STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1 Open-Label, Parallel-Design, Multiple-Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Bulevirtide in Participants with Normal and Impaired Renal Function
Study Phase:	1
Name of Test Drug:	Bulevirtide (BLV)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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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
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ET	early termination
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
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
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett’s formula
QTcF	QT interval corrected for heart rate using Fridericia’s formula

RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAP	statistical analysis plan
SD	standard deviation
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

PHARMACOKINETICS/PHARMACODYNAMICS 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}
A_e	amount of unchanged drug excreted in urine calculated either over a specific interval ($A_{e(interval)}$) or cumulatively over all collection intervals, calculated as (concentration of unchanged drug in urine) × (volume of urine collected)
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_{0-12}	area under the plasma concentration versus time curve from time zero to 12 hours post-dose
AUC_{0-24}	area under the plasma concentration versus time curve from time zero to 24 hours post-dose
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval
CL/F	apparent clearance after single dose administration of the drug. $CL/F = Dose/AUC_{inf}$
CLss/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
CL_r	renal clearance of unchanged drug in a specific interval ($CL_{r\ (interval)}$) or cumulatively over all collection intervals
C_{max}	maximum observed plasma concentration of drug
$C_{max,ss}$	maximum observed plasma concentration of drug at steady state
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
F_e	excreted fraction of administered drug in urine
$t_{½}$	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
Net AUC	positive portion of area under the baseline-adjusted biomarker concentration versus time curve over the dosing interval

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-589-6160. This SAP is based on the study protocol amendment 1 dated 02 February 2023 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 pharmacokinetic (PK) of Bulevirtide (BLV) in non-hepatitis D virus (HDV)/hepatitis B virus (HBV)-infected participants with renal impairment (RI) and in matched control participants with normal renal function

The secondary objectives of this study are as follows:

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

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}, Net AUC, and T_{max}
- The incidences of AEs and laboratory abnormalities

1.3. Study Design

This is a Phase 1, open-label, multiple-dose, parallel-group study to evaluate PK, PD, and safety of BLV in participants with severe RI and matched control participants with normal renal function. Additional groups of participants with mild and/or moderate RI (and with matched control participants) may be included pending evaluation of safety and PK results in severe RI participants.

An overview of the study design is described below and shown in Figure 1-1. In accordance with the objectives, a reduced study design starting in participants with severe RI was selected. The study will begin with Group A. Following completion and evaluation of PK and safety data from all participants in Group A, additional optional groups (Groups B, C, and D) may be evaluated as per the criteria detailed in protocol Section 3.1.1.1 and Figure 1-2.

The study groups are as follows:

Group A (BLV 2 mg severe RI): A total of up to 20 participants (10 participants with severe RI and 10 matched control participants) will be enrolled to obtain at least 16 evaluable participants (8 participants with severe RI and 8 matched control participants).

Optional Group B (BLV 10 mg severe RI): A total of up to 20 participants (10 participants with severe RI and 10 matched control participants) will be enrolled to obtain at least 16 evaluable participants (8 participants with severe RI and 8 matched control participants).

Optional Group C (BLV 2 mg or 10 mg moderate RI): A total of up to 20 participants (10 participants with moderate RI and 10 matched control participants) will be enrolled to obtain at least 16 evaluable participants (8 participants with moderate RI and 8 matched control participants).

Optional Group D (BLV 2 mg or 10 mg mild RI): A total of up to 20 participants (10 participants with mild RI and 10 matched control participants) will be enrolled to obtain at least 16 evaluable participants (8 participants with mild RI and 8 matched control participants).

Non-HDV/HBV-infected participants assigned male at birth and nonpregnant, nonlactating participants assigned female at birth, aged 18 through 79 years inclusive with a body mass index (BMI) from 18.0 kg/m² to 40.0 kg/m² will be enrolled in the study.

