STATISTICAL ANALYSIS PLAN

Study Title:	A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Participants with Chronic Hepatitis Delta
Name of Test Drug:	Bulevirtide
Study Number:	MYR301
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BLV	bulevirtide
BMI	body mass index
CHD	chronic hepatitis delta
CI	confidence interval
CRF	case report form
CRP	c-reactive protein
CS	clinically significant
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DT	delayed treatment
ECG	electrocardiogram
EOT	end of treatment
EQ-5D-3L	EuroQol 5-dimentions 3-levels
ET	early termination
FAS	full analysis set
FSS	fatigue severity scale
GGT	gamma glutamyl transferase
HAI	histological activity index
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HDV	hepatitis Delta virus
HQRQ	hepatitis quality of life questionnaire
HLT	high-level term
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LOD	limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
MEF	missing equals failure
NCS	not clinically significant

OC	observed case
PP	per protocol
PT	preferred term
Q1, Q3	first quartile, third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SVR24	sustained virological response 24 Weeks after scheduled end of treatment
SVR48	sustained virological response 48 Weeks after scheduled end of treatment
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
ULOQ	limit of quantification
VAS	visual analogue scale
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 MYR301 Week 144 end of treatment (EOT) analysis. This SAP is based on the study protocol Version 7.0 dated 25 January 2023 and the electronic case report form (eCRF). The SAP will be finalized before Week 144 database finalization. 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 to evaluate the efficacy of bulevirtide (BLV) administered subcutaneously for 48 weeks at a dose of 2mg or 10mg once daily for treatment of chronic hepatitis delta (CHD) in comparison to delayed treatment.

The secondary objectives of this study are:

- To evaluate optimal treatment duration
- To assess the safety of BLV

The exploratory objectives of this study are:

- To investigate the immunogenicity of BLV
- To investigate influence of BLV on quality of life
- To assess HBV/HDV genotyping
- To perform resistance testing

1.2. Study Design

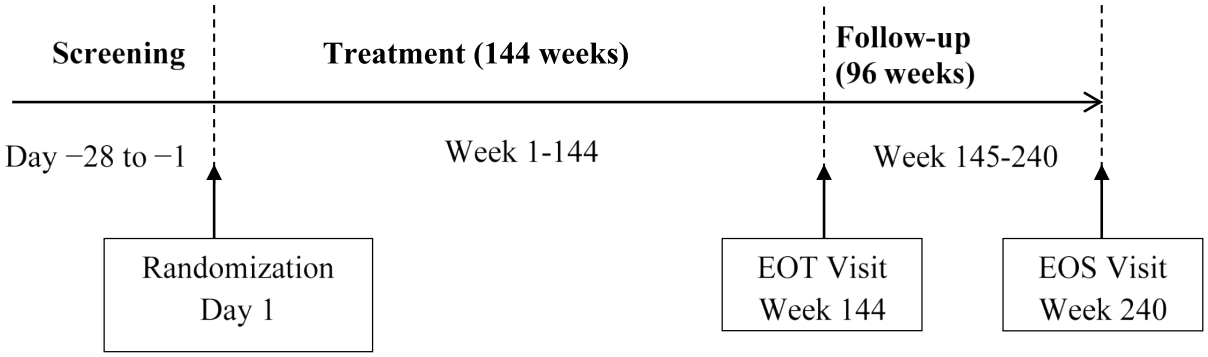
This is a randomized, open-label, parallel group, multicenter Phase 3 study to evaluate the efficacy and safety of BLV in participants with CHD who have no adequate treatment options.

A total of 150 participants were randomized, with stratification by presence of liver cirrhosis to 3 treatment arms in the ratio of 1:1:1 and treated as follows:

- Arm A (N = 51): Delayed treatment with BLV 10 mg/day for 96 weeks after an observational period of 48 weeks with a further follow-up period of 96 weeks
- Arm B (N = 49): BLV 2mg/day for 144 weeks with a further follow-up period of 96 weeks
- Arm C (N = 50): BLV 10mg/day for 144 weeks with a further follow-up period of 96 weeks

A scheme of the study design is presented in Figure 1. The schedule of events to be conducted during the 144-week treatment period and the safety follow-up period is presented in the Schedule of Assessments, Appendix 2.

Figure 1. Study Plan



EOT = end of treatment; EOS = end of study

1.3. Sample Size and Power

The primary analysis of the study is the separate comparisons of BLV 2mg and BLV 10mg with delayed treatment after a period of 48 weeks, respectively. The primary endpoint is defined as the response rate at Week 48 measured by undetectable HDV RNA or a decrease by ≥ 2 $\log_{10}$ IU/mL from baseline combined with normal ALT values within the reference range. The overall significance level is 0.05. An interim analysis was performed on the response rates at Week 24. To account for the repeated analysis of response, the nominal two-sided significance level was split among the time points with 0.01 for 24 weeks and 0.04 for 48 weeks. At each time point the BLV doses was compared to delayed treatment in terms of a hierarchical testing procedure starting with the higher dose at the respective adjusted two-sided significance levels.

The expected response rates at Week 48 for the BLV 2mg and BLV 10mg doses were 45% or greater. The conservative expectation for the delayed treatment response rates was 8% or less. These assumptions were based on results from the preceding Phase 2 study (MYR202).

With a sample size of 47 participants per treatment group, a Fisher's exact test with a 0.04 two-sided significance level has 97.8% power to detect this difference between the BLV 10mg and the delayed treatment proportions and between the BLV 2mg and the delayed treatment proportions. The power to reject both null hypotheses simultaneously is 95.6%.

This sample size was slightly increased to 50 participants per treatment group to account for a few potential early withdrawals. Hence 150 patients were randomized.

2. TYPE OF PLANNED ANALYSIS

2.1. Week 24 Analysis

The Week 24 analysis was conducted when all the participants completed the Week 24 visit or prematurely discontinued the study.

2.2. Week 48 Analysis (Primary Analysis)

The Week 48 analysis was conducted when all the participants completed the Week 48 visit or prematurely discontinued the study.

2.3. Week 96 Analysis

The Week 96 analysis was conducted when all the participants completed the Week 96 visit or prematurely discontinued the study.

2.4. Week 144 Analysis (End of Treatment)

The Week 144 analysis will be conducted when all the participants complete the Week 144 visit or prematurely discontinue the study.

2.5. Week 192 Analysis

The Week 192 analysis will be conducted when all the participants complete the Week 192 visit or prematurely discontinue the study.

2.6. Final Analysis (Week 240)

The final analysis will be performed after all participants complete the study or prematurely discontinue the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

This is the SAP for the Week 144 analysis. The details of the Week 24, 48, and 96 analysis methods were specified in the separate SAPs.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

All statistical tests will be two-sided and performed at the 5% significance level unless otherwise specified.

By-participant listings will be presented for all participants in the All Randomized Analysis Set and sorted by participant ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order for each participant. The treatment group to which participants were randomized will be used in the listings. Age, sex at birth, and race will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle for each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion, will be summarized by treatment group. In addition, the number and percentage of participants who were excluded from the Per Protocol (PP) Analysis Set and the reasons for their exclusion will be presented, and the corresponding listing will be provided.

3.1.1. All Randomized Analysis Set

The All Randomized Analysis Set includes all participants who were enrolled (informed consent signed) and randomized in the study. This is the primary analysis set for listings.

3.1.2. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all participants who were screened and enrolled in the study. The All Enrolled Analysis Set will be used for listings if it differs from the All Randomized Analysis Set.

3.1.3. Full Analysis Set

The Full Analysis Set (FAS) includes all participants who were randomized to BLV and took at least 1 dose of BLV or randomized to delayed treatment group. This is the primary analysis set for efficacy analyses.

3.1.4. Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set is defined as all participants of the FAS for whom no protocol deviations are judged to have an impact on the analysis of the primary efficacy endpoint of combined response (or on secondary efficacy endpoint of sustained virological response at follow-up Week 48 [SVR48], ie, study Week 192). The PP Analysis Set is the secondary analysis set for efficacy analyses.

There are three PP Analysis Sets in the study:

- The PP 24Week Analysis Set (defined for the Week 24 interim analysis)
- The PP 48Week Analysis Set (defined for the Week 48 primary efficacy analysis)
- The PP 192Week Analysis Set (defined for the Week 192 interim analysis)

The decision of whether a particular protocol deviation is considered as reason for exclusion from each of the PP Analysis Set should be made at data review meeting for each analysis and documented in each corresponding data review meeting report (ie, clean file report).

For Week 144 analysis, efficacy analyses using the PP 48Week Analysis Set will be repeated for primary efficacy endpoint of combined response at Week 48, key secondary endpoint of undetectable HDV RNA at Week 48, and secondary endpoint of ALT normalization at Week 48 and endpoint of virologic response at Week 48 (virologic response is defined as undetectable HDV RNA or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL from baseline) using the updated Week 144 database.

3.1.5. Safety Analysis Set

The Safety Analysis Set includes all participants who were randomized to the study and took at least 1 dose of BLV, or who were randomized to delayed treatment group. This is the primary analysis set for safety analyses.

3.1.6. Anti-drug Antibody Analysis Set

The Anti-drug Antibody (ADA) Analysis Set includes all participants who took at least 1 dose of BLV and had at least 1 non-missing ADA data. This is the primary analysis set for the immunogenicity analyses.

3.1.7. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes all randomized participants who took at least 1 dose of BLV and had at least 1 non-missing concentration value reported by the PK laboratory. This is the primary analysis set for the PK analyses.

