STATISTICAL ANALYSIS PLAN

Sponsor	Assembly Biosciences, Inc 331 Oyster Point Blvd South San Francisco, CA 94030
Protocol Number:	ABI-H0731-211
Protocol Title:	A Multi-center, Open-label, Long-term Extension Study of ABI-H0731+Nucleos(t)ide as Finite Treatment for Chronic Hepatitis B Patients
Product:	Vebicorvir (VBR; formerly ABI-H0731)
Protocol Version (Date):	Amendment 4 (14 October 2020)
Indication:	Chronic Hepatitis B Virus Infection
Analysis Type:	Final Analysis for Early Termination
Analysis Plan Version (Date):	Version 1.0 (30 June 2021)
Analysis Plan Author:	[redacted]

CONFIDENTIALITY STATEMENT

STATISTICAL ANALYSIS PLAN (SAP) APPROVAL FORM

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

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

Name and Title	Approval Signature/Date
[redacted]	See e-signature page
[redacted]	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
AST	aspartate aminotransferase
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
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	case report form
EDC	electronic data capture
ET	early termination
ETV	entecavir
FAS	full Analysis Set
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
HLGT	high-level group term
HLT	high-level term
ID	identification
INR	international normalized ratio
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
MMRM	mixed model for repeated measures
NrtI	Nucleos(t)ide reverse transcriptase inhibitor
PD	protocol deviation(s)
pgRNA	pregenomic ribonucleic acid

PT	preferred term
PK	pharmacokinetics
Q1, Q3	first quartile, third quartile
QD	once daily
RAV	resistance associated variants
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
VBR	vebicorvir
WHO	world health organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study ABI-H0731-211. This SAP is based on the Study Protocol Amendment 4 dated October 14, 2020 and the electronic case report form (eCRF). On December 8, 2020, Assembly made the decision to close the study early since the goals and objectives had been met based upon the predetermined study endpoints and available data generated by that date. The decision for early termination of the study was not related to any safety concern, but rather because there was no meaningful durable off-treatment virologic response despite a demonstrated deeper level of on-treatment viral suppression. Therefore, some efficacy analyses specified in the protocol will not be performed (Section 6.5). The SAP will be finalized before database lock. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the potential for combination therapy with vebicorvir (VBR; formerly ABI-H0731)+NrtI to increase sustained viral response (SVR) rates in subjects who have chronic hepatitis B virus infection (cHBV)

The secondary objectives of this study are as follows:

- To evaluate the longer-term safety and tolerability of VBR added to standard of care nucleos(t)ide reverse transcriptase inhibitor (NrtI) therapy
- To evaluate improvement in transaminases in subjects on treatment and post-treatment
- To evaluate the durability of changes in viral antigen and viral DNA after discontinuation of combination therapy

The exploratory objectives of this study are as follows:

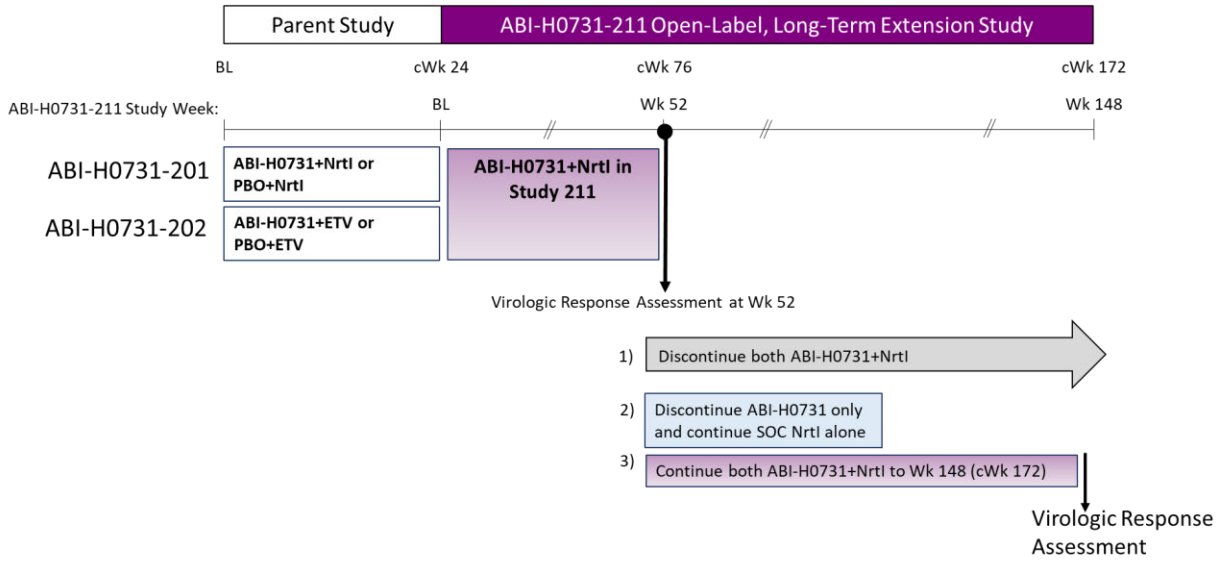
- To evaluate the kinetics of and absolute changes from Baseline in biomarkers of transcriptionally active covalently closed circular DNA (cccDNA; HBeAg and HBsAg)
- To assess the relationship between exploratory viral biomarkers, such as changes in viral pgRNA and hepatitis B core-related antigen (HBcrAg),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

