STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1 Open-Label, Parallel-group, Multiple-dose Study to Evaluate the Pharmacokinetics of Bulevirtide in Participants with Normal and Impaired Hepatic Function
Study Phase:	1
Name of Test Drug:	Bulevirtide (BLV)
Study Number:	GS-US-589-6162
Protocol Version (Date):	Amendment 2 (30 September 2024)
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

ADA	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BA	bile acid
BLQ	below the limit of quantitation
BLV	bulevirtide
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ET	early termination
GCV	geometric coefficient of variation
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
Hb	hemoglobin
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HI	Hepatic impaired
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
Q1, Q3	first quartile, third quartile
SAP	statistical analysis plan
SD	standard deviation
SI	International System of Units (Systeme International d'Unites)
SOC	system organ class

TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC/PHARMACODYNAMIC ABBREVIATIONS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma concentration of drug versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AUC	area under the plasma concentration versus time curve
AUC_{last}	area under the plasma concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the plasma concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval
$AUC_{x–xx}$	partial area under the concentration versus time curve from time "x" to time "xx"
CL_{ss}/F	apparent clearance at the steady state after administration of the drug: CLss/F = Dose/AUC_{tau}, where "Dose" is the dose of the drug per interval
C_{last}	last observed quantifiable plasma concentration of the drug
C_{max}	maximum observed plasma concentration of drug
$C_{max, ss}$	maximum observed plasma concentration of drug at steady-state
CL_{ss}	steady-state clearance
C_{tau}	observed drug concentration at the end of the dosing interval at the steady state
C_{trough}	plasma concentration at the end of the dosing interval
NetAUC	positive portion of area under the baseline-adjusted biomarker concentration versus time curve over the dosing interval
$t_{½}$	estimate of the terminal elimination half-life of the drug in plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
V_{ss}/F	apparent steady-state volume of distribution of the drug

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 final clinical study report (CSR) for Study GS-US-589-6162 following completion of all groups. This SAP is based on the study protocol amendment 2 dated 30 September 2024 and the electronic case report form (eCRF). The SAP will be finalized prior to database finalization. Any changes made after finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the steady-state plasma pharmacokinetics (PK) of Bulevirtide (BLV) in non-hepatitis D virus (HDV)/hepatitis B virus (HBV)-infected participants with hepatic impairment (HI) compared with matched controls with normal hepatic function

The secondary objectives of this study are as follows:

- To further characterize the plasma PK of BLV in participants with HI compared with matched controls with normal hepatic function
- To evaluate the pharmacodynamic (PD) effect of BLV on plasma bile acids (BA) in participants with HI compared with matched controls with normal hepatic function
- To evaluate the safety and tolerability of BLV following multiple dose administration in participants with HI compared with matched controls with normal hepatic function

The exploratory objectives of this study are as follows:

- To evaluate the plasma protein binding of BLV

1.2. Study Endpoints

Primary endpoints are the BLV steady-state plasma PK parameters AUC_{tau} and $C_{max,ss}$.

Secondary endpoints include the following

- Plasma PK parameters for BLV, as applicable: AUC_{0-24}, C_{max}, T_{max}, $t_{1/2}$, CL_{ss}/F, and V_{ss}/F
- Total BA concentrations in plasma and exposure parameters for total BA, as applicable: C_{trough}, C_{max}, AUC_{0-24}, NetAUC, T_{max}
- The incidences of AEs and laboratory abnormalities

Exploratory endpoint is percent of plasma protein binding which may be estimated.

1.3. Study Design

This is a Phase 1, open-label, multicenter, multiple-dose, parallel-group study to evaluate the steady state plasma PK following exposure to BLV in participants with hepatic impairment compared with matched controls with normal hepatic function. Up to 72 participants will be enrolled, with a goal of obtaining approximately 56 evaluable participants.

An approximately even distribution of participants assigned male at birth and nonpregnant, nonlactating participants assigned female at birth, aged 18 through 79 years will be enrolled into the study.

An overview of the study design is described below and shown in Figure 1. Participants will be enrolled into 1 of 4 study groups:

- **Group A** (BLV 2 mg in moderate hepatic impairment): 20 participants (10 with moderate hepatic impairment and 10 matched controls with normal hepatic function for a target of 8 evaluable participants per group)

- **Group B** (BLV 2 mg in severe hepatic impairment): Approximately 16 participants (8 with severe hepatic impairment and 8 matched controls with normal hepatic function for a target of 6 evaluable participants per group)

- **Group C** (Optional; BLV 10 mg in moderate hepatic impairment): 20 participants (10 with moderate hepatic impairment and 10 matched controls with normal hepatic function for a target of 8 evaluable participants per group)

- **Group D** (Optional; BLV 10 mg in severe hepatic impairment): Approximately 16 participants (8 with severe hepatic impairment and 8 matched controls with normal hepatic function for a target of 6 evaluable participants per group)

Classification of hepatic impairment will be assigned at screening as follows:

- Group A and Group C: Moderate hepatic impairment, Class B, CPT score of 7 to 9

- Group B and Group D: Severe hepatic impairment, Class C, CPT score of 10 to 15

The matched control group will consist of matched participants with normal hepatic function. Each control participant (normal hepatic function) will be matched for age (± 10 years), sex (assigned at birth), and BMI (± 20%, $18 \leq BMI \leq 40$ kg/m^2) with a participant in the hepatic impairment group.

Participants will be administered BLV by SC injection once daily for 6 days.