3.2. Participant Grouping

For analyses based on the All Randomized Analysis Set and FAS, participants will be grouped according to the treatment to which they were randomized. For analyses based on the PP Analysis Set, Safety Analysis Set, ADA Analysis Set, and PK Analysis Set, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

For cumulative data summary, data will be presented as listed below:

Group A:

- DT (ie, delayed treatment): baseline (ie, baseline at randomization) to prior to the first dose of BLV at Week 48 visit or to early termination (ET) before Week 48 visit (N = 51)
- DT to BLV 10mg: first dose of BLV at Week 48 visit to Week 144 visit (N = 50, 1 participant from DT group terminated early before the Week 48 visit). The baseline will be reset at Week 48 visit (ie, re-baseline)

Groups B and C (BLV 2mg and BLV 10mg):

- Baseline to Week 48 visit period or to ET before Week 48 visit (N = 49 for Group B, N = 50 for Group C)
- Overall BLV treatment period: baseline to Week 144 visit (N = 49 for Group B, N = 50 for Group C)

For by-visit summary, data will be presented as follows: DT group, DT to BLV 10mg group, Group B, and Group C. For Group A, the AEs that occurred prior to the first dose of BLV and lab values that were tested on or prior to the first dose of BLV, or up to premature discontinuation study before receiving BLV will be allocated to DT group, while the AEs occurring at or after the first dose of BLV and lab values generated after the first dose of BLV will be allocated to DT to BLV 10mg group.

For the DT to BLV 10mg group, the baseline will be reset as the last non-missing value on or prior to the first dose of BLV (the re-baseline liver stiffness is the available value from Week 48 visit).

For Groups B and C, the data prior to the Week 48 visit or up to ET before Week 48 visit will be allocated to the baseline to Week 48 visit period; the data up to Week 144 visit will be allocated to overall BLV treatment period.

3.3. Strata and Covariates

Participants eligible for the study were randomly assigned to treatment group via electronic randomization system in a 1:1:1 ratio using a stratified randomization schedule. Stratification was based on the following variables:

- Cirrhosis status at randomization (presence vs. absence)

Efficacy endpoints will be evaluated using stratification factors as covariates for analyses, as specified in Section 6.

3.4. Examination of Participant Subgroups

The efficacy endpoints will be examined using the following subgroups. Details will be specified in the corresponding sections.

- Cirrhosis status at randomization (presence vs. absence)
- Concomitant HBV treatment (Yes vs. No)

The safety endpoints will be examined using the following subgroups. Details will be specified in the corresponding sections.

- ADA incidence at Week 144 (positive vs. negative)

3.5. Multiple Comparisons

One interim analysis at Week 24 and one primary analysis at Week 48 were conducted to compare the efficacy of treatment groups using the primary efficacy endpoint. To account for the repeated analysis of response (interim analysis at Week 24 and primary analysis at Week 48) the nominal two-sided significance level of 0.05 was split among the time points with 0.01 for Week 24 and 0.04 for Week 48. At each time point, the BLV doses were compared to DT group in terms of a hierarchical testing procedure starting with the higher dose (BLV 10mg) at the respective adjusted two-sided significance levels.

Multiple group comparisons for the primary endpoint and a key secondary endpoint were handled with a hierarchical testing procedure. Details are described in Sections 6.2.1 and 6.3.1.

All other analyses will be considered explorative and no adjustment for multiple testing will be performed.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

The handling of missing or incomplete dates for AE is described in Appendix 3, and for prior and concomitant medications in Section 7.5. Imputation rules adopted in the efficacy analyses are specified in Section 6.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis, unless otherwise specified.

3.7. Data Handling Conventions and Transformations

In general, age in years at the time when informed consent was signed will be used for analyses and presented in listings. For DT to BLV 10mg group, re-baseline age in years at Week 48 visit will be used for the analyses.

For virology laboratory data, pharmacokinetics data, molecular analysis data, and gene expression analysis data, the following rules will be applied:

- Values below the lower limit of quantification (< LLOQ) with specification of target not detected (ie, < limit of detection [LOD]) will be imputed as 0.
- Values < LLOQ (without specification of target not detected) will be imputed as half of the LLOQ value, if LLOQ does not equal the LOD.
- Values < LLOQ (without specification of target not detected) will be imputed as 0, if LLOQ equals LOD (ie, HBV DNA by MLM).
- Values above the upper limit of quantification (ULOQ) will be imputed as the ULOQ.
- Non-measurable data will be considered as missing data.

For log10 transformed data, the following rules will be applied:

- Untransformable value of 0 will be imputed as 0 if LOD > 1.
- Untransformable value of 0 will be imputed as $\log_{10}(LOD/2)$ if LOD < 1.

The LLOQ, ULOQ and LOD for virology are specified in the Table 3-1.

Table 3-1. Virology LLOQ and LOD

Parameters	Lab Institutes	LLOQ	LOD
HDV RNA	University Hospital Frankfurt (data transferred through MLM)	50 IU/mL	6 IU/mL
HBV DNA	University Hospital Frankfurt (data transferred through MLM)	10 IU/mL	10 IU/mL
HBV DNA	Invitro	100 IU/mL	20 IU/mL
HBsAg	University Hospital Frankfurt (data transferred through MLM)	not applicable	0.05 IU/mL

Safety laboratory data that are continuous in nature but less than the LLOQ or above the ULOQ (reported in the form of "< xx.xx" or "> xx.xx") will be imputed as one half of LLOQ, or as the same as ULOQ to calculate summary statistics.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the randomization date for DT group or from the first dosing date of BLV for Group B/C and for DT to BLV 10mg group and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date (or randomization date for DT group) + 1
- For days prior to the first dose: Assessment Date – First Dosing Date (or randomization date for DT group)

Therefore, Study Day 1 is the day of randomization for DT group or the day of the first dose of BLV administration for Group B/C and DT to BLV 10mg group.

3.8.2. Analysis Visit Windows

The nominal visit as recorded on the CRF will be used when data are summarized by visit. However, when the nominal visit was made outside the analysis visit window, the value will not be included in analysis.

Table 3-2. Analysis Visit Windows for by Visit Assessments for Group A/B/C

Analysis Visit	Target Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	29	2	59
Week X*	X × 7+1	X × 7+1-30	X × 7+1+30

* For Group A BLV treated participants, the upper limit at Week 48 (exclude liver stiffness and biopsy) is First Dose Date of BLV – Study Day 1 + 1

Table 3-3. Analysis Visit Windows for by Visit Assessments for Group A DT group

Analysis Visit	Target Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	29	2	59
Week X	X × 7+1	X × 7+1-30	X × 7+1+30
Week 48*	337	307	First Dose Date of BLV – Study Day 1 + 1 (or 367 for participants not treated by BLV)

* Liver stiffness at Week 48 is the available value from Week 48 visit.

Table 3-4. Analysis Visit Windows for by Visit Assessments for Group A DT to BLV 10mg group

Analysis Visit	Target on-BLV Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline on BLV*	1	(none)	1
Week 4 on BLV	29	2	59
Week X on BLV	X × 7+1	X × 7+1-30	X × 7+1+30

* Liver stiffness baseline on BLV is the available value from Week 48 visit.

The data collected at unscheduled visits (including ET visits) will be used in the following ways:

- An unscheduled visit on or prior to the randomization for DT group or the first dose of BLV may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the randomization for DT group or the first dose of BLV will be included in determining the maximum postbaseline toxicity grade.

- Record from unscheduled visit will be assigned to a visit when there is no available data in the corresponding analysis visit window. If multiple measurements from unscheduled visits exist, the selection rule specified in Section 3.8.3 will be followed.

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

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value.

If multiple valid, non-missing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last non-missing value on or prior to the randomization date for the DT group, or to the first dosing BLV for all other groups will be selected, unless specified differently.

- For postbaseline values, record from ET visit will be selected. If there is no available ET record, the data from unscheduled visits will be selected as below.

  — The record closest to the target day for that visit will be selected.

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

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

A summary of participant enrollment will be provided by treatment group for each region. The summary will present the number and percentage of participants enrolled. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of participants in the randomization stratum will be the total number of enrolled participants.

A summary of participant disposition will be provided by treatment group. This summary will present the number of participants screened, the number of participants who met all eligibility criteria but were not randomized with reasons participants not randomized, the number of participants enrolled, the number of participants randomized, the number of participants randomized but not dosed, and the number of participants in each of the categories listed below:

- Safety Analysis Set
- Full Analysis Set
- Per-Protocol Analysis Set
- Completed Week 24
- Completed Week 48
- Completed Week 96
- Completed Week 144
- Continuing study at Week 144
- Did not complete the study with reasons for premature discontinuation of study

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

The following by-participant listings will be provided by participant identification (ID) number in ascending order to support the above summary tables:

- Reasons for premature study discontinuation

- Reasons for screen failure (will be provided by screening ID number in ascending order)

4.2. Extent of Study Drug Exposure and Compliance

The sponsor will capture, clean, and validate the missing doses that are not documented in the participant diary (hereafter referred to as "sponsor identified missed doses") in an excel file (included in the clean file report as an appendix).

4.2.1. Study Drug Exposure

The total duration of BLV exposure in weeks will be computed as (last dose date of BLV – first dose date of BLV + 1)/7 regardless of any temporary interruptions and will keep 2 decimal places (ie, 4.56 weeks).

The total dose of BLV (in mg) administered will be computed as the sum of all doses administered (as reported in the participant diary, which takes participant reported missed doses into consideration) minus sponsor identified missed doses (the number of days without dosing times the planned daily dose for BLV).

The dose intensity (in mg/week) will be computed as the total dose administered divided by the total duration of exposure.

4.2.2. Study Drug Compliance

The compliance rate of the full regimen will be computed as the ratio of the total dose administered to the expected full regimen dose and expressed as a percentage. The expected full regimen dose for BLV is defined as 96 weeks of planned daily dosage (10mg) for participants in DT to BLV 10mg group, and 144 weeks of planned daily dosage (2mg or 10mg) for participants in Groups B and Group C.

The total number of missed doses will be computed as the expected total number of doses minus the number of doses administered by Week 144, or study day 1006 (ie, 144×7-2 per protocol visit window), whichever comes first (as reported in the participant diary), plus the number of additional sponsor identified missed doses. If this results in a negative number, the total number of missed doses will be set to the number of sponsor identified missed doses, or zero if there were no sponsor identified missed doses.

The expected total number of BLV doses will be defined as:

(last on-treatment visit date, or study day 1006, or ET from study date, whichever comes first) – first dose date + 1

The proportion of missed doses will be computed as the ratio of the total number of missed doses to the expected total number of doses and expressed as a percentage.

