STATISTICAL ANALYSIS PLAN

Study Title:	A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients with Chronic Hepatitis Delta
Name of Test Drug:	Bulevirtide (BLV)
Study Number:	MYR301
Protocol Version (Date):	Version 7.0 dated 25 January 2023
Analysis Type:	Final (Week 240) Adverse Events of Interest Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	15 November 2024
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLV	bulevirtide
CHD	chronic hepatitis delta
CM	concomitant medication
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
DME	designated medical events
DT	delayed treatment
ECG	electrocardiogram
EOS	eosinophil
HDV	hepatitis D virus
HLGT	high-level group term
HLT	high-level term
HSAC	Hepatic Safety Adjudication Committee
ID	identification
INR	international normalized ratio
LLN	lower limit of normal
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MST	MedDRA search term
PT	preferred term
Q1	first quartile
Q3	third quartile
SAP	statistical analysis plan
SD	standard deviation
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in the Study MYR301 Final (Week 240) summary of adverse events of interest (AOIs). The safety data collected throughout the study will be included in the analysis. Unless otherwise specified, the same methods used for the analyses of safety specified in the MYR301 Final (Week 240) study SAP and/or protocol will be applied to the analysis of AOIs.

1.1. Study MYR301

This is a randomized, open-label, parallel group, multicenter Phase 3 study to evaluate the efficacy and safety of bulevirtide (BLV) in participants with chronic hepatitis delta (CHD) with or without compensated cirrhosis 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 and 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

2. 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), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

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

2.1. Analysis Sets

2.1.1. Safety Analysis Set

The Safety Analysis Set includes all participants who were randomized into the study and took at least 1 dose of BLV study drug, or who were randomized to the delayed treatment group. The Safety Analysis Set will be used for all AEs of interest analyses (excluding those analyses that present data collected only during the posttreatment period).

2.1.2. Posttreatment Safety Analysis Set

The Posttreatment 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 posttreatment period.

2.2. Participant Grouping and Presentation

Participants will be grouped according to the actual treatment received. The actual treatment received is defined as the randomized treatment except for participants who received treatment that differs from the randomized treatment for the entire treatment duration.

Group A

- Delayed Treatment (DT) (Baseline up to Week 48): includes AEs with onset date on or after randomization date and onset date/time 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/time 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 (Posttreatment 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 (groups are displayed separately)

- Group B and 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. If the Week 48 visit is missing, AEs with onset prior to Study Day 338 (48x7 + 2 days) are included. For lab data, the last analysis visit on/prior to Week 48 is selected [if visit is "not windowed" then the last value on/prior to Day 338 is selected].

- Group B and 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 and C (Posttreatment 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, if both the event date and time and BLV dosing date and time are used to determine the assigned treatment period and either of the 2 times is not available, then only event date and BLV dosing date will be compared to determine the assigned treatment period.

On-treatment and posttreatment data will be summarized on 2 separate tables for AOIs (where applicable). 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; posttreatment data (for BLV 2 mg, BLV 10 mg, and DT to BLV 10 mg groups) will be summarized for the Posttreatment Safety Analysis Set.

Cumulative summaries displayed by visit will use the analysis visit windows as specified in Section 3.8.2 of the study 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 reset as the last non-missing value on or prior to first dose of BLV.

3. EVALUATION OF ADVERSE EVENTS OF INTEREST

Adverse events of interest reported while the participant was on-treatment will be summarized for the following time periods. The AEs will be allocated to time periods based on AE onset (see Section 2.2 of this SAP).

- TEAEs prior to Week 48 visit for all groups
- TEAEs through Week 144 for Groups B and C
- TEAEs from Week 48 to Week 144 for the DT to BLV 10 mg group

3.1. Hepatic Adverse Events

All participants with hepatic AEs reported while the participant was on-treatment per Hepatic Safety Adjudication Committee (HSAC) criteria will be summarized by time period, treatment, and preferred term (PT). In addition, a data listing will be provided. The hepatic AEs per HSAC are defined as severe (CTCAE severity grade = 3, 4 or 5) events with:

- MedDRA System Organ Class (SOC) equals "Hepatobiliary disorders", OR
- MedDRA high-level group term (HLGT) equals "Hepatobiliary investigations".