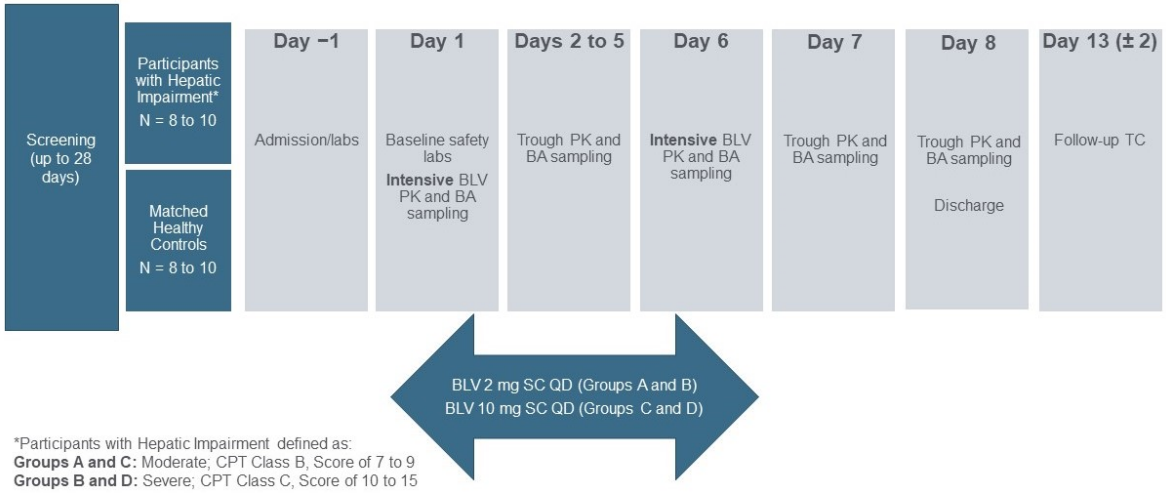
Study procedures (Section 14.1) will include safety and PK assessments for all participants. Clinical procedures in all groups will be identical to those described for Group A.

Groups A and B will begin enrollment simultaneously. Once the safety and PK data from all participants in Group A (2 mg moderate hepatic impairment) have been reviewed, Group C (10 mg moderate hepatic impairment) may be opened. Once the safety and PK data from all participants in Group B (2 mg severe hepatic impairment) have been reviewed, Group D (10 mg severe hepatic impairment) may be opened.

Within each group, once a participant with hepatic impairment is enrolled, a matched control to that participant will be allowed to enroll. Dosing of matched participant with normal hepatic function may begin after the corresponding participant with hepatic impairment in that group has completed the last PK assessment.

A matching control may serve as a matched control participant only once per study group. A participant with normal hepatic function may have their PK and BA data reused just once to serve as a matched control for another group, if the BLV dose is the same and the matching criteria are met.

Figure 1. Study Schema



BA = bile acids; BLV = bulevirtide; CPT = Child-Pugh-Turcotte; PK = pharmacokinetics; QD = once daily; SC = subcutaneous; TC = telephone call

Plasma Pharmacokinetic and Pharmacodynamic Assessments

Plasma PK and total BA sampling for PD will occur relative to the dosing of BLV at the following time points:

- Day 1 at predose (≤ 30 minutes before dose), 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 hours postdose;
- Day 2 at predose (≤ 30 minutes before dose);
- Day 3 at predose (≤ 30 minutes before dose);
- Day 4 at predose (≤ 30 minutes before dose);

- Day 5 at predose (≤ 30 minutes before dose);
- Day 6 at predose (≤ 30 minutes before dose), 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24 (Day 7), and 48 hours (Day 8) postdose, and at the early termination (ET) visit, as applicable (Section 14.1).

A time window of ± 10% will be allowed for samples collected through 4 hours postdose. All other samples collected beyond 4 hours postdose will have a ± 30-minute window. Clinical staff should make every effort to ensure that the sampling time is as close as possible to nominal time. The exact time and date of the blood draw must be recorded in the electronic data capture (EDC) system. For all plasma BA and plasma PK samples, a primary and backup sample will be collected and the backup sample will be stored for potential further analysis or reanalysis.

Plasma Protein Binding Evaluation: additional blood samples will be collected on Day 1 at predose (< 30 minutes prior to BLV dosing), 2 hours and 12 hours postdose, and at the ET visit (if applicable). These samples in addition to other predose and postdose PK samples may be utilized for plasma protein binding evaluation, and percent plasma protein binding may be determined.

Immunogenicity Assessments

The presence of antibodies to BLV will be assessed in plasma samples collected on Day 1 and Day 6 at the time points (≤ 30 minutes before dose) shown in Section 14.1. Antidrug antibodies (ADAs) may be further characterized (eg, for neutralizing activity).

Safety Assessments

Safety will be evaluated throughout the study. Refer to Section 14.1.

Safety assessments will include physical examination (complete or symptom-driven), vital signs, height, weight, clinical laboratory tests, urine drug and alcohol assessments, 12-lead ECG, pregnancy testing, and assessment of AEs.

All safety assessments will be completed predose unless otherwise specified.

1.4. Sample Size and Power

For Group A and Group C (if conducted), with 16 (8 hepatic impairment and 8 matched control [normal hepatic function]) evaluable participants, the estimated upper limit of 1-sided 95% CIs of the GLSM ratio of hepatic impairment group versus matched control, with regards to AUC_{tau} and $C_{max,ss}$ of BLV, would be less than 200% with at least 80% probability if the expected GLSM ratio is 1.0. This assumes a percentage coefficient of variation of no more than 51%, which is supported by the results from the previously conducted Gilead Sciences (Gilead) Study MYR102. Accounting for a 20% dropout rate, a total sample size of 20 participants (10 hepatic impairment and 10 matched control each) will be required. Furthermore, given the lower variability in BA concentrations compared with BLV concentrations observed in

Study MYR102 {Blank 2018}, this sample size will also provide at least 80% probability that the estimated upper limit of the 1-sided 95% CIs of the GLSM ratio of hepatic impairment group versus matched control, with regards to AUC_{tau} and $_{Cmax,ss}$ of plasma total BA, would be less than 200% if the expected GLSM ratio is 1.0.

For Group B and Group D (if conducted), given the challenges with enrolling participants with severe decompensated hepatic dysfunction, up to 16 participants (8 hepatic impairment and 8 matched control) will be enrolled in each conducted study group with a target of at least 12 (6 hepatic impairment and 6 matched control) evaluable participants. This may be lower than the power from the moderate groups but should provide sufficient characterization of BLV in the severe population. Note that based on the known metabolic pathway of linear peptides such as BLV, significant changes in the BLV PK are not expected in this population.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Safety Review Analysis

Groups A and B began enrollment simultaneously. For the purpose of making the decision to proceed to the subsequent groups, interim analyses of relevant safety and PK data were conducted by the Gilead safety review team (SRT). Once the safety and PK data from all participants in Group A (2 mg moderate hepatic impairment) were available and reviewed, Group C (10 mg moderate hepatic impairment) was opened. Once the safety and PK data from all participants in Group B (2 mg severe hepatic impairment) were available and reviewed, Group D (10 mg severe hepatic impairment) was opened. Safety assessments (eg, AEs, ECG, laboratory results) were displayed by hepatic function group to facilitate the decision to proceed to the next dose level or group.

2.1.2. Formal Interim Analysis

Prior to the final analysis, a formal interim analysis and interim clinical study report (CSR) were conducted following completion of Group A and Group B.

