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

NCT number: NCT03576066

Date: 06 Aug 2019

Statistical Analysis Plan

Sponsor:	Assembly Biosciences
Protocol No:	ABI-H0731-201
PRA Project Id:	ASM31201-731201
Protocol Version:	Amendment 3 v4.0 / 09 November 2018 Amendment 2 v3.0 / 09 September 2018 Amendment 1 v2.0 / 18 June 2018 Original v1.0 / 10 May 2018

Title:	A Phase 2a, Multi-center, Double-blind, Placebo-controlled Study Evaluating ABI-H0731 as Adjunctive Therapy in Virally-suppressed Patients with Chronic Hepatitis B
CRF Version Date:	15 Jan 2019
SAP No./Date	Final v1.0 / 06 Aug 2019

1.0 Approvals

Sponsor: Assembly Biosciences	
Representative/ Title:	[redacted]
Signature /Date:	
Representative/ Title:	
Signature /Date:	
PRA	
Project Manager/Title:	
Signature /Date:	
Biostatistician / Title (Owner):	
Signature /Date:	

Statistical Analysis Plan

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2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Assembly Biosciences Protocol ABI-H0731-201, "A Phase 2a, Multi-center, Double-blind, Placebo-controlled Study Evaluating ABI-H0731 as Adjunctive Therapy in Virally-suppressed Patients with Chronic Hepatitis B".

3.0 Scope

This plan is a living document that will be created during the trial start-up. The Statistical Analysis Plan will be drafted within three months of final CRF and maintained throughout the lifecycle of the trial. Each version of the SAP will require sign off from the Project Manager and the sponsor prior to programming starting or being updated as a result of an amended version of the SAP.

The SAP outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, efficacy analysis, concomitant medications, adverse events handling, laboratory data and physical examinations

4.0 Introduction

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the amended protocol v3.0 dated 09NOV2018 and CRF dated 15JAN2019. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Versions of the SAP up to sponsor approval will be known as a draft SAP. Programming activities will commence upon finalization and approval of the SAP. If necessary, changes following final approval of the SAP will be tracked in the SAP Change Log. The final sponsor approval of any amended version of the SAP will occur prior to database lock.

4.1 Changes from Protocol

Subjects entered study with additional NUCs not originally noted in the protocol. These NUCs are recorded as ongoing concomitant medications in the CRF.

Protocol Specified NUCs	Additional NUCs
entecavir (ETV)	Descovy (emtricitabine and tenofovir alafenamide)
tenofovir alafenamide fumarate (TAF)	Truvada (emtricitabine and tenofovir disoproxil fumarate)
tenofovir disoproxil fumarate (TDF)	Tenofovir (Tenofovir disoproxil fumarate) and entecavir

Following an increase in the number of subjects in the sister protocol (ABI-H0731-202), the timing of DMC meetings was changed to accommodate the two protocols in a single programmatic overview. As a result, instead of requiring all subjects in study 202 (and separately in study 201) to have completed Week 12 prior to triggering a DMC, the DMC trigger was based on 25% of subjects across BOTH studies completing a week 12 visit and 75% of all subjects completing a Week 12 visit.
PK sample collection for subjects to provide optional samples on Weeks 2 or 4, that were not able to provide optional PK samples on Day 1 was changed to: Optional sample collection on Day 1, Week 2, or Week 4 are not dependent on collection at any prior or subsequent sample collection time.

5.0 Study Objectives

5.1 Primary Objectives

The primary objective of the study is to evaluate the potential for ABI-H0731 to increase clinical cure rates in subjects with chronic hepatitis B infection (CHB) whose viral replication is stably suppressed on a standard of care (SOC) nucleos(t)ide (NUC) therapy, as measured by changes from Baseline in serum biomarkers (i.e. hepatitis B surface antigen [HBsAg] or hepatitis B e antigen [HBeAg]) of transcriptionally active covalently closed circular DNA (cccDNA).

5.2 Secondary Objectives

The following secondary objectives are defined for this study:

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

5.3 Exploratory Objectives

The following exploratory objectives are defined for this study:

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

6.0 Study Design

This Phase 2a, multi-center, randomized, double-blind, placebo-controlled study will assess the safety, efficacy, PK, and pharmacodynamics of 300 mg ABI-H0731 daily in combination with SOC NUC therapy in subjects with CHB virus infection who are already virally suppressed on SOC NUC therapy at entry to study. Seventy subjects will be stratified in a ratio of 9:5 (i.e. 45 HBeAg positive subjects: 25 HBeAg negative subjects) and randomized to treatment groups in a 3:2 ratio to receive investigational agent as add-on therapy to their current SOC NUC therapy for up to 6 months (24 weeks).

HBeAg Positive (N=45):

- 27 subjects will receive ABI-H0731 + NUC therapy
- 18 subjects will receive matching placebo + NUC therapy.

HBeAg Negative (N=25):

- 15 subjects will receive ABI-H0731 + NUC therapy
- 10 subjects will receive matching placebo + NUC therapy.

NUC treatment will continue uninterrupted for the duration of the study as well as during follow-up.

Safety will be monitored by a Data Monitoring Committee (DMC), including a safety analysis when approximately 25% and 75% subjects (across ABI-H0731-201 Amendment 3 v4.0 / 09 November 2018 and ABI-H0731-202 Amendment 1 v2.1 / 30 July 2018 [UK only] Amendment 1 v2.0 / 18 June 2018 [USA, Canada, NZ, HKG] studies) complete their Week 12 visit (or discontinues before completing Week 12). This timing differs from that defined in the protocol, following an amendment adding of 25 additional subjects to the ABI-H0731-201 protocol, to allow for earlier identification of potential safety events that may arise. There will be an assessment of PK data after all subjects have completed Week 4 (or discontinued study without completing Week 4) to confirm a lack of an important impact of ABI-H0731 on the steady-state PK of SOC NUC therapy.
At the end of the 24-week treatment period in this study, subjects will either continue their SOC NUC therapy and stop treatment with ABI-H0731/placebo, or they may elect to roll over onto the optional, open-label, extension study ABI-H0731-211.

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

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

6.1 Sample Size Considerations

As a proof-of-concept trial, there are no statistical hypotheses, per se, regarding treatment effects in this study. Rather, displays and comparisons of study results, regarding dose-related safety, efficacy, and PK profiles among the treatment groups, will primarily utilize descriptive statistics.

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

Subjects will be stratified 9:5 (HBeAg positive: HBeAg Negative). HBeAg positive subjects and HBeAg negative subjects will be evaluated both together and independently. With a sample size of 45 HBeAg positive subjects, randomized in a 3:2 ratio (27 active:18 placebo), a 2-sample t-test with a 2-sided α=0.05 significance level has 89.5% power to detect a difference of at least 0.5 log10 (IU/mL) in the mean change from Baseline in serum HBsAg or HBeAg at Week 24 (Table 1). A similar test has 80% power to detect a treatment difference of at least 0.6 log10 (IU/mL) in the change from Baseline in serum HBsAg at Week 24 in HBeAg negative subjects (Table 2). An equal standard deviation of 0.5 is assumed for both treatment groups.

Table 1 HBeAg Positive Subjects: Power Calculations under Various Mean Differences in the Change from Baseline in HBsAg (or HBeAg) levels at Week 24 between Treatment Groups

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

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

Table 2 HBeAg Negative Subjects: Power Calculations under Various Mean Differences in the Change from Baseline in HBsAg levels at Week 24 between Treatment Groups

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

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

6.2 Randomization

Approximately 70 subjects will be stratified 9:5 HBeAg positive to HBeAg negative and randomized in a 3:2 ratio by an independent Interactive Web Response System (IWRS) vendor to receive investigational agent as add-on therapy to their current SOC NUC therapy for up to 6 months (24 weeks).

