Statistical Analysis Plan

Study ID: 221854

Official Title of Study: A PHASE 1, 2-PART, OPEN-LABEL, FIXED-SEQUENCE STUDY EVALUATING POTENTIAL DRUG-DRUG INTERACTIONS BETWEEN GEMFIBROZIL (PART 1) OR DABIGATRAN ETEXILATE (PART 2) AND CAMLIPIXANT (BLU-5937) 50 mg TABLET IN HEALTHY PARTICIPANTS UNDER FASTING CONDITIONS

Date of Document: 27-Nov-2023 (The latest date on pg 3 is redacted as PI since it is a part of an individual's signature)

Statistical Analysis Plan for Interventional Studies (Early Phase)

Sponsor Name: Bellus Health

Protocol Number: 220265 (BUS-P1-12)

Protocol Title: A Phase 1, 2-Part, Open-label, Fixed-sequence Study Evaluating the Potential Drug-Drug Interactions between Gemfibrozil (Part 1) or Dabigatran Etexilate (Part 2) and Camlipixant (BLU-5937) 50 mg Tablet in Healthy Participants under Fasting Conditions

Protocol Version and Date: Final, 20-Jun-2023

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Authors: PPD, Principal Biostatistician

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Version	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	09-Nov-2023	PPD	Final

Approvals

I confirm that I have reviewed this document and agree with the content.

CCI Approval		
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Glossary of Abbreviations

Abbreviation	Description
AE	adverse event
AEMI	adverse event of medical interest
ANOVA	analysis of variance
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time zero to infinity, extrapolated
$AUC_{0\text{-}t}$	area under the concentration-time curve from time zero until the last observed concentration
CCI	
BLQ	below the lower limit of quantification
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
Cl/F	apparent clearance
C_{max}	maximal observed concentration
COVID-19	coronavirus 2019
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
K_{el}	terminal elimination rate constant
$K_{el\ Lower}$	the timepoint where ln-linear K_{el} calculation begins
$K_{el\ Upper}$	the actual sampling time of the last measurable concentration used to estimate the K_{el}
LLOQ	Lower limit of quantification
ln	natural logarithm
max	maximum

Abbreviation	Description
MedDRA®	Medical Dictionary for Regulatory Activities
min	minimum
N	number of subjects
n	number of observations
N/A	not applicable
NC	not calculated
NR	no result or not reportable
NS	no sample
PC	pharmacokinetic concentration
Pg-p	P-glycoprotein
PK	pharmacokinetic(s)
PT	preferred term
p-value	probability value
CCI	CCI
R^2	R-squared
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOP	standard operation procedure
$T_{½\ el}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{max}	time when the maximal concentration is observed
V_z/F	apparent volume of distribution
WHO DD	World Health Organization Global Drug Dictionary

1. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is based on the following documents:

- Protocol 220265 (BUS-P1-12) Final, dated 20-Jun-2023
- Electronic case report form (eCRF) version 1.00, dated 03-Aug-2023

The plan may change due to unforeseen circumstances; any changes made after the plan has been finalized will be documented. No revision to the SAP is required for changes which do not affect the statistical analysis methods, definitions, or rules defined in this document. If additional analyses are required to supplement the planned analyses described in the SAP, the changes and justification for the changes will be outlined in the associated clinical study report (CSR). No change will be made without prior written approval of the Sponsor.

When applicable, all methodologies and related processes will be conducted according to CCI [redacted] standard operating procedures (SOPs), as appropriate. Shells for all statistical tables, listings, and figures referred to in this SAP will be presented in a separate document.

1.1 Responsibilities

CCI [redacted] will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings (TFLs).

1.2 Timings of Analyses

The final safety, tolerability, and pharmacokinetic (PK) analysis will be completed after all participants complete the final study visit or discontinue from the study.

2. Study Objectives

- Primary Objectives:
    - To assess the effect of repeated oral doses of gemfibrozil, cytochrome P450 (CYP) 2C8 inhibitor, on the pharmacokinetics (PK) of a single oral dose of camlipixant (Part 1) administered to healthy participants.
    - To assess the effect of repeated oral doses of camlipixant on the PK of a single oral dose of dabigatran etexilate, a P-glycoprotein (P-gp) substrate (Part 2), administered to healthy participants.

- Secondary Objectives:
    - To evaluate the safety and tolerability of camlipixant when administered alone and in combination with gemfibrozil or dabigatran etexilate to healthy participants.

3. Study Description

This is a single-center, 2-part, Phase 1, open-label, fixed-sequence, drug-drug interaction (DDI) study designed to compare the PK of camlipixant when administered with and without gemfibrozil (Part 1) or to compare the PK of dabigatran when administered with and without camlipixant (Part 2) in healthy participants under fasting conditions. Participants will be enrolled to either Part 1 or Part 2. In each part, participants will receive the assigned treatment. The start of study conduct for Part 2 is independent from Part 1 study conduct.