4.2.3. Summaries of Study Drug Exposure and Compliance

Descriptive statistics for following parameters will be presented by treatment group (Group B, Group C, DT to BLV 10mg) for BLV at Week 144.

- Total duration of exposure
- Total dose administered
- Dose intensity
- Compliance rate
- Participants with ≥ 1 missed dose
- Total number of missed doses
- Proportion of missed doses

In addition, the by-participant listings of BLV administration and accountability will be provided. No formal statistical testing is planned.

4.3. Protocol Deviations

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

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations by deviation reason will be summarized by treatment group for the All Randomized Analysis Set. A by-participant listing will be provided for those participants with important protocol deviation.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which had an impact on the study conduct. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Protocol Deviations Due to COVID-19

A summary of important protocol deviations due to COVID-19 will be provided, similar to the summary described in the protocol deviations section (Section 4.3).

The number and percentage of participants with non-important protocol deviations related to COVID-19 by deviation reasons will be summarized by treatment group.

A by-participant listing will be provided for participants with important protocol deviations related to COVID-19, if applicable. A separate listing will be provided for participants with non-important protocol deviations related to COVID-19, if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic and baseline characteristics variables will be summarized by treatment group (eg, DT group, BLV 2mg group, BLV 10mg group, and DT to BLV 10mg group), and total, using descriptive statistics for continuous variables, and number and percentage of participants for categorical variables, where the total number is the sum of the DT group, BLV 2mg group, and BLV 10mg group. The summary of demographic and baseline characteristics data will be provided for the FAS and PP 48Week Analysis Set, for the following:

- Age (years)
- Sex (male, female)
- Race (Asian, Black or African American, White, Other)
- Height (cm)
- Body weight (kg)
- Body mass index (BMI, kg/m^2)
- BMI categories (<30 kg/m^2, ≥ 30 kg/m^2)

If the Safety Analysis Set differs from the FAS, or there are participants whose actual treatment differs from randomized treatment for the whole treatment period, this summary will be provided for the Safety Analysis Set as well.

A by-participant demographic and baseline characteristics listing, including the informed consent date will be provided. No formal statistical testing is planned.

5.2. Other Baseline Characteristics

Participants' other baseline characteristics variables will be summarized by treatment group, and total using descriptive statistics for continuous variables, and number and percentage of participants for categorical variables. The summary of other baseline characteristics data will be provided for the FAS and PP 48Week Analysis Set for the following:

- Cirrhosis status at randomization (Presence, Absence)
- Child–Pugh score for cirrhotic participants
- Child–Pugh class for cirrhotic participants

- Abdominal ultrasound (abnormal clinically significant [CS], abnormal not clinically significant [NCS], normal)
- Serum alpha-fetoprotein (AFP; IU/mL)
- Baseline alanine aminotransferase (ALT) (U/L)
- Baseline ALT (≤ upper limit of normal [ULN], > ULN to ≤ 1.5×ULN, > 1.5×ULN)
- Baseline creatinine clearance (mL/min)
- Baseline creatinine clearance (≥ 60 to < 90 mL/min vs. ≥ 90 mL/min)
- Baseline liver stiffness (kpa)
- Baseline liver stiffness (< 12 kPa, 12 to 20 kPa, > 20 kPa)
- Prior PEG-IFNα (prior medication preferred name contains the word 'interferon') (yes, no)
- HIV antibody (positive, negative, missing)
- HCV antibody (positive, negative, missing)
- HDV antibody (positive, negative, missing)
- HBeAg (positive, negative, missing)
- HBeAg antibody (positive, negative, missing)
- Qualitative HBV DNA at screening (positive, negative, missing)
- HDV genotype
- HBV genotype
- Baseline HDV RNA (log_{10} IU/mL)
- Baseline HBV DNA (log10 IU/mL)
- Baseline HBV DNA (< LLOQ target not detected, < LLOQ target detected, ≥LLOQ)
- Baseline HBsAg (log10 IU/mL)
- Baseline aspartate aminotransferase (AST) (U/L)
- Baseline alkaline phosphatase (ALP) (U/L)

- Baseline gamma glutamyl transferase (GGT) (U/L)
- Baseline platelet count ($\times 10^9$/L)
- Baseline total bilirubin (μmol/L)
- Baseline total bile salts (μmol/L)
- Concomitant HBV medication (Yes/No)

For DT to BLV 10mg, unless otherwise specified, a baseline value will be defined as the last measurement obtained on or prior to the date of first dose of BLV at Week 48 visit. And baseline liver stiffness is the available measurement from Week 48 visit.

In summary tables of demographic and baseline characteristics, the original baseline values at randomization will be used for the DT to BLV 10mg group for the following variables:

- Sex (male, female)
- Race (Asian, Black or African American, White, Other)
- Height (cm)
- Cirrhosis status at randomization (Presence, Absence)
- Child–Pugh score for cirrhotic participants
- Child–Pugh class for cirrhotic participants
- Abdominal ultrasound (abnormal clinically significant [CS], abnormal not clinically significant [NCS], normal)
- Serum alpha-fetoprotein (AFP; IU/mL)
- Prior PEG-IFNα (prior medication preferred name contains the word ‘interferon’) (yes, no)
- HIV antibody (positive, negative, missing)
- HCV antibody (positive, negative, missing)
- HDV antibody (positive, negative, missing)
- HBeAg (positive, negative, missing)
- HBeAg antibody (positive, negative, missing)

- Qualitative HBV DNA at screening (positive, negative, missing)
- HDV genotype
- HBV genotype

Estimated on-study creatinine clearance will be calculated by the Cockcroft-Gault method: creatinine clearance = [(140 – age (yrs)) × weight (kg) × (0.85 if female)] /(0.814 × creatinine (μmol/L)), where weight is total body mass in kilograms.

If the Safety Analysis Set differs from the Full Analysis Set, or there are participants whose actual treatment differs from randomized treatment for the whole treatment duration, this summary will be provided for Safety Analysis Set as well.

A by-participant listing of other baseline characteristics will be provided. No formal statistical testing is planned.

5.3. Substance Use

Participant substance use will be summarized by treatment group, and overall using number and percentage of participants. The summary will be provided for the FAS and PP 48Week Analysis Set, for the following:

- Alcohol breath test at screening (Positive, Negative)
- Alcohol breath test at baseline (Positive, Negative)
- Alcohol consumption status (Current, Former, Never)
- Smoking status (Current, Former, Never)
- Urine drug test at screening (Positive, Negative)
- Drug abuse status (Current, Former, Never)

5.4. Medical History

Medical history collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v26.0.

Medical history will be summarized for Safety Analysis Set by system organ class (SOC), preferred term (PT), treatment group, and overall. Participants who reported 2 or more medical history terms that are coded to the same SOC and/or PT will be counted only once by the unique coded term in the summary. No formal statistical is planned. A by-participant listing of medical history will be provided.

6. EFFICACY ANALYSES

6.1. General Considerations

The primary analysis set for efficacy analyses will be the FAS, defined in Section 3.1.2.

Derivation of Multi-component Endpoints

For the derivation of multi-component endpoints including combined response and virological response, the following steps will be used unless otherwise specified:

- Step 1: assign individual components to analysis visit windows specified in Section 3.8.2
- Step 2: impute missing data for individual components
- Step 3: derive the multi-component endpoint with the corresponding imputed individual components

Missing Data Imputation

Below are the descriptions for the imputation methods that will be used in the efficacy analyses:

- Missing Equals Failure (MEF): For binary response endpoints, missing value will be imputed as nonresponder. For all analyses of the primary endpoint and undetectable HDV RNA at Week 24 and Week 48 using FAS, MEF will be adopted when missing was not related to COVID-19. In addition, MEF will be adopted for all analyses of the secondary and exploratory endpoints using FAS.
- Last observation carrying forward (LOCF): Missing value will be imputed using the last observation (including observation from unscheduled visit). For all analyses (except the sensitivity analysis) of the primary efficacy endpoint and undetectable HDV RNA at Week 24 and Week 48 using FAS, LOCF will be used when missing was related to COVID-19.
- Observed Case (OC): Missing values remain missing. The OC will be used for analyses of continuous endpoints and analyses using PP 48Week Analysis Set.

6.2. Primary Efficacy Endpoints

The primary efficacy endpoint is combined response at Week 48. Combined response is defined as fulfilling both of the following 2 conditions simultaneously:

- Undetectable (< LLOQ, target not detected) HDV RNA or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL from baseline
- ALT normalization

6.2.1. Primary Analysis of the Primary Efficacy Endpoint

Two 2-sided Fisher's exact tests at an overall significance level of 0.05 will be performed to sequentially test the hypotheses:

H_{01}: $p_O = p_{M10mg}$ vs H_{11}: $p_O \neq p_{M10mg}$

H_{02}: $p_O = p_{M2mg}$ vs H_{12}: $p_O \neq p_{M2mg}$

where p_O, $p_{M2mg,}$ and p_{M10mg} are the expected response rate for delayed treatment, BLV 2mg and BLV 10mg, respectively. In terms of a hierarchical testing procedure, the second null hypothesis will not be rejected if the first null hypothesis could not be rejected. These hypotheses were tested at the Week 24 interim analysis and at the Week 48 primary analysis. To account for the repeated analysis, the nominal two-sided significance level of 0.05 will be split among these two time points with 0.01 for Week 24 and 0.04 for Week 48.

The primary analysis of combined response at Week 24 is the estimated rate difference between BLV and delayed treatment group with 99% exact unconditional CI for the difference based on the score statistic. The p-value from 2 two-sided Fisher's exact tests will also be provided. There is a statistically significant difference at Week 24 if $p < 0.01$. In addition, for each group, the response rate with Clopper-Pearson 95% CIs will be presented.

The primary analysis of combined response at Week 48 is the estimated rate difference between BLV and delayed treatment group with 96% exact unconditional confidence interval (CI) for the difference based on the score statistic. The p-value from 2 two-sided Fisher's exact tests will also be provided. There is a statistically significant difference at Week 48 if $p < 0.04$. The comparison of BLV 2mg versus delayed treatment is considered significant only if the comparison of BLV 10mg versus delayed treatment is significant. In addition, for each group, the response rate with Clopper-Pearson 95% CIs will be presented.