HBeAg positive subjects (N=45):

27 subjects will receive ABI-H0731 + NUC therapy: 18 subjects will receive matching placebo + NUC therapy.

HBeAg negative subjects (N=25):

15 subjects will receive ABI-H0731 + NUC therapy: 10 subjects will receive matching placebo + NUC therapy.

6.3 Schedule of Assessments

The study schedule of assessments per Amendment 3 v4.0 dated 09 November 2018 is noted in Table 3.

Table 3. Schedule of Assessments

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

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

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

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

c Any subjects with rash or ALT flare (defined as ALT≥2×Baseline and ≥10×ULN) should return to the clinic for an unscheduled visit as soon as possible, ideally within 3 days.

Unscheduled visit for ALT flare: All subjects should have the laboratory findings confirmed within 3 days of receipt of the original results. All subjects should undergo a symptom directed physical examination and the following laboratory tests: ALT, AST, total bilirubin, INR, and serum albumin. If the ALT flare is confirmed, perform the following tests: HBV DNA, quantitative HBV serologies (HBeAg [reflex qualitative HBeAg if quantitative HBeAg is negative] and HBsAg [reflex qualitative HBsAg if quantitative HBsAg is negative], HAV IgM, HCV RNA, HDV RNA, and HEV IgM

Unscheduled visit for rash: Digital photographs of the rash should be taken and blood samples should be taken (for erythrocyte sedimentation rate, complete blood count [with differential], creatinine, ALT, AST, and total bilirubin). If the rash diagnosis is uncertain, or if a rash is Grade 2, a referral to a dermatologist should be made and a biopsy should be conducted if recommended by the dermatologist. For a rash that is Grade 3 or higher, a referral to a dermatologist should be made and a biopsy should be requested of the

dermatologist. All dermatologist reports and biopsy results will be included in the source and eCRF. Digital photographs of the rash should be obtained at each visit to document any change in condition. Unscheduled visits should continue until the rash has resolved or declined to Grade 1 or less for two successive visits.

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

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

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

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

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

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

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

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

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

7.0 Study Endpoints, Variables and Covariates

7.1 Efficacy Endpoints and Variables

7.1.1 Primary Efficacy Endpoints

The primary endpoint is viral antigen decline (serum HBsAg or HBeAg), measured as the change in mean log_{10} serum viral antigen from Baseline to Week 24.

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7.1.2 Secondary Endpoints

The following secondary endpoints will be evaluated:

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

Safety endpoints as outlined in Section 7.2 will be evaluated.

7.1.3 Exploratory Endpoints

Blood samples for the assessment of exploratory efficacy endpoints are collected according to the Schedule of Assessments (Table 2). These variables include quantitative/qualitative HBsAg and HBeAg levels, HBsAg antibody (HBsAb) and HBeAg antibody (HBeAb), HBV DNA viral load, HBV RNA, and HBCrAg.

The primary efficacy variables, quantitative HBsAg and HBeAg, will be collected at Screening, Day 1, and Weeks 4, 8, 12, 16, 20, and 24 (or at the time of discontinuation).

Follow-up samples will be collected at Weeks 28 and 36 for subjects who do not continue treatment in the extension protocol. Subjects who enter the optional extension protocol (ABI-H0731-211) will have samples collected according to that protocol.

Reporting for assessments of HBeAg seroconversion (loss) will include only those subjects with detectable (positive) HBeAg viral antigen at baseline.

Reporting for assessments of HBV RNA will include only those subjects with detectable (positive) HBV RNA at baseline.

The assessments will be reported using Covance labs, or Assembly Labs. The incidence of LOQ values for each of these assessments will be reported and for numerical summaries the value at LOQ will be reported.

The following exploratory efficacy endpoints will be evaluated using these variables:

- The mean change from baseline in serum HBV RNA and HBCrAg levels at each time point where collected
- Percent of subjects with loss (defined as below LOQ) or decline in HBsAg or HBeAg (< 0.5 log_{10}, ≥ 0.5 to 1.0 log_{10}, or > 1.0 log_{10} decrease in viral antigen) at end of treatment and end of follow-up
- Percent of subjects with HBsAg seroconversion (loss of HBsAg and appearance of HBs antibody) or HBeAg seroconversion (loss of HBeAg and appearance of HBe antibody) at each timepoint
- Percent of subjects with HBV DNA “detectable” at Baseline whose HBV DNA becomes “non-detectable” at each timepoint
- Incidence of emergence of resistant HBV variants, if any

- For subjects who do NOT rollover onto the optional extension study, ABI-H0731-211:
    - Percent of subjects with suppression of detectable serum HBV RNA on treatment whose HBV RNA rebounds after discontinuing treatment during Post-Treatment follow-up with ABI-H0731 + SOC NUC as compared with placebo + SOC NUC
    - Percent of subjects with changes in HBsAg or HBeAg whose viral antigen rebounds after discontinuing treatment during Post-Treatment follow-up with ABI-H0731 + SOC NUC as compared with placebo + SOC NUC
    - Percent of subjects with HBsAg or HBeAg loss at Week 24 that is maintained through the end of Post Treatment follow-up (Week 36) after discontinuing treatment with ABI-H0731 + SOC NUC as compared with placebo + SOC NUC

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

Pharmacogenomic (PG) samples will be collected at Day 1 for subjects who provide separate informed consent. These samples may be saved for future research. If differences are noted in outcomes between racial or ethnic groups, the correlation between PG variables with clinical outcomes may be evaluated for subjects who provide optional informed consent.

7.2 Safety Endpoints and Variables

The safety variables noted in this section will be used to evaluate the following set of secondary safety endpoints:

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

7.2.1 Adverse Events

Adverse events will be coded using MedDRA 21.0 (March 2018) and graded by Medidata Rave Coding tool.

AEs will be monitored and reported from the time written informed consent is signed until completion of the Week 36 follow-up visit or until 30 days following cessation of the last dose of treatment with the study drug for subjects who discontinue from follow-up. For subjects who roll over into extension study ABI-H0731-211, AEs that have not resolved by time of rollover will continue to be followed in study ABI-H0731-211.

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

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

An AE will be considered a treatment-emergent AE (TEAE) if it first occurs or begins previous to and worsens on or after the first study drug dose date and before the last dose date + 30 days.

The following AE details will be recorded on the eCRFs:

- Adverse event (verbatim)
- Whether the AE is an adverse event of special interest (AESI). AESI's include rash and ALT flare.

- Start / end date of the AE
- Whether the AE is serious or not, and if yes, which category (AE resulted in death; AE is life-threatening; AE resulted in persistent or significant disability or incapacity; AE resulted in initial or prolonged hospitalization; AE is associated with a congenital anomaly or birth defect; AE is a medically important event not covered by other criteria).
- Relationship to Study Treatment (Not related; Unlikely related; Possibly related; Related)
- Action taken with Study Treatment (Dose not changed; Drug interrupted; Drug withdrawn; Not applicable; Unknown)
- Intensity (Mild (Grade 1); Moderate (Grade 2); Severe (Grade 3); Life threatening (Grade 4))
- Outcome (Fatal; Not recovered/not resolved; Recovered/resolved; Recovered/resolved with sequelae; Recovered/resolving; Unknown)
- Non-study drug treatment received for the AE

The intensity of each AE and laboratory abnormality will be assessed by the Investigator according to the modified Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (noted in APPENDIX II of the protocol), which grades the severity of clinical AEs and laboratory abnormalities in a four-category system.