- To assess steady state plasma levels of VBR and NrtI for possible correlation with markers of safety and efficacy

1.2. Study Design

This is an open-label, multi-center, long-term extension study evaluating the safety and efficacy of VBR in combination with NrtI in subjects with cHBV who have completed 24 weeks of treatment in one of two parent studies, ABI-H0731-201 (Study 201) or ABI-H0731-202 (Study 202) (Figure 1).

Figure 1. ABI-H0731-211 Study Overview



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

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

1) Discontinue both VBR+NrtI
2) Discontinue VBR only and continue NrtI alone
3) Continue both VBR+NrtI for up to 148 weeks

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

Table 1. Decision Criteria and Treatment Actions

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

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

As described in Table 1, based on the respective treatment action, additional follow-up visits may be undertaken. These visits are briefly summarized below.

3-Year Off-treatment Follow-up

All subjects who discontinue both VBR+NrtI will be followed for up to 3 years from the date of treatment discontinuation to assess the durability of virologic response. Subjects will return to

the clinic for follow-up every 4 weeks for visits at 4, 8, 12, 16, 20, and 24 weeks post-treatment discontinuation, then every 8 weeks for visits at 32, 40, and 48 weeks post-treatment discontinuation, and then every 12 weeks until completion of the 3-year follow-up. Additional unscheduled visits may be performed at the Investigator's discretion. Following completion of the visit 3 years after VBR+NrtI discontinuation, subjects will exit the study and be under the routine care of their physician.

12-Week Follow-up on NrtI Alone

All subjects who discontinue VBR only and continue NrtI alone will be followed for 12 weeks from the date of VBR discontinuation. Subjects will return to the clinic for follow-up visits at 4, 8, and 12 weeks after discontinuation of VBR. Additional unscheduled visits may be performed at the Investigator's discretion. Following completion of the visit 12 weeks after discontinuation of VBR, subjects will exit the study and be under the routine care of their physician.

Continuation of Treatment with VBR+NrtI

All subjects who continue VBR+NrtI beyond Week 52 will return to the clinic for visits every 4 weeks until Week 148. At Week 148, subjects will be evaluated for virologic response as described in the table above and will either discontinue both VBR and NrtI and be followed for up to 3 years (as described in the '3-Year Off-Treatment Follow-up') or discontinue VBR only and continue on NrtI alone and be followed for 12 weeks (as described in '12-Week Follow-up on NrtI Alone').

Criteria to Restart NrtI Following Discontinuation of Both VBR and NrtI

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

- Alanine aminotransferase (ALT) >10 × upper limit of normal (ULN)
- Direct bilirubin >2.0 × ULN
- International Normalized Ratio >1.5
- ALT >3 × ULN and HBV DNA >100,000 IU/mL
- ALT >ULN and HBV DNA >2000 IU/mL on 3 consecutive visits at least one month apart
- Any clinical decompensation, regardless of HBV DNA level
- Physician or subject's decision

Subjects who restart NrtI will return for follow-up visits at 4, 8, and 12 weeks after starting NrtI and will then complete participation in the study.

