBO and of ETV will be calculated. The last dose date for each drug will be the end date on the respective "Subject Disposition: End of the Treatment" eCRF. The last dose date of study drug will be defined as the maximum of the last dose dates of ABI-H2158/PBO and ETV in a treatment group.

Study day will be calculated from Study Day 1 and derived as follows:

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

For the follow-up period, the follow-up Study Day 1 is defined as the day after the last dose date of ABI-H2158/PBO and the follow-up study day will be calculated from the last dose date and derived as Assessment Date − Last Dose Date of ABI-H2158/PBO.

3.6.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. In general, the baseline value will be the last nonmissing value on or prior to the first dose date of study drug. The "on-treatment" period is defined up to the last dose date of ABI-H2158/PBO. The "off-treatment" period is defined after the last dose of ABI-H2158/PBO through the follow up period.

The assessment schedule is different in the Korea country specific protocol amendment. The analysis window will follow what is specified in the global protocol.

The analysis windows for on-treatment study assessments, including HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, adverse events, and clinical laboratories (chemistry, hematology, coagulation, urinalysis) are provided in Table 3-1.

Table 3-1. On-Treatment Analysis Visit Windows for Study Assessments

Nominal Visit	On-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	(none)	1
Week 2	14	2	21
Week 4	28	22	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	99	126
Week 20	140	127	154
Week 24	168	155	182
Week 28	196	183	210
Week 32	224	211	238
Week 36	252	239	266
Week 40	280	267	294
Week 44	308	295	322
Week 48	336	323	350
Week 52	364	351	378
Week 56	392	379	406
Week 60	420	407	434
Week 64	448	435	462
Week 68	476	463	490

Nominal Visit	On-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Week 72	504	491	≥504

The analysis windows for electrocardiograms (ECG) measurements are provided in Table 3-2.

Table 3-2. On-Treatment Analysis Visit Windows for ECG

Nominal Visit	On-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Day 1	1	(none)	1
Week 12	84	2	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	≥504

The analysis windows for off-treatment study assessments, including HBV DNA, HBV pgRNA, HBsAg, HBeAg, HBcrAg, vital signs, concomitant medications and adverse events, chemistry, hematology, coagulation and urinalysis are provided in Table 3-3.

Table 3-3. Off-Treatment Analysis Visit Windows for Study Assessments

Nominal Visit	Off-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
FU-Week 4	28	1	42
FU-Week 8	56	43	70
FU-Week 12	84	71	≥84

The analysis windows for ECG is provided in Table 3-4.

Table 3-4. Off-Treatment Analysis Visit Windows for ECG

Nominal Visit	Off-Treatment Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
FU-Week 12	84	1	≥84

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

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

- For Baseline, the last nonmissing value on or prior to the first dose date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity for categorical data (eg, normal will be selected over abnormal for safety ECG findings).

- For postbaseline values:

    - The record closest to the nominal day for that visit will be selected with the exception of virology parameters in which the latest record will be selected. For the virology parameters, the later record will be selected.

    - If there are 2 records that are equidistant from the nominal day, the later record will be selected.

    - If there is more than 1 record on the selected day with the same time, the retest record will be selected.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

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

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

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

- Full Analysis Set
- Safety Analysis Set

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

- Completed ABI-H2158/PBO
- Did not complete ABI-H2158/PBO and reasons for study drug discontinuation
- Completed ETV
- Did not complete ETV and reasons for study drug discontinuation
- Completed study
- Did not complete the study and reasons for study discontinuation

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

4.2. Extent of Study Drug Exposure

Extent of exposure to ABI-H2158/PBO and to ETV will be examined by assessing the total duration of exposure to each drug.