7.2.2 Clinical Laboratory Tests

Clinical laboratory tests will be performed at the timepoints indicated in the Schedule of Assessments (Table 3). The clinical laboratory assessments are listed in Table 4.

Table 4 Clinical Laboratory Tests

Panel	Tests
Clinical chemistries	Blood glucose levels, serum or plasma electrolytes (sodium, potassium, chloride, bicarbonate), calcium, blood urea nitrogen, creatinine, uric acid, total and direct bilirubin [a], ALT, aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, lactate dehydrogenase (LDH), amylase, triglycerides, total cholesterol, inorganic phosphate or total phosphate, total protein, albumin, lipase, and total serum or plasma globulins
In case of ALT flares	ALT, AST, total bilirubin, serum albumin, and INR
Hematology	Complete blood counts: hemoglobin, hematocrit, RBC indices (MCV, MCHC), reticulocyte counts, leukocyte counts (total and differential), and platelet counts
Coagulation	Prothrombin time, INR and aPTT
Urinalysis	pH, specific gravity, protein, glucose, ketones, and occult blood
Rash Panel	Erythrocyte sedimentation rate, complete blood count (with differential), creatinine, ALT, AST, and total bilirubin.
Other	AFP, HbA1c, and FSH
Pregnancy tests	For females only; a serum or plasma pregnancy test must be performed at screening, and both serum/plasma and urine are required Day 1; urine pregnancy test may be performed at all subsequent visits. A positive result disqualifies the subject for study treatment
Urine drug screening	Amphetamine/methamphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine metabolite, ecstasy, ethanol, opiates, phencyclidine, and propoxyphene. Note: If cannabinoids are not illegal in the subject's local, cannabinoids are not exclusionary
Antibodies	HCV, HDV, HAV IgM, HEV IgM, and HIV

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

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

During the study, any clinically significant laboratory abnormality or clinically significant change from Baseline will be recorded as an AE.

7.2.3 Vital Signs

Vital signs will be collected at screening, Day 1, and Weeks 2, 4, 8, 12, 16, 20, and 24 (or at the time of discontinuation). Follow-up samples will be collected at Weeks 28 and 36 for subjects who do not continue treatment in the extension protocol.

Variables will include temperature, systolic blood pressure, diastolic blood pressure, pulse rate, and respiratory rate. Additionally, height, weight, and body mass index (BMI) will be collected on the CRF at screening, with weight collected again at Day 1, and Weeks 4 and 24, and Week 36 for subjects who remain in the follow-up period.

7.2.4 12-Lead ECG

Twelve-lead ECGs will be collected at Screening, Day 1, and Weeks 12, 24, and 24 (or at the time of discontinuation). Follow-up ECGs will be collected at Week 36 for subjects who do not continue treatment in the extension protocol. During the study, any clinically significant ECG result should be confirmed, and if confirmed, should be recorded as an AE.

7.3 Pharmacokinetic Endpoints and Variables

The pharmacokinetic endpoints for this study are as follows:

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

Pre-dose drug concentration samples will be collected to determine trough concentrations of ABI-H0731 and the SOC NUC therapy. Post-dose samples for both ABI-H0731 and SOC NUC will be collected from subjects willing and able to provide the sample at 4 ± 2 hours after in-clinic dosing. Sample collection timing is outlined in Table 5.

Table 5 Pharmacokinetic Sample Collection

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

a A PK sample should be collected if an unscheduled or premature termination visit is performed.

b Sample collection times are targeted times. Samples collected outside of these targeted times will not be considered protocol deviations as long as the actual time the sample is collected is accurately recorded on source documentation and the case report form.

c Optional sample collection on day 1, week 2, or week 4 are not dependent on collection at any prior or subsequent sample collection time.

7.4 Other Variables

Other assessments that will be collected and included for analyses include:

- Demographic characteristics, including sex, ethnicity and race
- Liver screening using Fibroscan categorization method of F0 through F2.
- Prior and concomitant medications
- HBV treatment history
- Medical and surgical history
- Procedures
- Complete and symptom-directed physical examinations
- Drugs of Abuse testing
- Pregnancy testing
- Exposure and compliance to study medication

7.5 Predetermined Covariates and Prognostic Factors

Race, ethnicity, and HBV genotype (A, B, C, D, E-H) will be used as a covariate where indicated within the analysis.

8.0 Definitions

The following table will be used to define variables used within the statistical tables, figures, and listings.

Table 6 Variables and Definitions

Variable	Definition
Baseline	Baseline is defined as the value closest to but prior to the initiation of study drug administration.
Change from Baseline	Change from baseline will be defined as the post-baseline value minus the baseline value, where applicable (on a subject level). Change from baseline will only be calculated for subjects who have both baseline and at least one post-baseline value for any parameter.
Study Day	Study Day 1 will be based on the date of first dose. Events prior to this day will be reported as a negative study day (i.e. there will be no Day 0). The study day of an event will be calculated as (event date) – (first dose date) when the event occurred prior to first dose, and (event date) – (first dose date) + 1 when the event occurred after first dose.
Duration Variables	Duration variables (ex. time in study, exposure to study drug treatment, days since last visit, duration of AEs, etc.) will be calculated using the general formulas below: Duration (days) = (End date - Start date) + 1 Duration (weeks) = Duration (days) / 7 Duration (months) = Duration (days) / 30.25
Body Mass Index (BMI)	Where not collected on the eCRF, BMI will be calculated as: BMI = Weight (kg) / Height $(m)^2$

9.0 Analysis Sets

9.1 Intention-to-Treat

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

9.2 Safety

The safety population will include all randomized subjects who received any amount of study drug. Subjects in this population will be analyzed according to the actual treatment received.

9.3 Pharmacokinetic

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

Pharmacokinetic Population 2 (PK2): The PK2 population will include all subjects in the safety population who have SOC NUC PK data assessments available. Subpopulations of the PK 2 population will be defined by the specific SOC NUCs taken during the study: 1) SOC NUC TDF, 2) SOC NUC TAF, 3) SOC NUC ETV, 4) Any other combination. For SOC NUC of TDF + ETV, subjects will be included in both 1) and 3) SOC NUC subpopulations for PK2 population.

9.4 Pharmacogenomic

The pharmacogenomic population will consist of subjects who have consented to, and have provided, an optional PG sample. Subjects in this population will be analyzed according to the actual treatment received.

10.0 **Interim Analyses**

No formal interim analyses are planned. However, there will be a Week 4 PK analysis as well as a Data Monitoring Committee safety analysis for all data collected when approximately 25% and 75% subjects (across ABI-H0731-201 and ABI-H0731-202 studies) complete their Week 12 visit (or discontinues before completing Week 12). An unblinded statistician and programmer will provide these analyses.

An informal safety and efficacy analysis may be conducted opportunistically for presentation at interim medical conference.

10.1 Week 4 Pharmacokinetic Analysis

After all subjects have completed Week 4 (or discontinued before completing Week 4), PK data will be reviewed by an unblinded pharmacology reviewer from Assembly and/or a representative from PRA to verify whether NUC steady-state exposure levels are affected by combination treatment with ABI-H0731.