1.3. Sample Size and Power

It is anticipated that approximately 100 subjects will enroll in this trial and receive study medication. The sample size for this study is not based on statistical considerations and will be determined by optional enrollment from other VBR studies. All subjects who complete a prior

study of VBR and have not discontinued treatment in Studies 201 or 202 will have the opportunity to enroll in this study.

1.4. Methods of Assigning Subjects to Treatment

1.4.1. Randomization

This is an open-label, multi-center, long-term extension study with all subjects receiving VBR 300 mg QD + NrtI QD. There is no randomization performed in this study.

1.4.2. Blinding

This is an open-label, multi-center, long-term extension study and consequently there is no blinding concern.

2. TYPE OF PLANNED ANALYSES

2.1. Interim Analysis

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

2.2. Final Analysis

The study is early terminated. The final analysis will be performed after all subjects have discontinued or completed the early termination 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), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the All Enrolled 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 initially randomized in the parent Studies 201 and 202 will be included 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 the following sections. 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 by-subject listing of reasons for exclusion from analysis sets will be provided.

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set will include all subjects who were enrolled in Study 211.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) population will include all subjects who received any amount of study drug and who had at least one postdose assessment for the endpoint of interest.

3.1.3. Per-Protocol Population

The Per-Protocol (PP) Population will include subjects in the FAS subjects who are at least 80% compliant with scheduled study drug dosing, and who have no major protocol deviations. Given that the study was terminated early, PP analyses will not be performed.

3.1.4. Safety Population

The Safety Population will include all subjects who received at least 1 dose of study drug.

3.1.5. Pharmacokinetic Population 1

The Pharmacokinetic population 1 (PK1) will include all subjects in the Safety Population who have VBR PK data assessments available.

3.1.6. Pharmacokinetic Population 2

The Pharmacokinetic population 2 (PK2) will include all subjects in the Safety Population who have NrtI PK data assessments available.

3.2. Data Handling Conventions and Transformations

3.2.1. General

Subject's date of birth was collected at the Screening visit in the parent studies. The age is derived in the electronic data capture (EDC) based on the year of birth and the informed consent date of Study 211. The age will be used for analyses and presented in listings.

3.2.2. Non-PK Data

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 plus or minus 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 (Nehls and Akland, 1973).

3.2.3. PK Data

Sparse PK concentration values that are below the limit of quantitation (BLOQ) will be presented as "BLOQ" in the data listing.

3.3. Missing Data and Outliers

3.3.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified.

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

3.3.2. 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.

3.4. Analysis Phases and Visits

3.4.1. Definition of Phases

The analyses will include all the data collected in this study based on three phases defined as follows. The duration of each phase will be summarized.

- On-Treatment Phase: when a subject is undergoing treatment with VBR+NrtI (ie, from the first dose of VBR in Study 211 up to the last dose of VBR)
- Off-Treatment Phase: after a subject has discontinued both VBR+NrtI or discontinued VBR alone post treatment action and prior to NrtI restart if applicable (ie, after the last dose of VBR through the end of study or before the first dose of NrtI if it was restarted)
- NrtI-Restart Phase: after a subject has restarted NrtI, following the Off-Treatment Phase (ie, from the first dose of NrtI through the end of study)

3.4.2. Definition of Study Day

The study drug is VBR in Study 211. For On-Treatment Phase, Study Day 1 (or on-treatment Baseline) is defined as the first dose date of the study drug in Study 211. The last dose date of the study drug will be the end date on study drug administration eCRF. Study day will be calculated from Study Day 1 and is 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 Off-Treatment Phase, the Off-Treatment Day 1 (or Off-Treatment Baseline) will be defined as the last dose date of VBR. The off-treatment study day will be calculated from the last dose date and derived as Assessment Date − Last Dosing Date of VBR.

For the NrtI-Restart Phase, the NrtI-Restart Day 1 (or NrtI-Restart Baseline) will be defined as the first dose date of NrtI. The NrtI-Restart study day will be calculated from the first dose of NrtI and derived as Assessment Date – First Dosing Date of NrtI + 1.

