STATISTICAL ANALYSIS PLAN

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A Phase 4 Open-label, Randomized, Single Oral Dose, Two-way Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of Mirabegron in Healthy Chinese Subjects

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	adverse event
ANOVA	analysis of variance
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUC_{inf} (%extrap)	area under the concentration-time curve from the time of dosing extrapolated to time infinity as a percentage of total area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from the time of dosing to the last measurable concentration
BMI	body mass index
CI	confidence interval
CL	apparent total systemic clearance after extravascular dosing
C_{max}	maximum concentration
CSR	clinical study report
ECG	electrocardiogram
ESV	end-of-study visit
IP	investigational product
LS	least square(s)
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligrams
PD	protocol deviation
PK	pharmacokinetic
PKAS	pharmacokinetic analysis set
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{lag}	time prior to the time corresponding to the first measurable (nonzero) concentration
t_{max}	time of maximum concentration
V_z/F	apparent volume of distribution during the terminal elimination phase after extravascular dosing

List of Key Terms

Terms	Definition of terms
Baseline	Assessments of subjects as they enter a study before they receive any dosing.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. Note: Not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a subject into a study. Note: Once a subject has received the IP or placebo, the protocol applies to the subject.
Intervention	The drug, device, therapy or process under investigation in a study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test product or comparative drug (sometimes without randomization) is given to a subject, and continues until the last assessment after completing administration of the test product or comparative drug.
Randomization	The process of assigning subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias. NOTE: Unequal randomization is used to allocate subjects into groups at a differential rate; for example, 3 subjects may be assigned to a treatment group for every 1 assigned to the control group.
Screen failure	Potential subject who signed the ICF but did not meet 1 or more criteria required for participation in the study and was not randomized.
Screening	A process of active consideration of potential subjects for randomization in a study.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent form until just before the test product or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first study site initiation date to the last study site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes procedures for executing the statistical analysis to fulfil the objectives of the study.

The final SAP will be approved prior to database hardlock.

Changes from the planned analyses in the final SAP that impact the statistical analyses will be documented in the Clinical Study Report (CSR).

2 STUDY OBJECTIVE(S) AND DESIGN

2.1 Study Objective(s)

The primary objective of this study is to determine the effect of food on the pharmacokinetics of single oral doses of mirabegron in healthy Chinese male and female subjects.

The secondary objective is to evaluate the safety and tolerability of single oral doses of mirabegron in healthy Chinese male and female subjects.

The exploratory objective is to evaluate the pharmacokinetics of single oral doses of mirabegron in healthy Chinese male and female subjects.

2.2 Study Design

The study follows an open-label, randomized, 2-period, single oral dose crossover design at 2 dose levels in healthy Chinese male and female subjects. Each subject will participate in 2 periods separated by a washout of at least 10 days between IP administrations in each period.

Dose (mg)	Sequence	n	Period 1	Period 2
25	**1**	**6**	**Mirabegron (low-fat)**	**Mirabegron (fasted)**
	2	**6**	**Mirabegron (fasted)**	**Mirabegron (low-fat)**
50	**1**	**6**	**Mirabegron (low-fat)**	**Mirabegron (fasted)**
	2	**6**	**Mirabegron (fasted)**	**Mirabegron (low-fat)**

The dose under fed conditions will be administered following a low-fat breakfast (total calories approximately 450 kcal, with approximately 70 kcal from fat).

Pharmacokinetic samples will be collected predose on day 1 of each period and at multiple time points following each dose (see the Schedule of Assessments in the protocol.)

The study will be completed with an end-of-study visit (ESV). The ESV will take place 5 to 9 days after the last pharmacokinetic sample is collected or at early discontinuation from the study.

Details of the schedule of clinical assessments are available in the protocol.

2.3 Randomization

Randomization will be allocated through blocks. There will be no stratification variables.

3 SAMPLE SIZE

A total of 24 subjects (12 subjects per dose group) will be enrolled. Subjects who discontinue early from the study may be replaced at the discretion of the sponsor.

Based on data from Study 178-CL-091, a Chinese phase 1 study, the intrasubject coefficient of variation (CV) for pharmacokinetic parameters AUC_{inf}, AUC_{last} and C_{max} of the 50 mg mirabegron dose are estimated to be between 33% and 60%. Assuming the underlying variability is similar to 60% and an observed ratio between fasted and fed conditions of 100%, the 90% CI will lie within (60, 167) with > 80% probability.

4 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

The determination of whether subjects are included or excluded from the safety analysis set will be made prior to database hard-lock.

4.1 Safety Analysis Set

The safety analysis set (SAF) consists of all subjects who receive at least 1 dose of IP. The SAF will be used for all summaries and analyses of the safety data.

4.2 Pharmacokinetics Analysis Set

The pharmacokinetic analysis set (PKAS) consists of all subjects who receive at least 1 dose of IP for which concentration data are available to facilitate derivation of at least 1 primary pharmacokinetic parameter. Inclusion of subjects in the PKAS with missing data or major protocol deviations will be considered by the pharmacokineticist on a case-by-case basis.

The PKAS will be used for all summaries and analyses of the pharmacokinetic data.

5 PHARMACOKINETIC AND SAFETY ENDPOINTS

5.1 Pharmacokinetic Endpoint (Primary)

The primary PK endpoints will be Mirabegron plasma PK parameters: AUC_{inf}, AUC_{last} and C_{max}.

5.2 Safety Endpoints (Secondary)

Safety will be assessed by evaluation of the following endpoints:

- Nature, frequency and severity of AEs
- Clinical laboratory tests (biochemistry, hematology and urinalysis)

- Vital signs (blood pressure, body temperature and pulse)
- Routine 12-lead ECG

5.3 Exploratory Endpoints

The exploratory PK endpoints will be Mirabegron plasma PK parameters AUC_{inf}(%extrap), CL/F, $t_{½}$, t_{max}, t_{lag} and V_z/F.