Results will be provided once reviewed and will include trough levels and trough to peak ratios (as available) for ABI-H0731 and NUC concentrations in tabular and graphical format. The list of statistical outputs to be produced for the DMC members and the unblinded Sponsor statistician will be documented in the ABI-H0731-201 and ABI-H0731-202 DMC Data Transfer Plan and PK Data Transfer Plans as applicable.

These results will be provided for the PK1 and PK2 Populations in an unblinded manner by treatment group, delivered by the unblinded PRA statistician. The unblinded PK results will be posted on a user-restricted study portal to ensure that only the intended recipients have access to the results. The unblinded recipient(s) specified below will be notified when results are posted to complete their review of the unblinded PK data.

Name	Title and Company	Email
[redacted]		

10.2 Week 12 Safety Analysis

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

Details of the DMC will be outlined separately in a DMC Charter. The charter will detail data to be analyzed, and will identify members of the DMC, responsibility of those members, and frequency of meetings.

These results will be provided to the DMC members and the Sponsor's designated unblinded statistician in an unblinded manner delivered by the unblinded PRA statistician for posting on a user-restricted study portal, to ensure that only the intended recipients have access to the results. The unblinded recipients will be notified when results are posted. Details of the distribution of data outputs to the DMC members and sponsor's designated unblinded statistician will be outlined in the DMC Charter.

The list of statistical outputs to be produced for the DMC members and the unblinded Sponsor statistician will be documented in the ABI-H0731-201 and 202 DMC Data Transfer Plan; including a separate set of unblinded TFL shells for unblinded DMC members and the unblinded Sponsor statistician and a separate set of blinded TFLs for the blinded Sponsor team members.

11.0 **Data Review**

11.1 Data Handling and Transfer

Details regarding the data handling, including how data is received by external vendors and which data is included in cleaning and transfers of data, are referenced in the ABI-H0731-201 Data Management Plan.

11.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets and TFLs provides additional data screening. Presumed data issues will be output into SAS logs identified by the word “Problem” and extracted from the logs by a SAS macro and sent to Data Management.

The PRA statistician and the Sponsor must approve database lock.

12.0 **Statistical Methods**

12.1 General Considerations

All analyses will use SAS version 9.4 or higher. Results will be reported by stratification (HBeAg positive or HBeAg negative), and treatment group, based on the following test and reference product categories:

- **ABI-H0731**: This group will include subjects receiving test product ABI-H0731 in addition to their standard of care NUC therapy (which must include either entecavir [ETV], tenofovir alafenamide fumarate [TAF], or tenofovir disoproxil fumarate [TDF]).
- **Placebo:** This group will include subjects receiving placebo (matching placebo to ABI-H0731 tablets) in addition to their SOC NUC therapy

Data from each participating investigational study site will be pooled together for all analyses.

Adjustments for multiplicity will not be made since this is a proof-of concept study. Separate inferences will be drawn for assessment.

Unless otherwise noted, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% which will be displayed without any decimal places. Percentages will not be displayed for zero counts.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. The minimum and maximum values will be displayed to the same level of precision as the raw data, the mean and median to a further decimal place and the SD to two additional decimal places.

Confidence intervals will be two-sided and use the Clopper-Pearson (exact binomial) method at a 95% confidence level.

12.2 Handling of Missing Data / Imputation Methods

All attempts will be made to prevent missing data.

To assess robustness of the primary efficacy variables, sensitivity analysis with missing values imputed by MMRM Using Multiple imputation (MI) will be performed see Appendix 2 for multiple imputation method.

Missing data will only be imputed for the co-primary endpoints. Percent of subjects with missing visits, and total missing visits per lab assessment may be summarized for the primary, secondary, and exploratory endpoints to assess the effect on repeated measures analysis for these endpoints.

All missing and partial dates for adverse events will be queried for a value. If no value can be obtained, substitutions will be made as detailed in Table 7. These substitutions will be used in calculations, however, the actual value recorded on the eCRF will be presented in all listings.

Table 7. Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of treatment	Date of first dose of treatment
		M and/or Y not same as date of first dose of treatment	First day of month
	D and M	Y same as Y of first dose of treatment	Date of first dose of treatment
		Y prior to Y of first dose of treatment but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of treatment
Stop date for AEs	D	M and Y same as M and Y of last dose of treatment	Date of last dose of treatment
		M and/or Y not same as date of last dose of treatment	Use last day of month (i.e.. D may take on values of 28, 29, 30, or 31, depending on month)
	D and M	Y same as Y of last dose of treatment	Date of last dose of treatment
		Y not same as Y of last dose of treatment	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

D=day, M=month, Y=year
Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.
In all cases, if it cannot be determined if the AE occurred prior to or after the first dose of treatment, the AE should be defined as treatment emergent.

In the event that an AE has missing results for relationship to study treatment or intensity of AE, no imputation will be applied.

Table 7. Prior and Concomitant Medications Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for con meds	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date of first dose of study drug
Stop date for con meds	D only	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Last day of month
	M and D	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
	M, D, and Y	None - date completely missing and NOT ongoing	Date of last dose of study drug

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

For laboratory data, if the reported value of a parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value will be appropriately determined and used in the statistical analyses. In general, a value or lower limit of normal range such as '< 10' or '≤ 5' will be treated as '10' or '5' respectively, and a value or upper limit of normal range such as '> 100' will be treated as '100'. However, the actual values as reported in the database will be presented in data listings.

12.3 Subject Disposition

The number of screened subjects, subjects randomized, and subjects within each of the analysis populations (ITT, Safety, PK1, PK2, and PG) will be summarized by treatment group, and enrollment by site will be tabulated for subjects randomized into the study.

A list of subjects who did not meet all inclusion/exclusion criteria, and which criteria were not met, will be presented.

The number and percentage of subjects completing the study drug treatment period (up to and including Week 24), as well as the completion status of the study will be presented for each treatment group in the ITT population. Reasons for discontinuation from the study, as recorded on the eCRF, will be summarized (number and percentage) by treatment group. A listing of all subjects' disposition from the Treatment Phase and at end of study will be presented, along with the primary reason for discontinuation, as applicable. Percent of subjects who entered study 211 will be summarized by treatment group.

The number and percentage of subjects at each study visit will also be presented, and descriptive statistics will be used to summarize the total time in study from randomization in weeks.

All disposition data will be included within listings.

12.4 Protocol Deviations

Per PRA processes, protocol deviations data will be entered into a Clinical Trials Management System (CTMS). The study team and the sponsor will conduct on-going reviews of the deviation data from CTMS and the resulting set of evaluable subjects.

Deviations will be categorized into general categories: inclusion/exclusion criteria not met, study drug deviation (including storage issues, subject unblinding), prohibited medication received, overdose/misuse, study procedures not done (efficacy and safety), out of visit window, etc. The study team will also categorize protocol deviations as important or not important Final review of protocol deviations will be conducted and finalized prior to unblinding the database.

The number of subjects with at least one major protocol deviation and the number of subjects with at least one minor protocol deviation within each deviation category will be presented by treatment group for the ITT population. Major and minor protocol deviations are defined per the study Protocol Deviation Guidance document.

12.5 Demographic and Baseline Characteristics

Demographics will be summarized for the ITT, and Safety populations, and will include sex, race, ethnicity, age (in years, at time of signing informed consent), categorical age (i.e., < 65 years, ≥ 65 years – < 75 years, ≥ 75 years), weight, height, BMI, HBV genotype (A, B, C, D, E-H), pre-treatment ALT levels, and SOC NUC therapy reported at time of randomization, including combination therapies. Percent of subjects who entered study 211 will be summarized by treatment group.