2.2. Final Analysis

The final analysis will be performed after all participants in all groups have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoint will be conducted at the time of the final analysis.

2.3. Changes from Protocol-Specified Analysis

Changes from protocol-specified analyses are:

- In the protocol, PK/PD concentration values below the limit of quantitation (BLQ) were planned to be treated as missing for postdose time points in summary statistics. Instead in this SAP, the PK/PD concentration values that are BLQ will be treated as 0 at postdose time points, as it is more reasonable to assume PK/PD concentration values that are BLQ as 0 for summary statistics.

- Add parameter NetAUC to the secondary endpoint in section 1.2 Study Endpoints.

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.

By-participant listings will be presented for all participants in the All Enrolled Analysis Set, and sorted by participant identification (ID) number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within the participant. The study group and hepatic group to which participants were initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings.

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 of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion will be provided in the disposition table as detailed in Section 4. A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all participants who received a study participant identification number in the study after screening. This is the primary analysis set for safety listings.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all participants who took at least 1 dose of study drug BLV. This is the primary analysis set for safety analyses.

3.1.3. Pharmacokinetic Analysis Set

The plasma PK Analysis Set will include all enrolled participants who took at least 1 dose of BLV and had at least 1 measurable plasma PK concentration data reported by PK laboratory for the analyte BLV.

3.1.4. Pharmacodynamic Analysis Set

The plasma PD Analysis Set will include all enrolled participants who received at least 1 dose of study drug BLV and had at least 1 measurable plasma PD concentration value reported for the analyte BA.

3.1.5. Immunogenicity Analysis Set

The Immunogenicity Analysis Set will include all enrolled participants who received at least 1 dose of BLV and had at least 1 blood sample collected for immunogenicity evaluation before any BLV administration or had at least 1 blood sample collected after administration of BLV.

3.2. Strata and Covariates

This study does not use a stratified randomization schedule in enrolling participants. No covariates will be included in the analyses.

3.3. Examination of Participant Subgroups

There are no prespecified participant subgroupings for analyses.

3.4. Missing Data and Outliers

3.4.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2.

3.4.2. Outliers

Outliers of non-PK and non-PD data 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.

Outliers of PK and PD data may be identified during review of data by the PK scientist and biomarker scientist, and if necessary, selective sensitivity analyses may be conducted, excluding outliers. Anomalous concentration values are those that, after verification of bioanalytical validity, are grossly inconsistent with the known or expected pharmacokinetic or pharmacodynamic behavior of the drug. Individual concentrations, if deemed to be anomalous, will be flagged accordingly and may be excluded from the pharmacokinetic and pharmacodynamic analysis at the discretion of the PK scientist and biomarkers scientist. If an entire profile appears inconsistent with those of other participants or previous periods, then the PK scientist may use their discretion in reporting and may also consider using outlier tests to avoid biases in reporting. In the event that outliers are excluded, a rationale will be documented within the clinical study report, e.g., in table, figure, and listing formats. In some circumstances, it may be appropriate to exclude the anomalous value from the calculation of summary statistics (mean, median, etc.) of the concentrations and PK or PD parameter estimates.

3.5. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the enrollment date will be used instead of the Day 1 visit date. Age required for longitudinal and temporal calculations and analyses (e.g., estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK/PD Data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as the bullet point above.
- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

Natural logarithmic transformation will be used for analyzing concentrations and PK/PD parameters. Concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points and postdose time points for descriptive statistics summary purposes.

The following conventions will be used for the presentation of summary and order statistics for intensive PK/PD concentrations:

- If at least 1 participant has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the participants have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all participants have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) and summary statistics will be displayed as "BLQ."
- If more than 1/3 of the participants have a concentration data value of BLQ for a given time point, only order statistics will be presented.

Summary statistics (mean, median, etc.) of concentration-time data will be based on nominal sampling times.

3.6. Visit Definitions

3.6.1. Definition of Baseline, Postbaseline, Study Day

Baseline value is defined as the last available value collected prior to the first dose of study drug.

Postbaseline value is defined as any value collected after the first dose of study drug and before the date of the last dose of study drug plus 30 days.

Study Day will be calculated from the first dosing date of study drug and derived as follows:

- For days prior to the first dose: Assessment Date – First Dosing Date
- For postbaseline study days: Assessment Date – First Dosing Date + 1

Therefore, study day 1 is the day of first dose of study drug administration.

3.6.2. Analysis Visits

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point and in general will not be included in summaries. However, the following exceptions will be made:

- An unscheduled visit prior to the first dose of study drug may be included in the calculation of baseline value, if applicable.
- Unscheduled visits after the first dose of study drug will be included in determining the maximum postbaseline toxicity grade.
- For participants who prematurely discontinue from the study, early termination (ET) data will be summarized as a separate visit, labeled as "Early Termination".
- Data collected on a follow-up visit will be summarized as a separate visit, and labeled as "Follow-up".
- Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries but will be included in the listings.

3.6.3. Selection of Data in the Event of Multiple Records at the Same Visit

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

If multiple valid, nonmissing observations exist at a nominal visit, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last available non-missing record on or prior to the date and time of the first dose of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average (arithmetic or geometric mean, as appropriate) of the measurements for continuous data, or the measurement with the lowest severity (e.g., normal will be selected over abnormal for safety ECG findings) for categorical data.
- For postbaseline values, if there is more than 1 record on the same day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

Key study dates (i.e., first participant screened, first participant enrolled, last participant enrolled, last participant last visit for PK assessments, and last participant last visit for the clinical study report) will be provided.

A summary of participant enrollment will be provided for each country and investigator within a country by hepatic function group for each study group and overall. 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 disposition summary will be provided by hepatic function group for each study group and overall. This summary will present the number of participants enrolled, and the number and percentage of participants in each of the categories listed below.

- Safety Analysis Set
- Plasma PK Analysis Set for BLV
- Plasma PD Analysis Set for BA
- Immunogenicity Analysis Set
- Completed study drug
- Did not complete study drug with reason for premature discontinuation of study drug
- Completed the study
- Did not complete the study with reason for premature discontinuation of study

For the Safety Analysis Set category, the denominator for the percentage calculation will be the total number of participants enrolled for each column. For all other categories, the denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set for each column.

For the status of study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set corresponding to that column. In addition, the total number of participants who were enrolled, and the number of participants in each of the disposition categories listed above will be displayed in a flowchart.

