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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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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ADA	anti-drug antibody
AE	adverse event
AFP	alpha-fetoprotein
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
COVID-19	Coronavirus 2019
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
HQLQ	hepatitis quality of life questionnaire
HLT	high-level term
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LOD	limit of detection
LS	least squares

MedDRA	Medical Dictionary for Regulatory Activities
MEF	missing equals failure
MLM	MLM Medical Labs GmbH
MMRM	mixed effects model for repeated measurements
NCS	not clinically significant
NOCB	next observation carried backward
OC	observed case
PK	Pharmacokinetic
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
SAE	Serious Adverse Event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
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	upper 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 192 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 192 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 2 mg or 10 mg 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

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1.2. Study Design

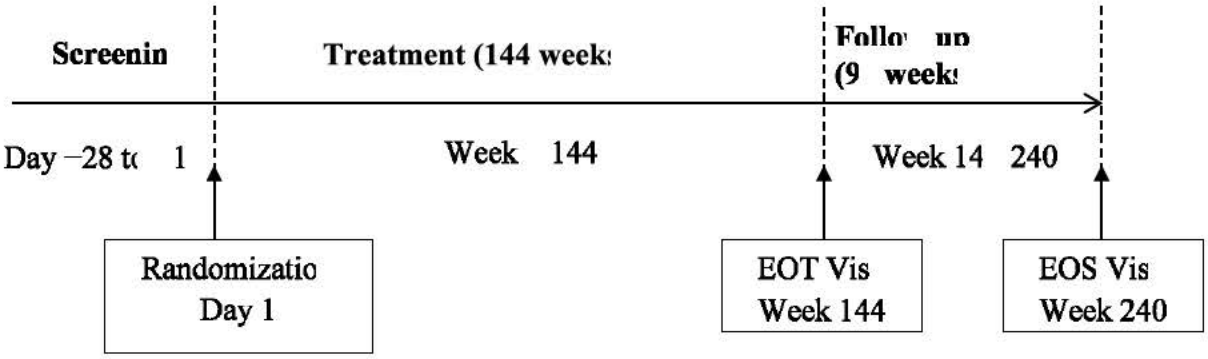
This is a randomized, open-label, parallel group, multicenter Phase 3 study to evaluate the efficacy and safety of BLV in participants with CHD who have no adequate treatment options.

A total of 150 participants were randomized in a 1:1:1 ratio, with stratification by presence of liver cirrhosis (yes, no) to 3 treatment arms 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 2 mg/day for 144 weeks with a further follow-up period of 96 weeks
- Arm C (N = 50): BLV 10 mg/day for 144 weeks with a further follow-up period of 96 weeks

A schema of the study design is presented in Figure 1. The schedule of events to be conducted during the 144-week treatment period and the 96 week off-treatment 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 was the separate comparisons of BLV 10 mg versus delayed treatment and BLV 2 mg versus delayed treatment after a period of 48 weeks. The primary endpoint was defined as the response rate at Week 48 measured by undetectable HDV RNA or a decrease of ≥ 2 $\log_{10}$ IU/mL from baseline combined with normal ALT (ALT value falls 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 between the time points with 0.01 for 24 weeks and 0.04 for 48 weeks. At each time point the BLV doses were 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 2 mg and BLV 10 mg doses were 45% or greater. The conservative expectation for the delayed treatment response rate 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 10 mg and the delayed treatment proportions and between the BLV 2 mg 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 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 participants completed the Week 48 visit or prematurely discontinued the study.

2.3. Week 96 Analysis

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

2.4. Week 144 Analysis (End of Treatment)

The Week 144 analysis was conducted when all the participants completed the Week 144 visit or prematurely discontinued 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 have completed the study (Week 240) or prematurely discontinued study, all 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 192 analysis. The details of the Week 24, 48, 96, and 144 statistical analysis methods were specified in separate SAPs for each of the analysis timepoints.

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 adverse event (AE) form, 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, separate listings will present the participants who were excluded from the Week 48 Per-Protocol (PP) and from the Week 192 PP Analysis Set and the reason(s) for their exclusion.

3.1.1. All Randomized Analysis Set

The All Randomized Analysis Set includes all participants who were enrolled (informed consent signed) and randomized into 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 the 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 was defined as all participants in the FAS for whom no protocol deviations were judged to have an impact on the analysis of the primary efficacy endpoint of combined response (PP 48W Analysis Set) or on the secondary efficacy endpoint of sustained virological response at follow-up Week 48, SVR48 (PP 192W Analysis Set). The PP Analysis Set is the secondary analysis set for efficacy analyses.