3.4.3. Analysis Visits

The nominal visit as recorded on the eCRF will be used when data are summarized by visit. Any data relating to unscheduled visits will be assigned to a particular visit or time point as follows:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the Baseline value, if applicable.
- Unscheduled visits after the first dose of study drug will be included in determining the maximum postbaseline toxicity grade.

The follow-up visits after discontinuing VBR will be summarized and labeled as "Off-Treatment" visits. The follow-up visits after NrtI was restarted will be summarized and labeled as "NrtI-Restart" visits.

3.4.4. Analysis by Phase

For the On-Treatment Phase, the analyses will be summarized by parent study (ie, Studies 201 and 202), HBV treatment history (ie, virologically suppressed or treatment naïve), HBeAg status (ie, HBeAg positive or HBeAg negative), and the randomized treatment group in parent studies (ie, VBR+NrtI or Placebo+NrtI). The total number of subjects by study population and parent study will be provided and the grand total may be provided where appropriate.

For the Off-Treatment Phase, the analyses will be summarized by treatment action in addition to parent study, HBV treatment history and HBeAg status. The total number of subjects following different treatment actions may be provided for safety analyses.

For the NrtI-Restart Phase, the analyses will be only applicable for subjects who discontinued both VBR and NrtI from Study 201. The analyses will be grouped by HBeAg status in parent studies.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided for each country, Investigator within a country, and overall. The summary will present the number and percentage of subjects enrolled. The denominator for the percentage calculation will be the total number of subjects analyzed for each column. A by-subject listing will be provided for the subject enrollment based on All Enrolled Analysis Set.

A summary of subject disposition will be provided. This summary will present the number of subjects enrolled, and the number of subjects in each of the categories listed below:

- Full Analysis Set
- Safety Population
- PK1 Population
- PK2 Population

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

- Completed study drug
- Did not complete study drug with reasons for study drug discontinuation
- Completed study
- Did not complete study with reasons for study discontinuation

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

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

- Reasons for premature study drug or study discontinuation
- Dispensed lot number and kit ID for VBR

A summary table will be provided with the number and percentage of subjects who completed 52 weeks of treatment and meet the treatment action criteria based on the virologic response as described in Table 1. The corresponding by-subject listing will be provided.

4.2. Extent of Study Drug Exposure

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug.

4.2.1. Duration of Exposure to Study Drug

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

The total duration of exposure to study drug will be summarized using descriptive statistics for the Safety Population. The distribution of subjects by the total number of weeks on therapy (ie, ≤24 weeks, >24 -48 weeks, >48 -72 weeks, >72-96 weeks, >96-120 weeks, >120 weeks) will be presented.

4.3. Protocol Deviations

Protocol deviations (PD) occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations (IPDs) by deviation reason (eg, non-compliance to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for All Enrolled Analysis Set. A by-subject listing will be provided for those subjects with IPD.

A table will be provided to summarize any COVID-19 related PDs with the deviation reason by treatment group. A by-subject listing of subjects who had study disruption due to COVID-19 may be provided with a description.

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 [in kg], height [in m], body mass index [BMI; in kg/m^2]) will be summarized using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary will be based on the Safety Population. Age, weight, and BMI will be measured at Study 211 Baseline. A by-subject listing will be provided by subject ID number in ascending order.

5.2. Baseline Disease Characteristics

Disease characteristics will be summarized at Stud 211 Baseline. 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
- Baseline NrtI type
- Years on current NrtI treatment
- Baseline HBV DNA (log10 IU/mL) (Cobas)
- Baseline HBV DNA (TD/TND) (Assembly)
- Baseline HBV pgRNA (log10 U/mL) (Assembly)
- Baseline Total Nucleic Acid (TNA) (Composite DNA + pgRNA) (Assembly)
- Baseline HBeAg (log10 IU/mL)
- Baseline HBeAg Status for subjects with HBeAg <LLOQ
- Baseline HBcrAg (log10 kU/mL)
- Baseline HBsAg (log10 IU/mL)
- HB e antibody (HBeAb)
- HB s antibody (HBsAb)
- Baseline ALT (U/L)
- ALT groups (>ULN [Covance], >ULN [AASLD])

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

6. EFFICACY ANALYSES

The efficacy analyses will be based on the FAS, defined in Section 3.1.2. The efficacy analyses will be based on all available data. If not specified, no imputation will be used for the missing data. No statistical comparison will be made. For continuous variables, descriptive statistics will include mean, SD, median, minimum, and maximum. For categorical variables, summary statistics will include the number and percentage of subjects who meet the endpoint criteria. A 95% confidence interval (CI) will be provided, where appropriate.