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

- Participants who prematurely discontinued study drug

- A by-participant listing of participants disposition including study group, hepatic function group, date of the last dose of study drugs (study days), study drug completion status, reason for study drug discontinuation, study completion status, reason for study discontinuation, and plasma PK analysis set status (indicating whether or not a participant is included in a PK analysis set), PD analysis set status (indicating whether or not a participant is included in a PD analysis set), and Immunogenicity analysis set status (indicating whether or not a participant is included in a Immunogenicity analysis set) will be provided by participant ID number in ascending order.

4.2. Extent of Exposure

A participant's extent of exposure to study drug data will be generated from the study drug administration page in the eCRF. Exposure data will be listed.

4.3. Protocol Deviations

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 violation) 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 category (e.g., eligibility criteria, informed consent) will be summarized by hepatic function group for each study group based on the All Enrolled Analysis Set. Any important deviations identified will be included in a by-participant listing, and evaluated to determine if it justifies excluding the participant from any analysis sets.

4.4. Assessment of COVID-19 Impact

Adverse events of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 SMQ narrow search. A by-participant listing of AEs of COVID-19 will be provided if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (i.e., age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized by hepatic group for each study group and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set.

A by-participant demographic listing, will be provided by participant ID number in ascending order. The informed consent date and version will also be listed.

5.2. Other Baseline Characteristics

Study Specific baseline characteristics will be summarized by hepatic group for each study group and overall. The summary of other baseline characteristics will be provided for the Safety Analysis Set.

- Alpha-fetoprotein
- Alkaline phosphatase
- Albumin
- Total bile acids from safety
- Total bilirubin
- International normailized ratio

No formal statistical testing is planned.

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

5.3. Medical History

Medical history data will be collected at screening and listed only. General medical history data will not be coded.

A by-participant listing of general medical history will be provided by participant ID number in ascending order. The listing will include relevant medical condition or procedure reported term, onset date, ongoing status, and resolution date (if applicable).

6. EFFICACY ANALYSES

Efficacy will not be evaluated in the study.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

Clinical and laboratory adverse events (AEs) will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). 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 by the investigator as Grade 1, 2, 3, 4, or 5 according to CTCAE toxicity grading scale, Version 5.0 as specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be presented last in the summary presentation.

7.1.2. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Yes" on the AE case report form (CRF) to the question of "Related to Study Treatment". 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. Relationship of Adverse Events to Study Procedure

Study procedure related AEs are those for which the investigator selected "Yes" on the AE case report form (CRF) to the question of "Related to Study Procedures". Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationships to study procedure will be considered related to study procedure for summary purposes. However, by-participant data listings will show the relationship as missing from that captured on the CRF.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definition of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Patient Safety Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

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

If the AE onset date is the same as the date of study drug start date then the AE onset time must be on or after the study drug start time. If the AE onset time is missing when the start dates are the same, the AE will be considered treatment emergent.

- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the date of first dose of study drug, and

- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the date of the first dose of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described below will be provided by hepatic function group and study group. All deaths observed in the study will also be included in this summary.

For the AE categories described below, summaries will be provided by SOC, PT, hepatic function group and study group:

- TEAEs
- TEAEs with Grade 3 or higher (if applicable)
- TEAEs with Grade 2 or higher (if applicable)
- TEAEs by severity
- TE treatment-related AEs
- TE treatment-related AEs by severity (if applicable)
- TEAEs related to study procedures (if applicable)
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug
- TEAEs leading to premature discontinuation of study (if applicable)
- TE SAEs leading to death (i.e., 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 HLT within each SOC if applicable) and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs and TE SAEs will be summarized by PT only, in descending order of total frequency.

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

- All AEs, indicating whether the event is treatment emergent
- AEs leading to death (if applicable)
- All deaths
- SAEs
- AEs leading to Premature Discontinuation of Study Drug
- AEs leading to Premature Discontinuation of Study

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Study Drug Related Injection Site Reactions

Additional analysis of AEs will be performed for injection site reaction (ISR) related to study drug, which is defined as an AE related to study drug reported as any event within the MedDRA HLT of "Injection Site Reactions". The following categories will be provided for participants in each hepatic function group and study group.

- Number of participants that received SC injection(s)
- Number and percentage of participants with study drug related ISRs
- Number and percentage of participants with study drug related ISRs by grade
- Number and percentage of participants with study drug related ISRs by PT

The denominator in the percentage calculation for the summary will be based on the total number of participants who receive at least 1 SC injection.

Duration of the ISR will also be calculated and summarized. Duration of a given ISR event is defined as the ISR stop date minus the ISR onset date plus 1 day. For ISRs with ongoing stop date, stop date will be imputed as last study date. Duration of ISR events in days will be summarized using descriptive statistics.

A by-participant listing for study drug-related ISRs and the corresponding duration will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days. The analysis will be based on values reported in conventional units. When values are BLQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.5. Hemolyzed test results will not be included in the analysis, but they will be listed in by-participant laboratory listings.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, chemistry, urinalysis, and coagulation separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

For each study group, descriptive statistics will be provided by hepatic function group and study group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

Baseline and postbaseline values will be defined as described in Section 3.6.1. 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.

Mean ± SD for total bile acids will be plotted by visit by hepatic function group for each study group.

In the case of multiple values in one visit, data will be selected for analysis as described in Section 3.6.3.

7.2.2. Graded Laboratory Values

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 (i.e., increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and hepatic function group for each study group; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values up to 30 days after last dosing date.

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

7.3. Vital Signs

Descriptive statistics will be provided by hepatic function group and study group for vital signs as follows:

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

Baseline and postbaseline values will be defined as described in Section 3.6.1. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Vital signs measured at unscheduled visits will be included for the baseline value selection.

In the case of multiple values in a visit, data will be selected for analysis as described in Section 3.6.3. 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, height, and BMI will be included in the vital signs listing, if space permits, otherwise they will be provided separately.

7.4. Prior and Concomitant Medications

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

Prior medications are defined as any medications taken before a participant took the first study drug. Concomitant medications are defined as medications taken while a participant took study drug.

Prior and concomitant medications will be separately summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of participants for each hepatic group, study group and overall. A participant reporting the same medication more than once will be counted only once within each ATC drug class when calculating the number and percentage of participants who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered, the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

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

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

7.5. Electrocardiogram Results

For each study group, a shift table of the investigators' assessment of ECG results at each time point compared with baseline values will be presented by hepatic function group for each study group based on Safety Analysis Set using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. 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 for each study group.