3.1 Subject Selection

A total of 36 healthy male or female, non-smoking participants, ≥18 and ≤55 years of age, with body mass index (BMI) >18.5 and <30.0 kg/m^2, and body weight ≥50.0 kg, are planned to be enrolled in this study. In Part 1, a total of 16 participants are to be enrolled. In Part 2, a total of 20 participants are to be enrolled in Part 2.

3.2 Determination of Sample Size

It is planned to enroll up to 16 participants in Part 1 and up to 20 participants in Part 2 for participation in this study (total of 36 participants) in order to have an adequate number of participants to characterize PK in both Part 1 and Part 2. No formal sample size calculation has been made. Based on experience from previous similar studies, a total of 36 participants (16 in Part 1 and 20 in Part 2) is considered sufficient to adequately characterize the potential for a clinical DDI.

3.3 Treatment Assignment

In each study part, participants will receive the assigned treatment according to the fixed-sequence scheme described below.

In Part 1, participants will receive a single oral dose of camlipixant on Day 1, followed by a 4-day washout period. Repeated oral doses of gemfibrozil will be administered CCI [redacted] on Days 5 through 11, with co-administration of a single oral dose of camlipixant with the morning dose of gemfibrozil on Day 9.

In Part 2, participants will receive a single dose of dabigatran etexilate on Day 1, followed by a 4-day washout period. Repeated oral doses of camlipixant will be administered CCI [redacted] on Days 5 through 9 and as CCI [redacted] on Day 10, with co-administration of a single dose of dabigatran etexilate with the morning dose of camlipixant on Day 10.

The planned dose levels and regimens are summarized in Table 3.3-1, below.

Table 3.3-1: Treatment Regimen

Study Part	Study Day(s)	Treatment(s)
Part 1	Day 1	1 x 50 mg camlipixant tablet
	Days 5-11	CCI mg gemfibrozil tablet CCI mg)
	Day 9	CCI mg gemfibrozil tablet CCI mg) and 1 x 50 mg camlipixant tablet [1 hour (± 2 minutes) after gemfibrozil]
Part 2	Day 1	CCI
	Days 5-10	1 x 50 mg camlipixant tablet CCI (total daily dose 100 mg) and CCI in the morning of Day 10
	Day 10	1 x 50 mg camlipixant tablet CCI CCI

3.4 Randomization and Blinding

This study will be an open-label study due to the objective nature of the data. Thus, no randomization and blinding measures will be applied. Participants will be administered each treatment according to the fixed-sequence scheme.

3.5 Participant Withdrawal and Replacement

Participants will be advised that they are free to withdraw from the study at any time. Over the course of the study, the Sponsor and the Investigator or designee may withdraw any participant from the study for one of the reasons described below; participant withdrawal will be done in accordance with the clinical site's SOP:

- Safety reason;
- Non-compliance with protocol requirements;
- Significant protocol deviation;
- Positive pregnancy test, drug screen, cotinine test, or alcohol breath test.

Participants who withdraw or are withdrawn from the study after dosing will not be replaced. However, in the event that the number of drop-outs exceeds initial expectations, participants who withdraw or are withdrawn might be replaced at the discretion of the Sponsor. Such replacement resulting in dosing more participants than planned in this protocol would be documented in a protocol amendment.

4. Endpoints

- Primary Endpoints:
    - PK parameters: Area under the concentration-time curve from time zero to infinity, extrapolated ($AUC_{0\text{-}inf}$), area under the concentration-time curve from time zero until the last observed concentration ($AUC_{0\text{-}t}$), and maximal observed concentration (C_{max}).

- Secondary Endpoints:
    - PK parameters: Time when the maximal concentration is observed (T_{max}), terminal elimination half-life ($T_{½\ el}$), residual area, terminal elimination rate constant (K_{el}), apparent clearance (Cl/F), and apparent volume of distribution (V_z/F).
    - Safety evaluation: Adverse events (AEs), serious AEs (SAEs), AEs of medical interest (AEMIs), vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature), 12-lead electrocardiogram (ECG) recordings, physical examinations, and clinical laboratory test results, including hematology, biochemistry, coagulation, and urinalysis.

5. Analysis Populations

All participants' inclusion status into each analysis population will be determined after database lock and before the final analysis. Participants will be analyzed according to the treatment received.

5.1 Safety Population

The safety population is defined as all participants who receive at least one dose of any study drug. The safety population will be used for all safety and tolerability summaries and analyses.