There are 3 different PP Analysis Sets that have been defined for the study:

- The PP 24W Analysis Set (defined prior to the Week 24 interim analysis) and not used for any of the analyses described in this Week 192 SAP
- The PP 48W Analysis Set (defined for the Week 48 primary efficacy analysis)
- The PP 192W Analysis Set (defined for the Week 192 analysis specifically for the SVR48 endpoint)

The decision as to whether a particular protocol deviation is considered as reason for exclusion of the participant from the PP Analysis Set (for the relevant analysis timepoint) should be made at the data review meeting for each analysis and documented in each corresponding data review meeting report (ie, clean file report). Additionally, participants with monitor-approved Bulevirtide/Hepcludex/Myrcludex rescue therapy recorded on the CM eCRF with a start date on or prior to the FU-Week 48 HDV RNA collection date will be excluded from the PP Week 192 Analysis Set. “Monitor-approved” is defined as no PD related to BLV rescue therapy.

For the Week 192 analysis, efficacy analyses using the PP 48W 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 the secondary endpoints of ALT normalization and virologic response at Week 48 using the updated Week 192 database. In addition, the secondary efficacy endpoint SVR48 will be analyzed using the PP 192W Analysis Set.

3.1.5. Safety Analysis Set

The Safety Analysis Set includes all participants who were randomized into the study and took at least 1 dose of BLV, or who were randomized to the delayed treatment group. This is the primary analysis set for safety analyses (with the exception of safety displays summarizing only post-treatment period data).

3.1.6. Post-Treatment Safety Analysis Set

The Post-Treatment Safety Analysis Set includes participants in the Safety Analysis Set who have at least 1 non-missing study assessment (eg, AE onset date, CM start date, laboratory collection, vital sign assessment, ECG assessment, physical exam, pregnancy, or death) performed after last BLV dose. This is the primary analysis set for safety displays during only the post-treatment period; and post-treatment potential liver-related clinical events.

3.1.7. 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.

3.1.8. 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. Analyses based on the Post-Treatment Safety Analysis Set will be based on the treatment received during the on-treatment period. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

Potential Liver-Related Clinical Events, AEs, and Laboratory Toxicity Grading summaries will use the following groupings to summarize data by treatment group and treatment period.

Group A

- Delayed Treatment [DT] (Baseline up to Week 48): includes AEs with onset date on or after randomization date and prior to the first dose of BLV. The last laboratory value with a collection date on or prior to the randomization date is the baseline value; postbaseline laboratory collections (DT group) will be those with laboratory collection dates after randomization date and prior to the first dose date of BLV. For participants who prematurely discontinue from study prior to Week 48, events will be included up to early discontinuation from study if not receiving BLV (N = 51)

- DT to BLV 10 mg (Overall BLV treatment period): includes AEs with an onset date/time on or after the first dose date/time of BLV and up to the last dose date of BLV. The last laboratory value with collection date/time on or prior to first BLV dose date/time is assigned to the baseline laboratory value (ie, baseline is reset); postbaseline "on-treatment" laboratory collections after first BLV dose date/time and up to last dose date of BLV will be included. (N = 50, 1 participant from DT group terminated early before Week 48 visit).

- DT to BLV 10 mg (Post-treatment period): includes AEs with an onset date after the last dose date of BLV and laboratory values with a collection date after the last dose date of BLV.

Groups B and C

- Group B or C (BLV treatment period [Baseline up to Week 48]): event meets criteria for overall BLV treatment period (see next bullet) and AE onset is prior to Week 48 visit (laboratory collection is at or prior to Week 48) or participant discontinued study drug at or prior to Week 48.

- Group B or C (Overall BLV treatment period): includes AEs with onset date/time on or after first dose date/time of BLV and up to last dose of BLV. The last laboratory value with collection date/time on or prior to BLV first dose date/time will be the baseline value; laboratory values with date/time of collection after first dose date/time of BLV and collection date up to last dose date of BLV) will be "on-treatment" values.

- Group B or C (Post-treatment period): includes AEs with an onset date after the last dose date of BLV, and laboratory values collected after the last dose date of BLV.

In the above descriptions, when both date and time are used in the comparison to determine period and at least one of the times is not available, then only the dates will be compared.

On-treatment and post-treatment data will be summarized on 2 separate tables for AEs, potential liver-related clinical events and laboratory toxicity grading. On-treatment displays will present data up to Week 48 (for comparison to control [DT group] through Week 48); and for all data collected while on BLV treatment (Weeks 0-144 for Groups B and C; Weeks 48-144 for DT to BLV 10 mg group for those dosed per protocol). On-treatment data will be summarized for the Safety Analysis Set; post-treatment data will be summarized for the Post-Treatment Safety Analysis Set.

Cumulative summaries displayed by visit will use the analysis visit windows as specified in Section 3.8.2 of the SAP to assign data to analysis visits. For the DT group, baseline will be the last value on or prior to randomization. For DT to BLV 10 mg group, baseline will be re-set as the last non-missing value on or prior to first dose of BLV (the re-baseline liver stiffness is the available value at Week 48).