7.6. Other Safety Measures

A by-participant listing of participant pregnancies during the study will be provided by participant ID number. No additional safety measures are specified in the protocol.

Although not necessarily related to safety, a by-participant listing of all comments received during the study on the comments form will be provided by participant ID number, and form for which the comment applies.

8. PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATION/ANALYSIS

8.1. Pharmacokinetic and Pharmacodynamic Sample Collection

Plasma PK and PD samples will be collected as specified in Section 1.3. The data handling for plasma bile acids will be conducted as in Section 14.2.

8.2. Estimation of Pharmacokinetic and Pharmacodynamic Parameters

Pharmacokinetic (PK) parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. Pharmacodynamic (PD) parameters will be estimated using SAS® software. The "Linear Up/Log Down" trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real time values, based on drug dosing times whenever possible.

All predose PK sample times before time-zero will be converted to zero.

PK samples that are BLQ at all other time points will be treated as missing data in WinNonlin. For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of zero to prevent overestimation of the initial AUC.

PK and PD parameters may not be able to be validlydetermined in cases of missing/incomplete PK or PD samples/data. PK parameters such as AUC_{inf}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of the drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist and will consider factors such as number of timepoints after C_{max} that are available to be included in the slope linear regression, regression coefficient of the slope, and percent of AUC_{inf} that is extrapolated.

8.3. Pharmacokinetic and Pharmacodynamic Parameters

Pharmacokinetic and pharmacodynamic parameters will be generated for all participants for whom valid parameters can be derived. The analytes presented in Table 8-1 will be evaluated if data are available.

Table 8-1. Study Treatments and Associated Analytes

Study Group	Treatment	Analyte(s)
A (moderate hepatic impairment)	BLV (2 mg), Single Dose, Day 1	Plasma BLV, Total Bile Acids
	BLV (2 mg), Multiple Doses, Day 6	
B (severe hepatic impairment)	BLV (2 mg), Single Dose, Day 1	
	BLV (2 mg), Multiple Doses, Day 6	
C (Optional, moderate hepatic impairment)	BLV (10 mg), Single Dose, Day 1	
	BLV (10 mg), Multiple Doses, Day 6	
D (Optional, severe hepatic impairment)	BLV (10 mg), Single Dose, Day 1	
	BLV (10 mg), Multiple Doses, Day 6	

The analytes and parameters presented in Table 8-2 will be used to evaluate the PK and PD objectives of the study. The primary PK parameters are AUC_{tau} and $C_{max,ss}$ of plasma BLV on Day 6. The PK and PD parameters are defined in the Pharmacokinetic/Pharmacodynamic Abbreviations section. Additional PK and PD parameters may be estimated and reported as applicable.

Table 8-2. Pharmacokinetic and Pharmacodynamic Parameters for Each Analyte and Sample Matrix

Analyte	Sample Matrix	Parameter
BLV	Plasma	Day 1: AUC_{0-24}, C_{max}, T_{max} Day 6: AUC_{tau}, AUC_{0-last}, $C_{max,ss}$, T_{max}, $t_{1/2}$, CL_{ss}/F, and V_{ss}/F Day 2-5, 7, 8: C_{trough}
Total Bile Acids (BA)	Plasma	Day 1 and Day 6: C_{max}, AUC_{0-24}, NetAUC, T_{max} Day 2-5, 7, 8: C_{trough}

Data on plasma concentration versus time profiles of BLV and total BA for each participant will be analyzed.

8.4. Statistical Analysis Methods for Plasma PK and PD

8.4.1. General Considerations

Individual participant plasma concentration data and individual participant BLV PK and total BA PD parameters will be listed and summarized using descriptive statistics by hepatic function group and study group. Summary statistics (numbers of participants, mean, SD, coefficient of variation [%CV], median, minimum, maximum, Q1, and Q3) will be presented for both individual participant concentration data by time point, and individual participant PK and PD parameters by hepatic group. Moreover, the geometric mean, 95% confidence interval (CI), geometric coefficient of variation (%GCV), and the mean and SD of the natural log transformed values will be presented for individual participant PK and PD parameter data.

Individual plasma concentration data listings and summaries will include all participants with available concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as zero at predose and postdose time points.

Individual plasma PK and PD parameter data listings and summaries will include all participants for whom valid PK and PD parameter(s) can be derived. The sample size for each PK and PD parameter will be based on the number of participants with nonmissing data for that PK and PD parameter.

The following tables will be provided for each analyte by hepatic function for each study group at each visit:

- Individual participant plasma PK BLV concentration data and summary statistics
- Individual participant plasma PK parameters and summary statistics
- Individual participant plasma total BA concentration data and summary statistics
- Individual participant plasma total BA parameters and summary statistics

The following figures will be provided for each analyte by hepatic function group for each study group at each visit:

- Individual participant plasma PK BLV concentration data versus time (on linear and semilogarithmic scales). Values of BLQ will be displayed as 0 on the linear scale and missing on the semi-logarithmic scale.
- Mean (± SD) plasma PK BLV concentration data versus time (on linear and semilogarithmic scales). If more than one-third of the values at a postdose timepoint are BLQ then the mean and SD will not be presented at that time point and remaining points connected. If lower error bar (mean-SD) is < 0 at a timepoint then it will not be presented at that timepoint.
- Median (Q1, Q3) plasma PK BLV concentration data versus time (on linear and semilogarithmic scales). If more than one-half of the values at a timepoint are BLQ then the median and quartile values will not be presented at that timepoint, and remaining points connected. If lower error bar (Q1) is BLQ at a timepoint then it will be presented as LLOQ at that timepoint.
- Geometric mean (95% CI) plasma PK BLV concentration data versus time (on linear and semilogarithmic scales). If more than one-third of the values at a postdose time point are BLQ then the geometric mean and 95% CI will not be presented at that timepoint and remaining points connected.

- Individual participant plasma total BA concentration data versus time (on linear and semilogarithmic scales).
- Mean (± SD) plasma total BA concentration data versus time (on linear and semilogarithmic scales). If lower error bar (mean-SD) is < 0 at a timepoint then it will not be presented at that timepoint.
- Median (Q1, Q3) plasma total BA concentration data versus time (on linear and semilogarithmic scales)
- Geometric mean (95% CI) plasma total BA concentration data versus time (on linear and semilogarithmic scales)

The following listings will be provided:

- Plasma PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age
- Plasma PD sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age
- Individual BLV data on determination of plasma half-life

8.4.2. Statistical Methodology

Within each study group, the statistical comparisons of the natural log-transformed plasma PK and PD parameters and hepatic function group comparison of interest will be based on the PK analysis set and PD analysis set accordingly. For each analyte, all participants with available data for the parameter under evaluation will be included in the modeling.