5.2 Pharmacokinetic Concentration Population

Part 1:
The pharmacokinetic concentration (PC) population for camlipixant will include all participants who received at least one dose of camlipixant drug at Day 1 or Day 9 and have at least one reportable concentration.

Part 2:
The PC population for dabigatran etexilate will include all participants who received at least one dose of dabigatran etexilate drug at Day 1 or Day 10 and have at least one reportable concentration.

The PC population will be used for summary and listing of concentrations.

5.3 Pharmacokinetic Parameter Population

Part 1:
The PK parameter population will include all participants for whom the Day 1 and Day 9 PK profiles of the victim drug camlipixant can be adequately characterized, specifically, when administered alone and in combination with gemfibrozil.

Part 2:
The PK parameter population will include all participants for whom the Day 1 and Day 10 PK profiles of the victim drug dabigatran can be adequately characterized, specifically, when administered alone and in combination with camlipixant.

The PK parameters population will be used for all PK parameter summaries and analyses.

Any participant who experienced emesis during the sampling interval will be evaluated on a case-by-case basis in order to determine whether the participant will be excluded from the descriptive statistics and statistical analyses. Individual PK parameters from participant excluded from the PK parameter population will be presented in the listing but will be excluded from the descriptive statistics and statistical analyses.

Here are some aspects to be considered (but not to be limited to) when determining data availability for the PK population: inclusion and exclusion criteria, acceptable times for study days/timepoints and measurements, compliance with the dosing timing and number of doses received for camlipixant and gemfibrozil treatments (Part 1), dabigatran etexilate and camlipixant treatments (Part 2), the nature and quality of the data, withdrawal, and any protocol deviation. The final responsibility of deciding which participants are to be included or excluded lies with the Investigator and/or the Sponsor.

5.4 Pharmacogenomic Population

The pharmacogenomic population will include all participants in the safety population who had at least one pharmacogenomic measurement data available.

6. General Aspects for Statistical Analysis

6.1 General Methods

CCI [redacted] (or more recent version) will be used to perform all statistical analyses. All relevant data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by study part, subject number, and assessment date/time. All listings and summaries will be presented separately for each study part. Unless otherwise stated, the descriptions of the analyses which follow will apply to all study parts.

The following labels for treatment will be used on all tabulations where the results are displayed by treatment, in the following order:

- Part 1:
  - Camlipixant
  - Gemfibrozil
  - Camlipixant + Gemfibrozil
- Part 2:
  - Dabigatran
  - Camlipixant
  - Camlipixant + Dabigatran

For Part 1, where applicable, the treatment phases considered for the safety summaries will be:

- Camlipixant alone – from Day 1 post-dose until Day 5 pre-dose of gemfibrozil;
- Gemfibrozil alone – from Day 5 dosing until Day 9 pre-dose of camlipixant;

- Gemfibrozil + Camlipixant – from camlipixant dosing on Day 9 until end of study.

For Part 2, where applicable, the treatment phases considered for the safety summaries will be:

- Dabigatran alone – from Day 1 post-dose until Day 5 pre-dose of camlipixant;
- Camlipixant alone – from Day 5 dosing until Day 10 pre-dose of dabigatran;
- Dabigatran + Camlipixant – from dabigatran dosing on Day 10 until end of study.

6.2 Summary Statistics:

Unless otherwise stated, continuous variables will be summarized using the number of observations (n), and the statistics mean, median, standard deviation (SD), minimum (min) and maximum (max). The min and max values will be presented to the same number of digits as recorded in the eCRF, mean and median will be presented to one more significant digit than the raw data, and the SD will be presented to two more significant digits than the raw data.

Summaries of change from baseline variables will include only participants who have both a baseline value and corresponding value at the timepoint of interest. Categorical and binary variables will be summarized with frequency counts and percentages. Percentages will be rounded to one decimal place, with the denominator being the number of participants (N) in the relevant population, unless otherwise stated.

All digits will be used for PK and statistical calculations. For PK tables and listings, the final reportable results or data will be presented by rounding off to two decimal digits, except for the following situations (this applies to individual data and descriptive statistics):

- K_{el} and R-squared (R^2) adjusted data shall be rounded off to four decimals.
- PK parameters related to time, such as T_{max}, the timepoint where ln-linear K_{el} calculation begins ($K_{el\ Lower}$), and the actual sampling time of the last measurable concentration used to estimate the K_{el} ($K_{el\ Upper}$), must be reported with the same precision as the actual sampling time, rounded to three decimals.
- Concentration versus time data, as well as C_{max} shall be reported as they appear in the corresponding dataset.
- Ratios and 90% CIs, intra- and inter-subject coefficients of variation (CV), and CV (%) will be presented to two decimal places.