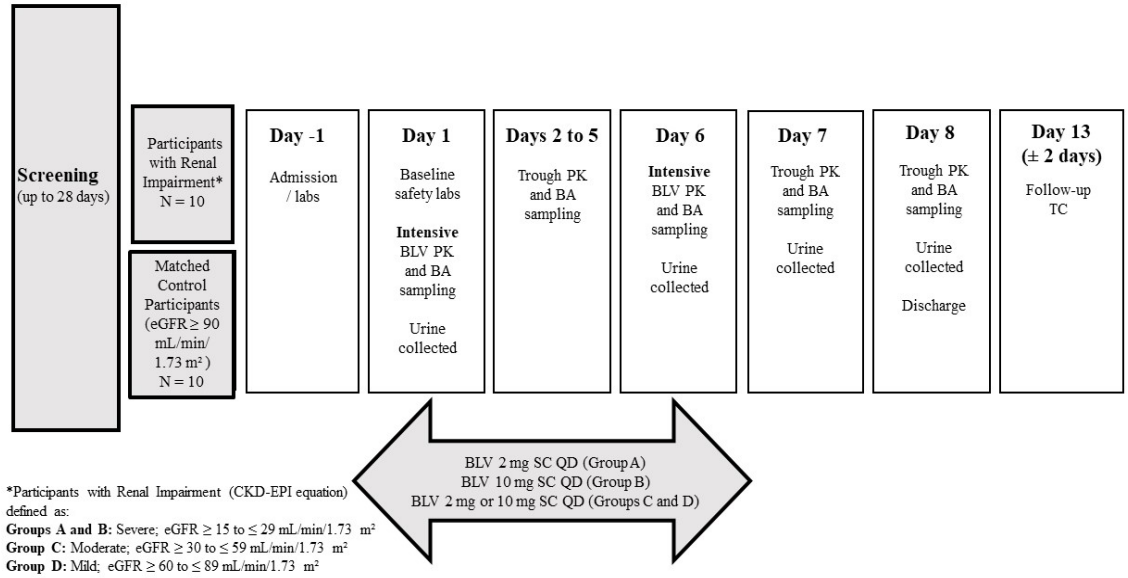
The matched control group will consist of matched participants with normal renal function. Each match participant (normal renal function i.e., eGFR ≥ 90 mL/min/1.73 m²) will be matched for age (± 10 years), sex (assigned at birth), and BMI (± 20%, 18.0 ≤ BMI ≤ 40.0 kg/m²) with a participant in the RI group.

Participants will undergo screening procedures to determine eligibility within 28 days prior to first dose of study drug.

Following the completion of screening procedures and study enrollment at admission, eligible participants will be admitted to the study clinic on Day -1 and will remain confined to the study clinic until completion of assessments on the morning of Day 8. Participants will receive a follow-up phone call on Day 13 ± 2 days to collect safety data since the participant's discharge.

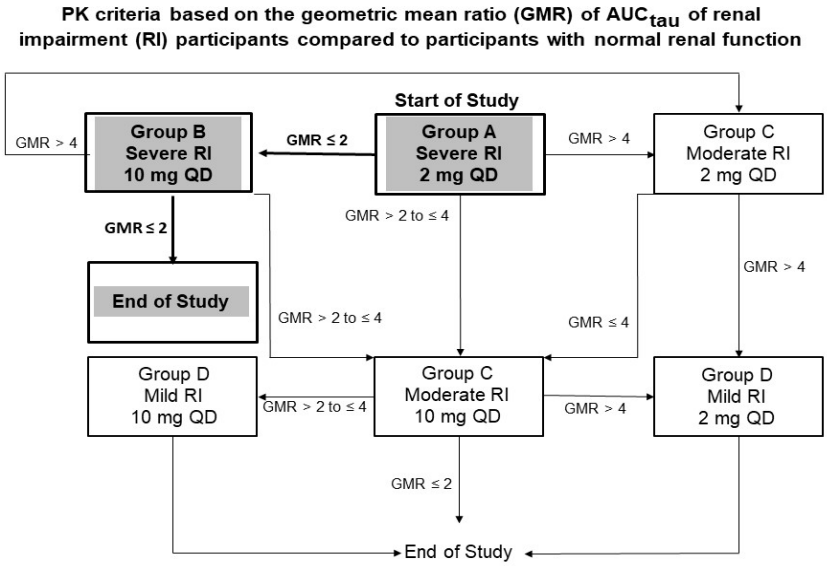
For each study group, participants will be administered BLV by SC injection by assigned study staff, once-daily (QD) at approximately the same time (± 30 minutes) each morning on Days 1-6 following an overnight fast for at least 8 hours prior to dosing.