3.3. Strata and Covariates

Participants eligible for the study were randomly assigned to treatment groups via an 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 primary efficacy endpoint combined response at Week 48 (and components [ALT normalization and virologic response]); all secondary endpoints (undetectable HDV RNA at Week 48, SVR24, SVR48, and liver stiffness by visit); by visit displays of categorical endpoints combined response, ALT normalization, and HBV DNA category (< LLOQ target not detected,< LLOQ target detected, and ≥ LLOQ); and continuous displays of ALT (U/L), HBV DNA (log_{10} IU/mL) and HBsAg (log_{10} IU/mL) and their respective changes from baseline will be examined using the following 2 subgroups:

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

Categorical endpoints HDV RNA decrease ≥ 2 log_{10} IU/mL, undetectable HDV RNA, and virologic response by visit; and continuous endpoint HDV RNA (log_{10} IU/mL) and change from baseline by visit will be displayed by cirrhosis status at randomization.

Treatment-emergent adverse events (TEAEs) while on treatment up to Week 48 will be examined using the ADA incidence by Week 48 (positive vs. negative). Treatment-emergent AEs while on treatment up to Week 144 will be examined using the ADA incidence by Week 144 (positive vs. negative). The geometric mean (95% CI) of BLV plasma concentration, and selected efficacy endpoints (complete response, ALT normalization, virologic response, and undetectable HDV RNA) will be examined by treatment group, visit, and 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 BLV 10 mg versus delayed treatment and BLV 2 mg versus delayed treatment 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 between the time points with 0.01 for Week 24 and 0.04 for Week 48. At each time point, the BLV dose was compared to DT group in terms of a hierarchical testing procedure starting with the higher dose (BLV 10 mg) 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 AEs 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 10 mg 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 $\log_{10}$ 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 10 mg 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 10 mg 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 [DT] Group (for Quality of Life Only) and Groups 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
Follow-up Week X (Group A [DT][$]/ B/C)	(144+X)×7+1	(144+X)×7+1-30	(144+X)×7+1+30

* For Group A BLV treated participants, the upper limit at Week 48 for DT group is First Dose Date of BLV – Study Day 1 + 1.
[$] Follow-Up visits for Group A (DT) group are only applicable for Quality of Life Assessments.

Table 3-3. Analysis Visit Windows Through Week 48 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 with BLV)

* Liver stiffness at Week 48 is the available value from Week 48 visit.
Not applicable for Quality of Life.

Table 3-4. Analysis Visit Windows for by Visit Assessments for Group A [DT to BLV 10 mg 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
Follow-up Week X	(96+X)×7+1	(96+X)×7+1-30	(96+X)×7+1+30

* Liver stiffness baseline on BLV is the available value from Week 48 visit; last available value on or prior to first dose of BLV otherwise.
Not applicable for Quality of Life.

The measurement at end of treatment (EOT) is defined as the record collected at the visit within (last dose date of BLV ± 7 days) for groups A (DT to BLV 10 mg), B, and C.

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

- An unscheduled visit on or prior to randomization for DT group or on or prior to the first dose of BLV may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after randomization and up to first BLV dose (or up to last dose for ET prior to Week 48) for DT group or after the first dose of BLV and up to last dose of BLV will be included in determining the maximum postbaseline toxicity grade while on treatment.
- Unscheduled visits after the first dose of BLV will be included in the determination of the value at EOT.
- Unscheduled visits after the last dose of BLV will be included when determining the maximum postbaseline toxicity grade during the post-treatment period.
- A record from an 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 rules 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 on or prior to the first dosing date for BLV for all other groups will be selected, unless specified differently.
- For postbaseline values, records from scheduled visits or an ET visit will be selected. If there is no available scheduled visit or ET record, the data from unscheduled visits will be selected as described 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 and overall 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 and overall. This summary will present the number of participants screened, the number of participants who met all eligibility criteria but were not randomized with the reasons participants were not randomized, 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
- Post-Treatment Safety Analysis Set
- Full Analysis Set
- Per-Protocol Week 48 Analysis Set
- Per-Protocol Week 192 Analysis Set
- Completed Week 24
- Completed Week 48
- Completed Week 96
- Completed Week 144
- Completed Week 192
- Continuing study after Week 192
- Did not complete the study with reasons for premature discontinuation of study

The number and percentage of participants discontinued from the study by Week 48, by Week 144, and for the study up to the Week 192 data cutoff will be presented along with the reasons for premature discontinuation. 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 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 study drug 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) study drug 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 (10 mg) for participants in DT to BLV 10 mg group, and 144 weeks of planned daily dosage (2 mg or 10 mg) 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 (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 study drug doses will be defined as:

Minimum of (last on-treatment visit, or study day 1006 [ie, study day 1006 = 144×7-2 per protocol visit window]) – 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 10 mg) for BLV study drug.