Only data from protocol scheduled (“nominal”) visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables (unless they were used as baseline) but will be included in the listings.

6.3 Key Definitions

Baseline:

Unless stated otherwise, baseline will be determined for each subject and will be defined as the last non-missing measurement (including repeated and unscheduled assessments) obtained prior to the first study drug administration. Post baseline will be considered as all measurements collected after first study drug administration. "Unknown", "Not Done", "Not Applicable" and other classifications of missing data will not be considered when calculating baseline observations unless the finding is a valid categorical observation.

Study Day:

Study day will be calculated using first study drug administration date as the reference date. If the date of interest occurs on or after the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date) + 1. If the date of interest occurs prior to the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date). There will be no study Day 0.

Prior and Concomitant Medication:

Prior medications are defined as medications that start and stop prior to the first dose of study drug. All other medications will be defined as concomitant medications including those that start prior to the first dose of study drug and continue thereafter. Any medications with an unknown start or stop date will be assumed to be concomitant medications unless a partial start or stop date indicates otherwise.

6.4 Missing Data

There will be no imputation for missing data, unless otherwise specified. Missing data shall be presented in subject listings as either "-" (unknown or not evaluated) or "N/A" (not applicable), with the corresponding definition in the footnotes. Missing descriptive statistics, or probability values (p-values), which cannot be estimated shall be presented as "-".

The listings will include the reported date/time, and the imputations rules below will be used if needed to classify as prior or concomitant medication, to determine if an AE is non-TEAE or TEAE, or to attribute to a particular treatment for the summaries.

For inclusion in concomitant medication tables, incomplete start and stop dates on the eCRF will be imputed as follows:

- If the start date is incomplete, the following rules will be applied:
    - Missing day: Assume the first day of the month; however, if the partial date and the date of first study drug administration lie within the same month and year and the date of first study drug administration is not after the stop date of the event/medication, set to the date of study drug administration. Otherwise, set to the stop date of the event/medication.

  - Missing day and month: Assume January 1st; however, if the partial date and the date of first study drug administration lie within the same year and the date of first study drug administration is not after the stop date of the event/medication, set to the date of first study drug administration. Otherwise, set to the stop date of the event/medication.
  - Missing day, month, and year: Assume date of first study drug administration if it is not after the stop date for the event/medication. Otherwise, set to the stop date for the event/medication.

- If the stop date is incomplete, the following rules will be applied:
  - Missing day: Assume the last day of the month
  - Missing day and month: Assume the last day of the year
  - Missing day, month, and year: Assume that the event/medication is continuing
  - In the case of the death of a subject, and if the imputed end date is after the date of death, the end date will be imputed as the date of death.
- If the stop date is incomplete, imputed end date will be used instead of reported end date.

AEs without an onset date or time, or AEs with an onset date on the date of first study drug administration but without an onset time, will be defined as treatment-emergent, unless an incomplete date (e.g., month and year) clearly indicates that the event started prior to administration of first study drug administration, or the AE stop date indicates that the event started and stopped prior to the first study drug administration.

In the case of withdrawal of consent, all data from participants who withdraw from the study will be included in all summaries up to the time of withdrawal. For all other withdrawals, all data captured will be included in the safety summaries.

For PK analysis, only observed concentration data will be used in the data analysis except for concentration values below the lower limit of quantification (BLQ); see section 8.1. No attempt will be made to extrapolate or interpolate estimates for missing data.

7. Study Population

7.1 Subject Disposition

The number of participants who were screened, enrolled, dosed, completed the study, and discontinued from the study, along with reasons for discontinuation, will be summarized. The data will be presented by study part, treatment, and overall (frequency counts and the percentage) and presented by participant in a data listing.

7.2 Protocol Deviations

Participant data will be examined for evidence of protocol deviations. All protocol deviations will be categorized (as critical, major or minor and important/non-important as per ICH E3 definition) and presented by participant in a data listing.

7.3 Inclusion and Exclusion Criteria

All recorded inclusion and exclusion criteria status will be presented by participant in a data listing. Each participant's inclusion or exclusion from each analysis population will also be presented in a data listing.

7.4 Demographics and Other Baseline Characteristics

All demographics and baseline body measurements will be summarized by study part and treatment for the safety, and PC and PK parameter populations (if different from safety population). All demographic characteristics will be presented by participant in a data listing.

Descriptive statistics (n, mean, SD, min, median, and max) will be calculated for continuous variables using the last results obtained (scheduled and unscheduled) prior to the first study drug administration. Frequency counts and percentages will be tabulated for categorical and binary variables.

7.5 Medical History

Medical history will be presented by participant in a data listing. The Medical Dictionary for Regulatory Activities (MedDRA), Version 26.0 (or more recent version) will be used to classify medical history terms by system organ class (SOC) and preferred term (PT). Output data will include the MedDRA version used in the study.

