Statistical Analysis Plan Amendment 2

Study ID: 221852

Official Title of Study: A phase 1, open-label study to investigate the pharmacokinetics and safety of camlipixant in male and female participants aged 18-75 years of age with hepatic impairment compared to matched healthy participants with normal hepatic function

NCT number: NCT06222892

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Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A phase 1, open-label study to investigate the pharmacokinetics and safety of camlipixant in male and female participants aged 18-75 years of age with hepatic impairment compared to matched healthy participants with normal hepatic function

Study Number: 221852

Compound Number: GSK5464714, camlipixant

Abbreviated Title: A study to investigate the pharmacokinetics and safety of camlipixant in male and female healthy participants and participants with hepatic impairment aged 18-75 years of age.

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	ID
IND	142905

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP 1.0	22 May 2024	Protocol Amendment 1 Final (29 Apr 2024)	Not Applicable	Original version
SAP 2.0	10 Dec 2024	Protocol Amendment 1 Final (29 Apr 2024)	Interim analysis decision of part 2 enrolment added in section 4.6. Add section 7 of changes from the planned analysis	Based on Part 1 Interim Analysis Summary & Decision (11 Jun 2024), mild HI participants and matched healthy control to mild HI participants will not be enrolled in part 2.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 221852. Details of the planned interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of hepatic impairment (HI) on the Pharmacokinetics (PK) of camlipixant in participants with HI compared to healthy control participants.	• $AUC_{(0-\infty)}$ and C_{max}.
Secondary	
• To evaluate the safety and tolerability of camlipixant in participants with HI compared to healthy control participants.	• Incidence of Adverse Events (AE), Serious Adverse Events (SAE) and Adverse Events of Special Interest (AESI). Incidence of participants with clinically relevant changes in clinical laboratory tests, electrocardiogram (ECG) and vital signs assessments.
• To assess the effect of HI on other PK parameters of camlipixant in participants with HI compared to healthy control participants.	• T_{max}, $t_{½}$, CL/F, and Vz/F.
CCI [redacted]	

$AUC_{(0-\infty)}$: Area under the concentration-time curve from 0 extrapolated to infinity, CCI [redacted] CCI [redacted] CCI [redacted], C_{max}: Maximum observed concentration, HI: Hepatic impairment, PK: Pharmacokinetics, T_{max}: Time of occurrence of C_{max}, $t_{½}$: apparent terminal phase

half-life, CCI [redacted]
CCI [redacted]

Primary Estimand

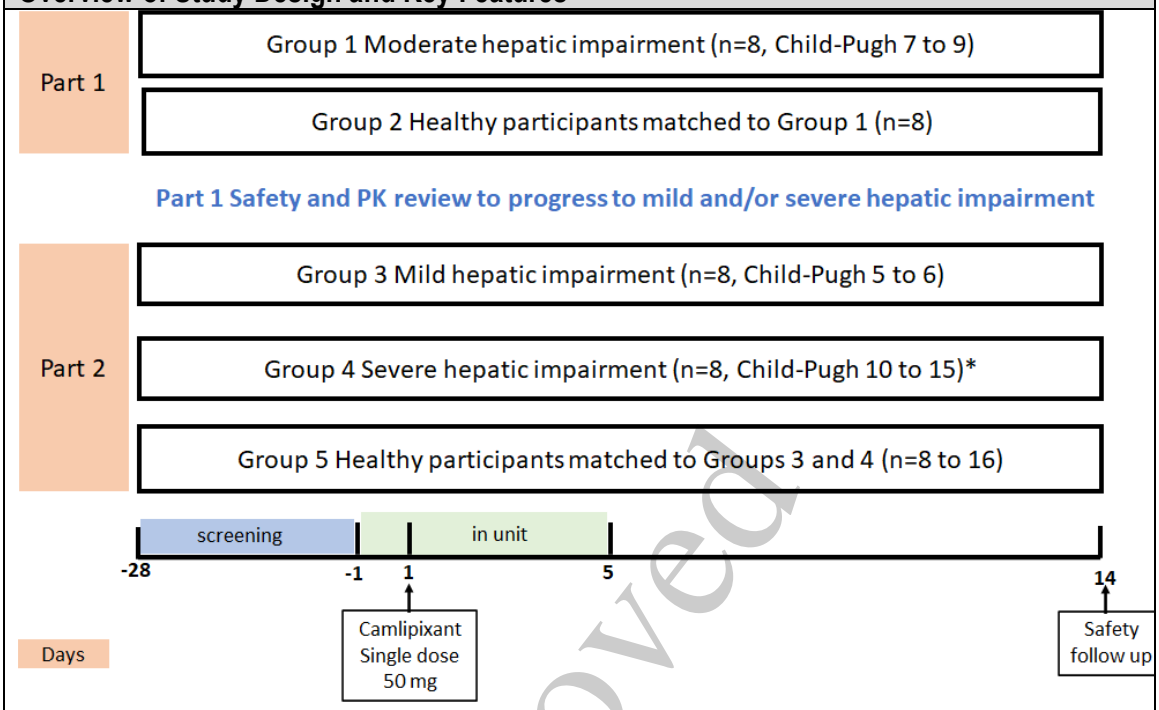
The geometric mean of PK parameters area under the concentration-time curve from time zero extrapolated to infinity [$AUC_{(0-\infty)}$] and maximum observed plasma concentration [C_{max}] in adult participants with HI vs. adult healthy control participants receiving 50 mg (or 25 mg in Scenario 3 defined in section 4.1 of protocol) of camlipixant where issues that affect exposure to study drug such as emesis, dosing errors, or important protocol violations will be handled with a while on-treatment strategy.