The primary analysis will be based on the FAS.

6.2.2. Sensitivity Analysis of the Primary Efficacy Endpoint

The same analysis as specified in Section 6.2.1 will be repeated using the data for which missing values were imputed as failure regardless of whether it was related to COVID-19 (Section 6.1).

6.2.3. Per-protocol Analysis of the Primary Efficacy Endpoint

The same analysis as specified in Section 6.2.1 will be repeated using the PP 48Week Analysis Set based on actual treatment on the observed cases without imputing missing values, as a supportive analysis.

6.2.4. Subgroup Analysis of the Primary Efficacy Endpoint

With an expected low number of responders in the delayed treatment group, the primary efficacy analysis will not be stratified by cirrhosis or other covariables. Descriptive analyses of combined response will be presented by subgroups for efficacy endpoints as defined in Section 3.4.

6.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Undetectable HDV RNA at Weeks 48 (key secondary efficacy endpoint)
- ALT normalization at Week 48
- Undetectable HDV RNA 24 weeks after scheduled end of treatment (SVR24)
- Undetectable HDV RNA 48 weeks after scheduled end of treatment (SVR48)
- Change from baseline in liver stiffness as measured by elastography at Weeks 48, 96, 144, 192, and 240

The SVR24, SVR48 and the change from baseline in liver stiffness at Weeks 192 and 240 will be analyzed in future analyses.

6.3.1. Analysis of Secondary Efficacy Endpoints

Undetectable HDV RNA at Weeks 48 (key secondary endpoint)

The proportion of participants with undetectable HDV RNA at Week 48 is the key secondary endpoint and will be used to test differences between the BLV doses and hence evaluate the dose response relationship.

A two-sided Fisher's exact test will be performed to test the hypotheses

$$H_{03}: r_{M2mg} = r_{M10mg} \text{ vs. } H_{13}: r_{M2mg} \neq r_{M10mg}$$

where r_{M2mg}, r_{M10mg} are the expected rates of participants with undetectable HDV RNA at Week 48 for BLV 2mg and BLV 10mg, respectively.

This test will only be performed if the two null-hypotheses for the primary variable (H_{01} and H_{02} in 6.2.1) both have been rejected. As for the primary analysis, the above hypotheses will also be tested at Week 24 and hence the nominal two-sided significance level of 0.05 will be split among the time points with 0.01 for Week 24 and 0.04 for Week 48, respectively.

The estimated rate differences between BLV 10mg and BLV 2mg with exact unconditional CI based on score statistic (99% CI for Week 24 and 96% CI for Week 48), and the p-value from

Fisher's exact test will be provided using FAS and PP 48Week Analysis Set. The Clopper-Pearson 95% CIs of undetectable HDV RNA rate in each group will also be presented. The same summary will be repeated by subgroups for efficacy endpoints as defined in Section 3.4.

ALT Normalization at Week 48

The proportion of participants with ALT normalization at Week 48 will be compared between BLV 2mg and the delayed treatment group and BLV 10mg and the delayed treatment group using two-sided Fisher's exact tests. Nominal p-values without multiple comparison adjustment and 95% exact unconditional confidence intervals based on score statistic for the proportion differences will be provided. The same analysis will be performed at Week 24 and at Week 48, using FAS and using PP 48Week Analysis Set. In addition, for each group, the Clopper-Pearson 95% CIs of response rate will also be presented. The same summary will be repeated by subgroups for efficacy endpoints as defined in Section 3.4.

Change from Baseline in Liver Stiffness at Week 48, Week 96, and Week 144

For the change from baseline in liver stiffness at Week 48, an ANCOVA model will be used to compare the least squares (LS) means between BLV 2mg and the delayed treatment group, and BLV 10mg and the delayed treatment group using FAS and PP 48Week Analysis Set. The model includes treatment, region, presence of cirrhosis and baseline liver stiffness as covariate. Nominal p-values without multiple comparison adjustment and the 95% CI for the LS mean difference between each BLV group and the delayed treatment group will be provided. In addition, for each treatment group, the LS mean will be provided.

For the change from baseline in liver stiffness at Week 96 and Week 144, a mixed-effects model for repeated measurements (MMRM) will be used to evaluate treatment effect using FAS. The model includes treatment (BLV 2mg, BLV 10mg, and DT to BLV 10mg group), region, presence of cirrhosis, visit and treatment by visit interaction as fixed effects, and baseline liver stiffness (the baseline for DT to BLV 10mg group is the reset baseline) as covariable. An unstructured variance-covariance matrix will be used. The Kenward-Roger method will be used to estimate the degrees of freedom. Restricted maximum likelihoods (REML) will be used to fit the model. Missing change values will not be otherwise imputed using MMRM. For each treatment group, the LS mean with 95% CI at Week 96 (for DT to BLV 10mg group, Group B and Group C) and at Week 144 (for Group B and Group C only) will be presented respectively. In addition, the difference in LS means and the 95% CI for the LS mean difference between BLV 2mg (Group B) and BLV 10mg (Group C) at each visit will be provided.

Descriptive statistics of liver stiffness at each visit, as well as the change from baseline, will be provided by treatment group. The summary will be repeated by subgroups for efficacy endpoints defined in Section 3.4 using FAS. The plots of mean ± SD of change from baseline in liver stiffness over time, as well as by subgroup of cirrhosis status, will be presented.

6.4. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Change from baseline in necroinflammation as assessed at liver biopsy
- Change from baseline in fibrosis as assessed at liver biopsies
- Combined response at all postbaseline assessments of HDV RNA and ALT
- HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL from baseline at all postbaseline assessments
- Undetectable HDV RNA at all postbaseline assessments
- HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL from baseline or undetectable HDV RNA at all postbaseline assessments (virologic response)
- Change from baseline in HDV RNA at all postbaseline assessments
- ALT normalization at all postbaseline assessments
- Change from baseline in ALT at all postbaseline assessments
- Change from baseline in serum alpha-2-macroglobulin (fibrosis marker) at all postbaseline assessments
- HBsAg response (HBsAg decrease by ≥ 1 $\log_{10}$ IU/mL) at all postbaseline assessments
- HBsAg loss without seroconversion at all postbaseline assessments
- HBsAg loss with seroconversion (presence of anti-HBsAg) at all postbaseline assessments
- Change from baseline in HBsAg ($\log_{10}$ IU/mL) at all postbaseline assessments
- Change from baseline in HBV DNA ($\log_{10}$ IU/mL) at all postbaseline assessments
- Liver-related clinical events (such as cirrhosis development; liver decompensation including development or worsening jaundice, coagulopathy, ascites, hepatic encephalopathy, bleeding from varices, and liver failure; HCC development; liver transplantation and liver-related death) at all postbaseline assessments
- Number of liver-related hospitalizations and duration of each hospitalization at all postbaseline assessments
- Change from baseline in quality of life assessed with questionnaires at all postbaseline assessments:
  - EuroQol (5 dimensions) (EQ-5D)
  - Fatigue Severity Scale (FSS)

— The Hepatitis Quality of Life Questionnaire™ (HQLQ™)

6.4.1. Definition of Exploratory Efficacy Endpoints

6.4.1.1. Necroinflammation and Fibrosis Assessed at Liver Biopsy

The analysis of the liver biopsy samples will be used to assess necroinflammation and fibrosis endpoints. The histological activity index (HAI) is an additive score calculated as the sum (range 0 to18) of the semi-quantitative scores for 3 individual features: periportal necrosis with the presence of bridge like necrosis or without them (range 0 to 10), intralobular degeneration and focal necrosis (range 0 to 4), and portal inflammation (range 0 to 4). Stage of histological activity based on Metavir score will be assigned as Metavir activity grade. The stage of liver fibrosis on a scale of Knodell, Ishak, Metavir will be assessed.

6.4.1.2. HBsAg Loss with/without Seroconversion

HBsAg loss is defined as undetectable HBsAg. Seroconversion is defined as presence of anti-HBsAg.

HBsAg loss without seroconversion response values are:

- Responder: HBsAg result less than the LOD, with negative anti-HBsAg
- Non-responder: participants who do not meet criteria of responder

HBsAg loss with seroconversion response values are:

- Responder: HBsAg result less than the LOD, with presence of anti-HBsAg
- Non-responder: participants who do not meet criteria of responder

6.4.1.3. Liver Related Clinical Events

The potential liver related clinical events include liver-related death, and other events as defined in the Table 6-1.

Table 6-1. Definition of Potential Liver Related Clinical Events

Potential Liver Related Clinical Events	MedDRA v26.0 Preferred Term
Cirrhosis development	• Hepatic cirrhosis
Development or worsening of jaundice	• Jaundice
Development or worsening of coagulopathy	• Coagulopathy
Development or worsening of ascites	• Ascites • Bacterascites • Spontaneous bacterial peritonitis
Development or worsening of hepatic encephalopathy	• Hepatic encephalopathy • Coma hepatic • Asterixis
Bleeding from varices	• Oesophageal varices haemorrhage • Gastric varices haemorrhage • Intestinal varices haemorrhage • Anorectal varices haemorrhage
Hepatocellular carcinoma development	• Hepatic cancer • Hepatocellular carcinoma • Liver carcinoma ruptured • Mixed hepatocellular cholangiocarcinoma
Liver transplantation	• Liver transplant • Renal and liver transplant
Liver failure	• Acute hepatic failure • Subacute hepatic failure • Acute on chronic liver failure • Hepatic failure • Hepatorenal syndrome • Hepatorenal failure • Hepatopulmonary syndrome
Liver-related death	Potential liver related clinical event with fatal outcome

6.4.1.4. EuroQol 5-Dimentions 3-Levels (EQ-5D-3L)

EQ-5D-3L is a standardized questionnaire describing health outcomes in 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 3 levels: no problems, some problems, and extreme problems. In addition to the five domains, the EQ visual analogue scale (EQ VAS) is used to assess the participant's self-rated health. The EQ VAS ranges from 0 to 100, and higher score indicates better health.