3.2. Other Adverse Events of Interest

3.2.1. Designated Medical Events (DMEs)

The TEAEs of designated medical events (DMEs) while on treatment will be summarized by time period, treatment, and PT. In addition, the corresponding data listing will be provided.

3.2.2. Injection Site Reactions

The participants with TEAEs of injection site reactions (High-Level Term (HLT) = "Injection site reactions") while on BLV treatment will be summarized by treatment (BLV 2 mg, BLV 10 mg, and DT to BLV 10 mg) and PT, and the corresponding listings will be provided.

In addition, the by-treatment (BLV 2 mg, BLV 10 mg, and DT to BLV 10 mg) summary tables and corresponding listings will be provided for participants experiencing TEAEs of injection site reactions while on BLV treatment with the concurrent events listed below:

- Concurrent AEs of eosinophilia or eosinophil (EOS) count increase (PT = "Eosinophilia" or "Eosinophil count increased"). Concurrence is defined as the onset of one event between 1 week before the onset and 1 week after the end of the other event.
- Concurrent absolute EOS > ULN while on-treatment. Concurrence is defined as any visit with absolute EOS > ULN with a laboratory collection date that was between 2 weeks before the onset and 2 weeks after the end of the injection site reaction event.

- Concurrent persistent absolute EOS increase (absolute EOS > ULN at ≥ 2 consecutive on-treatment visits). If multiple consecutive EOS laboratory collections meet criteria, the "event" starts on the date of the first laboratory collection and ends on the date of the last consecutive laboratory collection meeting criteria. Concurrence is defined as the onset of one event between 2 weeks before the onset and 2 weeks after the end of the other event.

3.2.3. Gallstone and Gallbladder Disorders

The participants with on-treatment TEAEs of gallstone related disorders (standardized MedDRA query [SMQ] narrow) and gallbladder related disorders (SMQ narrow) will be summarized by time period, treatment, and PT and the corresponding listing will be provided.

3.2.4. Hypersensitivity

The participants with on-treatment TEAEs of hypersensitivity (SMQ narrow) will be summarized by time period, treatment, and PT and the corresponding listing will be provided.

3.2.5. Sex Hormone Disorders

The participants with on-treatment TEAEs of sex hormone disorders (HLT = "Reproductive hormone analyses" or "Adrenal cortex tests", or HLGT = "Endocrine disorders of gonadal function" or "Adrenal gland disorders") will be summarized by time period, treatment, and PT and the corresponding listing will be provided.

3.2.6. Lipid Metabolism Disorders

The participants with on-treatment TEAEs of lipid metabolism disorders (HLGT = "Lipid analyses" or "Lipid metabolism disorders") will be summarized by time period, treatment, and PT, and the corresponding listing will be provided.

3.2.7. Bone Events or Loss of Bone Density

The participants with on-treatment TEAEs of bone events or loss of bone density, based on a MedDRA search term (MST) list will be summarized by time period, treatment, and PT, and the corresponding listing will be provided.

3.2.8. Eosinophilia or Eosinophil Count Increase

The participants with on-treatment TEAEs of eosinophilia or EOS count increase (PT = "Eosinophilia" or "Eosinophil count increased") will be summarized by time period, treatment, and PT, and the corresponding listing will be provided.

For the subset of participants with absolute EOS > ULN while on-treatment, the on-treatment TEAEs will be summarized by time period, treatment, and PT, and the corresponding listing will be provided. A similar table and listing will also be provided for participants with persistent absolute EOS increase (absolute EOS > ULN at >= 2 consecutive on-treatment visits).