The primary PK estimand is described by the following attributes:

- Population: male and female adult participants 18 to 75 years of age inclusive with mild, moderate, or severe HI vs. healthy male and female adult participants 18 to 75 years of age inclusive.
- Treatment condition: single dose of 50 mg camlipixant or a single dose of 25 mg in the severe hepatic impairment group in Scenario 3.
- Variable: $AUC_{(0-\infty)}$ and C_{max}.
- Summary measure: ratio of the geometric mean of each HI group vs. matched Healthy participants for $AUC_{(0-\infty)}$ and C_{max}.
- Intercurrent events: issues that affect exposure to study drug such as emesis, dosing errors, or important protocol violations will be handled with a while on-treatment strategy. Interest lies in estimating the effect of HI on the PK of camlipixant, when patients receive the single dose of camlipixant and while patients are sufficiently compliant with camlipixant to accurately assess exposure.

1.2. Study Design

Overview of Study Design and Key Features



*In Scenario 3, severe HI participants may receive a single dose of 25 mg Camlipixant on Day 1.

Design Features	• Phase 1, open-label, multi-center (3 planned), non-randomized, parallel-group, single dose, adaptive study in adults with moderate (Part 1) and mild and/or severe HI (Part 2) and matched healthy control participants with normal hepatic function (Part 1 and 2). • In Part 1, enrollment will begin for participants with moderate HI (Child-Pugh score of 7-9; n=8). Healthy control participants (n=8) will be matched in gender, race, age (±10 years), and weight (±20%) to participants with moderate HI. All participants will receive 50 mg of camlipixant as a single oral dose in the fasted state. Following safety and PK data review by the study team of a minimum of n=6 in each group of Part 1 a decision will be made about which HI category to be dosed on Part 2 according to the criteria in section 9.4 of protocol. • In Part 2, a single oral dose of camlipixant 50 mg (or 25 mg for severe HI in Scenario 3) will be administered to the selected group(s) and their matched healthy control participants in a fasted state. If the camlipixant dose is reduced to 25 mg for the severe HI participants, the matching healthy controls to the severe HI group will also be dosed with 25 mg. • In scenario 2 (defined in section 4.1 of the protocol), healthy participants in Group 5 can be matched to both mild (Group 3) and severe (Group 4) HI participants. In scenario 3 (defined in section

Overview of Study Design and Key Features	
	4.1 of the protocol), healthy participants can only be matched to either a mild or severe HI participant.
Study intervention	• Camlipixant 50/25 mg tablet
Study intervention Assignment	• All participants will receive a single 50 mg oral dose of camlipixant in a fasted state (or 25 mg for severe HI in scenario3)
Interim Analysis	• An interim analysis of the primary endpoint will be conducted following completion of Part 1 of the study, with possible progression to Part 2. Please refer to Section 4.7 for more details.

2. STATISTICAL HYPOTHESES

There is no formal research hypothesis that will be statistically tested in this study.

2.1. Multiplicity Adjustment

- There is no multiplicity adjustment requirement.