6.4.1.5. Fatigue Severity Scale (FSS)

The FSS is a 9 items scale measuring the severity of fatigue and its physical, social, and cognitive impact on participants' activities and lifestyle. Each item is scored using a 7-point Likert scale where a low value indicates strong disagreement with the statement, and a high value indicates agreement with the statement. An overall mean score will be computed as the arithmetic mean (range 1 to 7) of the item scores. The mean score will be computed when there are at least half of the item scores are non-missing; otherwise, the mean score will be set to "missing."

6.4.1.6. Hepatitis Quality of Life Questionnaire™ (HQLQ™)

The HQLQ™ assesses the functional health and well-being of the participant. It comprises 36 questions from the second version of the Short Form 36 Health Survey, and 15 additional questions that measure other generic health concepts. The Short Form 36 Health Survey items are organized into eight scales: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health. In addition, 2 summary measures are also constructed: physical component summary and mental component summary. The additional questions are organized into 5 scales: health distress, positive wellbeing, hepatitis-specific limitations, and hepatitis-specific health distress. The scale scores and summary measures will be computed by Optum®.

6.4.2. Analysis of Exploratory Efficacy Endpoints

The FAS will be used for analyses of exploratory efficacy endpoints. Descriptive statistics will be provided by treatment group at all scheduled visits for each exploratory efficacy endpoint and HBsAg loss. For binary endpoints, the Clopper-Pearson 95% CIs of response rate in each treatment group will be presented. Subgroup analysis specified in Section 3.4 will be performed for binary endpoints: proportions of participants achieving combined response, undetectable HDV RNA, virologic response, HDV RNA decrease ≥ 2 $\log_{10}$ from baseline, and ALT normalization. The subgroup analysis will be also provided for HDV RNA, ALT, HBsAg, and HBV DNA change from baseline by visit.

To analyze change from baseline in necroinflammation and fibrosis, the number and percentage of participants with change status (improving, no change or worsening) at Week 48 visit will be summarized by treatment group for Metavir histological activity grade, histological activity index (HAI), and Ishak, Knodell and Metavir fibrosis scores, respectively. The HAI original value (range 0 to18) will be categorized into category levels as in the table below for analysis, unless specified otherwise

HAI Original Value	HAI Category Level	HAI Clinical Interpretation
0	0	No inflammation
1-4	1	minimal inflammation

HAI Original Value	HAI Category Level	HAI Clinical Interpretation
5-8	2	Some inflammation
9-12	3	Moderate inflammation
13-18	4	Significant inflammation

The improving is defined as decrease at least 1 point (or 1 category level for HAI) from baseline, and the worsening is defined as increase at least 1 point (or 1 category level for HAI) from baseline. Participants with missing value at baseline or postbaseline will be summarized but will not be included in the denominator for percentage calculation.

The shift tables will be provided by showing changes in results from baseline to Week 48 by treatment group for Metavir histological activity grade, HAI, and Ishak, Knodell and Metavir fibrosis scores.

The number and percentage of participants having histological improvement (defined as decrease at least 2 points from baseline in HAI original value without worsening of Knodell fibrosis score) at Week 48 will be summarized by treatment group. The number and percentage of participants having at least 2 points reduction from baseline in HAI original valueat Week 48 will be also summarized by treatment group.

The potential liver-related clinical events will be summarized for the DT group, DT to BLV 10mg group, Group B/C baseline to Week 48 visit period and baseline to Week 144 visit period, respectively. The events will be allocated to treatment group based on event onset dates. A similar summary for liver related hospitalizations will also be provided, and the duration of hospitalization calculated as (end date – start date + 1) will be presented in the listing.
The proportions of participants achieving response will be plotted over time by treatment for combined response, ALT normalization, undetectable HDV RNA, and virologic response, as well as HDV RNA decrease ≥ 2 $\log_{10}$ from baseline. In addition, plots of mean ± SD of changes from baseline for HDV RNA and ALT will be presented. The same plots will be repeated by cirrhosis status.

In addition, a by-participant listing will be provided for combined response, virological response, HDV RNA decrease by ≥ 2 $\log_{10}$ IU/mL from baseline, undetectable HDV RNA, ALT normalization, HDV RNA, HDV RNA change from baseline, ALT, ALT change from baseline, liver stiffness, HBV DNA, and HBsAg at all visits. The same listing will be repeated for non-responders of combined response at Week 48.

Separate by-participant listings for other exploratory efficacy endpoints may be generated as appropriate.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

Clinical and laboratory adverse events (AEs) will be coded using the MedDRA v26.0. 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.

7.1.1. Adverse Event Severity

Adverse events are graded as Grade 1, 2, 3, 4, or 5 according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0). Events for which a CTCAE term cannot be found will be assigned a severity grade according to the classification of AEs specified in the study 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.

7.1.2. Relationship of Adverse Events to Study Drug

The related AEs for each study drug are those for which the investigator selected "Reasonable possibility" on the AE CRF to the question of causality. Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.3. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs meet the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAEs captured and stored in the Gilead global safety database before data finalization.

For SAEs with multiple reports (initial reports and one or more follow-up reports), only the last report will be included in the summary tables and listings.

7.1.4. Treatment-Emergent Adverse Events

7.1.4.1. Definition of Treatment-Emergent Adverse Events

For the DT group, treatment-emergent adverse events (TEAEs) are defined as the following:

- Any AEs with an onset date on or after the randomization date and before participants' BLV start date

- Any AEs with an onset date on or after the randomization date, and prior to the Week 48 visit date, or up to study discontinuation date if the participant discontinued the study before the Week 48 visit

For the DT to BLV 10mg group, BLV 2mg and BLV 10mg, TEAEs are defined as 1 or both of the following:

- Any AEs onset on or after the study drug start and no later than 30 days after permanent discontinuation of study drug

- Any AEs leading to premature discontinuation of study drug

For delayed treatment participants who switched to BLV 10mg, TEAEs with onset prior to the first dose of BLV will be allocated to the DT group. TEAEs onset on or after the first dose of BLV will be allocated to the DT to BLV 10mg group.

For BLV 2mg and BLV 10mg, TEAE onset prior to the Week 48 visit will be allocated to the baseline to Week 48 visit.

7.1.4.2. Incomplete Dates

If the onset or end date of an AE is fully or partially unknown, the incomplete date will be imputed before analysis according to the rules in Appendix 3.

7.1.5. Summaries of Adverse Events and Deaths

TEAEs will be summarized based on the Safety Analysis Set and repeated for the following categories. The AEs will be allocated to time periods based on AE onset dates.

- TEAE prior to Week 48 visit for all groups

- TEAE by Week 144 for the Group B and Group C

- TEAE from Week 48 to Week 144 for the DT to BLV 10mg group

7.1.5.1. Summaries of AE incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number and percentage of participants 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.

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and treatment group for the AE categories described below:

- TEAEs

- TEAEs with Grade 3 or higher
- TEAEs with Grade 2 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher
- TE treatment-related AEs with Grade 2 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug
- TEAEs leading to death (ie, outcome of death)

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC, and then by PT in descending order of BLV 2mg frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs, TEAEs with Grade 3 or higher, TEAEs occurring in ≥ 10% of participants of any treatment group, TE SAEs, TE treatment-related AEs, and TE treatment-related SAEs will be summarized by PT only, in descending order of BLV 2mg frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths
- All AEs with severity of Grade 3 or higher
- All AEs with severity of Grade 2 or higher
- All AEs leading to premature discontinuation of study drug

7.1.6. Additional Analysis of Adverse Events

7.1.6.1. Hepatic Adverse Events

Hepatic AEs potentially indicative of hepatitis flare will be identified using MedDRA v26.0 search terms. The number and percentage of participants who experienced any TE hepatic AE will be summarized by PT and treatment group. In addition, the hepatic AEs will be summarized as follows: from baseline to prior to Week 48 visit date for DT group, Group B and Group C, from baseline up to Week 144 for Group B and Group C, and from Week 48 to Week 144 for the DT to BLV 10mg group. The by-participant listing of hepatic AEs will also be provided.

7.1.6.2. Subgroup Analyses of Adverse Events

Treatment-emergent AEs by anti-drug antibody (ADA) incidence at Week 144 will be provided by PT and treatment group:

- For Group B and Group C, TEAEs from baseline to Week 144 will be summarized by treatment and ADA incidence at Week 144.
- For DT to BLV 10mg, TEAEs from Week 48 visit to Week 144 will be summarized by ADA incidence at Week 144. The ADA incidence will be derived using ADA data prior to the first dose of BLV at the Week 48 visit as baseline and ADA data after participants receive BLV as postbaseline assessments.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. All available data at the time of the database snapshot for participants who were ongoing at the time of an interim analysis. When values are below the LOQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

The summary of laboratory evaluation will be provided by:

- Prior to Week 48 visit for DT group, Group B and Group C
- Up to Week 144 for Group B and C
- From Week 48 to Week 144 for DT to BLV 10mg

For DT to BLV 10mg grouping, a baseline laboratory value will be defined as the last measurement obtained on or prior to the first dose of BLV at Week 48 visit.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, coagulogram, serum chemistry, total bile salts, and

urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate. No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics of baseline values, values at each postbaseline visit, change and percentage change from baseline at each postbaseline visit will be provided by treatment group for the following laboratory tests. White blood cell differential results from manual assay will not be included as they are not considered valid.