By-treatment summary tables, and corresponding listings will be provided for the following conditions (excluding DT group), respectively:

- Participants with on-treatment TEAE of hypersensitivity (defined in Section 3.2.4) and concurrent absolute EOS > ULN while on treatment. Concurrence is defined as any visit with absolute EOS > ULN between 2 weeks before the onset and 2 weeks after the end of the hypersensitivity event.

- Participants with on-treatment TE hepatic AEs (identified using MST) and concurrent absolute EOS > ULN while on treatment. Concurrence is defined as any visit with absolute EOS > ULN that was between 2 weeks before the onset and 2 weeks after the end of the hepatic AE.

- Participants with on-treatment potential hepatitis flare per AASLD criteria (ALT ≥ 3 × baseline and > 100 U/L) and concurrent (at the same visit) absolute EOS > ULN while on treatment.

- Participants that meet on-treatment potential DILI criteria and with concurrent (at the same visit) absolute EOS > ULN while on-treatment.

- Participants with on-treatment TEAE of hypersensitivity (defined in Section 3.2.4) and concurrent persistent absolute EOS increase (absolute EOS > ULN at ≥ 2 consecutive while on-treatment). Concurrence is defined as the onset of one event between 2 weeks before the onset and 2 weeks after the end of the other event.

- Participants with on-treatment TE hepatic AEs (identified using MST) and concurrent persistent absolute EOS increase (absolute EOS > ULN at ≥ 2 consecutive visits while on treatment). Concurrence is defined as the onset of one event between 2 weeks before the onset and 2 weeks after the end of the other event.

- Participants with on-treatment potential hepatitis flare per AASLD criteria (ALT ≥ 3 × baseline and > 100 U/L) and concurrent (at the same visit) persistent absolute EOS increase (absolute EOS > ULN at ≥ 2 consecutive visits while on treatment).

- Participants that meet potential on-treatment DILI criteria and with concurrent (at the same visit) persistent absolute EOS increase (absolute EOS > ULN at ≥ 2 consecutive visits while on treatment).

3.2.9. Vitamin D Deficiency

The number and proportion of participants with vitamin D deficiency (vitamin D < lower limit of normal [LLN]) will be summarized by treatment group and visit through the FU-96 visit (Week 240 on study). For the subset of participants with vitamin D deficiency while on treatment, TEAEs by time period, treatment, and PT will be summarized in a table, and a corresponding listing will be provided.

3.2.10. Renal Safety

A listing of on-treatment AEs of renal and urinary disorders (SOC = "Renal and urinary disorders") will be provided. In addition, on-treatment TEAEs will be summarized by time period, treatment, and PT for the subgroups of baseline creatinine clearance (≥ 60 to < 90 mL/min vs. ≥ 90 mL/min). A similar summary of adverse events that were reported after the last dose of BLV study drug will be provided by treatment group (BLV 2 mg, BLV 10 mg, and DT to BLV 10 mg), and PT for the subgroups of BLV baseline creatinine clearance clearance (≥ 60 to < 90 mL/min vs. ≥ 90 mL/min) for the Posttreatment Safety Analysis Set.

3.2.11. Cardiac Disorders

The participants with on-treatment TEAEs of cardiac disorders (SOC = "Cardiac disorders") will be summarized by time period, treatment, and PT and the corresponding listing will be provided.

For total bile salts (µmol/L) the baseline values, values at each postbaseline visit up to FU-96 (Week 240 on study) and change from baseline at each postbaseline visit will be summarized by treatment and subgroup of on-treatment TEAEs of cardiac disorders (presence vs. absence). In addition, the summary of the maximum postbaseline change (this may be in either the + or – direction) from baseline in total bile salts (µmol/L) while on treatment will be provided by treatment and subgroup of on-treatment TEAEs of cardiac disorders (presence vs. absence).

3.2.12. Skin and Subcutaneous Disorders

A listing of on-treatment TEAEs of skin and subcutaneous disorders (SOC = "Skin and subcutaneous tissue disorders") will be provided.

