Parexel International

Shanghai LianBio Development Co., Ltd.

LB2001-101

An Open-Label, Parallel-Group, Single-Center Phase 1 Clinical Study to Evaluate the Pharmacokinetics of a Single Oral Dose of Mavacamten in Healthy Adult Chinese Subjects

Statistical Analysis Plan

Version: <2.0>

Parexel Project Number: 256888

SPONSOR SIGNATURE PAGE

Approved by: _____ _____

Tuo Zhang *Date*

Senior Manager，Physician

Shanghai LianBio Development Co., Ltd.

Approved by: _____ _____

Mina Hsu *Date*

Senior Manager, Clinical Pharmacology

Shanghai LianBio Development Co., Ltd.

Approved by: _____ _____

Yupeng Li *Date*

Associate Manager, Biostatistics

Shanghai LianBio Development Co., Ltd.

Parexel SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	[Alex Liu] Project Role: Biostatistics Lead/Biostatistician

	Signatory
Author	[Novakovic Ana] Project Role: QCD Scientist

	Signatory
Reviewer	[Lifang Zhang] Project Role: Biostatistical Reviewer/Principle Biostatistician

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
2.0	28-Feb-2022	**1.** Pharmacokinetic parameters: DNCmax, DNAUC (0-last), DNAUC(0-inf), were added. **2.** Definition of PKS was updated to be: The pharmacokinetic (PK) analysis set consists of all subjects exposed to mavacamten with at least one plasma drug concentration result and without serious protocol violations affecting the PK parameter results. 3. Figure 1: Individual profiles for mavacamten: Plasma Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS) was revised to be Figure 1: Individual overlaid profiles for mavacamten (0-24h): Plasma Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS) 4. Figure 3: Mean (± SD) mavacamten per cohort: Plasma Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS) was revised to be Figure 3: Mean (± SD) mavacamten overlaid profiles per cohort (0-24h): Plasma Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS) 5. Figure 4: mavacamten Mean (± SD) overlaid profiles per cohort: Plasma Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS) was added. 6. Addition: Figure 7: Dose-Normalized Box plots of C_{max} (PKS) Figure 8: Dose-Normalized Box plots of $AUC_{0\text{-last}}$ (PKS) Figure 9: Dose-Normalized Box plots of $AUC_{0\text{-inf}}$ (PKS)

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-time Curve
$AUC_{(0\text{-}inf)}$	AUC from Time Zero Extrapolated to Infinity
$AUC_{(0\text{-}t)}$	AUC from Time Zero to the Last Quantifiable Concentration
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure
Bpm	Beats Per Minute
CL/F	Apparent Clearance
C_{max}	Maximum Plasma Drug Concentration
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CSP	Clinical Study Protocol
CV	Coefficient of Variation
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DRM	Data Review Meeting
ECG	Electrocardiogram
EOS	End-of-study
gCV%	Geometric Coefficient of Variation
GM	Geometric mean
HIV	Human Immunodeficiency Virus

Abbreviation / Acronym	Definition / Expansion
HR	Heart Rate
ICF	Informed Consent Form
IM	Intermediate Metabolizer
INR	International Normalized Ratio
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Available
NCS	Not Clinically Significant
NK	Not Known
NM	Normal Metabolizer
PK	Pharmacokinetic
PKS	Pharmacokinetic set
PM	Poor Metabolizers
PT	Preferred Term
PT	Prothrombin Time
QTc	Corrected QT Interval
QTcF	QT Corrected Using Fridericia's Formula
RBC	Red Blood Cell
RM	Rapid metabolizer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
$t_{½}$	Apparent Terminal Elimination Half-life
t_{max}	Time Corresponding to Occurrence of C_{max}
UM	Ultra-rapid Metabolizer
V_z/F	Apparent Volume of Distribution During Terminal Phase
WHO-DD	World Health Organisation - Drug Dictionary
λ_z	Terminal Elimination Rate Constant

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of Study LB2001-101, An Open label, Single-center Study on Pharmacokinetics of Single-Dose Mavacamten in Chinese Healthy Adults.

The content of this SAP is based on following study documents:

- Study Protocol, Version 1.0 (Apr 30, 2021)

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the pharmacokinetics (PK) of a single oral dose of mavacamten in healthy adult Chinese subjects with different CYP2C19 genotypes.

2.2 Secondary Objective

- To evaluate the safety and tolerability of a single oral dose of mavacamten in healthy adult Chinese subjects with different CYP2C19 genotypes.