7.6 Medications

Medications taken by participants that start and stop before first dosing will be documented as prior medications and whereas medications taken by participants after dosing (including those that start prior to the first dosing and continue thereafter) up to follow-up phone call will be documented as concomitant medications. Prior and concomitant medications will be presented by participant in a data listing. The World Health Organization Global Drug Dictionary (WHO DD), Version B3, March 2023 (or more recent version) will be used to classify medications by anatomical therapeutic chemical (ATC) classification code (3rd level) and preferred name. When 3rd level classification code is not available, 3rd level classification will be used instead. Output data will include the WHO DD version used in the study.

7.7 Drug, Cotinine, and Alcohol Screens

The results of urine drug, urine cotinine, and alcohol breath screen tests will be presented by participant in data listings.

7.8 Pregnancy Screening

Pregnancy tests will be performed for all females. The follicle-stimulating hormone (FSH) level will be tested in postmenopausal females only. All results will be presented by participant in data listings.

7.9 Additional Screening Tests

The results of serology tests and coronavirus 2019 (COVID-19) tests will be presented by participant in data listings.

8. Pharmacokinetic (PK) Analyses

CCI [redacted] or more recent version) will be used for all PK analyses. Statistical analyses will be performed using CCI [redacted]. Bioanalysis of all samples should be completed prior to the initiation of the PK and statistical analyses.

All PK concentration and PK parameter analyses will be conducted on the PK concentration population and PK parameter population, respectively.

PK concentrations, actual times, date/time of study drug administration and sample collection will be listed for the PK concentration population by nominal time for each study part, study day, participant and treatment, and summarized for the PC population for each study part by treatment and timepoint, using descriptive statistics (n, number of BLQs, arithmetic and geometric means, SD, geometric SD, CV%, geometric mean CV%, min, max, and median). Individual, mean (±SD) concentration and overlay of individual plasma concentration versus time profile will be presented for both linear and semi-logarithmic scales for each study part by treatment for the PC population. For ease of presentation, actual and nominal sampling times will be used to present results for individual and mean figures, respectively.

PK parameters will be presented in data listings and summarized in tables for each study part by study day and treatment (or day), using descriptive statistics (n, arithmetic mean, SD, %CV, geometric mean, geometric SD, geometric mean CV%, minimum, median, and maximum).

8.1 Data Handling

8.1.1 PK Parameters Calculation Rules

For all PK analyses, concentration values BLQ that occur before the first measurable concentration of the study drug will be set to “0.00”; BLQ values that occur after first measurable concentration will be set to “missing”. No imputations will be made on BLQ concentrations.

Invalid concentration values (due to bioanalytical or clinical issues) that occur prior to dosing will be replaced by “0.00”. Invalid concentration values that occur after dosing will be set to “missing” for tabulation, graphical representation, and calculation purposes.

The actual clock time for dosing and the actual clock time for each PK sample collection will be recorded. For all sampling times, the actual sampling duration will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times, expressed in hours and rounded off to three decimal digits, will be used to calculate the PK parameters. Pre-dose sampling times will always be reported as zero (0.000), regardless of the time difference. Nominal sampling times will be used in concentration tables and mean graphs, while actual sampling times for post-dose samples will be used in the individual graphs. Actual sampling times for post-dose samples also will be used for PK parameter derivation, unless the actual sampling time is missing, in which case, the nominal time will be used.

8.1.2 Data Presentation Rules

Non-measurable values reported in the plasma concentration data (i.e. values that are BLQ), will be entered as zero for the determination of summary statistics with the exception of geometric mean, geometric SD, and geometric CV%, where BLQ values will be imputed as half the lower limit of quantification (LLOQ) value. This also applies to any concentrations that are defined as PK parameters. Data recorded as "No Result" or "Not Reportable" (NR), "Not Calculated" (NC) or "No Sample" (NS) will be handled as missing (i.e. no assumption will be made about the actual concentration).

8.2 Pharmacokinetic (PK) Parameters

The PK parameters shown in Table 8.2-1 below, will be calculated, whenever possible, by standard non-compartmental methods for camlipixant (Part 1) and dabigatran (free and total) (Part 2):

Table 8.2-1: PK Parameters

Parameter	Definition
AUC_{0-t}	area under the concentration-time curve from time zero until the last observed concentration
AUC_{0-inf}	area under the concentration-time curve from time zero to infinity (extrapolated)
Cl/F	apparent clearance, calculated as Dose/AUC_{0-inf}
C_{max}	maximal observed concentration
K_{el}	terminal elimination rate constant
Residual area	percentage of AUC_{0-inf} due to extrapolation from the time of the last observed concentration to infinity, calculated as [1 - (AUC_{0-t}/AUC_{0-inf})] x 100
T_{max}	time when the maximal concentration is observed
$T_{½\ el}$	terminal elimination half-life, calculated as ln(2)/K_{el}
V_z/F	apparent volume of distribution, calculated as Dose/(K_{el} x AUC_{0-inf})

Additional PK parameters may be calculated as deemed necessary.