6 STATISTICAL METHODOLOGY

6.1 General Considerations

In general, all data will be summarized with descriptive statistics (n, mean, SD, median, minimum and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints, unless otherwise specified. Percentages by categories will be based on the number of subjects with no missing data (i.e., will add up to 100%).

For each sequence, the number and percentage of subjects will be characterized for all randomized subjects and by each analysis set.

6.2 Study Population

6.2.1 Disposition of Subjects

The number and percentage of subjects who completed and discontinued dosing and reasons for dosing discontinuation will be presented for all randomized subjects and for subjects in the SAF by dose group, sequence and overall. Similar tables for investigational period disposition and follow-up disposition will also be presented for all randomized subjects by dose group, sequence and overall. All disposition details and dates of first and last evaluations for each subject will be listed.

6.2.2 Protocol Deviations

The major protocol deviations are defined as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received incorrect dose,

PD4 - Received excluded concomitant treatment.

Major protocol deviations will be listed.

6.2.3 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, body weight, height and BMI) will be summarized by dose group, sequence and overall for all randomized subjects.

6.2.4 Previous and Concomitant Medications

Previous and concomitant treatment (medication and nonmedication therapy) will be listed.

6.2.5 Medical History

Medical history for each subject will be listed.

6.2.6 Investigational Product Exposure

The number and percentage of subjects exposed to IP will be summarized by dose group and sequence under fed and fasted conditions.

IP exposure data will be listed.

6.3 Analysis of Efficacy

Not applicable.

6.4 Analysis of Safety

6.4.1 Adverse Events

AEs will be coded using MedDRA. An AE with onset at any time from first dosing until last scheduled procedure will be classified as a TEAE for inclusion in the summary tabulations. An IP-related TEAE is defined as any TEAE with a causal relationship assessed as "yes" by the investigator, or records where the relationship is missing.

An overview and separate summaries of the number and percentage of subjects with TEAEs, drug-related TEAEs, TEAEs leading to withdrawal of dosing, IP-related TEAEs leading to withdrawal of dosing and TEAEs excluding SAEs that equal or exceed a threshold of 5% in any dose group under fed and fasted conditions will be presented by SOC, preferred term, by fed and fasted conditions for each dose group. Also included in the overview are the number and percentage of subjects with serious TEAEs, IP-related serious TEAEs, TEAEs leading to death and IP-related TEAEs leading to death.

AE data will be listed.

6.4.2 Clinical Laboratory Evaluation

For quantitative clinical laboratory measurements (hematology and biochemistry), descriptive statistics will be used to summarize results and change from baseline by fed and fasted conditions and visit for each dose group.

Baseline will be defined as the last nonmissing observation prior to administration of IP within each period.

Laboratory data will be listed.

6.4.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for subjects by fed and fasted conditions and time point for each dose group.

Vital signs data will be listed.

Baseline will be defined as the last nonmissing observation prior to administration of IP within each period.

6.4.4 Routine 12-lead Electrocardiogram

Routine 12-lead ECG data and interpretations will be listed.

6.5 Analysis of Pharmacokinetics

Descriptive statistics will include n, mean, SD, CV, geometric mean, geometric CV, median, minimum and maximum. For the pharmacokinetic parameters t_{max} and t_{lag}, only n, median, minimum and maximum will be calculated.

6.5.1 Plasma Concentrations

Plasma concentrations under both fasted and fed conditions will be listed and summarized using descriptive statistics by scheduled time point for each dose group. Standard graphics including mean plasma concentration-time profiles, overlay (spaghetti) plots and individual subject plasma concentration-time profiles will be produced.

6.5.2 Estimation of Pharmacokinetic Parameters

Noncompartmental analysis will be used for the calculation of plasma pharmacokinetic parameters using Phoenix® version 8.0 or higher(Certara LP, 100 Overlook Center, Suite 101, Princeton, NJ 08540, US).

Plasma pharmacokinetic parameters under both fasted and fed conditions will be listed and summarized using descriptive statistics for each dose group.

6.5.3 Statistical Analysis

To assess the effect of food on the pharmacokinetics of mirabegron, a mixed effects analysis of variance (ANOVA) model with fixed effects for food condition (fed or fasted) and period and subject as a random effect will be fitted on natural logarithm-transformed AUC_{inf}, AUC_{last} and C_{max} . Within the ANOVA, the least squares (LS) mean differences between fed and fasted, along with 90% CIs for the differences will be estimated.

The LS means for AUC_{inf}, AUC_{last} and C_{max} will be back-transformed to produce the geometric LS means and presented with the number of subjects for each food condition. The geometric LS mean ratios and their corresponding 90% CIs for each pharmacokinetic parameter will be presented by back-transforming and expressed as percentages. The ANOVA will be performed and results will be presented for 25mg and 50mg mirabegron doses separately.

The analysis will be repeated if all subjects did not complete both periods using an ANOVA with fixed effects for period, food condition and subject; this analysis will only include subjects with complete data in both periods.

6.6 Interim Analysis (and Early Discontinuation of the Clinical Study)

Not applicable.

6.7 Additional Conventions

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medications if they are missing on day of first IP administration. The imputed dates will be used to assess if the AEs or concomitant medications are treatment-emergent or concomitant, respectively.

Listings of AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

6.7.1 Analysis Windows

Not applicable.

7 REVISION AND RATIONALE

Not applicable.

8 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines)

9 APPENDICES

9.1 Appendix 1: Author and Approver Signatures

Completed by:

PPD

PPD

Signature dd/mmm/yyyy

(E-signatures are attached at the end of document.)