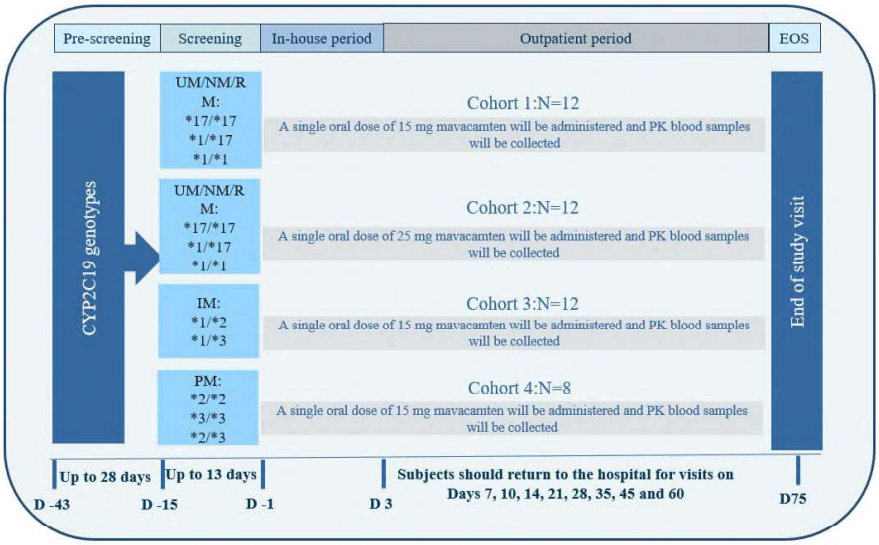
2.3 Exploratory Objective

- To evaluate the population PK.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is an open-label, parallel-group, single-center Phase 1 clinical trial. Healthy adult Chinese subjects with different CYP2C19 genotypes (Cohort 1 and Cohort 2: CYP2C19 ultra-rapid metabolizer (UM), rapid metabolizer (RM), or normal metabolizer (NM); Cohort 3: CYP2C19 intermediate metabolizer (IM); Cohort 4: CYP2C19 poor metabolizer (PM)) will be included and administered with a single oral dose of mavacamten to evaluate its PK profile. The doses administered include: 15 mg for cohort 1; 25 mg for Cohort 2; 15 mg for Cohort 3; 15 mg for Cohort 4. Blood samples will be collected from subjects at scheduled time points for PK testing. Series of safety assessments (including but not limited to AEs, laboratory tests, vital signs, and ECGs) will be performed during the whole study at specified time points.



Abbreviations: CYP = Cytochrome P450; EOS = end of study; IM = intermediate metabolizers; NM = normal metabolizer; PM = poor metabolizer; RM = rapid metabolizer; UM = ultra-rapid metabolizer.

Approximately 44 healthy adult Chinese subjects with different CYP2C19 genotypes will be enrolled in this clinical trial. This is a single-center study. Subjects will be divided into 4 cohorts.

- Cohorts 1 and 2: 12 healthy adult Chinese subjects to ensure that data will be obtained for at least 10 subjects; with their CYP2C19 genotypes being:
  - CYP2C19 UM: *17/*17 or
  - CYP2C19 RM: *1/*17 or
  - CYP2C19 NM: *1/*1;
- Cohort 3: 12 healthy adult Chinese subjects to ensure that data will be obtained for at least 10 subjects; with their CYP2C19 genotypes being:
  - CYP2C19 IM: *1/*2 or *1/*3;
- Cohort 4: 8 healthy adult Chinese subjects to ensure that data will be obtained for at least 6 subjects; with their CYP2C19 genotypes being:
  - CYP2C19 PM: *2/*2, *3/*3, or *2/*3.

3.2 Study Period

The overall study period for each subject is up to 16 weeks. The study periods are as follow:

- Pre-screening period: Day -43 to Day -15, up to 28 days;
- Screening period: Day-14 to Day -2, up to 13 days;
- In-house period: day -1 to Day 3, total 4 days;
- Outpatient period: Day 4 to Day 75, total 72 days;
- End of study visit: Day 75.

3.3 Endpoints and Associated Variables

3.3.1 Pharmacokinetic Variables

Pharmacokinetic concentration data will be obtained at the time points described in schedule of assessment (Table 1)**.**

The following PK parameters will be determined for mavacamten in plasma following single dose administration:

Table 3-1 Pharmacokinetic Parameters after Single Dose Administration

Parameter	WNL Name	CDISC Name	Definition
C_{max}	Cmax	CMAX	Maximum Plasma Drug Concentration
t_{max}	Tmax	TMAX	Time corresponding to occurrence of C_{max}
$t_{½}$	HL_Lambda_z	LAMZHL	Apparent terminal elimination half-life
$AUC_{(0\text{-}last)}$	AUClast	AUCLST	AUC from time zero to the last quantifiable concentration
$AUC_{(0\text{-}inf)}$	AUCINF_obs	AUCIFO	AUC from time zero extrapolated to infinity
$\%AUC_{ex}$	AUC_%Extrap_obs	AUCPEO	Percentage of $AUC_{(0\text{-}inf)}$ obtained by extrapolation t_{last}
CL/F	Cl_F_obs	CLFO	Apparent clearance following oral administration
V_z/F	Vz_F_obs	VZFO	Apparent volume of distribution during terminal phase
DNCmax	DNCmax	DNCMAX	Dose normalized Maximum Plasma Drug Concentration
$DNAUC_{(0\text{-}last)}$	DNAUClast	DNAUCLST	Dose normalized AUC from time zero to the last quantifiable concentration

Parameter	WNL Name	CDISC Name	Definition
$DNAUC_{(0\text{-}inf)}$	DNAUCINF_obs	DNAUCIFO	Dose normalized AUC from time zero extrapolated to infinity

3.3.2 Safety Variables

Safety will be assessed throughout the study, or at the time points described schedule of assessment (Table 1).

- Adverse events (AEs)

Adverse Event (AE)

An AE is any untoward medical occurrence in a subject after receiving the investigational product and does not necessarily have a clear causal relationship with the investigational drug. An AE can therefore be any unfavorable and unintended sign (e.g., tachycardia, enlarged liver, clinically significant or abnormal laboratory result), subject-reported symptom (e.g., nausea, chest pain), or evidence of any disease activity temporally associated with the use of a study medication, whether or not related to the use of the study medication.