- Total duration of exposure (weeks)
- Total dose administered (mg)
- Dose intensity (mg/week)
- Compliance rate (%)
- Participants with ≥ 1 missed dose
- Total number of missed doses
- Percentage 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 and overall 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 reason will be summarized by treatment group and overall.

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 2 mg group, BLV 10 mg group, and DT to BLV 10 mg 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 2 mg group, and BLV 10 mg group. The summary of demographic and baseline characteristics data will be provided for the FAS, PP 48W, and PP 192W Analysis Sets, for the following:

- Age (years)
- Sex (male, female)
- Race (Asian, Black or African American, White)
- Height (cm)
- Body weight (kg)
- Body mass index (BMI, kg/m^2)
- BMI category (<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, PP 48W, and PP 192W Analysis Sets 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 category (≥ 60 to < 90 mL/min vs. ≥ 90 mL/min)
- Baseline liver stiffness (kPa)
- Baseline liver stiffness category (< 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 (log_{10} IU/mL)
- Baseline HBV DNA category (< LLOQ target not detected, < LLOQ target detected, ≥LLOQ)
- Baseline HBsAg (log_{10} 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 Oral HBV medication (Yes/No)

For DT to BLV 10 mg, unless otherwise specified, a baseline value will be defined as the last measurement obtained on or prior to the first dose of BLV [at Week 48 visit]. Baseline liver stiffness is the available measurement from the 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 10 mg group for the following variables:

- Sex (male, female)
- Race (Asian, Black or African American, White)
- 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, PP 48W, and PP 192W Analysis Sets, 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) v26.1.

Medical history will be summarized for the 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 testing 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 component(s)
- Step 3: derive the multi-component endpoint using each individual component (or the imputed value from step 2 above, if the individual component is missing)

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, a missing value will be imputed as nonresponder.
  - For analyses of combined response at Week 24 and 48 (primary endpoint); undetectable HDV RNA at Week 24 and Week 48 (key secondary endpoint), SVR24, and SVR48 (secondary endpoint) using FAS, MEF will be adopted when missing was not related to COVID-19.
  - MEF adopted for sensitivity analyses of primary and key secondary endpoints.
  - In addition, MEF will be adopted for all analyses of binary endpoints for the secondary and CCI 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.
- Next observation carrying backward (NOCB): Missing value will be imputed using the next observation (including observation from unscheduled visit). For secondary efficacy endpoints of SVR24 and SVR48 using FAS, NOCB will be used when a missing value was related to COVID-19.

- Observed Case (OC): Missing values remain missing. The OC will be used for analyses of continuous endpoints, for SVR24 (using FAS), and analyses using the PP 48W and PP 192W Analysis Sets. By visit displays up to Week 192 for the following efficacy endpoints will be displayed using OC for the FAS: combined response, HDV RNA Undetectable, ALT normalization, virologic response, ≥ 2 $\log_{10}$ IU/mL decrease from baseline in HDV RNA, HBV DNA category, liver stiffness, and quality of life.

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:

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

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

where p_O, $p_{M2mg,}$ and p_{M10mg} are the expected response rate for delayed treatment, BLV 2 mg and BLV 10 mg, 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 between 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 a 2 two-sided Fisher's exact test 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 a 2 two-sided Fisher's exact test will also be provided. There is a statistically significant difference at Week 48 if $p < 0.04$. The comparison of BLV 2 mg versus delayed treatment is considered significant only if the comparison of BLV 10 mg 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 48W 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 Week 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 change from baseline in liver stiffness at Week 240 will be analyzed in the final CSR.

6.3.1. Analysis of Secondary Efficacy Endpoints

Undetectable HDV RNA at Week 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 hypothesis

H_{03}: $r_{M2mg} = r_{M10mg}$ 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 2 mg and BLV 10 mg, 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) have both been rejected. As for the primary analysis, the above hypothesis will also be tested at Week 24 and hence the nominal two-sided significance level of 0.05 will be split between the time points with 0.01 for Week 24 and 0.04 for Week 48, respectively.

The estimated rate differences between BLV 10 mg and BLV 2 mg with exact unconditional CI based on score statistic (99% CI for Week 24 and 96% CI for Week 48), and the p-value from a Fisher's exact test will be provided using FAS and PP 48W Analysis Set. The Clopper-Pearson 95% CIs on the 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 2 mg and the delayed treatment group and BLV 10 mg and the delayed treatment group using a two-sided Fisher's exact test. 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 48W Analysis Set. In addition, for each group, the Clopper-Pearson 95% CIs on the response rate will also be presented. The same summary will be repeated by subgroups for efficacy endpoints as defined in Section 3.4.