- Hematology
  - Haematocrit (%)
  - Haemoglobin (g/dL)
  - Platelet Count ($\times 10^9$/L)
  - Reticulocytes (ppth)
  - Red Blood Cells ($\times 10^{12}$/L)
  - White Blood Cells ($\times 10^9$/L)
  - Absolute Neutrophils ($\times 10^9$/L)
  - Relative Neutrophils (%)
  - Absolute Eosinophils ($\times 10^9$/L)
  - Relative Eosinophils (%)
  - Absolute Basophils ($\times 10^9$/L)
  - Relative Basophils (%)
  - Absolute Monocytes ($\times 10^9$/L)
  - Relative Monocytes (%)
  - Absolute Lymphocytes ($\times 10^9$/L)
  - Relative Lymphocytes (%)
- Total Bile Salts (μmol/L)

- Coagulogram
  - Prothrombin Time (%)
  - Activated Partial Thromboplastin Time (aPTT) (sec)
  - International Normalized Ratio (INR)
- Chemistry
  - Albumin (g/L)
  - ALP (U/L)
  - AST (U/L)
  - Total Bilirubin (µmol/L)
  - Direct Bilirubin (µmol/L)
  - C-Reactive Protein
  - Chloride (mmol/L)
  - Total Cholesterol (mmol/L)
  - Creatinine (µmol/L)
  - GGT (U/L)
  - Glucose (mmol/L)
  - Lipase (U/L)
  - Total Amylase (U/L)
  - Pancreatic Amylase (U/L)
  - Phosphate (mmol/L)
  - Potassium (mmol/L)
  - Total Protein (g/L)
  - Sodium (mmol/L)

- Urea (mmol/L)

- Urinalysis
  - pH
  - Specific Gravity (g/L)

A baseline laboratory value will be defined as the last measurement obtained on or prior to the first dose of BLV or to the randomization for the DT group. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values for these laboratory tests may be plotted using a line plot by treatment group and visit.

7.2.2. Summaries of Qualitative Laboratory Results

The summary of clinical assessment of laboratory variables (abnormal high CS, abnormal high NCS, normal, abnormal low NCS, abnormal low CS) will be provided by visit and treatment group for laboratory tests listed in Section 7.2.1 as well as for urinalysis of protein, glucose, bilirubin, urobilinogen, ketones, erythrocytes, leukocytes, and nitrites.

7.2.3. Graded Laboratory Values

The CTCAE Version 5.0 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. 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 BLV plus 30 days, or from randomization up to prior to the first dose of BLV or ET before Week 48 visit for DT group. 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 following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with non-missing postbaseline values up to 30 days after last dosing date, or prior to the first dose of BLV or up to ET before Week 48 visit for DT group.

A by-participant listing of treatment-emergent laboratory abnormalities will be provided by participant ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades or abnormal flags displayed. In addition, the listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will also be provided.

7.2.3.3. Potential Drug Induced Liver Injury (DILI)

The participants who meet any one of the following criteria for potential drug induced liver injury (DILI) at on-treatment visits will be summarized by treatment, and the corresponding listing will be provided:

- Criteria 1: ALT and/or AST > 3×ULN and total bilirubin > 2×ULN
- Criteria 2: ALT > 5×ULN
- Criteria 3: Total bilirubin > 2×ULN

7.2.4. Shifts Relative to the Baseline Value

Shift tables will be presented by showing changes in results from baseline value (abnormal high CS, abnormal high NCS, normal, abnormal low NCS, abnormal low CS) to Weeks 48, 96 and 144 for laboratory tests listed in Section7.2.1 and 7.2.2. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, and vital signs (systolic and diastolic blood pressures [mmHg], respiratory rate [breaths/min] and body temperature [C]) 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 the first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-participant listing of vital signs will be provided by participant ID number and visit in chronological order. Body weight will be included in the vital signs listing, if space permits. If not, they will be provided separately.

7.4. Physical Examination

For each type of local reaction at injection site, the number and percentage of participants with at least one instance reported as an AE will be summarized by severity and treatment, and the maximum severity grade of the reaction type will be presented. In addition, a by-participant listing will be provided for local reaction at injection site.

7.5. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the World Health Organization (WHO) Drug dictionary.

7.5.1. Prior and Concomitant Medications

Prior medications are defined as medications stopped prior to the first dose date of BLV (for Groups B, C, and DT to BLV 10mg group) or prior to randomization date for the DT group. For Group B, C, and DT to BLV 10mg group, concomitant medications are defined as ongoing medications or medications stopped on or after the first dose date of BLV, excluding medications started after the last dose date of BLV. For the DT group, concomitant medications are defined as ongoing medications or medications stopped on or after the date of randomization, excluding medications started on or after the first dose date of BLV.

If the medication start or stop date is partially unknown, the incomplete date will be imputed according to the rules in the Table 7-1. If a medication cannot be classified using the reported and/or imputed start and end dates, it will be considered as concomitant medication. The original reported dates will be presented in data listings.

Table 7-1. Imputed Partial Medication Dates

Scenario	Imputed Start Date	Imputed End Date
Unknown year	Missing	Missing

Scenario	Imputed Start Date	Imputed End Date
Unknown month	01 January	31 December
Unknown day	First day of month	Last day of month

Prior medications and concomitant medications will be summarized by therapeutic subgroup and preferred name using the number and percentage of participants for each treatment group and overall. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred term in order of descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned. In addition, by-participant listings will be provided.

7.5.2. HBV Medications

HBV medications are defined as oral medications with preferred names containing any of the following terms: tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, tenofovir disoproxil, entecavir, adefovir, adefovir dipivoxil, lamivudine, telbivudine.

The following HBV medications summaries will be provided by preferred name using the number and percentage of participants for each treatment group and overall; in addition, the corresponding listings will be generated:

- Participants with concomitant HBV medications
- HBV medications started before baseline and ongoing during treatment: participants with any HBV medication started prior to the first dose date of BLV or before randomization date for Group A DT group, and any concomitant HBV medication (same as or different from the previous one[s]) ongoing on/after the first dose date of BLV (randomization date for the DT group)
- Participants with prior HBV medications (stopped before baseline): participants with all HBV medications stopped before the first dose date of BLV or before randomization date for the DT group
- HBV medications started on-treatment: participants with all HBV medications started on/after the first dose date of BLV (randomization date for the DT group) and on/before the last dose date of BLV (before the first dose of BLV or until ET before Week 48 visit for the DT group)

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.6. Electrocardiogram Results

7.6.1. Investigator Electrocardiogram Assessment

The investigator's assessment of electrocardiogram (ECG) results (normal, abnormal NCS, abnormal CS, or missing) will be tabulated at each visit by treatment group. In addition, a shift table of the ECG assessment at each visit compared with baseline values will be presented by treatment group. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

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

7.6.2. Other Electrocardiogram Assessment

Descriptive statistics will be provided by visit and treatment group for ECG measurements and change from baseline including RR interval (msec), PQ interval (msec), QRS interval (msec), QT interval (msec), QT interval corrected for heart rate (QTc, Bazett) (msec), and heart rate (beats/min).

In addition, the number and percentage of participants with QTc values in each category below will be summarized by visit and treatment group:

- < 451 msec
- 451 to 480 msec
- 481 to 500 msec
- > 500 msec

The number and percentage of participants with QTc change from baseline values in each category below will be summarized by visit and treatment group:

- > 30 msec
- > 60 msec

In addition, a by-participant listing for ECG measurements will be provided. No formal statistical testing is planned.

7.7. Other Safety Measures

A data listing will be provided for participants who become pregnant during the study.

8. IMMUNOGENICITY ANALYSES

8.1. ADA Incidence and Prevalence

The evaluable population for ADA prevalence is participants with at least one non-missing ADA data at any visit, including the baseline. The evaluable population for ADA incidence is participants with at least one non-missing ADA data at postbaseline visits.

- ADA prevalence: participants with positive ADA at any visit including the baseline will be considered ADA positive. Otherwise, participants will be considered ADA negative.
- ADA incidence: defined in Table 8-1

Table 8-1. Definition of ADA Incidence

Baseline ADA	Postbaseline ADA	ADA Incidence
Negative/Missing	Positive (any visit)	Positive
Positive/Negative/Missing	Negative (all visits)	Negative
Positive	Positive (any visit)	Negative

The number and percentage of ADA prevalence and incidence at Weeks 48 and 144 will be summarized by treatment group. The corresponding listing will also be provided.

9. PHARMACOKINETIC (PK) ANALYSES

9.1. PK Sample Collection

For participants treated with BLV, blood samples for analysis of BLV concentration will be collected at all treatment visits. The sampling will be done 60 ±15 minutes after BLV injection.

9.2. PK Analyses

Descriptive statistics (including geometric mean, arithmetic coefficients of variation [%CV], and geometric %CV) of BLV plasma concentrations will be presented by treatment group and visit. In addition, the geometric mean of BLV plasma concentration will be plotted by treatment group and visit using a line plot. The by-participant listing of PK sampling details and PK concentrations will be provided.

10. OTHER EVALUATIONS

The analyses of variables from other evaluations will be conducted using the FAS.

10.1. HBeAg

HBeAg status and HBeAg antibody status will be summarized by visit and treatment group for participants who are positive for HBeAg at screening.

10.2. Liver Biopsy - Molecular Analysis and Gene Expression

Descriptive statistics will be presented by visit and treatment group on $\log_{10}$ transformed data for the following parameters (including the change from baseline). In addition, the by-participant listings will be provided.