All medical/surgical history, including those ongoing at screening, will be summarized in the ITT population based on the number and percentage of subjects reporting each event, as coded per Medical Dictionary for Regulatory Activities (MedDRA) v21.0. Current medical history events, denoted as ‘ongoing’ on the CRF, will be reported in a separate table.

All demographic and baseline characteristics, including HBV history (i.e. infection and diagnosis dates), and results from the screening liver examination, will be provided within data listings.

12.6 Treatments

12.6.1 HBV Treatment History

For each HBV treatment history reported at Screening (i.e. entecavir (ETV), tenofovir alafenamide fumarate (TAF), Tenofovir disoproxil fumarate (TDF), or Other SOC NUC), the outcome to treatment and ongoing status will be summarized by treatment group, and daily oral dose (mg), when reported, will be summarized using descriptive statistics. If a subject received the same HBV treatment more than once prior to entering the study, the most recent record, based on the treatment end date, will be summarized in this table for the given HBV treatment. In such cases, if none of the records note the treatment as ongoing, the end date month and/or year information will be used to determine most recent record, in the event of partial dates. A listing will be provided to include all information collected on the CRF regarding HBV treatment history. Data will be presented for the ITT population.

12.6.2 Prior and Concomitant Medications

Medications received prior to, or concomitantly with study drug will be categorized by Anatomical Therapeutic Classification (ATC) level 4 and preferred medication name, according to the WHODRUG dictionary (Version 2018MAR01 DDE B3). The number and percentage of subjects using each medication will be displayed by treatment group in the ITT population. Subjects will be counted only once for an ATC class and preferred term.

If a medication has an end date which occurs prior to the first dose of study drug, then it will be summarized as a prior medication. In the case where the medication end date is partially complete (i.e. missing day or month), then the month and/or year information will be used to determine if the medication was taken prior to study drug dosing, as applicable.

If a medication has a start date which occurs prior to the first dose of study drug and end date is after the first dose of study drug, then it will be summarized as a concomitant medication. All other medications with a start date after the first dose of study drug will be summarized as concomitant medications.

12.6.3 Procedures

Procedures will be recorded from 7 days prior to the informed consent date through to study completion defined as last study follow up visit or enrollment into study ABI-H0731-211. All procedures will be summarized in the ITT population based on the number and percentage of subjects reporting each procedure, as coded per MedDRA v21.0.

12.6.4 Compliance and Exposure to Study Drug

The summaries for compliance and exposure to study drug by treatment group will be presented for the Safety population.

For extent of study drug exposure, the duration will be calculated from Day 1 to the date of last study drug administration collected on the End of Treatment CRF. The expected total duration of on-treatment therapy for all subjects is 24 weeks. The distribution of subjects by the total number of weeks on therapy (i.e. < 1 week, 1-< 4 weeks, 4-< 8weeks, 8-< 12weeks, 12-< 16weeks, 16-< 20weeks, and >=20 weeks) will be presented as will descriptive statistics for the total duration of days on therapy. This duration will be calculated as defined in the Section 8 Definitions.

In order to assess compliance with scheduled study drug dosing in the 24-week treatment period, the drug dispensing and return information collected on the drug accountability Case Report Forms will be used. Per protocol, each subject is expected to take three 100mg tabs every day during the treatment phase. In a 24-week period, a total of 504 tabs would be expected.

The percent compliance in 24 weeks will be calculated as:

$$\% \text{ compliance} = 100 * \frac{Actual\ number\ of\ tables\ taken}{Expected\ number\ of\ tablets\ over\ 24\ weeks}$$

where the actual number of tablets taken will be calculated as the *sum of all tablets dispensed* minus the *sum of all tablets returned* as reported on the Study Drug Accountability CRF, plus the number of tablets taken at each of the in-clinic dosing visits as reported in the Study Drug Administration CRF on Day 1, and Weeks 2, 4, 12, and 24. The expected number of tablets over 24 weeks is 504 or (last date subject took study drug – start date subject took study drug) + 1 as days exposed multiplied by 3 tablets daily.

Descriptive statistics for treatment compliance and the number and percentage of subjects at least 80% compliant will be presented by treatment group.

12.7 Efficacy Analyses

Summary statistics will be presented in the ITT population, unless otherwise noted. For virology samples, a listing will be provided for the Safety population, and will include the following variables: HBsAg (IU/mL), HBsAg (qualitative), HBeAg (IU/mL), HBeAg (qualitative), HBV DNA (IU/mL), HBCrAg, and HBV RNA.

12.7.1 Primary Endpoint Assessments

The primary endpoint is viral antigen decline (serum HBsAg or HBeAg), measured as the mean change from baseline in $\log_{10}$ serum viral antigen from Baseline to Week 24.

For each endpoint variable, summary statistics will be provided by treatment group for the observed and change from baseline log_{10} results at all study visits. Summaries will be provided in the ITT population. Mean change from baseline and 95% confidence intervals will be presented.

A repeated measures analysis using observed data from all scheduled visits for change from baseline in HBV DNA will be performed on the ITT population. This analysis will compare treatment groups over time using a linear mixed effects repeated measure model which includes fixed effects for treatment, visit, treatment-by-visit interaction, baseline value, baseline-by-visit interaction, and baseline covariates (baseline ALT, HBV genotype, time on historical HBV treatment). Unstructured covariance matrix will be used. If there are convergence issues, then the use of first-order autoregressive (AR1) and/or the compound symmetry (CS) covariance matrices will be considered. The difference in least squares means between treatment groups and 95% confidence interval will be presented.

A similar analysis of the primary endpoints (serum HBsAg and HBeAg) as described above will be presented by stratum (HBeAg positive subjects vs HBeAg negative subjects) in the ITT population.

As this is a proof-of concept study, both primary endpoint parameters will be assessed independently. There is no plan to control for alpha for each of the primary variables, however, a significant difference for either of the primary variables at the Week 24 timepoint would be considered clinically desirable and may warrant further investigation.

Graphs will be used to illustrate the changes from baseline for all post-baseline results up to Week 24. Results from both treatment groups will be presented on the same graph.

12.7.2 Exploratory Efficacy Assessments

12.7.2.1 Serum HBV RNA and HBCrAg levels

For HBV RNA and HBCrAg variables, summary statistics will be provided by treatment group for the observed and change from baseline log_{10} serum results at all study visits. Summaries will be provided in the ITT population.

12.7.2.2 Serum HBsAg and HBeAg loss and seroconversion

The number and percentage of subjects with antigen loss (defined as below LOQ) or decline in HBsAg or HBeAg (< 0.5 log_{10}, ≥ 0.5 to 1.0 log_{10}, or >1.0 log_{10} decrease in viral antigen) will be tabulated for all measured visits in the ITT population. For HBeAg, the analytical measurement range is 0.11 –700.00 IU/mL. Samples with HBeAg concentrations greater than 700.00 IU/mL are diluted up to 1:2, extending the upper reporting limit to 1400.00 IU/mL. For HBsAg, the reportable range for the HBsAg quantitative assay is 0.05 – 124925.00 IU/mL. The analytical measurement range is 0.05 – 250.00 IU/mL. Samples with HBsAg concentrations greater than 250.00 IU/mL are diluted up to a maximum dilution of 1:500, extending the upper reporting limit to 124925.00 IU/mL.