SVR24 and SVR48

Response rate for SVR24 and SVR48 will be displayed and compared between the BLV 2 mg and [DT to BLV 10 mg group] and between the BLV 2 mg group and BLV 10 mg group using a two-sided Fisher's exact test. Nominal p-values without multiple comparison adjustment and 95% exact unconditional confidence intervals based on score statistic for the proportion differences will be provided for the SVR rates. For each group, the Clopper-Pearson 95% CI on the SVR rates will also be presented. Analysis will be performed for the FAS using NOCB for COVID-related missing values and MEF otherwise, for both SVR24 and SVR48. An analysis for the PP 192W Analysis Set using OC for SVR48; and FAS using OC for SVR24 will also be performed.

Analysis for FAS (NOCB for COVID-related missing values, and MEF otherwise) for SVR24 and SVR48, PP 192W Analysis Set using OC for SVR48, and FAS using OC for SVR24 will be repeated for the subgroups defined in Section 3.4.

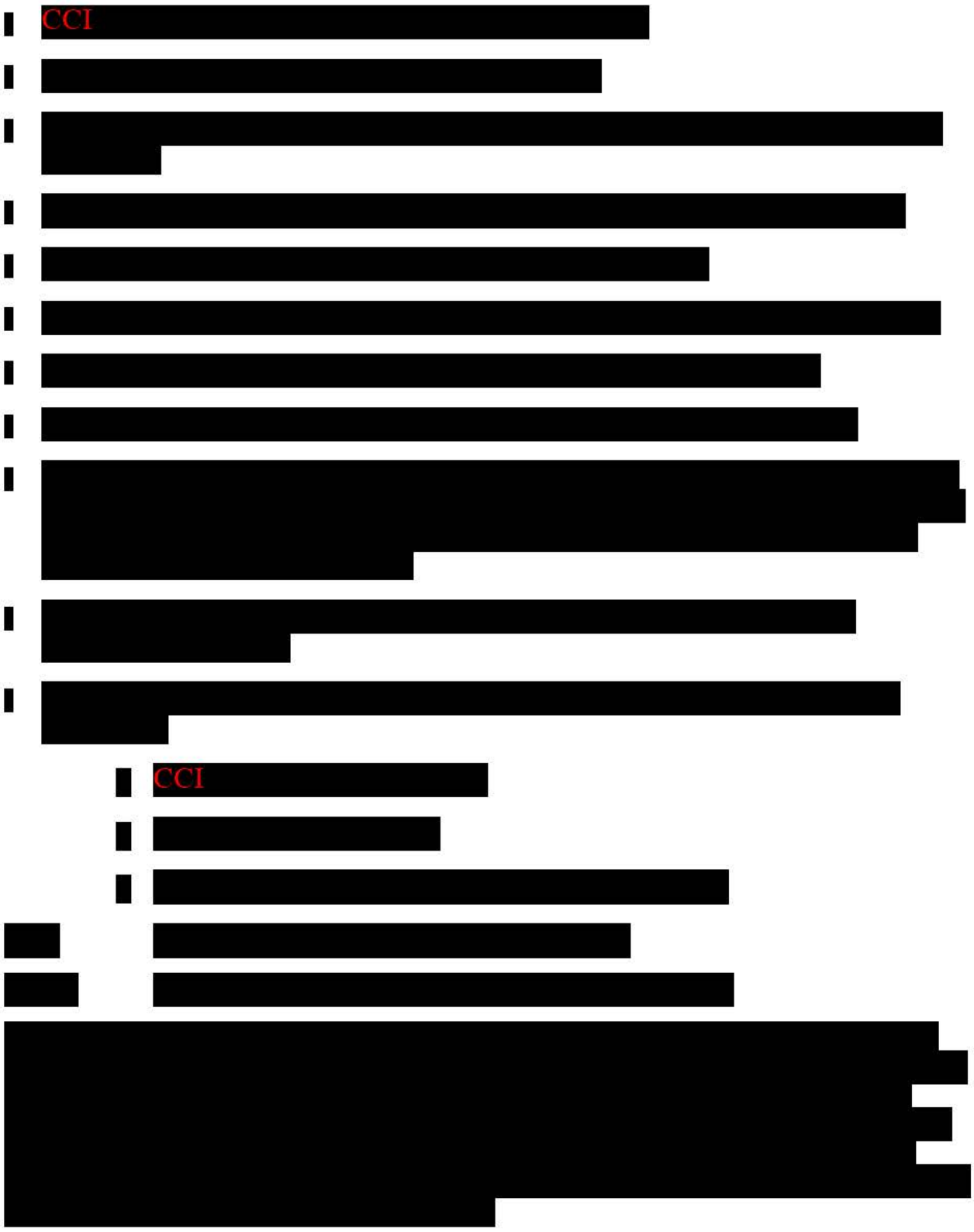
Results of SVR24 (Responder, Nonresponder) versus SVR48 (Responder, Nonresponder) will be displayed by treatment group (DT to BLV 10 mg, BLV 2 mg, and BLV 10 mg) for participants with a non-missing value at both timepoints to explore whether the outcomes at the 2 timepoints are correlated.