Molecular analysis:

- Relative expression level of HDV RNA
- Relative expression level HBV RNA (S region)
- Relative expression level of total HBV RNA (X region)
- Relative expression level of pregenomic HBV RNA
- HBV DNA (S region; copies/cell)
- Total HBV DNA (X region; copies/cell)
- HBsAg

Molecular analysis using immunofluorescence staining:

- HDAg, % of positive hepatocytes

Gene expression:

- Relative expression level of NTCP mRNA
- Relative expression level of CYP7A1 mRNA
- Relative expression level of CXCL10 mRNA
- Relative expression level of ISG15 mRNA

- Relative expression level of MX1 mRNA
- Relative expression level of OAS mRNA
- Relative expression level of HLA-E mRNA
- Relative expression level of TAP1 mRNA
- Relative expression level of USP18 mRNA
- Relative expression level of CXCL11 mRNA
- Relative expression level of CXCL9 mRNA
- Relative expression level of CXCR3 mRNA
- Relative expression level of CCL5 mRNA
- Relative expression level of CXCL8 mRNA
- Relative expression level of IL18 mRNA
- Relative expression level of TGFB1 mRNA

For the following parameters only the by-participant listings will be provided:

- Molecular analysis: DNA content (ng/µL), RNA content (ng/µL), Beta globin (copies), cccDNA (copies/cell).
- Gene expression: GAPDH CT, RPL30CT, SERPINA1 mRNA CT

11. SOFTWARE

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

12. APPENDICES

Appendix 1. Sample SAS Code

The following statement will be used to construct the confidence interval for the binomial proportions described in Section 6:

```
proc freq data = final;
   table trtp*aval/riskdiff (cl=exact) fisher alpha=0.0x;
   exact riskdiff;
   where trtp = "Arm X" | trtp = "Arm Y";
run;
```

For combined reponse and undetectable HDV RNA, alpha=0.01 at Week 24 and alpha=0.04 at Week 48. Otherwise, alpha=0.05.

```
proc freq data = final;
    by trtp;
    table aval/bnomial;
    exact binomial;
run;
```

The following statement will be used to construct ANCOVA described in Section 6:

```
proc mixed data = final;
   class usubjid trtp region;
   model chg = base region strata trtp /ddfm=kr;
   lsmeans trtp /diff cl alpha=0.05;
run;
```

The following statement will be used to construct MMRM model described in Section 6:

```
proc mixed data = final;
   class usubjid trtp avisit region strata;
   model chg = base region strata trtp avisit trtp*avisit/ddfm = kr;
   repeated avisit/subject=usubjid type=un;
   lsmeans trtp*avisit/diff cl;
run;
```

Appendix 2. Schedule of Assessments

	Screening	144-week Treatment Phase (app. 3 years)*					96-week Follow-up Phase		
	SCR	**V1**	**V2–V7**	**V8**	**V9–V18**	**V19**	**FU 1**	**FU 2-5**	**FU 6/EOS**
Study Phase V (Visit)/ W (Week)/ D (Day) Procedures[1]	**D-28 to D-1 ****	**W0/D1**	**± 2 days: W4, W8, W16, W24, W32, W40**	**± 2 days: W48**	**± 2 days: W52, W56, W64, W72, W80, W88, W96, W108, W120, W132**	**± 2 days: W144**	**± 3 days: W148**	**±7 days: W156 (FU 2), W168 (FU 3), W180 (FU 3.1), W192 (FU 4), W216 (FU 5)**	**±7 days W240**
CLINICAL AND INSTRUMENTAL EVALUATIONS									
Informed consent [2]	X								
Demographics [3]	X								
Medical history, prior therapy [4]	X								
Weight, height, BMI (height and BMI at SCR only)	X	X	X	X	X	X	X	X	X
Physical examination [5]	X	X [6]	X	X	X	X	X	X	X
Assessment of local reactions at the bulevirtide injection site[7]		X	X	X	X	X	X		
Vital signs [8]	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)	X		X (W8, W24 only)	X	X (W72, W96, W120 only)	X		X (W192 only)	X
Abdominal ultrasound	X								
Transient elastometry (FibroScan)	X			X	X (W96 only)	X		X (W192 only)	X
Breath alcohol test	X	X							
Inclusion/Exclusion criteria	X	X							
Adverse events (including liver-related clinical events starting from randomization)	X (SAE only)	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X

	Screening	144-week Treatment Phase (app. 3 years)*					96-week Follow-up Phase		
	SCR	V1	V2–V7	V8	V9–V18	V19	FU 1	FU 2-5	FU 6/EOS
Study Phase V (Visit)/ W (Week)/ D (Day) Procedures[1]	D-28 to D-1 **	W0/D1	± 2 days: W4, W8, W16, W24, W32, W40	± 2 days: W48	± 2 days: W52, W56, W64, W72, W80, W88, W96, W108, W120, W132	± 2 days: W144	± 3 days: W148	±7 days: W156 (FU 2), W168 (FU 3), W180 (FU 3.1), W192 (FU 4), W216 (FU 5)	±7 days W240
Randomization [9]		X							

	Screening	144-week Treatment Phase (app. 3 years)*					96-week Follow-up Phase		
	SCR	**V1**	**V2–V7**	**V8**	**V9–V18**	**V19**	**FU 1**	**FU 2-5**	**FU 6/EOS**
Study Phase V (Visit)/ W (Week)/ D (Day) Procedures[1]	**D-28 to D-1 ****	**W0/D1**	**± 2 days: W4, W8, W16, W24, W32, W40**	**± 2 days: W48**	**± 2 days: W52, W56, W64, W72, W80, W88, W96, W108, W120, W132**	**± 2 days: W144**	**± 3 days: W148**	**±7 days: W156 (FU 2), W168 (FU 3), W180 (FU 3.1), W192 (FU 4), W216 (FU 5)**	**±7 days W240**
TREATMENT DISPENSING/RETURN									
Bulevirtide [10]		X [7, 10]	X [7, 10]	X [10]	X [10]	X [10]			
Treatment compliance assessment			X[7]	X	X	X			
Patient Diary Dispensing/Review/Collection		X[7]	X[7]	X	X	X			
Quality of life questionnaires (EQ-5D, FSS, HQLQ™)		X	X (W24, W40 only)	X	X (W72, W96 only)	X		X (W192 only)	X
LOCAL LABORATORY/STUDY SITE									
Urine pregnancy test [11]	X	X	X	X	X	X	X	X	X
Urine drug screening test	X								
ANALYSES PERFORMED IN CENTRAL LABORATORY/SAMPLES TO BE SENT TO CENTRAL LABORATORY AT ONCE									
Serology (anti-HIV, anti-HCV, anti-HDV)	X								
HCV RNA (if anti-HCV positive at SCR)	X								
HBeAg and HBeAg antibodies	X								
Urinalysis	X	X [6]	X [12]	X	X [12]	X		X [12]	X
Hematology [13]	X	X [6]	X	X	X	X	X	X	X
Biochemistry (full panel) [14]	X	X [6]	X (W24 only)	X	X (W72, W96, W120 only)	X			X
Biochemistry (abbreviated panel) [15]			X (W4, W8, W16, W32, W40 only)		X (W52, W56, W64, W80, W88, W108, W132		X	X	

	Screening	144-week Treatment Phase (app. 3 years)*					96-week Follow-up Phase		
	SCR	**V1**	**V2–V7**	**V8**	**V9–V18**	**V19**	**FU 1**	**FU 2-5**	**FU 6/EOS**
Study Phase V (Visit)/ W (Week)/ D (Day) Procedures[1]	**D-28 to D-1 ****	**W0/D1**	**± 2 days: W4, W8, W16, W24, W32, W40**	**± 2 days: W48**	**± 2 days: W52, W56, W64, W72, W80, W88, W96, W108, W120, W132**	**± 2 days: W144**	**± 3 days: W148**	**±7 days: W156 (FU 2), W168 (FU 3), W180 (FU 3.1), W192 (FU 4), W216 (FU 5)**	**±7 days W240**
					only)				

	Screening	144-week Treatment Phase (app. 3 years)*					96-week Follow-up Phase		
	SCR	**V1**	**V2–V7**	**V8**	**V9–V18**	**V19**	**FU 1**	**FU 2-5**	**FU 6/EOS**
Study Phase V (Visit)/ W (Week)/ D (Day) Procedures[1]	**D-28 to D-1 ****	**W0/D1**	**± 2 days: W4, W8, W16, W24, W32, W40**	**± 2 days: W48**	**± 2 days: W52, W56, W64, W72, W80, W88, W96, W108, W120, W132**	**± 2 days: W144**	**± 3 days: W148**	**±7 days: W156 (FU 2), W168 (FU 3), W180 (FU 3.1), W192 (FU 4), W216 (FU 5)**	**±7 days W240**
Coagulogram [16]	X	X [6]	X (W8, W24, W40 only)	X	X (W64, W80, W96, W108, W120, W132 only)	X		X (W168, W192, and W216 only)	X
Total blood bile salts		X	X	X	X	X	X	X	X
Alpha-fetoprotein test	X								
Vitamin D		X	X (W24 only)	X	X (W72, W96, W120 only)	X		X (W168 and W192 only)	X
HBV DNA for pts. not receiving nucleoside/nucleotide analogues	X								
Serum alpha-2-macroglobulin		X		X	X (W96 only)	X		X (W168 and W192 only)	X
ANALYSIS PERFORMED IN CENTRAL VIROLOGY LABORATORY/SAMPLES TO BE SENT TO CENTRAL LABORATORY AT ONCE									
HDV RNA	X								
ANALYSIS PERFORMED IN CENTRAL VIROLOGY LABORATORY/SAMPLES TO BE STORED AT SITE									
HDV genotyping		X							
HDV RNA		X	X	X	X	X	X	X	X
HBV DNA (HBV genotyping at first positive HBV DNA)		X	X	X	X	X	X	X	X
HBsAg		X	X	X	X	X	X	X	X
HBsAg antibodies [17]		X	X (W24 only)	X	X (W96 only)	X		X (W168 only)	X
HBeAg and HBeAg antibodies [18]		X		X	X (W96 only)	X			X

	Screening	144-week Treatment Phase (app. 3 years)*					96-week Follow-up Phase		
	SCR	**V1**	**V2–V7**	**V8**	**V9–V18**	**V19**	**FU 1**	**FU 2-5**	**FU 6/EOS**
Study Phase V (Visit)/ W (Week)/ D (Day) Procedures[1]	**D-28 to D-1 ****	**W0/D1**	**± 2 days: W4, W8, W16, W24, W32, W40**	**± 2 days: W48**	**± 2 days: W52, W56, W64, W72, W80, W88, W96, W108, W120, W132**	**± 2 days: W144**	**± 3 days: W148**	**±7 days: W156 (FU 2), W168 (FU 3), W180 (FU 3.1), W192 (FU 4), W216 (FU 5)**	**±7 days W240**
ANALYSIS PERFORMED IN CENTRAL LABORATORY/SAMPLES TO BE STORED AT SITE									
Immunogenicity (bulevirtide antibodies) [19]		X	X (W16, W24 only)	X	X (W64, W72, W96, W120 only)	X		X (W168)	X
NTCP polymorphism[20]		X							
Resistance test [21] (HBV genome sequencing, phenotypic assay, and HDV genome sequencing)		X	X	X	X	X	X	X	X
Pharmacokinetics		X [22]	X [22]	X [22]	X [22]	X [22]			
Liver biopsy	X[23]			X[24]				X [24, 25] (W192 or W216)	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CRP = C-reactive protein; DNA = deoxyribonucleic acid; EOS = end of study; EQ-5D = EuroQol (5 dimensions); FSS = Fatigue Severity Scale; FU = follow-up; GGT = gamma-glutamyl transferase; HBeAg = hepatitis B e antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis delta virus; HIV = human immunodeficiency virus; HQLQ = Hepatitis Quality of Life Questionnaire; NTCP = sodium-taurocholate cotransporting polypeptide; RBC = red blood cell; RNA = ribonucleic acid; SCR = screening; ULN = upper limit of normal; WBC = white blood cell