Drug Taken Period Adverse Event

A drug taken period AE will be defined as any AE that emerge during treatment (i.e., AE which started after study drug administration or pre-existed that worsened in severity after study drug administration).

Adverse Events of Special Interest (AESI)

Symptomatic overdose, outcomes of a pregnancy, and LVEF≤30% as determined by local site are considered as Adverse Events of Special Interests (AESIs).

Serious Adverse Event (SAE)

A SAE is an AE that fulfills one or more of the following criteria in the opinion of the investigator or sponsor:

- Results in death;
- is immediately life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires subject hospitalization or prolongation of existing hospitalization;
- Resulting in persistent or significant disability or incapability or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital abnormality or birth defect.

Is an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a SAE when, based upon appropriate medical judgment, it may require medical or surgical intervention to prevent one of the outcomes listed above.

- Physical examination findings:

Complete physical examination: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, and musculoskeletal, cardiovascular, neurological, and respiratory systems.

Brief physical examination: cardiovascular and respiratory examinations.

- ECG parameters: HR, rhythm, PR interval, QRS interval, QT interval, P wave, QRS complex, T wave morphology, ST segment displacement.
- Vital signs: Systolic blood pressure (SBP) [mmHg], Diastolic blood pressure (DBP) [mmHg] Respiratory rate (bpm), Heart rate (bpm), temperature [°C].
- Clinical laboratory tests:

Table 3-2 Laboratory Tests

Hematology	Coagulation function	Blood chemistry	Urinalysis[a]
• White blood cell count including differential • Red blood cell count • Hemoglobin • Haematocrit • Platelet count	• PT • INR • APTT • TT • FIB	• Sodium • Potassium • Chloride • Calcium • Magnesium • Urea nitrogen • Creatinine • Uric acid • ALP • ALT • AST • Total bilirubin • Direct bilirubin • Total protein • Albumin • CK • Glucose	• Specific gravity urine • Urine pH • Protein urine • Urine glucose • Urine leukocyte esterase • Urine ketone body • Red blood cells urine • White blood cells urine

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CK = creatine kinase; FIB = fibrinogen; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PT = prothrombin time; SAE = serious AE; TT = thrombin time.

[a]Urine microscopy will be performed if there is a significant abnormality in the dipstick.

Safety laboratory assessments (hematology, blood chemistry, coagulation test, urinalysis) has no need to be repeated on Day -1 if latest results are within 7 days.

The following non-safety laboratory parameters will be measured at screening:

• Hepatitis virus test (HBV and HCV): HBV antigen, HCV antibody;

• HIV test: HIV antibody

• FSH (post-menopausal females only);

• Pregnancy test (β-hCG) (all women of childbearing potential);

• Alcohol or drug abuse test

3.3.3 Exploratory Variables

Population PK model may be assessed to investigate ethnic differences on key PK parameters including clearance and volume of distribution.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

'Baseline' is defined as the last available pre-treatment assessment. 'End of Study' is defined as the last available post-treatment assessment.

Continuous data will be summarized in terms of the mean, standard deviation (SD), upper quartile, median, lower quartile, minimum, maximum and number of observations, unless otherwise stated.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

4.3 Software

All report outputs will be produced using SAS® version [9.4] or a later version in a secure and validated environment.

PK analyses will be produced using Phoenix® WinNonLin (WNL) version [8.2] or a later version in a secure and validated environment.

All report outputs will be provided to the Sponsor in RTF format and can be combined to a whole PDF file.

4.4 Study Subjects

4.4.1 Analysis Sets

Enrolled Analysis Set (ENR)：All subjects who have signed informed consent without screening failure.
Pharmacokinetics Set (PKS): The pharmacokinetic (PK) analysis set consists of all subjects exposed to mavacamten with at least one plasma drug concentration result and without serious protocol violations affecting the PK parameter results. The PKS will be used for PK analysis.

Safety Analysis Set (SAS): All subjects exposed to mavacamten, regardless of the doses administered, will be included in the SAS. The SAS is used for safety analysis.

A summary table with the number of subjects in each of the analysis set will be provided and this table will be displayed by cohort and overall, for ENR. A listing of subjects excluded from analysis sets will also be provided including reason of exclusion for ENR.

A by-subject listing of analysis set details will be provided. This listing will be presented by cohort and include subject identifier, inclusion/exclusion flag and reason for exclusion from each analysis set. All subjects screened will appear on this listing.

4.4.2 Disposition of Subjects

Screening failures (i.e., subjects who signed the ICF but do not receive study treatment) and the associated reasons for failure will be tabulated overall.

A summary of study treatment status will be provided for the ENR. This display will show the number and percentage of subjects who have completed the study or have discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment.

A -by subject listing of study treatment discontinuation will be presented for the ENR. The listing will include reasons for discontinuation of study treatment.

4.4.3 Protocol Deviations

All protocol deviations are predefined in the separate document, Protocol Deviation Specification.

4.4.3.1 Protocol Deviations with Non-PK Implications

The defined protocol deviations will be collected during the study period by site monitor/clinical team and programming team. All deviations related to study inclusion or exclusion criteria, conduct of the study, subject management or subject assessment, and handling of the subject's rights will be described.