Change from Baseline in Liver Stiffness at Week 48, Week 96, Week 144, and Week 192

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 2 mg and the delayed treatment group, and BLV 10 mg and the delayed treatment group using FAS and PP 48W Analysis Set. The model includes treatment, region, presence of cirrhosis and baseline liver stiffness as a 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, Week 144, and Week 192, a mixed-effects model for repeated measurements (MMRM) will be used to evaluate treatment effect using FAS. The model includes treatment (BLV 2 mg, BLV 10 mg, and DT to BLV 10 mg group), region, presence of cirrhosis, visit, and treatment by visit interaction as fixed effects, and baseline liver stiffness (the baseline for DT to BLV 10 mg 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 and FU-48 (for DT to BLV 10 mg 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 2 mg (Group B) and BLV 10 mg (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.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7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

Clinical and laboratory adverse events (AEs) will be coded using the MedDRA v26.1. 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 eCRF 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 randomization date and before 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 DT to BLV 10 mg, BLV 2 mg and BLV 10 mg groups, TEAEs are defined as 1 or both of the following:

- Any AEs with an onset on or after 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 10 mg, TEAEs with onset prior to the first dose of BLV will be allocated to the DT group. TEAEs with onset on or after the first dose of BLV will be allocated to the DT to BLV 10 mg group.

For BLV 2 mg and BLV 10 mg groups, TEAEs with onset prior to the Week 48 visit will be allocated to the baseline to Week 48 period.

7.1.4.2. Definition of Post Treatment Adverse Events

For DT to BLV 10 mg, BLV 2 mg and BLV 10 mg groups, post-treatment AEs are defined as:

- Any AE with an onset after the last dose of BLV study drug

7.1.4.3. 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 Treatment-Emergent Adverse Events and Deaths (On-Treatment Period)

Treatment-emergent AEs while on treatment will be summarized based on the Safety Analysis Set. The AEs will be allocated to "on-treatment time periods" based on AE onset, randomization date (DT group only), Week 48 visit date, and the start and end of BLV dosing (see Section 3.2).

- TEAEs up to Week 48 (DT, BLV 2 mg, BLV 10 mg groups)
- TEAEs up to Week 144 (BLV 2 mg and BLV 10 mg groups)
- TEAEs Week 48 (first BLV dose) up to Week 144 (DT to BLV 10 mg group)

7.1.5.1. Summaries of AE incidence in Combined Severity Grade Subsets (On-Treatment Period)

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE while on treatment in the categories described below will be provided by treatment group and "on-treatment time period". All AEs with outcome of death with an onset while on treatment will also be included in this summary.

The number and percentage of participants who experienced at least 1 TEAE while on treatment during the "on-treatment" periods described above 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 2 mg frequency (baseline up to Week 144 period) 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 and treatment period.

In addition to the above summary tables, all TEAEs, TEAEs with Grade 3 or higher, TEAEs occurring in ≥ 10% of participants in any treatment group, TE SAEs, AEs leading to premature discontinuation of BLV, TE treatment-related AEs, and TE treatment-related SAEs will be summarized by PT only, in descending order of BLV 2 mg frequency (baseline up to Week 144 period).

In addition data listings that include events reported throughout the duration of the study 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

Adverse events with an onset or resolution date after last dose of BLV study drug will be flagged with the symbol '~' and the number of days post last dose of BLV will be presented for the column "Days" in the listing.

7.1.6. Additional Analysis of Adverse Events (On-Treatment Period)

7.1.6.1. Hepatic Adverse Events

Hepatic AEs potentially indicative of hepatitis flares will be identified using MedDRA v26.1 search terms. The number and percentage of participants who experienced any TE hepatic AE while on treatment will be summarized by PT, treatment group, and "on-treatment period".

The by-participant listing of hepatic AEs will also be provided and will include events reported throughout the duration of the study. Hepatic AEs with an onset or resolution date after last dose of BLV study drug will be flagged with the symbol '~' and the number of days post last dose of BLV will be presented for "Days" column in the listing.

7.1.6.2. Subgroup Analyses of Treatment-Emergent Adverse Events

Treatment-emergent AEs while on treatment by anti-drug antibody (ADA) incidence at Week 48 will be provided by PT and treatment group:

- For DT, Group B and Group C, TEAEs (while on treatment for Groups B and C) from baseline up to Week 48 will be summarized by treatment and ADA incidence at Week 48.

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

- For Group B and Group C, TEAEs while on treatment from baseline up to Week 144 will be summarized by treatment and ADA incidence.
- For DT to BLV 10 mg, TEAEs while on treatment from BLV first dose (ie, Week 48) up to Week 144 will be summarized by ADA incidence. 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.

7.1.7. Summaries of Adverse Events (Post-Treatment Period)

Posttreatment AEs will be summarized for the Post-Treatment Safety Analysis Set for the treatment groups BLV 2 mg, BLV 10 mg, and DT to BLV 10 mg.