Time to HBsAg loss and HBeAg loss will be evaluated using Kaplan-Meier estimates for each treatment group. The summary will be provided based on results observed up to Week 24. A subject will be identified as having loss if the HBsAg, HBeAg result of < LOQ is observed for the subject, and all subsequent measurements of HBsAg, HBeAg are < LOQ. Subjects will be considered censored for the Kaplan-Meier analysis if any of the following occur: 1) Subjects who are not observed to have encountered viral suppression by Week 24 (HBV DNA of <20 IU/mL) will be censored at their last observed visit up to week 24, 2) If a subject rebounds within the 24-week period, HBsAg, HBeAg are >= LOQ then the overall status for that subject will be considered as censored at the first occurrence of a rebound, 3) if a subject discontinues study participation prior to an occurrence of). This rebound censoring technique adequately accounts for seroreversions. Patients who are not observed to have encountered loss by Week 24 will be censored at their last observed visit up to week 24. The 25th, 50th (median), and 75th percentiles for time to loss in weeks will be reported, along with the corresponding 95% confidence interval. An unstratified log-rank test will be used to assess differences in loss rates between treatment groups.

Additionally, a Cox regression analysis will be used to determine association of the following baseline covariates on HBsAg and HBeAg loss: gender (male, female), race (Asian vs non-Asian, and Black vs non-Black), ethnicity (Hispanic/Latino, Non-Hispanic/Latino), and HBV genotype (A, B, C, D, E-H). Hazard ratios and corresponding 95% Wald confidence limits will be provided in a summary table, along with the Wald Chi-Square p-value comparing the loss rates between the treatment groups.

Seroconversion status will be summarized at all post-baseline time points when antibodies for HBsAg and HBeAg are collected (i.e. Weeks 12, 24, and 36). For subjects where antibody is present, subjects with seroconversion will be presented as the number of subjects who also observed loss (i.e. HBsAg below LOQ, or HBeAg below LOQ) at the identified timepoint. Results will be provided by treatment group in the ITT population.

12.7.2.3 HBsAg, HBeAg, HBCrAg, and HBV RNA levels

For HBsAg, HBeAg, HBCrAg, and HBV RNA variables, summary statistics will be provided by treatment group for the observed and change from baseline $\log_{10}$ serum results at each study visit. Summaries will be provided in the ITT population. Mean change from baseline and 95% confidence intervals will be presented.

A repeated measures analysis using observed data from all scheduled visits for change from baseline in HBsAg, HBeAg, HBCrAg, and HBV RNA will be performed on the ITT population. This analysis will compare treatment groups over time using a linear mixed effects repeated measure model which includes fixed effects for treatment, visit, treatment-by-visit interaction, baseline value, baseline-by-visit interaction, and baseline covariates (baseline ALT, HBV genotype, time on historical HBV treatment). Unstructured covariance matrix will be used. If there are convergence issues, then the use of first-order autoregressive (AR1) and/or the compound symmetry (CS) covariance matrices will be considered. The difference in least squares means between treatment groups and 95% confidence interval will be presented.

12.7.2.4 HBV DNA

For subjects reporting detectable HBV DNA at Baseline, the number and percentage of those with loss at each post-baseline assessment will be tabulated in the ITT population. The categories for loss will be similar as those used in the HBsAg and HBeAg analysis indicated above, including subjects who achieve below LOQ results (i.e. reported as < 20 IU/mL, or No HBV DNA detected).

Additionally, summary statistics will be provided by treatment group for the observed and change from baseline $\log_{10}$ serum results at all study visits. Mean change from baseline and 95% confidence intervals will be presented.

A repeated measures analysis using observed data from all scheduled visits for change from baseline in HBV DNA will be performed on the ITT population. This analysis will compare treatment groups over time using a linear mixed effects repeated measure model which includes fixed effects for treatment, visit, treatment-by-visit interaction, baseline value, baseline-by-visit interaction, and baseline covariates (baseline ALT, HBV genotype, time on historical HBV treatment). Unstructured covariance matrix will be used. If there are convergence issues, then the use of first-order autoregressive (AR1) and/or the compound symmetry (CS) covariance matrices will be considered. The difference in least squares means between treatment groups and 95% confidence interval will be presented.

12.7.2.5 Follow-up Subject Assessments

Follow-up efficacy assessments will be performed on ITT subjects who do not rollover onto the optional extension study, ABI-H0731-211.

For subjects with suppression of detectable serum HBV RNA (i.e. HBV RNA below LOQ at Week 24), the number of subjects whose HBV RNA rebounds after discontinuing treatment will be presented at Weeks 28 and 36 in both treatment groups. Similar analyses will be presented for both HBsAg and HBeAg for subjects with loss at Week 24, to determine whether results have rebounded following the treatment phase.

12.7.2.6 Pharmacogenomic Assessments

Pharmacogenomic samples will be collected at Day 1 for subjects who consent to this procedure. These samples may be saved for future research. If differences are noted in outcomes between racial or ethnic groups from the Cox regression analysis defined in **Section 12.7.2.2**, the correlation between PG variables with clinical outcomes may be evaluated for subjects who provide optional informed consent.

A listing of PG results will be provided for the Safety population.

12.8 Safety Analyses

12.8.1 Adverse Events

Verbatim descriptions of AEs will be coded using Version 21.0 of MedDRA. Summary tables will be provided for all treatment-emergent adverse events (TEAEs) in the Safety Population.

A treatment-emergent AE is defined as any AE that newly appeared or worsened in severity on or after the first dose of study drug but not more than 30 days after the subject's last dose. If the start date of the AE is partial or missing, Table 6 in Section 12.2 will be used to determine the flag for treatment emergence.

An overall summary of TEAEs will be presented by treatment group and overall, and will include the following tabulations:

- the number of subjects reporting at least one TEAE, and the total the number of events reported
- the number of subjects with an Adverse Event of Special Interest (AESI) (i.e. ALT flare, rash, or other)
- the number of subjects with a treatment-related TEAE (i.e. either Possibly Related or Related)
- the number of subjects with Grade ≥ 3 (severe) TEAE
- the number subjects discontinuing the study due to a TEAE
- the number of subjects with at least one serious TEAE
- the number of subjects with a TEAE resulting in death.

Additionally, AEs will also be summarized as categorized by body system and preferred term coded according to the MedDRA dictionary. Tabulations will be by subject, such that subjects are only counted once within each body system or preferred term. These summaries will be provided for the following:

- all TEAEs, and the total number of events reported
- TEAEs of special interest
- TEAEs per SOC NUC at randomization
- TEAEs related to study treatment (i.e. Related or Possibly Related)
- TEAEs with Grade ≥ 3 (severe)
- TEAEs leading to study discontinuation
- Serious TEAE's
- TEAEs resulting in death

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed.

Rash assessments will be listed separately for subjects with this AESI.

12.8.2 Deaths and Serious Adverse Events

Subjects with treatment-emergent adverse events with an outcome of death will be summarized. A listing of all deaths that occurred following the first dose of treatment will be presented in a listing. Similarly, all AEs noted as serious will be displayed in a listing.

12.8.3 Central Laboratory Data

Laboratory data will be summarized in the Safety Population using descriptive statistics (based on SI units) for the observed and change from baseline results for hematology and clinical chemistry by treatment group at each visit. Only the numeric part in laboratory values that contain non-numeric qualifiers, such as less than (<) a certain value, or greater than (>) a certain value, will be used in the summary statistics.