Figure 1-1. Study Schema



BA = bile acids; BLV = bulevirtide; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; N = number of participants; PK = pharmacokinetics; QD = once-daily; SC = subcutaneous; TC = telephone call
Note: Refer to Figure 1-2 for PK criteria for dose selection and renal population of the subsequent study groups.

Figure 1-2. PK Decision Criteria for Progression to Subsequent Study Groups



BLV = bulevirtide; GMR = geometric mean ratio; PK = pharmacokinetic; QD = once-daily; RI = renal impairment
Boxes in bold and shaded indicate the most likely scenario to be pursued.

The study procedures to be conducted for each participant enrolled in the study are detailed in Section 12.1.

Plasma Pharmacokinetic and Pharmacodynamic Assessments

Intensive plasma PK and total plasma 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, 12 hours postdose, and at the ET visit, as applicable.

Day 6 at predose (≤ 30 minutes before dose), 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 hours postdose, and at the ET visit, as applicable.

A trough (predose) PK and PD biomarker BA sample (≤ 30 minutes before dose) will be collected 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).

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.

Plasma Protein Binding Evaluation: additional blood samples for Day 1 at predose (≤ 30 minutes prior to BLV dosing), 2 hours and 12 hours postdose, and at the ET visit (if applicable).

Urine Pharmacokinetic Assessments

Urine PK sampling will occur on Day 1 and Day 6.

- Day 1: Predose (-60 to 0 minutes prior to dosing), 0 to 6, 6 to 12, and 12 to 24 hours postdose
- Day 6: Predose (-60 to 0 minutes prior to dosing), 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours postdose

CYP3A4 metabolic activity: The predose urine voided (-60 to 0 minutes interval) on Day 1 and the 0 to 6 hour postdose urine interval on Day 6 may be analyzed for determining the 6 beta-hydroxycortisol to cortisol ratio as a marker of CYP3A4 metabolic activity.

Immunogenicity Assessments

Immunogenicity sampling will occur on Days 1 and 6 at predose (≤ 30 minutes before dosing). Plasma will be evaluated for the presence of ADA to BLV.

Safety Assessments

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, fourth generation HIV antibody/antigen test, HBsAb, HBsAg, HCV antibody, and HCV RNA testing, and assessment of AEs.

All safety assessments will be completed predose unless otherwise specified. The Day 1 safety labs will be used for baseline values. Safety will be evaluated throughout the study. Refer to Section 12.1 for a schedule of assessments.

1.4. Sample Size and Power

For study Group A, with 16 (8 RI and 8 matched control [normal renal function]) evaluable participants, the estimated upper limit of the one-sided 95% CIs of the GLSM ratio of RI group versus matched control group with regards to AUC_{tau} and C_{max} of BLV, would be less than 200% with ≥ 80% probability if the expected GLSM ratio is 1.0. This assumes a percentage coefficient of variation (CV%) of no more than 51%, which is supported by previously conducted Study MYR102. Accounting for a 20% dropout rate, a total sample size of 20 participants (10 RI and 10 matched control each) will be required.

Furthermore, given the lower degree of variability in BA concentrations compared to BLV, plasma concentrations observed in Study MYR102 {Blank 2018}, this sample size will also provide ≥ 80% probability that the estimated upper limit of the one-sided 95% CIs of the GLSM ratio of RI group versus matched control group with regards to AUC_{tau} and C_{max} of total plasma BA would be less than 200% if the expected GLSM ratio is 1.0. If additional

optional groups (Groups B, C, and D) are conducted, a total of up to 20 participants (10 RI and 10 matched controls with normal renal function) will be enrolled in each conducted study group in order to adequately power each subgroup.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

Prior to the final analysis, interim analyses will be conducted at the end of each group and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

2.1.1. Safety Review Analysis

For the purpose of subsequent optional groups, a safety review team (SRT) will review all PK and safety data from completed Group A before opening Group B or Group C; and from completed Group B before opening Group C; and from completed Group C before opening Group D. Safety assessments (e.g., AEs, ECG, and laboratory results) will be displayed by renal group to facilitate the decision to optional groups.

Decision Criteria for subsequent groups can be found in Figure 1-2.

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

No changes from protocol-specified analyses are planned.

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 renal 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 respective analyte. The urine PK Analysis Set will include all enrolled participants who received at least 1 dose of BLV and had at least 1 measurable urine PK concentration data reported by PK laboratory for BLV.