7.1.7.1. Summaries of Posttreatment AEs by Preferred Term

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

- AEs in the post-treatment period
- AEs with Grade 3 or higher in the post-treatment period
- SAEs in the post-treatment period
- AEs leading to death (ie, outcome of death) in the post-treatment period
- AEs that occurred in ≥ 5% of Participants in Any Treatment Group during the post-treatment period

Multiple events with the same PT will be counted only once per participant in each summary. Posttreatment AEs will be summarized by PT in descending order of BLV 2 mg frequency and then alphabetically by PT for those AEs with the same BLV 2 mg frequency. 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.

7.1.8. Additional Analysis of Adverse Events (Post-Treatment Period)

7.1.8.1. Hepatic Adverse Events

A post-treatment summary of hepatic AEs potentially indicative of hepatitis flare (identified using MedDRA v26.1 search terms) will be displayed for BLV 2 mg, BLV 10 mg, and DT to BLV 10 mg groups.

7.1.8.2. Adverse Events Reported After Administration of Commercial BLV

Adverse events with an onset date on or after the start date of commercial BLV drug (identified by Bulevirtide/Hepcludex/Myrcludex recorded on the concomitant medication [CM] eCRF) in the post-treatment period will be listed.

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 will be included 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.

Separate by-participant listings for laboratory test results throughout the duration of the study will be provided by participant ID number and visit in chronological order for hematology, coagulogram, serum chemistry, total bile salts, and urinalysis. 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 (including post-treatment visits through Follow-Up Week 48 [Study Week 192]), and change from baseline at each postbaseline visit will be provided on a single table for the Safety Analysis Set 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 (‰)
  - 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 (mg/L)
  - 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)
  - Vitamin D (ng/mL)

- 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 on or prior to 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 will be plotted for the Safety Analysis Set using a line plot by treatment group and visit.

For laboratory data collected at follow-up visits during the post-treatment period, the change from EOT at each post-treatment visit will also be included in the change from baseline tables (described above) for the following laboratory tests: platelets, white blood cell (WBC), absolute and relative eosinophils, total bile salts, total bilirubin, direct bilirubin, albumin, GGT, Vitamin D, AST, total amylase, pancreatic amylase, INR, and creatinine.

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 (including post-treatment visits through Follow-Up Week 48 [Study Week 192]) 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. 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, 144, and FU-48 (ie, Study Week 192) for laboratory tests listed in Section 7.2.1 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 at the postbaseline visit will not be included in the denominator for percentage calculation at the visit.

7.2.4. 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.

7.2.4.1. Treatment-Emergent Laboratory Abnormalities (On-Treatment Period)

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline for postbaseline values up to BLV first dose or ET for DT group; or up to last BLV dose date + 30 days for other groups. Baseline value is the last laboratory value collected on or prior to randomization for DT group and last value collected on or prior to first BLV dose for other groups. 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.

The summary of TE laboratory abnormalities in the on-treatment period will be provided for:

- TE laboratory abnormalities up to Week 48 (DT, BLV 2 mg, BLV 10 mg groups)
- TE laboratory abnormalities up to Week 144 (BLV 2 mg and BLV 10 mg groups)
- TE laboratory abnormalities from Week 48 (first BLV dose) up to Week 144 (DT to BLV 10 mg group)

TE lab abnormalities will be allocated to "on-treatment time periods" based on laboratory collection date, randomization date (DT group only), Week 48 visit date, and the start and end of BLV dosing (see Section 3.2).

7.2.4.2. Summaries of Laboratory Abnormalities (On-Treatment Period)

The following summaries (number and percentage of participants) for TE laboratory abnormalities while on treatment (up to Week 48 and up to Week 144) will be presented:

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities while on treatment, the denominator is the number of participants with non-missing postbaseline values during the relevant treatment period. Participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test during the treatment period.

A by-participant listing of treatment-emergent laboratory abnormalities while on treatment 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 (highest grade from randomization up to Week 48 for DT group, and while on treatment during the "on-treatment" period for all other groups) displayed. A similar by-participant listing of treatment-emergent Grade 3 or 4 laboratory abnormalities while on treatment will also be provided.

7.2.4.3. Summaries of Laboratory Abnormalities (Post-Treatment Period)

The number and percentage of participants categorized by the most severe post-treatment toxicity grade collected during the post-treatment follow-up period will be summarized by treatment group for each laboratory parameter (including hyper and hypo directions with toxicity-grading [when applicable]) and overall (for all laboratory tests at the participant level) for all lab tests with toxicity grading. Denominator for percentage calculation will be the number of participants with a non-missing value in the post-treatment period.

A listing will include test results collected throughout the study for the laboratory test with at least 1 Grade 3 or 4 toxicity grade during the post-treatment period. Laboratory collection dates after last dose of BLV study drug will be flagged with the symbol '~' for the number of days post last dose of BLV in the "Days" column for that date in the listing. All applicable severity grades and/or abnormal flags will be presented in the listing with the highest severity for a laboratory test and participant during the post-treatment period flagged.