6.1. Primary Efficacy Endpoint

6.1.1. Definition of Primary Efficacy Endpoint

The primary efficacy endpoint is the sustained viral response (SVR) rate at 24 weeks off treatment. The viral response is defined as HBV DNA <LLOQ where LLOQ is defined as 20 IU/mL using the COBAS TaqMan Version 2.0 HBV DNA assay.

6.1.2. Analysis of Primary Efficacy Endpoint

The number and percentage of subjects reaching SVR at off-treatment Week 24 will be presented with 95% CI based on Clopper-Pearson method.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

The secondary endpoints include the following:

- Incidence of subjects with abnormal ALT at Baseline who have normal ALT at end of treatment (EOT) and end of study (EOS)
- Incidence of subjects with suppression/loss of viral antigen/DNA on combination treatment whose viral antigens rebound off therapy

6.2.2. Analysis of Secondary Efficacy Endpoints

The ALT normalization at EOT and EOS will be summarized for subjects who have abnormal ALT (ie, >ULN based on Covance lab) at Baseline. The number and proportion of subjects with normal ALT will also be summarized over time by phase regardless of Baseline status. The normal ranges are specified by both central lab and AASLD criteria. In addition, the change from Baseline in ALT will be analyzed descriptively over time by phase using the summary statistics and a line plot with mean (SE) will be provided by phase.

The viral antigen rebound off therapy is defined as a ≥ 1 $\log_{10}$ increase in viral antigen from the off-treatment Baseline or a change in viral antigen from <LLOQ on treatment to ≥LLOQ off treatment. A table and listing will be provided for subjects who had reached the suppression or

loss of a viral antigen and DNA on combination treatment but had a viral antigen rebound while off treatment.

6.3. Exploratory Efficacy Endpoints

6.3.1. Definition of Exploratory Efficacy Endpoints

Exploratory endpoints include the following:

- Mean change from Baseline in $\log_{10}$ serum HBeAg.
- Mean change from Baseline in $\log_{10}$ serum HBsAg.
- Incidence of subjects with loss or change in $\log_{10}$ HBsAg or $\log_{10}$ HBeAg (<0.5, ≥0.5 to 1.0, or >1.0 in viral antigens) at EOT and end of follow-up.
- Incidence of subjects with HBsAg seroconversion (loss of HBsAg and appearance of HBsAg antibody) or HBeAg seroconversion (loss of HBeAg and appearance of HBeAg antibody).
- Incidence of subjects with "detectable" HBV DNA by polymerase chain reaction at Baseline whose HBV DNA becomes "target not detected".
- Quantitative changes from Baselines in viral pgRNA on treatment and through end of follow-up.
- Quantitative changes in serum HBcrAg levels on treatment and through end of follow-up.
- Incidence of HBsAg or HBeAg seroreversion in "Complete Responders" up to 3 years off therapy.
- Incidence of subjects requiring retreatment following SVR through 3 years off therapy.
- Incidence of subjects with emergence of HBV RAVs.

The loss of HBsAg is defined as HBsAg ≥LLOQ at Baseline plus HBsAg <LLOQ at a post-Baseline visit. The loss of HBeAg is defined as HBeAg ≥LLOQ at Baseline plus HBeAg <LLOQ and HBeAg status negative at a post-Baseline visit.

HBsAg seroconversion is defined as loss of HBsAg and appearance of HBsAg antibody. The appearance of HBsAg antibody is defined as negative antibody at Baseline plus positive or borderline HBsAg antibody at a post-Baseline visit. HBeAg seroconversion is defined as loss of HBeAg and appearance of HBeAg antibody. The appearance of HBeAg antibody is defined as negative HBeAg antibody at Baseline plus positive or borderline HBeAg antibody at a post-Baseline visit.