3.1.4. 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.

3.1.5. 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 each respective analyte.

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 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 subjects 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. For screen failures, the date the first informed consent was signed will be used for the age derivation. 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 summarizing concentrations, and PK and 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 and 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 Predose, Postdose, Study Day

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

Postdose 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 postdose 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 predose 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 Visit”.

- Data collected on a follow-up visit will be summarized as a separate visit, and labeled as “Follow-up Visit”.

- Data obtained after the follow-up visit or last dose date plus 9 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 predose 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 predose, 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 predose 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 postdose 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 enrolled, last participant enrolled, last participant last visit for PK assessment, and last participant last visit for the clinical study report) will be provided.

A summary of participant enrollment will be provided for each investigator by renal function group and overall for each study group. 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 renal function group and overall for each study group. 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
- Plasma PK Analysis Set for Protein Binding
- Urine PK Analysis Set for BLV
- Urine Analysis Set for CYP3A4
- 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, renal 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) 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 renal 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

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

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 renal group and overall for each study group 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, including the informed consent date, type and version, will be provided by participant ID number in ascending order.

5.2. Other Baseline Characteristics

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

- eGFR
- ECG results (normal, non-clinically significant abnormal, clinically significant abnormal)
- AST
- ALT
- Hemoglobin

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 toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be 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 "Caused by Investigational Product". 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 Procedure or Activity". 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 Global 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 renal function group and dose level. 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, renal 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
- All 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 each SC injection visit and overall for participants in each renal function 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 by visit summary and the overall summary will be based on the total number of participants who receive at least 1 SC injection at the visit of interest and the total number of subjects who receive at least 1 SC injection at any injection visit, respectively.

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 9 days for participants who have permanently discontinued study drug or all available data at the time of the database snapshot. 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, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

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

- Baseline values

- Values at each postdose visit
- Change from baseline at each postdose visit

Baseline and postdose values will be defined as described in Section 3.6.1. Change from baseline to a postdose visit will be defined as the visit value minus the baseline value. Laboratory test results collected at unscheduled visits will be included for the baseline and postdose maximum and minimum toxicity grade selection. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the absolute values for selected laboratory tests, including eGFR and serum creatinine will be plotted using a line plot by renal group and postdose visit 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 postdose time point, up to and including the date of last dose of study drug plus 9 days for participants who permanently discontinued study drug , or the last available date in the database snapshot. 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 postdose visit.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and renal function group for each study group; participants will be categorized according to the most severe postdose 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 postdose 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 renal function group and dose level for vital signs as follows:

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

Baseline and postdose values will be defined as described in Section 3.6.1. Change from baseline to a postdose visit will be defined as the postdose value minus the baseline value. Body weight and 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.

A summary of prior and concomitant medications will be provided.

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.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first study drug.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once within each ATC drug class when calculating the number and percentage of subjects who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by 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.

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

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by ATC drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once within each ATC drug class will be counted only once when calculating the number and percentage of subjects who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by preferred term in 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 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.

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 renal function group 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 postdose will not be included in the denominator for percentage calculation.

ECG parameter values (HR, QT, QTcF, QTcB, PR, RR, QRS) and change from baseline at each visit will be summarized for the Safety Analysis Set by renal function group using descriptive statistics for each study group.

In addition, the maximum postdose ECG parameter values will be summarized for the Safety Analysis Set by renal function group by category for each study group.

- The maximum postdose QTcF interval: > 450 msec, > 480 msec, > 500 msec.
- The maximum postdose change in QTcF interval: > 30 msec, > 60 msec.
- The maximum postdose PR (> 200 msec) and QRS (> 110 msec).

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.

8. PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATION/ANALYSIS

8.1. Pharmacokinetic and Pharmacodynamic Sample Collection

Plasma and urine PK samples will be collected as specified in Section 1.3.

The data handling for PD plasma bile acids will be conducted as in Section 12.2. Data handling for PK Non-Compartmental (NCA) analysis will be specified with details in Section 12.4.

8.2. Estimation of Pharmacokinetic and Pharmacodynamic Parameters

Pharmacokinetic (PK) and pharmacodynamic (PD) parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental (NCA) methods specified in Sections 12.3 and 12.4. PD parameters may also be estimated using SAS® software. For PK analysis, 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/urine concentration, and corresponding realtime values, based on drug dosing times whenever possible.