4.4.3.2 Protocol Deviations with PK Implications

Protocol deviations that may potentially impact PK parameter derivation include, but are not limited to:

- Emetic episode in case of orally administered study drug
- Missed PK samples that impact estimation of PK parameter(s)
- Concomitant medications not authorized by protocol

- PK samples obtained out of allowance window that may impact the estimation of PK parameter(s)

Protocol deviations (mentioned in Sections 4.4.3.1 and 4.4.3.2) and analysis sets will be reviewed in the data review meeting (DRM) to decide analyses sets and to decide if special subject's data will be excluded from certain analyses. Decisions regarding the exclusion of subjects and/or data from analyses will be made prior to database lock and will be documented and approved.

A -by subject listing of major and minor protocol deviations will be provided including subject identifier; leading to exclusion from specific analysis sets; and protocol deviation classification, and protocol deviation description.

4.5 Demographics and Baseline Characteristics

The demographic characteristics (age, gender, ethnic, height, body weight, body mass index [BMI]), CYP2C19 genotypes will be summarized by cohort and overall and listed by subject for the SAS.

4.6 Medical History and Concomitant Illnesses

All medical history and concomitant illnesses will be coded to System Organ Class (SOC) and Preferred Term (PT) using the MedDRA version 24.0 or later version. All medical history and concomitant illnesses will be summarized by SOC and PT by cohort and overall for the SAS.

A by-subject listing of medical history and concomitant illnesses will be also provided.

4.7 Prior and Concomitant Medications

Medications will be considered as prior if they with a stop date prior to administration of the study drug.

Medications will be considered as concomitant if they are stopped on or after administration of the study drug.

All concomitant medications will be coded to Anatomical Therapeutic Chemical (ATC) classification and PT using the World Health Organization Drug Dictionary (WHO-DD) SEP 2020 or later version. All concomitant medications will be summarized by ATC and PT for the SAS.

A by-subject listing will be provided with relevant information for prior and concomitant medications.

4.8 Pharmacokinetics

4.8.1 Pharmacokinetic Concentrations

Concentration Listings:

Pharmacokinetic concentration data for mavacamten, will be listed by cohort and subject for the PKS. Concentration listings will include nominal PK sampling time, actual sampling times relative to dose administration, deviation from nominal time, and percent deviation from nominal time, and concentrations. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as below the lower limit of quantification (BLQ) in the listings. Missing PK samples will be reported as no sample (NS) and/or not reportable (NR) and considered to be excluded from PK analysis.

In concentration listings, the individual concentrations will be reported to the same precision as the source data (for example, if the source data is presented to five significant digits in Bioanalytical

Lab deliverable, it will be programmed to same precision in SDTM and ADaM PK concentration datasets, and the individual values in the listings will be presented to five significant digits).

Concentration Summary Tables:

Tabular summaries for concentration-time data will report N (number of subjects who received treatment) and n (number of subjects with non-missing values).

Concentration for mavacamten will be summarized by cohort, and nominal timepoint for the PKS. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: N, n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the SD of the log-transformed values), median, minimum, and maximum values.

The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of subject level concentrations and summary tables of concentration are as follows:

- Source data will be used for calculation of concentration summary statistics.
- For presentation in concentration summary tables if less than 4 significant digits, all summary statistics will be tabulated to one more significant digit compared to the source data, otherwise up to a maximum of four significant digits, except that N and n will be presented as whole numbers.
- CV% and gCV% will be presented in one decimal place.

Concentration Figures:

To visualize subject-level concentrations and the comparison between each cohort, the descriptive PK graphs listed below will be generated.

- Figure 1: Individual overlaid profiles for mavacamten (0-24h): Plasma Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS)
- Figure 2: Overlaid individual subject profiles for mavacamten: Plasma Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS)
- Figure 3: Mean (± SD) mavacamten overlaid profiles per cohort (0-24h): Plasma Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS)
- Figure 4: mavacamten Mean (± SD) overlaid profiles per cohort: Plasma Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS)

Figures will be generated in color using unique line style and marker for each plot in the graph. For all PK concentration-time plots, linear scale will be used for x-axis (e.g., do not use an ordinal scale).

4.8.2 Handling of Concentration Values Below the Limit of Quantification (BLQ)

Derivation of plasma PK parameters

- BLQs at the beginning of a subject profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero.
- BLQs at the end of a subject profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
- Single BLQs which fall between two measurable concentrations will be set to missing.

- Consecutive BLQs (2 or more) which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will also be set to missing.

Concentration Listings:

All BLQ concentrations will be labeled as "BLQ" in the concentration data listings, and LLOQ value presented as a footnote.

Concentration Figures:

For arithmetic mean linear/linear graphs, all BLQ values will be substituted with zero for calculation of arithmetic mean and for log/linear graphs the log transformed arithmetic mean will be displayed (this should not include zero).

For individual linear/linear and log/linear graphs all BLQ values will be substituted as follows:

- BLQs at the beginning of a subject profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero (except for intravenous administration when these BLQs should not be displayed). When using log/linear scale, these timepoints will be considered missing.
- BLQs at the end of a subject profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
- Single BLQs which fall between two measurable concentrations will be set to missing.
- Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will be set to missing.

Concentration Tables:

For summary tables, all BLQs will be considered zero, and number of BLQs and non-BLQs at each scheduled time point will be reported. Summary Statistics will not be calculated if non-BLQ concentrations at a scheduled time point is <3 and reported as NC.