*Visits at W0-W8 and W48-W56 are performed every 28 ± 2 days; at W8-W48 and W56-W96: every 56 ± 2 days; at W96-W144: every 84 ± 2 days

**Screening can be shorter than 28 days as soon as eligibility of patient is confirmed.

1. Detailed description of all study procedures can be found in Section 6 of the protocol.
2. Signed and dated informed consent must be obtained before any procedure specific to the protocol.
3. Demographics include date of birth, sex, race, smoking/alcohol/drugs abuse history and current use.
4. Information about diseases, conditions and surgeries related to the liver is collected for a lifelong period; Information about other diseases, conditions and surgeries is collected if they have occurred within 5 years before the Screening or regardless of the time if they are considered to be relevant by investigator. All previous treatment for viral hepatitis should be recorded. Prior therapy for other diseases is collected for therapies that patient receives currently and therapies that were discontinued within 3 months before Screening.
5. A complete physical examination is performed at Screening (SCR), Randomization (V1), Week 24, Week 48, Week 96, and Week 144. A complete physical examination includes evaluation of general appearance, skin, head, eyes, ears, nose, and throat, lymph nodes, respiratory, cardiovascular, gastrointestinal including hepatobiliary assessment, musculoskeletal, endocrine system, nervous systems, and urogenital system. At all other visits, a symptom directed physical examination is performed.
6. If at Screening was done over 14 days ago.
7. Arm A: starting from W48.

8. Vital signs include body temperature, heart rate, and blood pressure.
9. Patients eligible for the study are randomized after completion of all procedures scheduled for Screening and Day 1 (except study drug administration, Patient Diary dispensing and assessment of adverse events, sample collection for pharmacokinetics) and confirmation of participant's eligibility.
10. Patients should be instructed NOT to administer study drug at home at days of visits to study sites. At these days study drug is administered at study site in accordance with schedule of events for assessment of immunogenicity and pharmacokinetics of the study drug.
11. Only for women of childbearing potential.
12. Urinalysis is not needed at V2 (W4), V9 (W52), and FU 3 (W168), and FU 3.1 (W180).
13. Hematology includes hemoglobin, hematocrit, reticulocytes, RBC, platelet count, WBC with differential (absolute counts and percentage for neutrophils, eosinophils, basophils, monocytes, and lymphocytes).
14. Participants must attend study sites after fasting for at least 9 hours (water and concomitant medications are permitted) for the purpose of conducting the biochemistry. Full biochemistry includes total protein, albumin, ALT [this sample will be used to obtain ALT results for efficacy assessment as described in Section 6.5.4], AST, GGT, P-amylase, alkaline phosphatase, lipase, total bilirubin, direct bilirubin, total cholesterol, creatinine, urea, glucose, potassium, sodium, chloride, phosphorus, and CRP.
15. Participants must attend study sites after fasting for at least 9 hours (water and concomitant medications are permitted) for the purpose of conducting the biochemistry. Abbreviated biochemistry includes:includes albumin, ALT [this sample will be used to obtain ALT results for efficacy assessment as described in Section 6.5.4], AST, GGT, total bilirubin, direct bilirubin, creatinine, lipase, P-amylase, CRP.
16. Coagulogram includes prothrombin time, international normalized ratio, and activated partial thromboplastin time.
17. Collection of anti-HBsAg samples at designated time points; testing only if HBsAg becomes undetectable.
18. Collection and testing of HBeAg and HBeAg antibodies only if patient is HBeAg positive at SCR.
19. Samples for immunogenicity assessment should be taken before administration of the study drug, during first 48 weeks immunogenicity samples are taken only for Arms B and C.
20. Blood samples for determination of NTCP polymorphism are collected at Day 1 for all the patients. NTCP polymorphism will be performed in central laboratory as detailed in Section 6.4.4 of the protocol.
21. Dedicated samples for phenotypic assay are collected only at Day 1. For other resistance tests (HBV genome sequencing and HDV genome sequencing) and phenotypic assay at the other time points back-up virology samples are used. Full resistance tests are performed as detailed in Section 6.4.4 of the protocol.
22. During first 48 weeks pharmacokinetics samples are taken only for Arms B and C. One sample at each visit 1 hour ± 15 minutes post bulevirtide dose.
23. At Screening liver biopsy is performed after confirmation of eligibility. If a liver biopsy was performed within 1 year prior to Screening, and a patient can provide biopsy records and appropriate biopsy specimens, the available specimens can be used for the baseline evaluation and biopsy at Screening is not required. Otherwise, liver biopsy at screening is performed if feasible provided that patient is considered to be eligible after the review of all eligibility criteria.
24. Liver biopsy should be performed within ± 7 days from the date of the visit for patients who do not have medical contraindications for the procedure. If baseline liver biopsy samples are not available (were not provided to central laboratory or were considered as non-evaluable by central laboratory) subsequent liver biopsy should not be performed.
25. Optional Liver biopsy should be performed at W192, or (if not possible at W192) at W216 in patients who previously had a baseline liver biopsy and who have provided their separate and specific consent.

Appendix 3. Imputation of incomplete AE start or end date

1 For Group B and Group C

1.1 to impute partial AE date if **year and month are available**:

	Imputed start date	Imputed end date
If AE year/month same as 1st dose year/month	Same as 1st dose date or AE end date whichever comes first.	Last of the month
If AE year/month before 1st dose year/month	First of the month	Last of the month
If AE year/month after 1st dose year/month	First of the month	Last of the month

1.2 to impute partial AE date if **only year is available**:

	Imputed start month/date	Imputed end month/date
If AE year same as 1st dose year	Same as 1st dose month/date or AE end month/date whichever comes first	December 31
If AE year before 1st dose year	January 1	December 31
If AE year after 1st dose year	January 1	December 31

1.3 to impute partial AE **start** date if **neither year nor month** is available:

	Imputed AE start year/month/date
If AE end date is before 1st dose date	AE end date
If AE end date is at/after 1st dose date	Same as 1st dose date

1.4 to impute partial AE **end** date if **neither year nor month** is available:

Impute the missing AE end date using the last visit date in database for this participant, or AE start date, whichever comes last.

2 For Arm A (i.e., delayed treatment)

2.1 to impute partial AE date if **year and month are available**:

	Imputed start date	Imputed end date
If AE year/month before randomization year/month	First of the month	Last of the month
If AE year/month same as randomization year/month	Same as randomization date or AE end date whichever comes first.	Last of the month
If AE year/month after randomization year/month but before 1st BLV dose year/month	First of the month	Last of the month
If AE year/month at 1st BLV dose year/month	1) if Relationship to bulevirtide=’not applicable (bulevirtide not administred)’, then first of the month 2) if Relationship to bulevirtide **not** equal to ’not applicable (bulevirtide not administred)’, then same as 1st BLV dose date or AE end date whichever comes first.	Last of the month
If AE year/month after 1st BLV dose year/month	First of the month	Last of the month

2.2 to impute partial AE date if **only year is available**:

	Imputed start month/date	Imputed end month/date
If AE year before randomization year	January 1	December 31
If AE year same as randomization year and before 1st BLV dose year (randomization year < 1st BLV year)	Same as randomization month/date or AE end month/date whichever comes first	December 31
If AE year same as 1st BLV dose year (randomization year = 1st BLV year)	1) if Relationship to bulevirtide=’not applicable (bulevirtide not administred)’, then same as randomization month/date or AE end month/date whichever comes first. 2) if Relationship to bulevirtide **not** equal to ’not applicable (bulevirtide not administred)’, then same as 1st BLV dose month/date or AE end month/date whichever comes first.	December 31

If AE year same as 1st BLV dose year (randomization year < 1st BLV year)	1) if Relationship to bulevirtide=’not applicable (bulevirtide not administred)’, then January 1. 2) if Relationship to bulevirtide **not** equal to ’not applicable (bulevirtide not administred)’, then same as 1st BLV dose month/date or AE end month/date whichever comes first.	December 31
If AE year after 1st BLV dose year	January 1	December 31

2.3 to impute partial AE **start** date if **neither year nor month** is available:

	Imputed AE start year/month/date
If AE end date is before randomization date	AE end date.
If AE end date is at/after randomization date but before 1st BLV dose date	Same as randomization date
If AE end date is at/after 1st BLV dose date	if Relationship to bulevirtide=’not applicable (bulevirtide not administered)’, then same as Randomization date. 2) if Relationship to bulevirtide **not** equal to ’not applicable (bulevirtide not administered)’, then same as 1st BLV dose date.

2.4 to impute partial AE **end** date if **neither year nor month** is available**:**

Impute the missing AE end date using the last visit date in database for this participant, or AE start date, whichever comes last.

Appendix 4. Version History

Version	Date	Description of Changes
1.0	06 June, 2023	Week 144 Final 1.0 corresponding to database lock on 8 June 2023.
2.0	21 June, 2023	Added biopsy analysis in Section 6.4.2 and 10.2 corresponding to database lock expected on 30 June 2023 to include biopsy data. Corrected the typo of 48 to 144 in Section 4.2.2.

MYR301 W144 SAP v2.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
Dmitry Manuilov	Clinical Development eSigned	26-Jun-2023 22:47:37
YaPei Liu03	Biostatistics eSigned	26-Jun-2023 22:50:19