3. ANALYSIS SETS

For analyses purposes, the following populations are defined:

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Enrolled	• All participants who entered the study (who received study intervention or underwent a post-screening procedure) • NOTE: screening failures (who never passed screening even if re-screened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled Analysis set as they did not enter the study.	• Study Population
Assigned	• All participants who were assigned to study intervention in the study.	• Study Population
Safety	• Participants who received study intervention.	• Safety
Pharmacokinetic (PK)	• All participants in the safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK

Analysis Set	Definition / Criteria	Analyses Evaluated
	• Data will be reported according to the actual study intervention.	

4. STATISTICAL ANALYSES

4.1. General Considerations

Schedule of activities are outlined in protocol section 1.3.

4.1.1. General Methodology

Participants who prematurely withdrew from study may be replaced at the discretion of the sponsor if they were not discontinued due to AEs or SAEs.

Data will be listed and summarized for each cohort of the study according to GSK reporting standards wherever applicable. Unless otherwise specified, descriptive summaries for untransformed continuous variables will include n, mean (95%CI; PK parameters only), standard deviation (SD), CV% (PK parameters only), median, minimum, and maximum. For Tmax, only median, minimum and maximum will be reported. CI and CV% will not be reported for safety summaries. Parameters which are log-transformed prior to analysis will be summarized using n, geometric mean (95% CI), SD (Log), geometric between subject CV (CVb%) and arithmetic mean (95% CI), SD, median, minimum, and maximum. For the geometric ratio and mean difference, a 90% CI will be presented. Categorical data will be summarized as number and percentage of participants in each category.

All data displays will follow the GSK integrated data standards library (IDSL) display standards. Final analyses will be performed after the completion of the study and final dataset authorization.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of endpoints

Pharmacokinetic analysis will be performed by or under the direct auspices of Clinical Pharmacology Modelling & Simulation, GSK. Pharmacokinetic parameters will be calculated by standard CCI [redacted] analysis according to current working practices and using the currently supported version of *Phoenix WinNonlin.* All calculations of CCI [redacted] parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
$AUC_{(0-\infty)}$	Area under the concentration-time curve from time zero extrapolated to infinity, using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. $AUC_{(0-\infty)} = AUC_{(0-t)} + C_{(t)}/\lambda_z$ where $C_{(t)}$ is the last quantifiable concentration and λ_z is terminal phase elimination rate constant. AUC_{ex} = The percentage of $AUC_{(0-\infty)}$ obtained by extrapolation (%AUC_{ex}) will be calculated as: $(AUC_{(0-\infty)} - AUC_{(0-t)}) / AUC_{(0-\infty)} \times 100$ It is acceptable to include data from profiles with >20% extrapolated as long as at least 80% of the profiles in the study have <20% of the $AUC_{(0-\infty)}$ as extrapolated area. It is unacceptable to use $AUC_{(0-\infty)}$ data if >40% of the AUC has been extrapolated.
C_{max}	Maximum observed concentration, determined directly from the concentration-time data.

4.2.2. Main analytical approach

The primary PK analyses will be based on the PK Analysis Set unless otherwise specified. Plasma camlipixant concentration-time data will be listed for each participant and standard summary statistics will be calculated (i.e. N [number of subjects in the cohort), n [number of evaluable values), No. imputed [number of values imputed), arithmetic mean, 95% CI, standard deviation, CV%, median, minimum and maximum) by cohort (healthy versus hepatic impairment group) and planned sampling time.

Individual, mean and median plasma camlipixant concentration-time profiles will be plotted for each cohort on both linear and log-linear scales. A reference line indicating the lower limit of quantitation (LLOQ) will be included in plots. For handling concentrations which are below the limit of quantitation (i.e. NQ, non-quantifiable) the following will be applied:

For plasma concentration data, concentrations below the limit of quantification (NQs) at the beginning of a participant profile (i.e. before the first incidence of a measurable concentration) will be assigned to be zero. For NQs at the end of the participant profile (i.e. after the last incidence of a measurable concentration):

- for individual plots and pharmacokinetic analyses, these will be dropped (set to missing)
- for summary statistics, these will be set to 0
- Individual NQs which fall between 2 measurable concentrations will be set to missing

Strategy for Intercurrent (Post-Randomization) Events

Issues that affect exposure to study drug such as emesis, dosing errors, or important protocol violations will be handled with an on-treatment strategy i.e., use available data up until the intercurrent event. Interest lies in estimating the effect of HI on the PK of camlipixant, when patients receive the single dose of camlipixant and while patients are sufficiently compliant with camlipixant to accurately assess exposure.