4.8.3 Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by non-compartmental analysis methods from the concentration-time data using Phoenix® WinNonlin® (Version 8.2) or higher following these guidelines:

- Actual time from dose will be used in the calculation of all derived pharmacokinetic parameters, except when parameters are calculated for safety/dose escalation meetings when nominal times may be used to calculate PK parameters.
- There will be no imputation of missing data.
- Any subjects with missing concentration data will be included in the PK analysis set provided that at least C_{max} and $AUC_{0\text{-}last}$ can be reliably calculated.

- Pharmacokinetic parameters will be estimated according to the following guidelines:

Table 4-1 Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
C_{max}, t_{max}	Obtained directly from the observed concentration-time data

Parameter	Guideline for Derivation
$AUC_{0\text{-last}}$	The AUC from zero time (pre-dose) to the time of last quantifiable concentration will be calculated by a combination of linear and logarithmic trapezoidal methods. Unless specifically requested and justified the linear up/log down trapezoidal method will be employed. The $AUC_{0\text{-last}}$ is the sum of areas up to the time of the last quantifiable sample: $$AUC_{0-last} = \int_0^t C(t)dt$$
$AUC_{0\text{-inf}}$	The area from zero time extrapolated to infinite time will be calculated as follows: $$AUC_{0\text{-}inf} = AUC_{0\text{-}t} + \frac{C_t}{\lambda_z}$$ where C_t is the last observed quantifiable concentration.
$\%AUC_{ex}$	The percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation will be calculated as follows: $$\%AUC_{ex} = \frac{AUC_{0-inf} - AUC_{0-t}}{AUC_{0-inf}} * 100$$ Unless otherwise determined by PK Scientist's best knowledge and judgment, if the $\%AUC_{ex}$ is greater than 30% the value, $\%AUC_{ex}$ and all dependent parameters (ie, $AUC_{0\text{-inf}}$, MRT, Vz and CL) will be flagged in listings and excluded from summary tables and statistical analysis of PK parameters, and if the $\%AUC_{ex}$ is greater than 20% but less than or equal to 30% the value, $\%AUC_{ex}$ and all dependent parameters (ie, $AUC_{0\text{-inf}}$, MRT, Vz and CL) will be flagged in listings, but not excluded from summary tables and statistical analysis of PK parameters. The reason for exclusion will be footnoted in parameter listings.
t½	1. The apparent terminal phase rate-constant (λz) will be estimated by linear regression of concentration versus time data presented in a log-linear scale. 2. Data are primarily monotonically decreasing in magnitude and are representative of the actual decline in the log concentration-time curve. 3. Only those data points that are judged to describe the terminal log-linear decline will be used in the regression. 4. A minimum number of three data points in the terminal phase will be used in calculating λz with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope). Unless otherwise determined by PK Scientist's best knowledge and judgment, if the adjusted correlation coefficient (R^2 adjusted) is <0.8, it will be excluded from the summary tables and statistical analysis of PK parameters, and λz and all the λz dependent parameters (i.e. t½, $AUC_{0\text{-inf}}$, CL, MRT, and Vz) will also be flagged and excluded from summary tables and statistical analysis. Any value of R^2 between 0.8 and 0.9 will be flagged but may be used at the PK Scientist's best knowledge and judgement. The reason for exclusion will be footnoted in parameter listings. 5. The interval used to determine λz should be equal or greater than 1.5-fold the estimated t½ or otherwise flagged and used at the PK Scientist's best knowledge and judgement. All derived parameters (i.e. t½, AUC0-inf, CL, MRT, and Vz) will also be flagged or excluded from statistical analysis of PK parameters accordingly. The reason for flagging and/or exclusion will be footnoted in parameter listings 6. The t½ will be calculated as follows: $t_{½} = \ln 2 / \lambda z$ 7. Data points may be dropped from the linear regression if the PK Scientist considers the reported values to be anomalous. Any data points so designated should remain in the listings with a footnote and be identified in the study report with a rationale for exclusion.
CL or CL/F	Following IV administration, systemic clearance of parent drug will be calculated from: $CL = \frac{Dose}{AUC_{0-inf}}$ If desired, apparent clearance (CL/F) following extravascular (eg, oral) dosing

Parameter	Guideline for Derivation
	may also be calculated. In the case of steady state administration $AUC_{0-\tau}$ will be the denominator.
V_z or V_z/F	Volume of distribution at terminal phase following either intravascular or extravascular dosing may be calculated from: $V_z \text{ or } {}^{V_z}/_{F} = \frac{Dose}{\lambda_z * AUC_{0-inf}} = {}^{CL}/_{\lambda_z} \text{ or } {}^{(CL/F)}/_{\lambda_z}$ Likewise, if derived for steady state administration $AUC_{0-\tau}$ will be used.
DNC_{max}, $DNAUC_{0-last}$ and $DNAUC_{0-inf}$	DNC_{max}, $DNAUC_{0-last}$ and $DNAUC_{0-inSf}$ divided by dose

PK Parameters Listings:

For final analysis, Biostatistics group will be responsible for reporting individual PK parameters in the listing(s).

Individual PK parameters will be presented to four significant digits, with the exception of t_{max}, which will be presented to two decimal places. Parameters derived directly from source data (e.g. C_{max},) shall be reported with the same precision as the source data (if this is not four significant digits).