All predose PK/PD sample times before time-zero will be converted to zero and PK/PD 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 validily determined in cases of missing/incomplete PK or PD samples/data. Pharmacokinetic parameters such as AUC_{inf} (or other AUC values requiring extrapolation from the last observed concentration), CL/F, V/F, 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. Additionally, the calculation of $AUC_{tau,ss}$ may be estimated in absence of having both pre-dose and C_{trough} values using the pre-dose or C_{trough} sample value twice: as both the time zero and for time τ. If this occurs, a footnote will indicate the re-use of the pre-dose or C_{trough} sample.

8.3. Pharmacokinetic and Pharmacodynamic Parameters

Pharmacokinetic and pharmacodynamic parameters will be generated for all participants in PK/PD analysis set. 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	BLV (2 mg), Single Dose, Day 1	BLV, Total BA
	BLV (2 mg), Multiple Doses, Day 6	
[redacted]		

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. Other PK and PD parameters to be estimated in this study are listed and defined in the Pharmacokinetic 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}, $C_{max,Day1}$, $T_{max,}$ AUC_{0-12}, $AUC_{inf,}$ t1/2, CL_{day1}/F, and V_{day1}/F Day 6: AUC_{tau}, AUC_{0-last}, AUC_{0-12}, $C_{max\ ss,}$ T_{max}, $t_{1/2}$, CL_{ss}/F, and V_{ss}/F Day 2-5, 7, 8: C_{trough}
	Urine	Day 1 and Day 6: A_{et1-t2}, A_e*, CL_r#, and F_e*
Total BA	Plasma	Day 1 and 6: C_{max}, AUC_{0-24}, Net AUC Day 2-5, 7, 8: C_{trough}

* If any interval is missing, total A_e is not calculated (reported as missing). F_e: time interval of A_e and AUC must match.
# $CLr=A_{e,0-t}/AUC_{0-t}$

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 renal 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 study group and by renal function 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. The PK and PD parameters T_{max} and $T_{1/2}$ will be reported with the following summary statistics: number of participants, median, range (minimum, maximum).

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 PK and PD parameter(s) can be derived. Special considerations for PK parameters are listed in Section 12.4.4. PK parameters that are flagged out will be excluded from individual PK parameter summary descriptions. 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 renal function for each study group:

- Individual participant plasma PK BLV concentration data by time point and summary statistics by study group and renal function
- Individual participant plasma PK parameters and summary statistics by study group and renal function
- Individual participant plasma total BA concentration data and summary statistics by study group and renal function
- Individual participant plasma total BA parameters and summary statistics by study group and renal function

The following figures will be provided for each analyte for each study group:

- Individual participant plasma PK concentration data versus time (on linear and semilogarithmic scales)
- Mean (± SD) plasma PK BLV concentration data versus time (on linear and semilogarithmic scales) by renal function group on Day 1 and Day 6 separately
- Median (Q1, Q3) plasma PK BLV concentration data versus time (on linear and semilogarithmic scales) by renal function group on Day 1 and Day 6 separately

- Geometric mean (95% CI) plasma PK BLV concentration data versus time (on linear and semilogarithmic scales) by renal function group on Day 1 and Day 6 separately

- 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) by renal function group

- Mean (± SD) plasma total BA concentration data versus time (on linear and semilogarithmic scales) by renal function group on Day 1 and Day 6 separately

- Median (Q1, Q3) plasma total BA concentration data versus time (on linear and semilogarithmic scales) by renal function group on Day 1 and Day 6 separately

- Geometric mean (95% CI) plasma total BA concentration data versus time (on linear and semilogarithmic scales) by renal function group on Day 1 and Day 6 separately

Individual, mean, and median postdose concentration values that are ≤ LOQ will not be displayed in the figures and remaining points connected.