7.2.5. Liver-related Laboratory Evaluations

7.2.5.1. Potential Drug Induced Liver Injury (DILI) While on Treatment

The participants who meet any one of the following criteria for potential drug induced liver injury (DILI) will be summarized by treatment group and on-treatment period, 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

Events will be allocated to "on-treatment periods" based on the laboratory collection date, randomization date (DT group only), Week 48 visit date, and the start and end of BLV dosing (see Section 3.2).

7.2.5.2. Posttreatment ALT > 5 x ULN and ALT > 10 x ULN

The number and percentage of participants with posttreatment ALT values meeting the criteria below will be displayed by treatment group for the Post-treatment Safety Analysis Set:

- ALT > 5 x ULN
- ALT > 10 x ULN

The denominator for percentage calculation will be the number of participants in the treatment group with at least 1 post-treatment ALT value collected. A supporting listing of participants meeting criteria will be created.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group and visit (including post-treatment visits through Follow-Up Week 48 [Study Week 192]) for participants in the Safety Analysis Set 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 BLV study drug for the DT to BLV 10 mg, BLV 2 mg, and BLV 10 mg groups, and the last value on or prior to randomization for the DT group. 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, Concomitant, and Post-Treatment Medications

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

7.5.1. Prior, Concomitant, and Post-Treatment Medications

Prior medications are defined as medications stopped prior to the first dose of BLV (for Groups B, C, and DT to BLV 10 mg group) or prior to randomization date for the DT group. For Group B, C, and DT to BLV 10 mg group, concomitant medications are defined as ongoing medications or medications stopped on or after the first dose of BLV, excluding medications started after the last dose 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 of BLV. Post-treatment medications are defined as medications that start after the last dose 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
Unknown month	01 January	31 December
Unknown day	First day of month	Last day of month

7.5.2. Summaries of Non-Study Drug Medications

Prior medications, concomitant medications, and post-treatment medications will be summarized by 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.

Prior and concomitant summaries will be based on the Safety Analysis Set; post-treatment summaries will be based on the Post-Treatment Safety Analysis Set. No formal statistical testing is planned. In addition, a by-participant listing will be provided.

7.5.3. 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
- Participants with HBV medications started in the post-treatment period (based on the Post-Treatment Safety Analysis Set)
- HBV medications started before baseline and ongoing during treatment: participants with any HBV medication started prior to the first dose of BLV or before randomization 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 of BLV (randomization for the DT group)

- Participants with prior HBV medications (stopped before baseline): participants with all HBV medications stopped before the first dose of BLV or before randomization for the DT group

- HBV medications started on-treatment: participants with all HBV medications started on/after the first dose of BLV (randomization for the DT group) and on/before the last dose 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 (except where specifically noted otherwise). No formal statistical testing is planned.

7.5.4. Commercial BLV

A listing of participants who started commercial BLV drug (Bulevirtide/Hepcludex/Myrcludex recorded on the concomitant medication [CM] eCRF) will be provided. The first and last dose date of BLV study drug and the number of days post last dose for start and end date (when applicable) of administration of commercial BLV drug will be included in the listing.

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 for the Safety Analysis Set at each visit (including post-treatment visits through Follow-Up Week 48 [Study Week 192]) 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. A baseline value will be defined as the last available value collected on or prior to the date/time of the first dose of BLV study drug for the DT to BLV 10 mg, BLV 2 mg, and BLV 10 mg groups, and the last value on or prior to randomization for the DT 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 (including post-treatment visits through Follow-Up Week 48 [Study Week 192]) 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

Participants with a value at the visit will be included in the denominator for percentage calculation (all participants had a baseline value). 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, 144, and 168 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 and arithmetic coefficients of variation [%CV]) of BLV plasma concentrations will be presented by treatment group and visit. In addition, the geometric mean (95% CI) of BLV plasma concentration will be plotted by treatment group and visit using a line plot. Descriptive statistics and a line plot of the geometric mean (95% CI) of BLV plasma concentration will also be presented by treatment group, visit, and ADA incidence by Week 144 (positive, negative).

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 were presented by visit and treatment group on $\log_{10}$ transformed data for the following parameters (including the change from baseline) at Week 48 primary analysis and results were described in the interim Week 48 CSR dated 13 July 2022. In addition, the by-participant listings were 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)

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 were 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							
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

	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**
Biochemistry (abbreviated panel) [15]			X (W4, W8, W16, W32, W40 only)		X (W52, W56, W64, W80, W88, W108, W132 only)		X	X	
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

	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**
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
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. CCI [redacted]
CCI [redacted]

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.

MYR301_ W192_SAP_v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	PPD
PPD	Clinical Development eSigned	PPD