PK parameters will be listed by-subject for the PKS. PK parameters that will be excluded from summary tables and statistical analyses of PK parameters will be flagged and footnoted with the reason for exclusion.

PK Parameter Summary Tables:

Biostatistics group will use derived PK parameters source data without rounding for calculation of PK parameters summary statistics tables.

PK parameters will be summarized by cohort for the PKS.

Tabular summaries for PK parameters will report N (number of subjects who received treatment) and n (number of subjects with non-missing values).

Descriptive statistics for calculated PK parameters will include N, n, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum values. For t_{max}, only n, median, minimum and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

The rules followed for presentation of PK parameters data with regards to the number of decimal places/significant digits for the listings of subject level PK parameters and summary tables of PK parameters are as follows:

- all summary statistics will be tabulated to a maximum of 4 significant digits, with exception of t_{max} that is presented to 2 decimal places and N and n that will be presented as whole numbers. Comparative estimates will be presented in 3 decimal places and confidence intervals in the form of percentages, CV%, and $\%AUC_{ex}$ will be presented to two decimal places.

PK Parameter Figures

To visualize the comparison between each cohort on PK parameter level, Box plots of dose-normalized C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ and Dose-Normalized Box plots of C_{max} (PKS), $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ will be generated according to CYP2C19 genotype (cohort):

- Figure 4: Box plots of C_{max} (PKS)
- Figure 5: Box plots of $AUC_{0\text{-last}}$ (PKS)
- Figure 6: Box plots of $AUC_{0\text{-inf}}$ (PKS)
- Figure 7: Dose-Normalized Box plots of C_{max} (PKS)
- Figure 8: Dose-Normalized Box plots of $AUC_{0\text{-last}}$ (PKS)
- Figure 9: Dose-Normalized Box plots of $AUC_{0\text{-inf}}$ (PKS)

4.8.4 Pharmacokinetic Analysis

To examine the exposure to mavacamten for subjects with the UM/RM/NM vs IM vs PM genotype, analysis of variance (ANOVA) model will be constructed using log-transformed $AUC_{(0\text{–last})}$, $AUC_{(0\text{–inf})}$ and C_{max}. The dependent variable will be the ln-transformed primary PK parameters ($AUC_{(0\text{–last})}$, $AUC_{(0\text{–inf})}$ and C_{max}) and the independent variables will include fixed effects for cohort and subject as a random effect.

The reference group will be cohort 1 and test groups will be cohort 2 to cohort 4. Geometric least-squares means for each cohort (cohort 1 and cohort2:UM/RM/NM, cohort 3:IM, cohort 4: PM), point estimates and associated 90% CIs for the ratios for each primary PK parameter will be produced in tabular format. Estimates of between -participant variability (%CVb) will also be provided.

4.8.5 Population PK (PopPK) Analysis

PopPK analysis will be conducted with the pooled data from the current study LB2001-101 and other mavacamten studies. Additional details on PopPK model development and analysis will be provided in a separate PopPK data analysis plan(DAP).

4.9 Safety Evaluation

All safety summaries and analyses will be based upon the SAS as defined in Section 4.4.1.

4.9.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 or higher.

All AE summaries should provide the number and percentages of subjects reporting at least one AE and the total number of events reported.

Summaries of AEs will include the following:

- Incidence of AEs - Overview (by cohort and overall)
- Incidence of drug taken period AEs(by cohort and overall, SOC, and PT)
- Incidence of drug taken period AEs by maximum relationship (by cohort and overall, SOC, and PT)
- Incidence of drug taken period AEs by maximum severity (mild/moderate/severe, by cohort and overall, SOC, and PT)

- Incidence of AESIs (by cohort and overall, SOC, and PT)

Summary tables will contain counts of subjects, percentages of subjects in parentheses, and the number of events where applicable. A subject who has multiple events in the same SOC and PT will be counted only once in the subject counts, but all events will be included.

A by-subject listing of all adverse events (including non-treatment-emergent events) will be provided. This listing will be presented by cohort and will include: subject identifier, age, sex, race, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, severity, seriousness, action taken, outcome and causality.

All Adverse Events (AEs)

All AEs will be listed including pre-treatment AEs, and pre-treatment SAE will be listed separately.

Drug Taken Period Adverse Event

Drug taken period AEs will be summarized by SOC and PT, including the number and percentage of subjects experiencing events, separately.

Severity

Drug taken period AEs will be summarized by SOC, PT, and severity, including the number and percentage of subjects experiencing events. If a subject reports the same drug taken period AE more than once within that SOC and PT, the drug taken period AE with the highest severity will be used in the corresponding severity summaries.

In summaries including severity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Subjects who experience the same event multiple times will be included in the most severe category. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

Relationship (Causality)

Drug taken period AEs will be summarized by SOC, PT, and causality, including the number and percentage of subjects experiencing events. Relationship to study drug will be tabulated respectively. In summaries including severity, the following relationships will be summarized: 'unrelated', 'Related'. If a subject reports the same drug taken period AE more than once within that SOC and PT, the drug taken period AE with the worst case relationship to study drug will be used in the corresponding relationship summaries. Events with missing relationship will be considered as 'Related' to the last given study drug for summary purposes but recorded as missing in the listings.

Adverse Events of Special Interests (AESIs)

Adverse events of special interests (AESIs) will be summarized by SOC and PT, including the number and percentage of subjects experiencing events. Listing of AESI will be provided.