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 and corresponding regression correlation coefficient

8.4.2. Statistical Methodology

Within each study group, the statistical comparisons of the natural log-transformed plasma PK and PD parameters and renal function group comparison of interest will be based on the plasma 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 Renal Function within Each Study Group

Analytes	Parameter	Comparison	
		Test	Reference
BLV (Day 6)	AUC_{tau}	Impaired renal function	Normal renal function
	$C_{max\ ss}$		
Total BA (Day 6)	AUC_{0-24}	Impaired renal function	Normal renal function
	Net AUC		
	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 renal function group as a fixed effect. The following SAS® PROC MIXED code will provide the comparison between the renal function groups and the 90% CI calculations for natural log-transformed PK parameters.

```
proc mixed;
  by analyte paramcd;
  class renalgrp subjid;
  model lnest = renalgrp / ddfm=kr;
  lsmeans renalgrp / diff cl alpha = 0.1;
  estimate 'Impaired vs. Normal' renalgrp -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 1 sided 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. Examples of exclusion are as below:

- PK parameters based on adjusted R^2 below 0.85 and $\%AUC_{extrap}$ above 20% will be flagged in the listing, but excluded from descriptive and inferential statistics.

- $t_{1/2}$: to be excluded from analysis/summaries if the following criteria are not met: extrapolation, regression.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9. 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.

10. SOFTWARE

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

Phoenix WinNonlin® 8.1. Pharsight Corporation, Princeton, NJ, USA.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision
08 AUG 2024	3.1.5 and 8.5.2	Urine PD bile acids analysis was removed from SAP	Urine PD BA was not applicable for the study
	8	1. PD parameters will be estimated using WinNonlin instead of SAS Day 1 and 6: Net AUC 2. More PK variables were added in Table 8-2: Day 1: AUC_{0-12}, $AUC_{inf,}$ t1/2, CL_{day1}/F, and V_{day1}/F Day 6: AUC_{0-12} 3. More summary tfl were added in section 8.4.1 4. Net AUC was added in Table 8-4 for statistical model	More PD parameters were required for the study using WinNonlin.
	8.3	Table 8-2, Parameters for Total BA of Day 1 and Day 6, are Cmax, AUC0-24 and Net AUC	
	8.5.3	ADA definitions and related TFLs were added	It is required per Gilead shell templated version Dec 2023.
	8.5.4	Protein binding will be summarized at predose instead of selected timepoints	
	12.1	Schedule of Assessment table was updated	Missing one page of assessments in version 1.0
	12.2	Definition and calculations of baseline-adjusted total BA and Net AUC were added	Net AUC was required for the study
	12.3	Added section 12.3 for PD analysis.	
	12.3.4 and 12.3.5	Reworded header for 12.3.4 and 12.3.5	

12. APPENDICES

12.1. 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

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**		
										in the morning of following days/before blood PK sampling: Day 2 through Day 5, Day 7, and discharge (Day 8), and at ET visit (if applicable).
12-Lead ECG	X	X	X	X	X		X		X	12-Lead ECG: screening, admission (Day –1), Day 1 (4 hours postdose), Day 3 (4 hours postdose), Day 6 (4 hours postdose) and discharge (Day 8), and at ET visit (if applicable).
HIV, HBV, and HCV testing	X									Fourth generation HIV antibody/antigen test, HBsAg, HBsAb, HCV antibody, and HCV RNA testing.
eGFR[e]	X	X	X	X	X	X	X		X	eGFR will be estimated at screening, admission (Day –1), predose Day 1 to 6, Day 7, and at discharge (Day 8), and at ET visit if applicable. eGFR will be calculated using the CKD-EPI equation (2021) for allocation to the RI group based on serum creatinine as measured at screening.
Hematology[d,e]	X	X	X	X	X	X	X		X	8 hours fasting required.
Chemistry[d,e]	X	X	X	X	X	X	X		X	8 hours fasting required. Assessment of total BA for safety.
Urinalysis[d,e]	X	X	X	X	X	X	X		X	8 hours fasting required.
Urine drug and alcohol screen	X	X								If study site cannot perform urine alcohol or obtain results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.

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**		
Coagulation[d,e]	X	X	X	X	X		X		X	Prothrombin time, partial thromboplastin time, and international normalized ratio.
Serum pregnancy test	X	X								Required for participants assigned female at birth and of childbearing potential only. Point of care 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.
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					Day 1 to Day 6, BLV SC injection, QD.
Intensive plasma BLV PK and plasma BA for PD			X		X				X	Intensive BLV PK and total plasma BA for PD biomarker 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) at 0.5, 1, 1.5, 2, 3, 4, 6, 9, and 12 hours postdose; and, at ET visit (as 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**		