For continuous data, the following hematology tests will be summarized for observed and change from baseline values:

- Basophils (% and abs), Blasts (% and abs), Eosinophils (% and abs), Hematocrit, Hemoglobin, Lymphocytes (% and abs), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), Monocytes (% and abs), Neutrophils (% and abs), Platelets, red blood cell (RBC) count, RBC Morphology, Reticulocyte Count (% and abs), white blood cell (WBC) count

The following chemistry tests will be summarized for observed and change from baseline values:

- Alkaline Phosphatase, Albumin, ALT (SGPT), Amylase, AST (SGOT), Bicarbonate, Bilirubin (direct), Bilirubin (indirect), Bilirubin (total), Calcium, Chloride, Cholesterol, Creatinine, estimated GFR (eGFR) CKD, GGT, Globulin, lactate dehydrogenase (LDH), Lipase, Phosphorus, Potassium, Serum Glucose, Sodium, Total Protein, Triglycerides, Urea Nitrogen (BUN), Uric Acid

The following coagulation factors will be summarized for observed and change from baseline values:

- International normalized ratio (INR), Prothrombin time (PT) and activated partial thromboplastin time (aPTT).

The following urinalysis parameters will be summarized for observed and change from baseline values:

- Continuous parameters: pH, Specific gravity
- Categorical parameters: protein, glucose, ketones, blood

Clinically abnormal laboratory values will be applied based on the modified Division of AIDS (DAIDS) Table for Grading Severity of Adult Adverse Experiences (2017), as noted in **Appendix 3**. In the summary tables, values of grading will be displayed as 0, 1, 2, 3, or 4, where a grade of '0' will be assigned if the lab value was non-missing but did not meet a grading criterion (i.e. defined as normal). The maximum post-baseline grade observed up to end of study will be tabulated for each laboratory test, and percentages will be based on the number of subjects with a post-baseline evaluation of the specific laboratory test.

Additionally, a shift table will be used to tabulate the grading observed at Baseline to the maximum post-Baseline result up to the end of study for each lab parameter, in order to highlight important grading differences noted during the study.

The DAIDS grades will be applied within the Covance central lab datasets for the following parameters:

- Hematology: Hemoglobin, Lymphocytes (absolute), Neutrophils (absolute), Platelets, and WBC.
- Chemistry: Alkaline Phosphatase, Albumin, ALT (SGPT), Amylase, AST (SGOT), Bicarbonate, Bilirubin (total), Calcium, Creatinine, eGFR CKD, GGT, Lipase, Phosphorus, Potassium, Serum Glucose, Sodium, Uric Acid

- Coagulation: PT, aPTT, and INR

For subjects reporting an AESI of ALT Flare, a separate summary lab data associated with the flare will be presented for both treatment groups. Data may include results for clinical chemistries (i.e. AST, ALT, GGT, alkaline phosphatase, total bilirubin, and albumin).

For subjects with abnormal ALT at Baseline (defined as modified DAIDS grading of ≥ 1), the number and percentage of subjects who have normal ALT at Week 24 (i.e. a grading of 0) will be presented.

A shift table will be used to tabulate the ALT levels observed at baseline to post-baseline measurements up to end of the study for the following categories: Normal (ALT < ULN), ALT >= 1xULN to < 3xULN, ALT >= 3xULN to < 5xULN, ALT >= 5xULN to < 20xULN, ALT >= 20xULN.

By-patient listings will be provided for hematology, clinical chemistry, coagulation, and urinalysis. Laboratory values outside normal limits will be identified in the subject data listings with flags for low (L) and high (H).

Additional listings will be provided for other laboratory assessments, including serum alpha fetoprotein (AFP), hemoglobin A1c (HbA1c), and follicle-stimulating hormone (FSH; females only) as collected, as well as information collected regarding drug abuse from the urine drug results (i.e. amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, propoxyphene, ethanol, opiates, and phencyclidine).

Antibody tests for hepatitis B surface antigen (HBsAb), hepatitis B “e” antigen (HBeAb), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis A virus immunoglobulin M (HAV IgM), hepatitis E virus immunoglobulin M (HEV IgM), HBV core protein (HBCrAb), and human immunodeficiency virus (HIV) will be listed by subject as collected.

12.8.4 Vital Signs

Blood pressure (systolic and diastolic), respiratory rate (breaths/min), pulse rate (beats/min), and temperature (ºC) will be summarized in the Safety Population using descriptive statistics, for both the absolute and the change from baseline assessments over time. Timepoints will include screening, Baseline (Day 1), and Weeks 2, 4, 8, 12, 16, 20, and 24, and follow-up samples will be collected Weeks 28 and 36 for subjects who do not continue treatment in the extension protocol. Weight (kg) will also be included in the summary table, for the following timepoints: screening, Baseline (Day 1), and Weeks 4, 24, and Week 36 for subjects who remain in the follow-up period.

12.8.5 Physical Examinations, ECGs, and Other Observations Related to Safety

Physical examination results will be summarized in the Safety Population by body system for each timepoint based on the frequency and percentage of subjects with interpretations of normal, abnormal – clinically significant, abnormal – not clinically significant, or not done. Results of 12-lead ECG interpretations will be presented by timepoint in a similar manner.

For female subjects in the Safety Population, results from blood (serum β-hCG) and urine pregnancy tests will be tabulated. All results will be presented in a data listing.

12.9 Pharmacokinetics

For ABI-H0731-treated subjects with a PK assessment (i.e. subjects in Pharmacokinetic Set 1), summary statistics will be presented for trough PK plasma concentrations observed at Baseline, Weeks 2, 4, 12, and 24, as well as Week 28 for subjects who enter the follow-up phase. If a subject provides consent to optional post-dose PK sample collections, then the post-dose (peak) concentration, and the trough to peak ratio will be summarized descriptively at Baseline, Week 2 and Week 4.

For all subjects receiving SOC NUC (either entecavir [ETV], tenofovir alafenamide fumarate [TAF], tenofovir disoproxil fumarate [TDF]) with a PK assessment (i.e. subjects in Pharmacokinetic Set 2), a similar analysis as described above will be provided, for both treatment groups. Each SOC NUC will be

analyzed separately. For SOC NUC Other Combinations, only the TDF, TAF, and ETV components will be measured for the PK assessment.

For subjects in Pharmacokinetic Set 2, the comparisons of SOC NUC trough concentration between treatment arms (ABI-H0731 vs Placebo) will be presented in a table. The comparisons will be based on the geometric mean ratio (with 90% CI) obtained from a two-sample t-test that compares the natural log-transformed trough PK measurements between treatment arms.

Trough plasma concentrations for ABI-H0731 and NUC levels at Baseline, Week 2, Week 4, Week 12, and Week 24, as well as Week 28 (for subjects who enter the follow-up phase) will be presented side-by-side in a graph. At each timepoint, the following 2 results will be plotted: SOC NUC PK levels in ABI-H0731 subjects, and SOC NUC PK levels in Placebo subjects.

Drug-drug interaction effects of SOC NUC at Baseline, Week 2, and Week 4 will be presented in a graph. At each time point the geometric mean ratio of trough SOC NUC PK values for [ABI-H0731 + SOC NUC / SOC NUC alone] will be plotted.

13.0 Validation

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately.