The following information will be presented for gemfibrozil (Part 1): pre-dose concentrations on the morning of Days 5, 6, 7, 8, and 9. The following information will be presented for camlipixant (Part 2): pre-dose concentrations on the morning of Days 5, 7, 8, 9, and 10. These data will be listed. Any additional PK data will be presented as appropriate.

Note: Area under the concentration-time curve (AUC) parameters will be calculated using the linear up log down trapezoidal method, where the linear trapezoidal rule is used any time the concentration data are increasing, and the logarithmic trapezoidal rule is used any time that the concentration data are decreasing.

Note: K_{el} will be the negative of the estimated slope of the linear regression of the ln-transformed plasma concentration versus time profile in the terminal elimination phase. The best fit method will be used to calculate the K_{el} from at least three concentration data points, excluding C_{max}. R^2 adjusted, the goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of K_{el} must be ≥ 0.8. If the K_{el} cannot be measured (e.g.: there are fewer than three non-zero concentrations in the terminal elimination phase), the PK parameters derived from K_{el} will be presented in listing(s) but excluded from descriptive statistics in tables.

All the derived parameters (i.e., $AUC_{0\text{-}inf}$, $T_{½\ el}$, Cl/F and V_d/F) will be also flagged accordingly. The timepoint where ln-linear K_{el} calculation begins ($K_{el\ Lower}$), the actual sampling time of the last measurable concentration used to estimate the K_{el} ($K_{el\ Upper}$), and the R^2 adjusted for the ln-linear regression for the calculation of the elimination rate constant will be reported. If the Residual area is greater than 20%, the individual result should be flagged in the listing, and $AUC_{0\text{-}inf}$ removed from descriptive statistics and statistical analyses.. The derived parameters (i.e., $AUC_{0\text{-}inf}$, Cl/F and V_d/F) will be also flagged accordingly in the listing.

Some PK parameters may not be calculated for all or some subjects, at the discretion of the CCI pharmacokineticist if the concentration data is not deemed to be amenable to evaluation. Explanations for PK parameters that could not be estimated will be provided in the CSR.

8.3 Assessment of Gemfibrozil Effect (Part 1)

CCI

CCI [redacted]

8.4 Assessment of Camlipixant Effect (Part 2)

CCI [redacted]

PK parameters for free dabigatran will also be calculated as above and presented as supportive data.

8.5 Attainment of Steady State

As supportive data, to assess attainment of steady state, descriptive statistics on pre-dose concentrations of gemfibrozil in Part 1 (Days 7, 8, and 9) and camlipixant in Part 2 (Days 8, 9, and 10) will be presented. If necessary, additional data may be presented.

9. Pharmacogenomic Analyses

CCI [redacted]

Other possible exploratory markers may be considered as deemed necessary. If applicable, a data listing will be provided for the pharmacogenomic population.

10. Safety

Safety and tolerability analysis will be performed for all subjects in the safety population. No inferential statistical analysis of safety data is planned.

10.1 Exposure

Study drug administration will be listed by participant.

10.2 Adverse Events (AEs)

AEs will be coded using MedDRA, Version 26.0 (or more recent version). Output data will include the MedDRA version used in the study. AEs will be grouped by SOC and PT and summarized by actual treatment phase. The summary tables will present the number and percentage of total participants and number of events by SOC and by PT.

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), defined as AEs that commence on or after the time of first study drug administration. Any AE that first occurs pre-dose but worsens in severity after the first study drug administration will also be considered a TEAE. TEAEs will be attributed to the appropriate treatment phase as defined previously based on their onset date and time. TEAEs continuing after administration on the next treatment phase will be evaluated on a case-by-case basis (e.g: If there was no worsening in severity, it would be attributed to the treatment phase that coincides with the AE onset. If there was worsening in severity, it would be attributed to the treatment phase during which the worsening of the AE has occurred. The relationships could also be considered in this determination).

The relationships for each TEAE will be evaluated separately for the two drugs administered during the treatment phase of respective study part and will be classified according to the study protocol as definite, possible, probable, unlikely or not related to respective study drugs. The severity of TEAEs will be classified as mild, moderate or severe.

The number and percentage of subjects experiencing TEAEs and the number of TEAEs will be tabulated. Subjects who experience the same TEAE (in terms of MedDRA PT) more than once will only be counted once, however, the total number of events will be counted per category. This also applies to sub-categories (e.g.: SOC, PT) displayed in the summaries.