Trough plasma PK and trough plasma BA for PD				X		X	X		X	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 at 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.
Urine BLV PK for PD			X	X	X	X	X			CCI [redacted] All urine voided will be collected and pooled. All urine samples will be collected predose (void; within a 60-minute period prior to Day 1 and Day 6 dose), and over the following collection intervals after Day 1 at: 0 to 6, 6 to 12, and 12 to 24 hours postdose, and after dosing on Day 6 at: 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours postdose.
CCI [redacted]										

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**		**Notes**
Immunogenicity			X		X					ADA to BLV. Collected predose (≤ 30 minutes before dose).
Meal monitoring		X	X	X	X	X	X			Record the percentage of meal consumed (0-25%, 25-50%, >50%).
Review AEs & 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.

ADA = antidrug antibodies; AE = adverse events; BA = bile acids; BLV = bulevirtide; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; ECG = electrocardiogram; eCRF = electronic case report forms; eGFR = estimated glomerular filtration rate; ET = early termination; FSH = follicle-stimulating hormone;
HBsAb= hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; PK = pharmacokinetics; QD = once-daily; RI = renal impairment; SAE = serious adverse event; SC = subcutaneous

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 ie, 7 days (± 2 days) following last administration of study drug.
c. ET assessments will be performed within 24 hours of prematurely discontinuing from the study (prior to Day 8), if possible.
d. Performed at screening, admission (Day −1), predose on Days 1 to 6, Day 7, at discharge (Day 8), and at ET visit, if applicable. Predose collections are to be performed ≤ 30 minutes before dose. Coagulation tests will not be performed on Day 7.
e Safety laboratory tests will be collected upon study site admission (Day –1); 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 labs will be maintained with the source documents and will not be entered in the electronic data capture at the site. Day 1 safety labs will be used for baseline values.

12.2. Data handling for Pharmacodynamic plasma bile acid panel

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. If the individual bile acid is below the limit of quantification, the corresponding BLQ value will be entered.

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. In addition, baseline-adjusted total bile acid values will be calculated by subtracting the baseline value at Day 1 predose from post-dose values at each dosing period (Day 1 or Day 6). Baseline-adjusted value at Day 1 predose will be zero.

1) Conversion formula from ng/mL to µM and conjugation status 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 subject. If baseline-adjusted value results in a negative value, the value will be set equal to 0. (reference FDA bioequivalence guidance)

12.3. PD Analysis

For total BA concentrations that are BLQ, including predose and postdose time points, the concentrations will be treated as zero.

The following key PD parameters will be derived:

- C_{max}: The maximum total BA concentration observed during intensive sampling days of Day 1 or Day 6.
- $AUC_{0\text{-}24}$: Area under the total BA-time curve will be derived using Phoenix WinNonlin® software and the "Linear Up/Linear Down" trapezoidal rule will be applied. Day 1 and Day 6 $AUC_{0\text{-}24}$ will be calculated separately
- NetAUC will be calculated based on baseline-adjusted total BA concentration- time profile using Phoenix WinNonlin® software and the "Linear Up/Linear Down" trapezoidal rule. Day 1 and Day 6 netAUC will be calculated separately.

12.4. PK NCA analysis

12.4.1. BLQ samples for NCA using WinNonlin

All predose sample times before time-zero will be converted to zero and samples that are BLQ at all other time points will be treated as missing data. For AUC calculations, BLQ samples 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.

For handling of BLQ samples for TFLs, please refer to Section 3.5.

12.4.2. Nominal versus Actual Times (for NCA using WinNonlin):

For the final analysis (using the PK merge dataset from the QA data), the actual time will be used for all individual analyses (NCA) and recorded as such in the report. For computing partial AUC, e.g., $AUC_{0\text{-}12}$ and $AUC_{0\text{-}t}$, actual durations will be used.

Summary statistics (mean, median, etc.) of concentration-time data will be based on nominal sampling times; samples that have a significant time deviation in the opinion of the PK scientist will be flagged accordingly and considered as "missing" for the calculation of summary statistics only. A footnote indicating the exclusion of samples due to time deviations from collection time should be included.