4.9.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

The following summaries will be provided by cohort and by MedDRA SOC and PT:

- SAEs
- Drug taken period SAEs
- Related SAEs to the study drug
- AEs leading to study discontinuation

- AEs leading to death

The following listings are to be provided:

- A by-subject listing of all deaths that occurred during the study
- A by-subject listing of all SAEs
- A by-subject listing of all AEs leading to discontinuation of study

4.9.3 Clinical Laboratory Evaluation

Descriptive statistics (for non-categorical data including hematology, coagulation function and blood chemistry) will be presented by cohort and time-point for both absolute values and changes from baseline.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented by cohort and time-point.

Shift tables will be presented for select laboratory parameters (Blood chemistry, coagulation function and hematology).

Laboratory values (hematology, coagulation, biochemistry and urinalysis) will be listed by subject and study time point, including changes from baseline (with the exception of urinalysis).

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory values will be recorded by the Investigator as AEs.

4.9.4 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital Signs

Descriptive statistics will be presented by cohort and time-point for absolute values and changes from baseline.

A by-subject listing of all vital sign measurements and change from baseline will be presented by cohort and time point.

ECG

Descriptive statistics will be presented by cohort and time-point for absolute values and changes from baseline.

A summary of the number and percentage of subjects with QTc exceeding some predefined upper limits (e.g. >450ms, >480ms, >500ms, >520ms, >550ms for measured values as well as. >30ms, >60ms for changes from baseline) of ECG parameters will be displayed in a frequency table.

All ECG parameters will be listed by subject for each cohort and time point including changes from baseline.

The listing of ECG abnormality will be presented separately.

Physical Examination

The full physical examination includes an assessment of general appearance and a review of systems (general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, and musculoskeletal, cardiovascular, neurological, and respiratory systems).

The brief physical examination includes an assessment of the cardiovascular and respiratory examinations.

Clinically significant physical exam findings will be listed.

4.10 Handling of Dropouts or Missing Data

No imputation of missing data will be performed except for partial dates imputation mention in Section 6.3.

4.11 Planned Interim Analysis

No interim analysis will be performed for this study.

4.12 Determination of Sample Size

No formal hypothesis testing will be conducted. The number of subjects in each cohort is expected to provide sufficient data to allow the assessment of the safety, tolerability and PK profile of mavacamten in Chinese subjects. Hence approximately 8-12 subjects will be enrolled in Phase I to obtain adequate PK and safety data based on China regulatory consideration.

4.13 Explanation for Inconsistency with Planned Analysis

In the study protocol, one of the laboratory biochemistry parameters collected is urea nitrogen, but since urea nitrogen is no longer applicable at the site, the item actually collected in the eCRF is urea. It is hereby stated that in this statistical analysis plan, urea nitrogen described in the protocol was changed to be urea, and indicators of urea actually collected were used for analysis.

In the study protocol, the pharmacokinetic analysis set (PKS) was defined as: The pharmacokinetic (PK) analysis set consists of all subjects exposed to mavacamten with at least one plasma drug concentration result.

In this analysis plan, the definition of pharmacokinetic analysis set (PKS) was additionally described. That subjects without serious protocol violations affecting PK parameter results were included in the analysis set was added to more accurately describe the PKS analysis set. The modified definition is as follows: The pharmacokinetic (PK) analysis set consists of all subjects exposed to mavacamten with at least one plasma drug concentration result and without serious protocol violations affecting PK parameter results. It is hereby stated.

5 REFERENCES

[1] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
[2] Phoenix®WinNonlin® Professional Software Version 8.2. https://www.certara.com

6 APPENDICES

6.1 Schedule of Assessments

Table 2 Study Flow Chart

Weeks	Pre-screening	Screening Period	In-house Period				Outpatient Period								End of study visit
Days	**D-43 to D-15**	**D-14 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D7**	**D10**	**D14**	**D21**	**D28**	**D35**	**D45**	**D60**	**D75**
Visit Window (day)							**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Signing the pre-screening ICF[1]	X														
Demographics[2]	X														
CYP2C19 genotyping	X														
Signing the main ICF		X													
Inclusion/exclusion criteria		X	X												
Assign subject number	X	X	X												
Medical history		X													
Vital signs[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[4]		X	X			X									X
Weight, height[5]		X													X
12-lead ECG[6]		X	X	X		X					X			X	X
Echocardiography		X													
Hematology[7]		X	X								X				X
Blood chemistry[8]		X	X			X					X				X
Urinalysis[9]		X	X								X				X

Weeks	Pre-screening	Screening Period	In-house Period				Outpatient Period								End of study visit
Days	**D-43 to D-15**	**D-14 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D7**	**D10**	**D14**	**D21**	**D28**	**D35**	**D45**	**D60**	**D75**
Visit Window (day)							**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Coagulation[10]		X	X			X					X				X
FSH[11]		X													
Serum pregnancy test[12]		X													X
Urine Pregnancy test[12]			X								X			X	
Hepatitis B, C, and HIV virology		X													
Alcohol or drug abuse test[13]		X	X												
Investigational drug[14]				X											
PK blood sampling[15]				X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BP = blood pressure; CK = creatine kinase; CYP = cytochrome P450; ECG = electrocardiogram; EOS = end of study; FIB = fibrinogen; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; HR = heart rate; ICF = informed consent form; INR = international normalized ratio; PK = pharmacokinetic; PT = prothrombin time; QD = once daily; RBC = red blood cell; SAE = serious AE; TT = thrombin time; WBC = white blood cell.
Note: Safety laboratory assessments (Hematology, Biochemistry, Coagulation test, Urinalysis) has no need to be repeated on Day -1 if latest results are within 7 days.