The descriptive statistics of baseline values, values at each postbaseline visit up to FU-96 (Week 240 on study) and change from baseline at each postbaseline visit for total bile salts by treatment and subgroup of on-treatment TEAEs of pruritus (PT= "Pruritus"; presence vs. absence) will be provided. The corresponding line plots of mean (± SD) and median (Q1, Q3) change in total bile salts by treatment and visit for pruritis (presence vs. absence) will also be presented for the BLV 2 mg and BLV 10 mg groups.

3.2.13. Laboratory Related Adverse Events

The number and proportion of participants with elevated on-treatment total bile salts (total bile salts > ULN) will be provided by treatment group (Group B, Group C and DT to BLV 10 mg) and visit.

The descriptive statistics of on-treatment total bile salts measurements (multiple records per participant) will be provided by time period and treatment (Week 0-48 and Week 0-144 for BLV 2mg, BLV 10 mg, and BLV 2 mg + BLV 10 mg; and Week 48-144 for DT to BLV 10 mg group); and corresponding boxplots for BLV 2 mg and BLV 10 mg (Week 0-144) will be provided for the following subgroups (presence vs. absence), respectively:

- On-treatment TEAEs of pruritus (PT= "Pruritus")

- On-treatment TEAEs of skin and subcutaneous disorders (SOC = “Skin and subcutaneous tissue disorders”)
- On-treatment TEAEs of eosinophilia or EOS count increase (PT = “Eosinophilia” or “Eosinophil count increased”)
- On-treatment persistent absolute EOS increase (absolute EOS > ULN at >= 2 consecutive on-treatment visits)
- On-treatment TEAEs of cardiac disorders (SOC = “Cardiac disorders”)
- On-treatment TEAE of bradycardia (PT= “Bradycardia” or “Sinus bradycardia”)
- On-treatment Vitamin D deficiency (Vitamin D < LLN at any on-treatment visit)
- On-treatment TEAEs of hypersensitivity (SMQ narrow)
- On-treatment TEAEs of gallstone related disorders (SMQ narrow) and gallbladder related disorders (SMQ narrow)
- On-treatment TEAEs of lipid metabolism disorders (HLGT = “Lipid analyses” or “Lipid metabolism disorders”)
- On-treatment TEAEs of sex hormone disorders (HLT = “Reproductive hormone analyses” or “Adrenal cortex tests”, or HLGT = “Endocrine disorders of gonadal function” or “Adrenal gland disorders”)
- On-treatment TEAE of bone events or loss of bone density (MST)

The descriptive statistics of total bile salts will be provided by treatment group, visit, and subgroup of baseline creatinine clearance (≥ 60 to < 90 mL/min vs. ≥ 90 mL/min) through FU-96 (study Week 240), and the corresponding line plots of mean (± SD) and median (Q1, Q3) of total bile salts will be presented for the BLV 2 mg and BLV 10 mg groups.

3.3. Other Analyses

Treatment-emergent AEs while on treatment will be summarized by time period, treatment, and PT at the maximum severity (for the PT). In addition, the TEAEs while on treatment will be summarized by time period, treatment, and PT for the subgroups of cirrhosis status (ie, stratification factor: presence vs. absence).

AEs with an onset date after last dose date of BLV study drug will be summarized by treatment groups (BLV 2 mg, BLV 10 mg, and DT to BLV 10 mg) and PT at the maximum severity (for the PT). In addition, the posttreatment AEs will be summarized by treatment group and PT for the subgroups of cirrhosis status (ie, stratification factor: presence vs. absence) for the same treatment groups during the posttreatment period. The Posttreatment Safety Analysis Set will be used to produce both posttreatment displays of adverse events.

MYR301 W240 AOI_SAP_v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	16-Nov-2024 20:00:48
PPD	Patient Safety eSigned	18-Nov-2024 16:39:40
PPD	Global Development Lead (GDL) eSigned	20-Nov-2024 04:54:53