Comparisons of interest are shown in Table 8-3.

Table 8-3. Statistical Comparisons for Plasma Pharmacokinetic and Pharmacodynamic Analyses between Normal and Impaired Hepatic Function within Each Study Group

Analytes	Parameter	Comparison	
		Test	Reference
BLV (Day 6)	AUC_{tau}	Impaired hepatic function	Normal hepatic function
	$C_{max,ss}$		
Total Bile Acids (Day 6)	AUC_{0-24h}	Impaired hepatic function	Normal hepatic function
	NetAUC		
	C_{max}		

For each plasma PK and PD parameter, a parametric (normal theory) ANOVA model will be fitted to the natural log-transformed values of the multiple dose PK parameter (Day 6) under evaluation within each study group.

The statistical model will include hepatic function group as a fixed effect. The following SAS® PROC MIXED code will provide the comparison between the hepatic function groups and the 90% CI calculations for natural log-transformed PK parameters.

```
proc mixed;
  by analyte paramcd;
  class hepaticgrp subjid;
  model lnest = hepaticgrp / ddfm=kr;
  lsmeans hepaticgrp / diff cl alpha = 0.1;
  estimate 'Impaired vs.  Normal' hepaticgrp -1 1 / cl alpha = 0.1;
  ods output Estimates = LSDiffs LSMeans = LSMeans CovParms = MSE;
run;
```

The ESTIMATE statement will be used to produce the point estimate and the corresponding 90% CI of the difference in PK and PD parameters of interest on a logarithmic scale. The test-to-reference ratio and associated 90% CI will be calculated by exponentiation of the point estimate and the corresponding lower and upper limits, which is consistent with the two 1sided tests approach {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2001, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2003}.

8.4.3. Sensitivity Analysis

Sensitivity analysis may be conducted for the key PK or PD analyses if the PK scientist or biomarker scientist identifies PK or PD data as questionable. The sensitivity analysis will exclude specific data from analyses, if appropriate. If a sensitivity analysis is deemed necessary, a listing of the PK and PD data being excluded, with associated reason(s) provided by the PK scientist and biomarker scientist, will be generated.

8.5. Exploratory Analysis

8.5.1. Individual, Conjugated and Unconjugated Plasma Bile Acid Analysis

Exploratory analysis may be conducted for each individual BA, unconjugated and conjugated BA if applicable (see Appendix 14.2 for conjugation status). Individual plasma concentration data listings and summaries will include all participants with available concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as zero at predose and postdose time points.

The following tables will be provided for each analyte by hepatic function for each study group at each visit:

- Individual participant plasma concentration data and summary statistics for each individual BA
- Individual participant plasma taurine-conjugated BA concentration data and summary statistics
- Individual participant plasma glycine-conjugated BA concentration data and summary statistics
- Individual participant plasma unconjugated BA concentration data and summary statistics

The following figures will be provided for each analyte by hepatic function group for each study group at each visit:

- Individual participant plasma concentration data versus time for each individual BA (on linear and semilogarithmic scales). Values of BLQ will be displayed as 0 on the linear scale and missing on the semi-logarithmic scale.
- Individual participant plasma BA concentration data versus time by conjugation status groups (taurine-conjugated, glycine-conjugated, and unconjugated) (on linear and semilogarithmic scales)
- Mean (± SD) plasma individual BA concentration data versus time (on linear and semilogarithmic scales). If more than one-third of the values at a postdose timepoint are BLQ then the mean and SD will not be presented at that time point and remaining points connected. If lower error bar (mean-SD) is < 0 at a timepoint then it will not be presented at that timepoint.
- Mean (± SD) plasma BA concentration data versus time by conjugation status groups (taurine-conjugated, glycine-conjugated, and unconjugated) (on linear and semilogarithmic scales). If lower error bar (mean-SD) is < 0 at a timepoint then it will not be presented at that timepoint.
- Median (Q1, Q3) plasma individual BA concentration data versus time (on linear and semilogarithmic scales). If more than one-half of the values at a timepoint are BLQ then the median and quartile values will not be presented at that timepoint, and remaining points connected. If lower error bar (Q1) is BLQ at a timepoint then it will be presented as LLOQ at that timepoint.
- Median (Q1, Q3) plasma BA concentration data versus time by conjugation status groups (taurine-conjugated, glycine-conjugated, and unconjugated) (on linear and semilogarithmic scales)

- Geometric mean (95% CI) plasma individual BA concentration data versus time (on linear and semilogarithmic scales). If more than one-third of the values at a postdose time point are BLQ then the geometric mean and 95% CI will not be presented at that timepoint and remaining points connected.

- Geometric mean (95% CI) plasma BA concentration data versus time by conjugation status groups (taurine-conjugated, glycine-conjugated, and unconjugated) (on linear and semilogarithmic scales)

8.5.2. PK-PD Analysis

The PK-PD relationship using plasma BLV PK concentrations and plasma total BA concentrations may be evaluated using a graphic approach for Day 1 and Day 6.

9. IMMUNOGENICITY ANALYSIS

9.1. Definition of Terminology

Participants Evaluable for ADA Prevalence: participants who have at least one reportable ADA result at baseline or postbaseline.

Participants Evaluable for ADA Incidence: prticipants who have at least one reportable ADA result at postbaseline.

ADA Prevalence: the proportion of participants who have at least one positive ADA sample (baseline or postbaseline) among all participants evaluable for ADA prevalence.

ADA Incidence: the proportion of participants who have treatment-emergent ADA among all participants evaluable for ADA incidence.

Treatment-Emergent ADA: either treatment-boosted or treatment-induced ADA.

Treatment-Boosted ADA: defined as positive baseline ADA sample and at least one positive postbaseline ADA sample and the (max titer of the postbaseline ADA) / (titer of baseline ADA) ≥ 4. The proportion of participants who have treatment-boosted ADA is calculated based on the total number of participants evaluable for ADA incidence as the denominator.

Treatment-Induced ADA: defined as negative or missing baseline ADA sample and at least one positive postbaseline ADA sample. The proportion of participants who have treatment-induced ADA is calculated based on the total number of participants evaluable for ADA incidence as the denominator.