Strategy for Missing Data

No Sample (NS), No Result, i.e. lost sample (NR), Insufficient Sample (IS) and Not Analyzed (NA) are truly missing and should be set to missing for reporting including summary statistics and graphical presentation.

4.2.2.1. Statistical Analyses / Methods

After log transforming PK parameters $AUC_{(0-\infty)}$ and C_{max} for camlipixant, they will be analyzed using a mixed effects model with the cohort included as a fixed effect and a matching variable (indicating the matching of each healthy participant for each impairment participant) as a random effect. This matching variable will be categorical taking values 1, …., k where k is the total number of matched sets.

Statistical Methodology Specification:

Endpoint / Variables
• Log transformed $AUC_{(0-\infty)}$, and C_{max} for camlipixant plasma concentrations. If there is not sufficient data to analyze $AUC_{(0-\infty)}$ with a linear model, then $AUC_{(0-t)}$ will be calculated and analyzed.
Model Specification
CCI [redacted]

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[redacted]

Subgroup Analyses
• Not applicable.
Sensitivity and Supportive Analyses
• Not applicable.

Summary statistics (arithmetic mean, geometric mean, median, 95% CI [arithmetic and geometric], SD [arithmetic and on ln-scale], minimum, maximum, and CVb% [SQRT (exp (SD^2) – 1) x 100]) for plasma camlipixant PK parameters will be summarized by cohort.

4.3. Secondary Endpoints Analyses

4.3.1. Secondary endpoints

4.3.1.1. Definition of endpoints

Safety Endpoints:

- Incidence of AEs, SAEs, AESIs.
- Incidence of participants with clinically relevant changes in clinical laboratory tests, ECG and vital signs assessments.

PK Endpoints:

Pharmacokinetic parameters will be calculated by standard CCI [redacted] analysis according to current working practices and using the currently supported version of *Phoenix WinNonlin*. All calculations of CCI [redacted] parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
$t_{1/2}$	Apparent terminal phase half-life calculated as: $t_{½} = \ln 2 / \lambda z$
CL/F	Apparent clearance calculated as: $CL/F=Dose/AUC_{(0-\infty)}$ If $AUC_{(0-\infty)}$ cannot be accurately estimated, CL/F and Vz/F will not be calculated.
T_{max}	Time of occurrence of C_{max}, determined directly from the concentration-time data.
Vz/F	Apparent terminal phase volume of distribution calculated as: $Vz/F=(CL/F)/ \lambda z$

NOTES:

- Additional parameters may be included as required.

4.3.1.2. Main analytical approach

Safety Analysis:

All safety analyses will be performed on the Safety Analysis Set.

Analyses related to safety endpoints (AEs, ECGs, vital signs, and clinical laboratory tests) are described in section 4.5.

PK Analysis:

Summary statistics will be summarized by cohort based on the PK Analysis Set. For T_{max}, only median, minimum and maximum will be generated. For $t_{1/2}$, CL/F, and Vz/F, the summary statistics specified for log transformed data (Section 4.1.1) will be generated.

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[redacted]

4.4.2. Main analytical approach

PK Endpoints:

Summary statistics for exploratory plasma and urine PK parameters described in Section 4.4.1 will be summarized as appropriate based on the PK Analysis Set.

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CCI [redacted]

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CCI [redacted]
CCI [redacted]

The relationship between camlipixant PK parameters and measures of HI (e.g., bilirubin, albumin, Child-Pugh score) may be examined in an exploratory manner via a linear regression approach or other appropriate methods.

Strategy for Missing Data:

No Sample (NS), No Result, i.e. lost sample (NR), Insufficient Sample (IS) and Not Analyzed (NA) are truly missing and should be set to missing for reporting including summary statistics and graphical presentation. In case of one or more NQ data they will be assigned a value of zero concentration.

4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

Safety endpoints that are included as secondary endpoints are included in section 4.3.

4.5.1. Extent of Exposure

A listing of study drug exposure data will be produced on Safety Analysis Set.

4.5.2. Adverse Events

The definitions of AE, treatment-emergent AE (TEAE), SAE refer to section 10.3 of protocol.

AEs will be coded using the most current version 27.0 of Medical Dictionary for Regulatory Activities (MedDRA). A by participant AE, SAE and AESI data listing including verbatim term, coded term, treatment, severity (mild, moderate and severe), and relationship to treatment will be provided. A listing of taste AE questionnaire will be provided for any participants who spontaneously reports a taste disturbance AE.