6.2 Schedule of PK Sampling

3mL whole blood will be collected at each following time point for PK analysis.

Blood samples will be obtained to determine mavacamten concentrations at pre-dose and 10min, 20min, 30min, 45min, 1h, 1.5h, 2h, 3h, 4h, 8h, 12h, 24h, and 48 hours after administration of mavacamten. Additional blood samples will be collected at Days 7, 10, 14, 21, 28, 35, 45, 60 and 75 (**Table 2**).

Table 2 PK Sampling Schedule

	In-house Period			**Outpatient Period**								**End of study visit**
Days	**D 1**	**D 2**	**D 3**	**D 7**	**D 10**	**D 14**	**D 21**	**D 28**	**D 35**	**D 45**	**D 60**	**D 75**
Visit Window (day)	**0**	**0**	**0**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Collection time points	Pre-dose (within 60 min before dosing) 10 min±2 min 20 min±2 min 30 min±2 min 45 min±2 min 1 h±2 min 1.5 h±3 min 2 h±3 min 3 h±3 min 4 h±3 min 8 h±5 min 12 h±5 min	24 h ± 1 h post-dose	48 h ± 1 h post-dose	Outpatient visits: 144 h ± 24 h post-dose on Day 1	Outpatient visits: 216 h ± 24 h post-dose on Day 1	Outpatient visits: 312 h ± 24 h post-dose on Day 1	Outpatient visits: 480 h ± 24 h post-dose on Day 1	Outpatient visits: 648 h ± 24 h post-dose on Day 1	Outpatient visits: 816 h ± 24 h post-dose on Day 1	Outpatient visits: 1056 h ± 24 h post-dose on Day 1	Outpatient visits: 1416 h ± 24 h post-dose on Day 1	EOS Visit: 1776 h ± 24 h post-dose on Day 1

6.3 Imputation Rules for Partial Dates

Imputed dates will NOT be presented in the listings. In general, when calculating the relative study days, the imputation of the partial dates will be as follows:

Incomplete Start Date

- If only day is missing, date imputed will be 1st of the month.
- If both month and day are missing, January 1 will be imputed.

Incomplete End Date

- If only day is missing, date imputed will be last day of the month.
- If both month and day are missing, December 31 will be imputed.

Table and Table 3 present algorithm for imputing partial dates for drug taken period AE and prior/concomitant medication respectively.

Table 3 Algorithm for Drug Taken Period Adverse Events:

Start/Increase Severity Date	Stop Date	Action
Known	Known	Considered as a drug taken period AE if start date on or after the date of the dose of investigational product (IP)
	Partial	Considered as a drug taken period AE if start date on or after the date of the dose of IP. The last day of the month and the last month (i.e., December) will be used if the stop day/month is missing.
	Missing	Considered as a drug taken period AE if start date on or after the date of the dose of IP
Partial, but known components show that it cannot be on or after first IP taken date	Known	Not a drug taken period AE. The first day of the month and January will be used if the start day/month is missing.

Start/Increase Severity Date	Stop Date	Action
	Partial	Not a drug taken period AE. The first day of the month and January will be used if the start day/month is missing. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Not a drug taken period AE. The first day of the month and January will be used if the start day/month is missing.
Partial, could be on or after first IP taken date	Known	Considered as a drug taken period AE, if stop date is after first IP taken date. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date Considered as not drug taken period AE, if stop date is prior to first IP taken date. The first day of the month and January will be used if the start day/month is missing.
	Partial	Considered as a drug taken period AE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Considered as a drug taken period AE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date.

Start/Increase Severity Date	Stop Date	Action
Missing	Known	Considered as a drug taken period AE if stop date is on or after the date of the dose of IP.
	Partial	The last day of the month and the last month (ie, December) will be used if the stop day/month is missing. If the imputed stop date is on or after the dose of IP considered as a drug taken period AE; if the year is missing, considered as a drug taken period AE.
	Missing	Considered as a drug taken period AE

Table 3 Algorithm for Prior/Concomitant Medications:

Start Date	Stop Date	Action
Known	Known	If stop date is prior to the date for the dose of IP, considered as prior; if stop date are on or after the date for the dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the dose of IP, considered as prior; if the imputed stop date are on or after the date for the dose of IP, considered as concomitant.
	Missing	Considered as concomitant.
Partial	Known	The first day of the month and January will be used if the start day/month is missing. If stop date is prior to the date for the dose of IP, considered as prior; If stop date are on or after the date for the dose of IP, considered as concomitant.
	Partial	The first day of the month and January will be used if the start day/month is missing.The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the imputed stop date is prior to the date for the dose of IP, considered as prior; If imputed stop date are on or after the date for the dose of IP, considered as concomitant.
	Missing	Considered as concomitant.
Missing	Known	If stop date is prior to the date for the dose of IP, considered as prior; if stop date is on or after the date for the dose of IP, considered as concomitant.

Start Date	Stop Date	Action
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the imputed stop date is prior to the date for the dose of IP, considered as prior; if he imputed stop date is on or after the date for the dose of IP, considered as concomitant.
	Missing	Considered as concomitant.