9.2. Evaluation of Immunogenicity Data

The number and percentage of participants within each ADA category described above will be summarized by hepatic function group for each study group and overall using the Immunogenicity Analysis Set. In addition, the number and percentage of positive ADA samples will be summarized by visit. ADA titer values in positive ADA samples will be summarized (including median, Q1, Q3, minimum and maximum titer values) by visit. A by-participant listing of ADA result, titer, NAb result (if available), and corresponding PK concentration by participant ID number and visit for all participants in the Immunogenicity Analysis Set will be provided. A separate listing will be produced for participants with any positive ADA results.

10. PLASMA PROTEIN BINDING

Percentage of protein binding will be listed and summarized based on PK analysis set using descriptive statistics by hepatic function group and study group at each visit. Bound protein percentage will be calculated as 100% - unbound protein percentage. The following table will be provided for protein binding by hepatic function for each study group:

- Unbound and bound protein percentage at selected timepoint(s)

11. REFERENCES

Blank A, Eidam A, Haag M, Hohmann N, Burhenne J, Schwab M, et al. The NTCP-inhibitor Myrcludex B: Effects on Bile Acid Disposition and Tenofovir Pharmacokinetics. Clin Pharmacol Ther 2018;103 (2):341-8.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Statistical Approaches to Establishing Bioequivalence. January, 2001.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (Revision 1). March, 2003.

12. SOFTWARE

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

nQuery Advisor® Version 9.2. Statistical Solutions, Cork, Ireland.

Phoenix WinNonlin® 8.2. Pharsight Corporation, Princeton, NJ, USA.

13. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision
20 May 2024	3.1.5 8.5	Administrative changes: Changed the last 'and' to 'or' in Section 3.1.5; Fixed Section 8.5 title typo.	1. Made Section 3.1.5 consistent with Section 8.5.3. 2. Fixed the Section 8.5 title typo.
15 July 2025	2.3 3.5 4.1 4.4 5.2 7.1.7.1 7.2.1 8.2 8.3 8.4.1 8.4.2 8.5.1 9 10 14.2	• Clarified that the PK/PD concentration values that are BLQ will be treated as 0 instead of missing at postdose time points for summary statistics in Section 2.3 • Specified that NetAUC is added to the secondary endpoint in Section 2.3 • Clarified the PD data handling conventions in Section 3.5 • Clarified that the summary tables will be presented by hapatic fuction group for each study group and overall, remove the PK analysis set for protein binding in Section 4.1 • Removed the analysis for protocol deviations related to COVID-19 in Section 4.4 • Removed the summary of CPT score in Section 5.2 • Clarified that the analysis of ISR will only be performed overall in Section 7.1.7.1 • Clarified that the analysis for numeric lab results will be provided by hapatic fuction group and study group; added the mean±SD plots for total bile acids in Section 7.2.1 • Clarifed that the PD parameters will be estimated by SAS in Section 8.2 • Table 8-2, Parameters for Total BA of Day 1 and Day 6, are Cmax, AUC0-24 and NetAUC in section 8.3 • Updated the data handling rules for PK/PD plots in Section 8.4.1 and 8.5.1 • Table 8-3, add Total BA parameter NetAUC in Section 8.4.2	• Updated the SAP according to Protocol Amendment 2 • Added clarifications to make definitions more accurate • Updated the data handling rules for figures to align with corresponding tables • Added and removed analyses as needed for alignment and feasibility

		• Clarified the ADA definition and analyses in Section 9 • Clarified the Bound protein percentage calculation in Section 10 • Clarified that values BLQ for the individual bile acids will be treated as 0 in Section 14.2 • Definition and calculations of baseline-adjusted total BA and NetAUC were added in Section 14.2	

14. APPENDICES

14.1. Schedule of Assessments

Study Procedure	Screening	Admission	Evaluation Period				Discharge[a]	Follow-up[b]	ET[c]	Notes
Study Day:		−1	1	2-5	6	7	8	13		
Window:	≤ 28 Days Prior to Dosing							± 2 Days		
Written informed consent	X									
Clinic confinement		X	X	X	X	X	X			
Review study restrictions	X	X					X	X		
Complete medical history	X									
Complete physical examination	X	X					X		X	Symptom-driven physical examination may occur at any other visits if clinically indicated.
Weight, height, and BMI	X	X								
COVID-19 testing		X								Must receive a negative PCR result for enrollment. If study site cannot obtain results from the local laboratory in time for Day 1 dosing, then COVID-19 rapid antigen test/rapid PCR is acceptable.
Vital signs	X	X	X	X	X	X	X		X	Vital signs include resting blood pressure, heart rate, and body temperature at: screening, admission (Day −1), Day 1 (predose and approximately 2 hours postdose), Day 6 (predose and approximately 2 hours postdose), then once in the morning of following days/before blood PK sampling: Day 2 through Day 5, Day 7, discharge (Day 8), and at the ET visit (if applicable).

Study Procedure	Screening	Admission	Evaluation Period				Discharge[a]	Follow-up[b]	ET[c]	Notes
Study Day:		**−1**	**1**	**2-5**	**6**	**7**	**8**	**13**		
Window:	**≤ 28 Days Prior to Dosing**							**± 2 Days**		
12-Lead ECG	X	X	X	X	X		X		X	12-Lead ECG will be performed at screening, admission (Day −1), Day 1 (4 hours postdose), Day 3 (4 hours postdose), Day 6 (4 hours postdose), discharge (Day 8), and at the ET visit (if applicable).
HIV, HBV, and HCV testing	X									Fourth generation HIV antibody/antigen test, hepatitis B surface antibody, hepatitis B surface antigen, HCV antibody, and HCV RNA testing (at screening only).
Creatinine clearance	X	X	X	X	X	X	X		X	Creatinine clearance will only be calculated via Cockcroft-Gault method on days chemistry is performed.
Hematology[d,e]	X	X	X	X	X	X	X		X	8-hour fasting required.
Chemistry[d,e]	X	X	X	X	X	X	X		X	8-hour fasting required
Urinalysis[d,e]	X	X	X	X	X	X	X		X	8-hour fasting required.
Urine drug and alcohol screen[e]	X	X								If study site cannot perform urine alcohol or receive results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.
Coagulation[e,f]	X	X	X	X	X		X		X	Prothrombin time, partial thromboplastin time, and INR.
Alpha-fetoprotein	X									
Immunogenicity			X		X					Collected predose (≤ 30 minutes before dose).
Serum pregnancy test	X	X								Required for participants assigned female at birth and of childbearing potential only. Point of care (urine) pregnancy test may be used at site if serum test result is not available prior to dosing.
FSH testing	X									FSH testing required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.