Summary of incidence of AEs, SAEs and AESIs will be tabulated by system organ class (SOC) and preferred teams (PT) for each cohort.

An overview summary of AEs, including counts and percentages of participants with any AE, TEAEs, treatment-related TEAE, severe TEAE, treatment-related severe TEAE, death due to TEAE, TEAE caused study discontinuation, SAEs, treatment-related SAEs, Fatality and any AESI will be produced by cohort.

The number of participants reporting the TEAEs and the number of TEAEs reported will be summarized for each cohort. Separate summary tables including all AEs by maximum severity, treatment-related AEs, AEs caused study discontinuation, SAEs, and AESI will be generated as well. These summary tables will be presented by SOC and PT. In summary tables which are presented by SOC and PT, SOCs will be sorted in descending order of the total incidence then alphabetically, PTs will be sorted in descending order of the total incidence then alphabetically within the SOC. For the calculations in tables by maximum severity, each participant's AEs will be counted once under the maximum severity. For the calculations in tables by relationship to study treatment, each participant's AEs will be counted once under treatment-related.

If treatment relationship and severity of AEs are missing, no imputation will be performed.

The definition of TEAE and AESI are described in Section 10.3.6 and Section 8.4.4 of the protocol, respectively.

4.5.2.1. Cardiovascular Events

The definition of cardiovascular events refers to Section 10.3.5 of protocol.

Listings of cardiovascular events assessment (including abnormal physical exams) and CV status will be provided.

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

Laboratory summaries will be presented by cohort. Absolute values and change from baseline in laboratory parameters will be summarized with descriptive statistics by timepoint. All laboratory data related to chemistry, hematology, urinalysis and other laboratory characters will be listed separately for participants. A listing will be produced including laboratory data with character results. Shift tables describing out of reference range shifts will be provided for clinical laboratory (hematology and chemistry) results.

Liver function laboratory tests and pregnancy tests (for female only) will be included with chemistry lab tests.

4.5.3.1.1. Liver Events

Liver monitoring reporting will be listed. The liver monitoring criteria are described in the protocol Section 7.1.1.

4.5.3.2. ECG Data

ECG values will include measurements of heart rate, PR, QRS, uncorrected QT, and QTcF intervals. ECG data summaries will be reported by cohort. Absolute values and change from baseline will be summarized with descriptive statistics by timepoint for ECG values. A separate summary table of ECG findings will be created. All ECG values and all ECG findings will be listed separately.

4.5.3.3. Vital Signs Data

Vital signs data summaries will be reported by study treatment. Vital sign assessments will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature. Absolute values and change from baseline over time in vital signs will be summarized with descriptive statistics by timepoint. All vital signs data will be listed.

4.6. Interim Analyses

An informal interim analysis of the primary endpoint will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria:

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[redacted]

The interim analysis will be conducted after Part 1 is complete. Safety listings for AEs, Labs, ECG, and concomitant medications will be created by Data Management team. The two primary PK outputs, for PK variables $AUC_{(0-\infty)}$ and C_{max}, will be created based on plasma concentration data and nominal time. Actual time may also be used as data permit. See section 4.2.2 for details of analysis method.

Based on the decision after interim analysis review, the first criterion is met. Mild HI participants will not be enrolled in Part 2 and only severe HI participants will be enrolled in Part 2.

5. SAMPLE SIZE DETERMINATION

Eight participants will be enrolled in each HI group (i.e., Groups 1, 3, and 4). Eight healthy participants will be enrolled in Group 2 and 8 to 16 healthy participants in Group 5 will be enrolled with normal hepatic function, matched to the age (±10 years), weight (±20%), race and gender (1:1) of a participant in Group 1, 3, and/or 4.

CCI

[redacted]

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the summary will also be grouped by cohort (mild HI, moderate HI, severe HI and matched healthy controls to moderate HI, matched healthy controls to mild and severe HI and pooled healthy controls) for Screened, Enrolled and Safety Analysis Sets.

In this multi-centre global study, enrolment will be listed by site.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be listed and summarized.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention, or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention.