The following summaries will be presented:

- Overall summary of TEAEs

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and relationship to each study drug
- Serious AEs by SOC and PT
- AEMIs by SOC and PT

AEMIs for this study include the following, but not limited to:

- CCI [redacted]
- CCI [redacted]
- CCI [redacted].

All AEs will be listed. The following listings will be included: Non-TEAEs, TEAEs, serious AEs, AEMIs and CCI [redacted]

10.3 Laboratory Evaluations

Laboratory data, including biochemistry, hematology, coagulation, and urinalysis, will be listed by participant and summarized overall separately by study day. Observed values and changes from baseline will be presented.

In addition, a shift table representing the categorical change (low, normal, high) from baseline to each post baseline study day will be presented.

The categorical results of urinalysis will be summarized overall as number and percentage separately by study day.

Abnormal results will be flagged in the listings.

If more than one clinical laboratory is used, a formula that takes into consideration the relative normal ranges of each test of the laboratories will be utilized to normalize these data[a]. The conversion formula used for each test will depend on the typical distribution of the normal range for the test[b]. Prior to applying these formulas, units will be adjusted, as necessary. The laboratory which has the most results for each parameter will be considered primary in the formulas.

10.4 Vital Signs

Vital sign measurements will be listed by participant and summarized overall separatelyby study day. Observed values and changes from baseline will also be presented.

In addition, a shift table representing the categorical change from baseline to each post baseline study day will be presented.

Abnormal results will be flagged in the listings. The normal ranges as per clinical SOP (refer to the table below) will also be included in the listing and the summary tables.

Vital Sign Parameters	Normal Range (inclusive)
Systolic blood pressure	90 to 140 mmHg
Diastolic blood pressure	50 to 90 mmHg

Hearth rate	50 to 100 beats/min
Respiratory rate	8 to 20 breaths/min
Oral temperature	35.8 to 37.6 °C

10.5 Electrocardiograms (ECGs)

ECG values will be listed by participant and summarized overall separately by study day. Observed values and changes from baseline will be presented.

In addition, a shift table representing the categorical change in overall interpretation (normal, abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline study day will be presented.

Abnormal results will be flagged in the listings. The normal ranges as per clinical SOP (refer to the table below) will also be included in the listing and the summary tables.

ECG Parameter	**Normal Range (inclusive)**
Hearth rate	50 to 100 beats/min
PR interval	120 to 200 msec
QRS interval	70 to 110 msec
QT interval	≤ 450 msec
QTcF interval	≤ 450 msec

10.6 Physical Examination

The results of physical examinations will be listed by participant. Abnormal results will be flagged in the listings.

11. Changes from Analysis Planned in the Protocol

No changes were made to planned analyses.

12. Programming Considerations

All TFLs and statistical analyses will be generated using [redacted] (or more recent version) [redacted] software in accordance with Food and Drug Administration (FDA) guidelines. [redacted] (or more recent version) [redacted] will be used for all PK analyses. This software was validated by [redacted] in compliance with US 21 CFR Part 11 regulation.

12.1 General Considerations

- One [redacted] program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in rich text format that can be manipulated in MS Word.
- Numbering of TFLs will follow International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E3[c].

12.2 Table, Listing, and Figure Format

12.2.1 General

- TFLs will be produced in landscape format. The orientation may be changed to portrait, as necessary to allow additional rows to be presented.
- TFLs will be produced using the Times New Roman font, size 9. The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all four sides.
- Unless otherwise specified, TFLs will be in black and white (no color).
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used; see below.
- Standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- TFLs will be produced using sentence case, unless otherwise specified.

12.2.2 Headers and Footers

- Times New Roman font, size 9 will be used for TFL headers and footers.
- All outputs will have the following at the top of each page: Bellus Health Protocol: 220265 (BUS-P1-12).
- All outputs will have page x of y at the top or bottom right corner of each page. TFLs are individually paginated in relation to total length (i.e., the page number appears sequentially as page x of y, where y is the total number of pages in the output).
- The data source will be included in the footer, as applicable.
- The date and time the output was generated will appear, along with the program name, at the bottom of each page.

12.2.3 Display Titles

Each display title includes the appropriate designation ("Table", "Figure", or "Listing") and a numeral, along with a descriptive name (e.g., Table 14.1-1 Subject Enrollment and Disposition). The analysis population should also be included in each title. ICH E3 numbering is strongly recommended, but Sponsor preferences are obtained for final determination. Display titles are left aligned, single spaced, and presented in title case. A solid line spanning the margins will separate display titles from column headings.