6.3.2. Analysis of Exploratory Efficacy Endpoints

The change from Baseline in $\log_{10}$ serum HBV DNA (Cobas), pgRNA, HBeAg, HBsAg, and HBcrAg will be analyzed descriptively over time and EOT by phase using the summary statistics. Mean ± SE of the change from Baseline values will be plotted using a line plot over time by phase. The change from Baseline in $\log_{10}$ TNA (Assembly) will be summarized and plotted for the On-Treatment Phase.

The number and percentage subject with loss or change in $\log_{10}$ HBsAg and $\log_{10}$ HBeAg (<0.5, ≥0.5 to 1.0, or >1.0) at EOT and EOS will be summarized.

The number and percentage of subjects with HBsAg seroconversion and HBeAg seroconversion will be summarized at EOT and EOS.

A summary will be provided for subjects with "detectable" HBV DNA (Cobas) at Baseline and becomes "target not detected" at any post-Baseline visit during the On-Treatment Phase.

The proportion of subjects with ≥1 $\log_{10}$ IU/mL increase in on-treatment HBV DNA from on-treatment nadir will be summarized and their virology data will be listed. The incidence of HBV variants with reduced susceptibility to VBR will be assessed in the virology report.

In addition, the number and percentage of subjects reaching HBV DNA (Cobas) <LLOQ will be summarized by visit and phase. The categories of HBV DNA (Cobas) <LLOQ TD and TND will also be summarized. For the HBV DNA measured by Assembly lab, the summary of the number and percentage of subjects with TD and TND will be provided.

Subjects who restarted NrtI will be summarized with the associated reasons as described in Section 1.2.

6.4. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

6.5. Changes From Protocol-Specified Efficacy Analyses

Due to study early termination and limited follow up time, the protocol-specified exploratory endpoint of incidence of HBsAg or HBeAg seroreversion in "Complete Responders" up to 3 years off therapy, will not be analyzed. In addition, the analysis of subjects with emergence of HBV RAVs will be provided separately by a virology report. The pharmacogenomic data will not be analyzed in this CSR but may be explored in the future.

In addition, the per-protocol and subgroup analyses will not be performed for the primary endpoint since no subjects reached SVR at off-treatment Week 24.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version (v) 21.0. 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 study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

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

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing 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 month or after the month and year (or year) of the first dosing date of study drug, and

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

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered as 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 dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

TEAEs will be summarized based on the Safety Population for the On-Treatment Phase.

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. All deaths observed in the study will also be included in this summary. In addition, the number and percentage of subjects will be provided by SOC, PT, and treatment group for each AE category as well as by PT only in descending order of total frequency:

- TEAEs

- TEAEs by severity grade

- Treatment-related TEAEs

- TE SAEs

- Treatment-related TE SAEs

- TEAEs leading to study drug discontinuation

- TEAEs leading to study discontinuation

- TEAEs leading to death (outcome of death)

- COVID-19 specific TEAEs

- COVID-19 specific TE SAEs

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetical order by SOC, and then by PT in descending order of total frequency within each SOC. 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 summary table by PT will also be provided for the above relevant AE categories that occurred during the Off-Treatment and NrtI-Restart phases. For the Off-Treatment Phase, the AEs are counted from the 29 days after the last dose of VBR and before the first dose of NrtI if it was restarted. For the NrtI-Restart Phase, the AEs are counted from the first dose of NrtI though the end of study.

Data listings will be provided for the following:

- All AEs
- All treatment-related AEs
- All SAEs
- All treatment-related SAEs
- All AEs with severity of Grade 3 or higher
- All AEs leading to discontinuation of study drug
- All AEs leading to discontinuation of study
- All deaths

7.1.7. Additional Analysis of Adverse Events

Additional analysis will be performed for the rash AEs during each phase. A summary will be provided for the number and percentage of subjects with PTs of rash, rash erythematous, rash macular, rash papular, ad rash pruritic. A data listing will be provided for subjects with any rash AEs.

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 Population. The laboratory values that are below LLOQ or above the upper LOQ will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.4.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, coagulation, and urinalysis separately. Values falling outside of the relevant reference range and/or having a United States National Institutes of Health Division of AIDS (DAIDS) severity grade of 1 or higher will be flagged in the data listings, as appropriate.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline visit
- Change and percentage change from baseline at each postbaseline visit

A Baseline laboratory value will be defined as the last measurement obtained 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 for the On-Treatment Phase.