4.2.1. Duration of Exposure to Study Drug

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

The total duration of exposure to ABI-H2158/PBO and to ETV will be summarized using descriptive statistics. Summaries will be provided by treatment group for the Safety Analysis Set. The expected total duration of on-treatment therapy for all subjects is 72 weeks. The distribution of subjects by the total number of weeks on therapy (ie, <12 weeks, 12 -<24 weeks, 24 -<48 weeks, ≥48 weeks) will be presented. The cumulative distribution of subjects will also be presented using the following cutoffs: at least 1 dose, ≥2 weeks, ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥24 weeks, ≥36 weeks, ≥48 weeks, and ≥72 weeks.

4.2.2. Study Drug Compliance

The total number of tablets administered and average daily dose will be summarized using descriptive statistics.

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

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

4.2.2.1. On-Treatment Compliance

The level of on-treatment compliance to ABI-H2158/PBO and to ETV will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period.

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

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

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

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

4.3. Protocol Deviations

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

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

A table will be provided to summarize any COVID-19 related PDs with the deviation reason by treatment group. A table will also be provided to summarize visits that were not performed along with the reason they were not performed. A by-subject listing of subjects who missed visits along with reasons for missed visit will be provided.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, age group [<50/ ≥50 years], sex, race, and ethnicity), baseline characteristics (body weight, height, body mass index [BMI; in kg/m^2]) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set.

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

5.2. Baseline Disease Characteristics

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

- Years positive for HBV
- HBV Genotype
- Baseline HBV DNA (log_{10} IU/mL)
- Baseline HBV DNA groups: ⩾8.0 log_{10} IU/mL and <8.0 log_{10} IU/mL for Cohort 1, and ⩾6.0 log_{10} IU/mL, <6.0 log_{10} IU/mL for Cohort 2
- Baseline HBV pgRNA (log_{10} U/mL)
- Baseline HBeAg (log_{10} IU/mL)
- HBeAg group (< LLOQ)
- Baseline HBcrAg (log_{10} kU/mL)
- HBcrAg group (< LLOQ)
- Baseline HBsAg (log_{10} IU/mL)
- HBsAg group (< LLOQ)
- Baseline HBeAg antibody (HBeAb)

- Baseline HBsAg antibody (HBsAb)
- Baseline antibody to the HBV core-related antigen (HBcrAb)
- Baseline ALT (U/L)
- ALT group (>ULN [Covance], >ULN [AASLD])
- Fibroscan result
- Metavir Fibrosis Stage

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

5.3. Medical History

Medical history collected at Screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v23.0. Medical history will be summarized by preferred term (PT), treatment group and overall. Subjects who report 2 or more medical history items that are coded to the same PT will be counted only once by the unique coded term in the summary. The summary will be provided for the Safety Analysis Set.

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

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

6. EFFICACY ANALYSES

The primary analysis set for efficacy analyses will be the FAS, defined in Section 3.1.2. The efficacy analyses will be performed for the 2 cohorts separately. Nominal p-values will be presented for any treatment comparisons. No multiplicity adjustment will be made.

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the change in mean $\log_{10}$ HBV DNA from Baseline to Week 24 for ABI-H2158+ETV compared to PBO+ETV.

6.1.2. Primary Analysis of the Primary Efficacy Endpoint

The primary comparison will be made using an analysis of covariance (ANCOVA) model, including baseline value, stratification factors, and treatment group. The estimated least square means of treatment effects and estimated difference in treatment effects between treatment groups at Week 24 will be presented along with the 95% CIs and p-values. The primary analysis will be based on observed data.

Summary statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided for the observed and change from Baseline by treatment group and study visit.

Analysis will be based on observed data only. No imputation will be done for missing data.

6.2. Changes From Protocol-Specified Efficacy Analyses

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

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v23.0. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the Investigator selected "Related" on the AE eCRF to the question of "Relationship to Study Treatment" based on the his/her clinical assessment. Events for which the Investigator misses to record a relationship to ABI-H2158/PBO or to ETV will be considered related to the corresponding drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs with an onset date on or after first dose date of study drug and no later than 28 days after permanent discontinuation of ABI-H2158/PBO.