Study Procedure	Screening	Admission	Evaluation Period				Discharge[a]	Follow-up[b]	ET[c]	Notes
Study Day:		**−1**	**1**	**2-5**	**6**	**7**	**8**	**13**		
Window:	**≤ 28 Days Prior to Dosing**							**± 2 Days**		
Enrollment			X							Participants will be considered enrolled after eligibility is confirmed and a participant number is assigned on Day 1 prior to dosing.
Study drug administration			X	X	X					
Intensive plasma PK and BA sampling for PD			X		X				X	Intensive PK and total BA sampling will occur relative to the dosing of BLV at the following time points: Day 1 and Day 6 at predose (≤ 30 minutes before dose), 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 hours postdose, and at the ET visit (if applicable).
Trough plasma PK and BA for PD				X		X	X		X	Trough PK and total BA sampling will occur predose (≤ 30 minutes before dose) on Day 2 through Day 5 and at 24 hours post Day 6 dose (Day 7) and 48 hours post Day 6 dose (Day 8), and the ET visit (as applicable). The Day 2 predose trough sample of plasma PK and plasma BA will serve as the 24 hours post Day 1 dose sample for intensive plasma PK and plasma BA, respectively, and would be interpolated programmatically at the time of PK analysis.
Plasma sample for protein binding			X							On Day 1, at predose, and 2 and 12 hours postdose.
CCI										
Meal monitoring		X	X	X	X	X	X			Record the percentage of meal consumed (0%-25%, 25%-50%, > 50%).

Study Procedure	Screening	Admission	Evaluation Period				Discharge[a]	Follow-up[b]	ET[c]	
Study Day:		**−1**	**1**	**2-5**	**6**	**7**	**8**	**13**		
Window:	**≤ 28 Days Prior to Dosing**							**± 2 Days**		**Notes**
Review AEs and concomitant medications	X	X	X	X	X	X	X	X	X	From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any nonserious AEs related to protocol-mandated procedures, on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be captured on the medical history eCRF.

AE = adverse event; BA = bile acids; BLV = bulevirtide; BMI = body mass index; ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event

a Participants will be discharged from the clinic on Day 8 per investigator's discretion, following all morning assessments.

b Participants will be contacted for evaluation of AEs by telephone on Day 13 ± 2 days, 7 days (± 2 days) following the last administration of study drug.

c ET assessments will be performed within 24 hours of prematurely discontinuing from the study (prior to Day 8).

d Performed at screening, admission (Day −1), Day 1 (predose), Day 3 (predose), Day 6 (predose), Day 7, at discharge on Day 8, and at the ET visit, if applicable. Predose collections are to be performed ≤ 30 minutes before study drug administration.

e Safety laboratory tests will be performed upon study site admission (Day −1) and will be evaluated at the site's local laboratory to obtain results for participant's eligibility prior to dosing on Day 1. Results of the Day −1 safety laboratory tests will be maintained with the source documents and will not be entered in the electronic data capture at the site. Baseline safety laboratory assessments will be performed on Day 1 and then participants will be administered daily injections of BLV.

f Coagulation tests will be performed at screening, admission (Day −1), Day 1 (predose), Day 3 (predose), Day 6 (predose), at discharge on Day 8, and at the ET visit, if applicable. Predose collections are to be performed ≤ 30 minutes before study drug administration.

14.2. Data Handling for Plasma Bile Acids

The plasma bile acid panel consists of 15 individual bile acids and each will be reported in ng/mL units. The method developed for laboratory raw data collection was for 5-5000 ng/mL range of each individual bile acid and will be validated as such. Values BLQ for the individual bile acids will be treated as 0.

After converted from ng/mL to μM (using the molecular weight of each individual bile acid to transform the data), the 15 individual bile acids will be summed up to be reported as the total bile acids in μM.

1. Conversion formula from ng/mL to μM for the 15 individual bile acids:

Bile Acid Abbreviation	**Bile Acid Name**	**Molecular Weight (MW) (g/mol)**	**Conjugation Status**
CA	Cholic acid	408.57	Unconjugated
CDCA	Chenodeoxycholic acid	392.57	Unconjugated
DCA	Deoxycholic acid	392.572	Unconjugated
UDCA	Ursodeoxycholic acid	392.56	Unconjugated
LCA	Lithocholic acid	376.5726	Unconjugated
GCA	Glycocholic acid	465.631	Glycine-conjugated
GCDCA	Glycochenodeoxycholic acid	449.6233	Glycine-conjugated
GDCA	Glycodeoxycholic acid	449.6233	Glycine-conjugated
GUDCA	Glycoursodeoxycholic acid	449.6233	Glycine-conjugated
GLCA	Glycolithocholic acid	433.6239	Glycine-conjugated
TCA	Taurocholic acid	515.7058	Taurine-conjugated
TCDCA	Taurochenodeoxycholic acid	499.71	Taurine-conjugated
TDCA	Taurodeoxycholic acid	499.71	Taurine-conjugated
TUDCA	Tauroursodeoxycholic acid	499.7036	Taurine-conjugated
TLCA	Taurolithocholic acid	483.71	Taurine-conjugated
Formula to transform ng/mL to μM	1 ng/mL = 1 μg/L; Divide the ng/mL value by the molecular weight to get the number of μmol/L or μM.		

2. Summation over the 15 individual bile acids to get the total bile acids:

At each collection timepoint for one participant per protocol,

$$Total\ BA\ at\ a\ timepoint = \sum_{i=1}^{15} individual\_bile\_acid_i\ (\mu M)\ at\ that\ timepoint$$

3. Baseline-adjusted total bile acids: Using Day 1 pre-dose as baseline, baseline-adjusted BA will be derived by subtracting the baseline level from the total BA concentration from all postdose time points (including Day 1 and Day 6) for each participant. If baseline-adjusted value results in a negative value, the value will be set equal to 0. (reference FDA bioequivalence guidance)

4. NetAUC will be calculated based on baseline-adjusted total BA concentration- time profile using SAS software.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	16-Jul-2025 16:17:34
PPD	Global Development Lead (GDL) eSigned	16-Jul-2025 19:02:58
PPD	Clinical Pharmacology eSigned	16-Jul-2025 21:58:55