7.2.2. Summaries of Categorical Laboratory Results

For categorical urinalysis parameters, the number and percentage of subjects in each category will be presented by treatment group at each visit in the On-Treatment Phase.

7.2.3. 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 Appendix 2 of the protocol 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.

7.2.3.1. 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 study drug plus 28 days for the On-Treatment Phase. 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.

7.2.3.2. Summaries of Laboratory Abnormalities

The summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by laboratory 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 dosing date.

The maximum postbaseline grade observed up to 28 days after last dosing 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.

All the graded lab abnormalities will be summarized for the Off-Treatment and NrtI-Restart phases. For the Off-Treatment Phase, the lab abnormalities are included from the 29 days after the last dose of VBR and before the first dose of NrtI if it was restarted. For the NrtI-Restart Phase, the lab abnormalities are included from the first dose of NrtI though the end of study.

A by-subject listing of treatment-emergent 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 laboratory test of interest, with all applicable severity grades displayed.

7.2.4. ALT Flare and Elevation

An ALT flare is defined as:

- ALT >2 × Baseline and ≥10 × ULN, or
- ALT >2 × on-treatment nadir and ≥10 × ULN

ALT elevation with declining hepatic function is defined as:

- ALT ≥2 × (Baseline or nadir) and >2 × ULN AND
- Direct bilirubin increase to ≥2 × Baseline and ≥2 × ULN, OR
- An albumin decline ≥0.5 g/dL or international normalized ratio (INR) >2 × Baseline,

  OR

- Symptoms of liver inflammation (fatigue, weakness, lack of appetite, nausea, vomiting, jaundice, or discolored feces).

The number and subjects meeting the above criteria will be summarized by phase. 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 Population who have nonmissing postbaseline values. A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group during the On-Treatment Phase for body weight, BMI, and vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min], respiration rate [breaths/min], and body temperature [ºC]) as follows:

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

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

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. In the same manner, a by-subject listing of body weight, height, and BMI will be provided separately.

7.4. Concomitant Medications

Medications collected during the study will be coded using the World Health Organization (WHO) Drug dictionary (WHODrug Global Sep2018).

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant 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. 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 PT 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 any one of the following criteria:

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

medication with the month and year (if day is missing) or year (if day and month are missing) after the date of first study drug.

- A medication started and stopped on the same day as the first dosing date or the last dosing date of study drug
- Medications with completely missing start and stop dates, unless otherwise specified.

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

Summaries of concomitant medications will be provided based on the Safety Population.

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

7.5. Electrocardiogram Results

A shift table of the Investigators' assessment of electrocardiogram (ECG) results at each visit during the On-Treatment Phase compared with Baseline values will be presented by treatment group using the following categories:

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

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

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

7.6. Other Safety Measures

No additional safety measures are specified in the protocol.

7.7. Changes From Protocol-Specified Safety Analyses

In the protocol, the rash and ALT flare were defined as AESIs. However, further review has determined these events are appropriately described as TEAEs. These events were monitored closely and discussed in detail in this report but are not defined as AESIs. Rash events are

recorded in the AE listings and will be summarized in a table. Events of ALT elevation (ALT≥ 10xULN is one of the requirements of ALT flare) will be provided in a table.

In addition, COVID-19 related safety analyses are added per regulatory guidance.

8. PHARMACOKINETIC (PK) ANALYSES

For VBR-treated subjects with a PK assessment (ie, subjects in PK Set 1), summary statistics will be presented for trough PK plasma concentrations at Week 48 when predose (trough) concentration is available. For all subjects receiving NrtI with a PK assessment (ie, subjects in PK Set 2), a similar analysis as described above will be provided for each NrtI.

Individual subject concentration data for VBR and NrtI will be listed and summarized using descriptive statistics. The sample size will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented.

The listings will be provided for PK sampling details and PK concentrations by subject.

The correlation between the plasma levels of VBR and NrtI with markers of safety and efficacy may be explored in a future population PK-Pharmacodynamic model.

9. REFERENCES

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

10. SOFTWARE

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

11. DOCUMENT HISTORY

Version	Date (DD MMM YYYY)	Summary of Changes

Signature Page for VV-TMF-12297 v1.0

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