7.1.5.2. Incomplete Dates

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

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

- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 28 days after the date of the last dose of ABI-H2158/PBO

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

7.1.6. Summaries of Adverse Events and Deaths

Treatment emergent AEs will be summarized based on the Safety Analysis Set.

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

- TEAEs

- TEAEs by severity grade

- TE SAEs

- TEAEs leading to ABI-H2158/PBO discontinuation

- TEAEs leading to ETV discontinuation

- TEAEs leading to study discontinuation

- TEAEs related to ABI-H2158/PBO

- TEAEs related to ETV

- TE SAEs related to ABI-H2158/PBO

- TE SAEs related to ETV

- COVID-19 specific TEAEs

- COVID-19 specific TE SAEs

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

A brief, high-level summary of the number and percentage of subjects who experienced at least 1 off-treatment AE in the same categories as the TEAEs except for the AEs leading to ABI-H2158/PBO discontinuation will be provided by treatment group. In addition, a table for each category showing the number and percentage of subjects will be provided by PT and treatment group in descending order of total frequency. The off-treatment AEs are counted starting from 29 days after the last dose of ABI-H2158/PBO.

A data listing containing all AEs will be provided.

7.2. Laboratory Evaluations

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

7.2.1. Graded Laboratory Values

The criteria specified in the study protocol will be used to grade laboratory results as normal (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3) or potentially life threatening (Grade 4). See Protocol Appendix 2 for detailed DAIDS grading criteria on the relevant laboratory tests. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.1.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from Baseline at any postbaseline time point, up to and including the date of last dose of ABI-H2158/PBO plus 28 days or subjects who permanently discontinued ABI-H2158/PBO. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.1.2. Summaries of Laboratory Abnormalities

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

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 28 days after last dose date of ABI-H2158/PBO.

The maximum postbaseline grade observed up to 28 days after last dose date will be tabulated for each laboratory test, and percentages will be based on the number of subjects with a postbaseline evaluation of the specific laboratory test.

Graded lab abnormalities will be also be summarized for the off-treatment period. Lab abnormalities are included starting from 29 days after the last dose of ABI-H2158/PBO.

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

7.2.2. ALT Elevation

7.2.2.1. ALT Elevation without Declining Hepatic Function

A confirmed ALT elevation on treatment is defined as ALT >2 × Baseline or on-treatment nadir and ≥10 × ULN(Covance) at 2 consecutive visits.

7.2.2.2. ALT Elevation with Declining Hepatic Function

A confirmed ALT elevation with evidence of declining hepatic function is defined as meeting the following criteria at 2 consecutive visits:

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

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

7.3. Vital Signs

Descriptive statistics will be provided by treatment group for vital signs including heart rate, respiration rate, blood pressure, and body temperature as follows:

- Baseline value
- Values at each postbaseline time visit

- Change from Baseline at each postbaseline visit

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

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

A by-subject listing of vital signs (systolic and diastolic blood pressure [mmHg], respiration rate [breaths/min], heart rate [bpm] and body temperature) will be provided by subject ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using WHODrug-Global-B3 v202003 of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

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

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

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

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

Summaries will be based on the Safety Analysis Set.

7.4.2. Concomitant Medications

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

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

- A medication with a start date prior to or on the first dose date of study drug, and continued to be taken after the first dose date.
- A medication started after the first dose date but prior to or on the last dose date of study drug.
- If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) before study drug stop date and the stop date after the first dose date of study drug. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the first dose date of study drug
- A medication started and stopped on the same day as the first dose date or the last dose date of study drug
- Medications with completely missing start and stop dates, unless otherwise specified.

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

Summaries will be based on the Safety Analysis Set.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram Results

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

- normal

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

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

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

8. REFERENCES

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

9. SOFTWARE

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

10. SAP REVISION

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

Signature Page for [redacted]

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 25-Jan-2022 19:22:38 GMT+0000

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