14.0 References

None.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	adverse event
AESI	adverse event of special interest
AFP	alpha fetoprotein
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomic therapeutic classification
AUC	area under the concentration-time curve
BMI	body mass index
cccDNA	covalently closed circular DNA
CHB	chronic hepatitis B infection
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	confidence interval
CRF	case report form
CRO	Clinical Research Organization (PRA Health Sciences)
CTMS	Clinical Trials Management System (PRA)
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
dsDNA	double-stranded DNA
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ETV	entecavir
FSH	follicle-stimulating hormone
GFR	glomerular filtration rate
HAV	hepatitis A virus
HbA1c	hemoglobin A1c
HBCrAb	antibody to the HBV core protein
HBCrAg	hepatitis B core-related antigen
HBeAb	HBeAg antibody
HBeAg	hepatitis B “e” antigen
HBsAb	HBsAg antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
ICF	Informed Consent Form
IgM	immunoglobulin M
INR	International Normalized Ratio
ITT	intent-to-treat

IWRS	Interactive Web Response System
LOQ	limit of quantitation
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NUC	nucleos(t)ide inhibitors of the HBV polymerase; also called nucleos(t)ide analogues or nucleos(t)ides
PG	pharmacogenomic
pgRNA	pre-genomic RNA
PK	pharmacokinetic(s)
PK1	Pharmacokinetic Population 1
PK2	Pharmacokinetic Population 2
PT	prothrombin time
rcDNA	relaxed circular DNA
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

Appendix 2 Tables, Figures, Listings, and Supportive SAS Output Appendices

Please refer to the Table, Figure and Listing shells to support this SAP, provided in a separate document.

Isolated missing values will be imputed by Markov Chain Monte Carlo (SAS PROC MI, MCMC) first to make the missing pattern monotone and then imputed by monotone linear regression. SAS PROC MI and PROC MIXED will be used to obtain MMRM estimates of treatment difference. SAS PROC MIANALYZE will be used to combine estimates and to generate the average test statistics for hypothesis testing. The Missing at Random method will be used with the following parameters: MAR – assume missing at random, number of imputation=100, seed= SEED11 (for MCMC) and SEED12 (for MONOTONE REG) for imputation.

Appendix 3 Grading of Laboratory Values

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

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

Laboratory Values*: Chemistries

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Acidosis	NA	pH≤7.3 to <LLN	pH<7.3 without life-threatening consequences	pH<7.3 with life- threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN 30 to < LLN	≥ 2.0 to < 3.0 ≥ 20 to < 30	< 2.0 < 20	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0 × ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin *Direct Bilirubin, High*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity	> ULN with life- threatening consequences (e.g., signs and symptoms of liver failure)
Total Bilirubin, High	1.1 to <1.6×ULN	1.6 to <2.6×ULN	2.6 to <5.0×ULN	≥5.0 × ULN
Calcium, High (mg/dL; *mmol/L*)	10.6 to <11.5 *2.65 to <2.88*	11.5 to <12.5 *2.88 to <3.13*	12.5 to <13.5 *3.13 to <3.38*	≥ 13.5 *≥3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	>ULN to <6.0 *>ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 *≥1.8*
Calcium, Low (mg/dL; *mmol/L*)	7.8 to <8.4 *1.95 to <2.10*	7.0 to <7.8 *1.75 to <1.95*	6.1 to <7.0 *1.53 to <1.75*	<6.1 *<1.53*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 *<LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 *<0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to <6×ULN	6 to <10×ULN	10 to <20×ULN	≥20 × ULN
Creatinine, High **Report only one*	1.1 to 1.3×ULN	>1.3 to 1.8×ULN OR Increase to 1.3 to <1.5×participant's baseline	>1.8 to <3.5×ULN OR Increase to 1.5 to <2.0×participant's baseline	≥3.5 × ULN OR Increase of ≥2.0 × participant's baseline

Laboratory Values*: Chemistries

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Creatinine Clearance 13 or eGFR, Low **Report only one*	NA	<90 to 60 ml/min or ml/min/1.73 m_2 OR 10 to <30% decrease from participant's baseline	<60 to 30 ml/min or ml/min/1.73 m_2 OR 30 to <50% decrease from participant's baseline	<30 ml/min or ml/min/1.73 m_2 OR ≥50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to <6.95*	>125 to 250 *6.95 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Nonfasting, High	116 to 160 *6.44 to <8.89*	>160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75*	≥500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*)	55 to 64 *3.05 to <3.55*	40 to <55 *2.22 to <3.05*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
Lactate, High	ULN to <2.0×ULN without acidosis	≥2.0×ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences 3.0 to <5.0×ULN	Increased lactate with pH <7.3 with life- threatening consequences
Lipase, High	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0 × ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High***	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	NA
LDL, Fasting, High	130 to <160 *3.37 to <4.12*	160 to <190 *4.12 to <4.90*	≥190 *≥4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to <1,000 *>5.7 to 11.4*	>1,000 *>11.4*
Magnesium 14, Low (mEq/L; *mmol/L*)	1.2 to <1.4 *0.60 to <0.70*	0.9 to <1.2 *0.45 to <0.60*	0.6 to <0.9 *0.30 to <0.45*	<0.6 *<0.30*
Phosphate, Low (mg/dL; *mmol/L*)	2.0 to <LLN *0.65 to <LLN*	1.4 to <2.0 *0.45 to <0.65*	1.0 to <1.4 *0.32 to <0.45*	<1.0 *<0.32*
Potassium, High (mEq/L; *mmol/L*)	5.6 to <6.0 *5.6 to <6.0*	6.0 to <6.5 *6.0 to <6.5*	6.5 to <7.0 *6.5 to <7.0*	≥7.0 *≥7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to <3.4 *3.0 to <3.4*	2.5 to <3.0 *2.5 to <3.0*	2.0 to <2.5 *2.0 to <2.5*	<2.0 *<2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to <150 *146 to <150*	150 to <154 *150 to <154*	154 to <160 *154 to <160*	≥160 *≥160*
Sodium, Low (mEq/L; *mmol/L*)	130 to <135 *130 to <135*	125 to <130 *125 to <130*	121 to <125 *121 to <125*	<121 <121
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to <10.0 *0.45 to <0.59*	10.0 to <12.0 *0.59 to <0.71*	12.0 to <15.0 *0.71 to <0.89*	≥15.0 *≥0.89*

Hematology				
Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life- Threatening**
Absolute CD4+ Count, Low (cell/mm3; *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/mm3; *cells/L*) *(not HIV infected)*	600 to <650 *0.600×10⁹ to <0.650×10⁹*	500 to <600 *0.500×10⁹ to <0.600×10⁹*	350 to <500 *0.350×10⁹ to <0.500×10⁹*	<350 *<0.350×10⁹*
Absolute Neutrophil Count (ANC), Low (cells/mm3; *cells/L*)	800 to 1,000 *0.800×10⁹ to 1.000×10⁹*	600 to 799 *0.600×10⁹ to 0.799×10⁹*	400 to 599 *0.400×10⁹ to 0.599×10⁹*	<400 *<0.400×10⁹*
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/mm3; *cells/L*)	100,000 to <125,000 *100.000×10⁹ to <125.000×10⁹*	50,000 to <100,000 *50.000×10⁹ to <100.000×10⁹*	25,000 to <50,000 *25.000×10⁹ to <50.000×10⁹*	<25,000 *<25.000×10⁹*
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/mm3; *cells/L*)	2,000 to 2,499 *2.000×10⁹ to 2.499×10⁹*	1,500 to 1,999 *1.500×10⁹ to 1.999×10⁹*	1,000 to 1,499 *1.000×10⁹ to 1.499×10⁹*	<1,000 *<1.000×10⁹*

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