12.2.4 Column and Row Headings

- Column and row headings are presented in title case, with the exception of complete sentences, which will be presented in sentence case.
- In efficacy or pharmacokinetic tables, the variable (or characteristic) column will be on the far left, followed by the group columns and overall column (if applicable). P-values may be presented under the overall column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- Column and row headings will include "Unit" for numeric variables, as appropriate.
- Column and row headings will include the number of subjects in the analysis population for each group, presented as (N=xx). This is different from the 'n' used in descriptive statistics, which represents the number of observations.
- The order of treatments in the tables and listings will be placebo first, in placebo-controlled studies, and active comparators first, in active comparator trials, with "overall" (if applicable) last.

12.2.5 Body of the Data Display

12.2.5.1 General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left aligned.

- Whole numbers (e.g., counts) or numerical data are centered aligned.

12.2.5.2 Table Conventions

- Units will be included, where available.
- If the categories of a parameter are ordered, all categories between the maximum and minimum category are presented in the table, even if n=0 for all groups in a category between the minimum and maximum level for that parameter. See the example for the frequency distribution for symptom severity below. If percentages are presented in these tables, 0% will not be presented, therefore, counts of zero will be presented as "0", not "0 (0%)".

Severity Rating	N
Severe	0
Moderate	8
Mild	3

- Where the categories are not ordered (e.g., Reason for Discontinuation), only those categories for which there is at least one subject represented will be included.
- An "Unknown" or "Missing" category will be added to each parameter for which information is unavailable for one or more subjects.
- P-values are presented in the format: 0.xxxx, where xxxx is the value. If the p-value is less than 0.0001, it will be presented as "<0.0001." If the p-value is >0.999, it will be presented as ">0.999."
- Percentage values are presented in parentheses with no spaces, one space after the count [e.g., 7 (12.8%), 13 (5.4%)]. Unless otherwise noted, for all percentages, the denominator will be the number of subjects in the analysis population for the group that has an observation. Percentages after zero counts are not displayed, and percentages equating to 100% are presented as "100%" (without decimal places).
- Unless otherwise noted, tabular displays of data for medical history, prior/concomitant medications, and AEs data are presented in alphabetical order.
- The percentage of subjects is typically calculated as a proportion of the number of subjects assessed in the relevant group (or overall) for the analysis population presented; however, careful consideration is required in many instances, due to the complicated nature of selecting the denominator. Details of this will be presented in footnotes or programming notes.
- In categorical summaries where a subject can be included in more than one category, a footnote or programming note will specify whether the subject is included in the summary statistics for all relevant categories or just one category and the criteria for selecting the category.
- Where a category with a subheading (such as SOC) must be split over more than one page, present the subheading followed by "(cont.)" at the top of each subsequent page. The overall summary statistics for the subheading will only be presented on the first relevant page.

12.2.5.3 Listing Conventions

- Unless otherwise noted, listings will be sorted for presentation in order of subject number, visit/collection day, visit/collection time, and parameter (alphabetic order).
- Dates are printed in CCI [redacted] (e.g., "ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (e.g.,--JUL2000). Dates that are missing because they are not applicable for the subject are presented as "N/A", unless otherwise specified.
- All observed time values are presented using a 24-hour clock HH:MM:SS or HH:MM format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included, where available.

12.2.5.4 Figure Conventions

- For safety figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values will be displayed on the Y-axis, unless otherwise specified.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- Units will be included, where available.

12.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left aligned, with single spacing, immediately below the solid line beneath the data display.
- Informational footnotes begin with "Note:". Reference footnotes begin with a reference number or letter (e.g., 1, 2, 3 or a, b, c).
- Each new footnote starts on a new line, where possible.
- Subject-specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or data listing. If more than six lines of footnotes are planned, a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

13. Quality Control

CCI [redacted] programs are developed to produce outputs such as analysis data sets, summary tables, data listings, figures, and statistical analyses. These are developed and undergo quality control in accordance with the latest versions of SOP 2800[d] and SOP 2801[e].

14. Reference List

[a]Chuang-Stein, C., PhD, Research Support Biostatistics Unit, 9164–32–2, The Upjohn Company, Kalamazoo, Michigan. (1992). Summarizing Laboratory Data with Different Reference Ranges in Multi-Center Clinical Trials. Drug Information Journal, 26(1), 77-84. doi:10.1177/009286159202600108

[b]Karvanen, J., Signal Processing Laboratory, Helsinki University of Technology, Helsinki, Finland. (2003). The Statistical Basis of Laboratory Data Normalization. Drug Information Journal, 37(1), 101-107. doi:10.1177/009286150303700112

[c]International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (1996). Guideline for Industry, Structure and Content of Clinical Study Reports (ICH E3).

CCI [redacted]

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