A summary of analysis populations and listing of subjects excluded from any analysis set based on the Screened Analysis Set described in Section 3 will be provided. In this summary table, the number and percentage participants in each of the analysis set (Screened/ Enrolled/ Assigned/ Safety/ PK) will be produced.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, race, height/weight/body mass index (BMI) and HI status at baseline will be summarized with descriptive statistics based on the Safety Analysis Set.

Demographic characteristics will also be listed. It will include baseline HI status (Child-Pugh classification) and clinical and biochemical parameters (encephalopathy grade, ascites, serum bilirubin, serum albumin, prothrombin time, prothrombin time) at baseline.

Past medical conditions and current medical conditions including CV events as of screening will be listed and summarized by cohort respectively.

6.1.3. Protocol Deviations

Important protocol deviations will be listed and summarized. The summary table will be grouped by cohort and total based on Enrolled Analysis Set.

Protocol deviations will be tracked by the study team following the Protocol Deviation Rules throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorized in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Participants with I/E criteria deviations will also be listed.

6.1.4. Prior and Concomitant Medications

Concomitant medications and Anatomical Therapeutic Chemical (ATC) Classification (level 4)/preferred term (PT) will be listed by participant in Enrolled Analysis Set and coded using the most current version September 2023 or higher of WHO Drug dictionary.

Concomitant medications include any medication that was taken at some point during the on-intervention period as defined in Section 6.8 of the protocol.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

In addition, the following criteria will be used to flag potential clinical importance (PCI):

Parameters	Unit	PCI Range
QTc	msec	Participants with bundle branch block: <450 at baseline and >500 at post-baseline; 450-480 at baseline and ≥530 at post-baseline
QTcF interval	msec	>500; change from baseline >60
ALT-absolute	U/L	≥3×ULN
ALT and Total Bilirubin (Direct Bilirubin)	U/L; umol/L; umol/L	ALT ≥3×ULN and total bilirubin >2×ULN (>35% direct bilirubin)

Parameters	Unit	PCI Range
ALT and INR		ALT ≥3×ULN and INR>1.5

6.2.2. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Pre-Intervention is defined as time prior to the first dose of study intervention.

On-Intervention is defined as time from first dose to last date plus five days. If time of assessment or study intervention is not collected, the following assessment on the first dose date will be assumed to be taken prior to the first dose and therefore considered pre-intervention: ECG, Lab, and vital signs, and first dose date is considered on-intervention for AE and concomitant medication.

Follow-up is defined 14 + / - 2 days after (inclusive) study drug administration or end of study.

6.2.3. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The study day is calculated as below:

- Assessment Date = Missing
  → Study Day = Missing
- Assessment Date < First Study Administration Date
  → Study Day = Assessment Date – First Study Administration Date
- Assessment Data ≥ First Study Administration Date
  → Study Day = Assessment Date – First Study Administration Date + 1

6.2.4. Assessment Window

- Actual times will be used in the derivation of PK parameters and in the individual concentration-time plots. Planned times will be used in the descriptive summaries and in mean and median plots. Samples that are collected outside the collection window will be flagged in data listings.
- PK concentration listings shall have both the planned and actual times.
- Planned time will be used for all other analysis.
- For data summaries by visit, the nominal visit description will be used. If there are multiple assessments within the same window, a scheduled visit will be prioritized over un-scheduled visits.

6.2.5. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in participant listing displays.
However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

• If month and year of start date = month and year of study intervention start date, then

– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.

– Else set start date = study intervention start date.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:

• If year of start date = year of study intervention start date, then

– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.

– Else set start date = study intervention start date.

Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>Concomitant Medications/Medical History</td><td>
• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e., participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
– Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
• If year of start date = year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
– Else set start date = study. intervention start date.
Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Age</td><td>• For Integrated Data Standards Library (IDSL) reporting, AGE will need to be imputed from year of birth, which is being collected on demographics eCRF, following calculation as (First Dose Date - JUN30 of Collected Birth Year + 1)/365.25.</td></tr>
</table>

6.2.6. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies	Trademarks not owned by the GlaxoSmithKline Group of Companies
None	WinNonlin

Trademarks of the GlaxoSmithKline Group of Companies

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
MedDRA

7. CHANGES FROM THE PLANNED ANALYSIS

Based on the decision after interim analysis review, mild HI participants and matched healthy controls to mild HI participants will not be enrolled in Part 2. In this case, mild HI cohort will be deleted from analysis. Matched healthy controls to mild HI and severe HI cohort will be changed to matched healthy controls to severe HI.

8. REFERENCES

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