12.4.3. Outliers

Anomalous concentration values are those that, after verification of bioanalytical validity, are grossly inconsistent with the known or expected pharmacokinetic behavior of the drug. For example, a BLQ value that is between two quantifiable values or a non-BLQ value prior to first dose may be considered as anomalous. Individual concentrations, if deemed to be anomalous, should be flagged accordingly and may be excluded from the pharmacokinetic analysis at the discretion of the PK scientist. If an entire profile appears inconsistent with those of other subjects or previous periods, then the PK scientist should use their discretion in reporting and should also consider using outlier tests to avoid biases in reporting. Exclusion of data from analyses is not encouraged and in the event that outliers are excluded, a strong rationale must 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 parameter estimates. In other circumstances, e.g., when a concentration datapoint has been excluded from the terminal elimination phase estimation, the exclusion from summary statistics may not be appropriate.

12.4.4. PK NCA parameters

In line with the analysis plan, the PK parameters listed in Table 8-2 will be estimated. In the instances where a PK parameter cannot be estimated (e.g., the terminal phase regression coefficient <0.85 or percentage of AUC0-24 extrapolation >20% or percetange of observed AUC extrapolation >20%), the term "NR" (not reported) may be used to denote that a value cannot be reported for a particular parameter; this should be considered a reserved abbreviation.

Special considerations for PK parameter estimation:

- λ_z: Elimination rate constant estimated as the slope of the linear regression of the terminal phase using the natural logarithm of the concentration-time profiles. When estimating the elimination rate constant value, the following requirements should be met:

  — To estimate the slope of the terminal phase, a minimum of 3 timepoints not including Tmax are required.

  — The regression coefficient (r^2) should be ≥0.85. Values below 0.85 may be flagged by the PK scientist (in the PK parameter file with the rationale for exclusion) or regression re-examined for possible data elimination

Failure to meet the above criteria may lead to insufficient information for the estimation of λz and therefore it will be reported along with $t_{1/2}$ as not determined (ND) with a footnote listing and the criteria provided for λ_z estimation in the statistical analysis plan.

- $AUC_{0\text{-}inf}$: calculated as $AUC_{0\text{-}last}+C^*/\lambda_z$. Where C* is the estimated concentration at the time of the last quantifiable concentration. The percentage of the area that is extrapolated from the last time point to infinity should not exceed 20% of the total $AUC_{0\text{-}inf}$. If the percentage extrapolated is greater than 20% of the total $AUC_{0\text{-}inf}$ the recommendation is not to report it and if reported, a footnote will be needed indicating that the % extrapolated was greater than 20% for all subjects or some of the subjects analyzed. The rationale for the inclusion of $AUC_{0\text{-}inf}$ when extrapolation is greater than 20% needs to be provided in the body of the report. If λ_z is ND, $AUC_{0\text{-}inf}$ will also be presented as ND, and additional parameters ($t_{1/2}$, CL_{ss}/F, V_{ss}/F) should also be reported as ND. Similar criteria apply for the calculation of the extrapolated part of $AUMC_{0\text{-}inf}$ for the extrapolated portion of $AUC_{0\text{-}inf}$.

- In this study, when calculating AUC_{tau} for Day 6, the concentrations at 24 hours postdose might be BLQ and Clast could be from 9 or 12 hours postdose. The percentage of the area extrapolated from $AUC_{0\text{-}last}$ to $AUC_{0\text{-}24}$ hours should not exceed 20% of $AUC_{0\text{-}24}$ by extrapolation. If greater than 20% of $AUC_{0\text{-}24}$ extrapolated, the recommendation is not to report it and ND will be reported with a footnote indicating that the % extrapolated for $AUC_{0\text{-}24}$ was greater than 20%. When the sample size for evaluable AUCtau is less than 8, other applicable AUC parameters, such as $AUC_{0\text{-}12}$ and $AUC_{0\text{-}last}$ will be derived.

- Geometric mean ratio (GMR) of AUCtau for RI vs healthy match is used for PK decision criteria in this study. When sample size of AUC_{tau} is less than 8, GMR based on other AUC parameters such as $AUC_{0\text{-}12}$ and $AUC_{0\text{-}last}$ will also be considered.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Pharmacology eSigned	25-Oct-2024 04:40:26
PPD	Biostatistics eSigned	25-Oct-2024 06:00:38
PPD	Global Development Lead (GDL) eSigned	25-Oct-2024 23:38:57