Statistical Analysis Plan (SAP)

Sponsor Protocol No. : MS200084_0028
CCI CCI

Study Title:
A randomized phase I, open-label, active-controlled study assessing the bioequivalence between single doses of 500 mg Glucophage® XR Reduced Mass tablets and 500 mg Glucophage® XR tablets under fasted and fed state in two 2-way crossover groups of healthy subjects

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Date	Summary of amendments	Author
1.0	2021-11-30	None (First version)	PPD
2.0	2022-04-08	Added safety analysis of Blood Sugar Test (BST)	PPD

2. INTRODUCTION

This SAP described a statistical analysis plan for the CCI study. It was written based on the BE Study Protocol, and the analysis plan follows PPD SOP and the finally approved BE Study Protocol. If there is a difference between SAP and SOP, the one specified in SAP shall be given a priority.

2.1 STUDY OBJECTIVES

2.1.1 Primary Objectives

To demonstrate the bioequivalence of the newly developed "Glucophage® XR Reduced Mass tablet" (containing metformin hydrochloride 500 mg) and the current marketed "Glucophage® XR tablet" (containing metformin hydrochloride 500 mg) after single oral administration under fasted and fed conditions.

2.1.2 Secondary Objectives

- To evaluate the safety and tolerability of the metformin formulations after single dose treatment under fasted and fed conditions.
- To characterize other PK parameters of the metformin formulations under fasted and fed conditions.

2.2 STUDY DESIGN

This bioequivalence study is divided into two parts according to the method of administration of the Investigational Medicinal Products (IMPs): Part 1 (Fasted state) and Part 2 (Fed state).

Each part of the study is performed by an open label, randomized, 2-period, 2-sequence, single oral dose and crossover design.

A detailed description of the study design is specified in Table of Contents 4 of the BE Study Protocol.

2.3 SAMPLE SIZE

Eighty-two (82) healthy adult subjects will be included in the study: 48 in the fasted group (Part 1) and 34 in the fed group (Part 2).

1) Part 1: Fasted state (N=48)

Variability estimates were obtained from the preliminary PK data (CCI [redacted] [fasted] and CCI [redacted] [fed]) and intra-subject variability of the major pharmacokinetic parameters AUC_{last} and C_{max} of metformin were about 19.1 % and 25.0%, respectively. Based on the intra-subject variability of the C_{max}, the difference of log-transformed mean values of the evaluation parameters of Reference Drug and Test Drug was used as log 0.95. Sample size of 19 subjects per sequence, totally 38 subjects meeting 2-period 2-sequence crossover study design, has significance level of 0.05 and a power of 90%. Considering the dropout rate (about 20%) during the study, 24 subjects per sequence, totally 48 subjects will be recruited.

2) Part 2: Fed state (N=34)

Variability estimates were obtained from the preliminary PK data (CCI [redacted] [fasted] and CCI [redacted] [fed]) and intra-subject variability of the major pharmacokinetic constants AUC_{last} and C_{max} of metformin were about 13.1% and 18.7%, respectively. Based on the intra-subject variability of the C_{max}, the difference log of log-transformed mean values of the evaluation parameters of Reference Drug and Test Drug was used as log 0.95. Sample size of 11 subjects per sequence, totally 22 subjects meeting 2-period 2-sequence crossover study design, has significance level of 0.05 and a power of 90%. Considering the dropout rate (about 35%) during the study, 17 subjects per sequence, totally 34 subjects will be recruited.

- R: Glucophage® XR tablet (Reference Drug)
- T: Glucophage® XR Reduced Mass tablet

Part	Sequence	Period		
		1	Washout	2
Part 1 (n=48)	1(n=24): RT	R	≥ 7 days	T
	2(n=24): TR	T		R

Part	Sequence	Period		
		1	Washout	2
Part 2 (n=34)	1(n=17): RT	R	≥ 7 days	T
	2(n=17): TR	T		R

3. HYPOTHESES AND DECISION RULES

3.1 STATISTICAL HYPOTHESES

The alternative hypothesis (H_1: $\theta_L <= \mu_T - \mu_R <= \theta_U$) and null hypothesis ($H_0$: $\mu_T - \mu_R < \theta_L$ or $\mu_T - \mu_R > \theta_U$) of BE Study can be expressed as two one-sided hypotheses:

- H_{0A}: $\mu_T - \mu_R < \theta_L$, H_{1A}: $\theta_L <= \mu_T - \mu_R$
- H_{0B}: $\mu_T - \mu_R > \theta_U$, H_{1B}: $\mu_T - \mu_R <= \theta_U$

μ_T and μ_R are the geometric mean of C_{max} and AUC, respectively, and $[\theta_L, \theta_U] = [0.80, 1.25]$ defines the acceptance range of bioequivalence. Bioequivalence will be tested for both Part 1 and Part 2. Overall, bioequivalence can be concluded if all 8 null hypotheses (H_{0A} and H_{0B} for both AUC and C_{max}, in Part 1 and in Part 2) can be rejected with an alpha of 5%.

3.2 STATISTICAL DECISION RULES

When log transformation and statistical evaluation on comparative parameters of the reference and test drug except T_{max} are performed, the 90% confidence intervals for the difference in mean values between the test and reference should be within log 0.8 to log 1.25. Even if this is not the case, equivalence is achieved if all of the following conditions are met

- When the difference in average values of logarithmic AUC_{last} and C_{max} parameters to be assessed between two products are between log0.9 to log1.11.
- When the comparative dissolution test is conducted according to “Standard on Pharmaceutical Equivalence Study”, all values are equivalent under all conditions described. However, products containing poorly soluble drugs and enteric-coated products containing poorly soluble drugs are not applicable to this provision. In case of extended-release products, the average dissolutions of the test drug are within that of the reference drug ±10% at three appropriate time points when the average dissolution of the reference drug are around 30%, 50%, and 80%.
- The total sample size of the bioequivalence study population is not less than 24 (n=12/group).

4. ANALYSIS SETS AND HANDLING OF DEVIATIONS

The populations for analyses were defined as three analysis groups:

Data Sets	Definition Usage
All Randomized	Demographic Information is evaluated for those participants who participated in the bioequivalence study (i.e., all participants who were randomized). However, the participants who were replaced by the stand-by participants before the first administration of Study Interventions will be excluded from the analysis.
Safety	Safety is evaluated for those participants who were administered at least one dose of the Study Interventions.
PK	Pharmacokinetics is evaluated for those participants whose pharmacokinetics evaluation is possible by the completion of all planned pharmacokinetics blood collection schedules according to the Protocol, who do not exhibit concentrations exceeding 5% of the maximum plasma concentration (C_{max}) of the drug in the pharmacokinetics sample of prior to dosing and who have valid primary endpoints for both treatments. In the case of drop-outs, they are excluded from statistical analysis.

5. PHARMACOKINETIC AND SAFETY VARIABLES

5.1 PHARMACOKINETIC ENDPOINTS

Blood collection for pharmacokinetic analysis follows the schedule given in the BE Study Protocol. Pharmacokinetic parameters are calculated from the blood concentration-time data of 'metformin' using a non-compartmental method.

Parameter	Definition	Measuring method
AUC_{last}	Area under the plasma concentration versus time data pairs, where last is the time of the last quantifiable concentration	Linear trapezoidal method
AUC_{inf}	Area under the plasma concentration versus time data pairs, with extrapolation to infinity	$AUC_{last} + C_{last} / K_{el}$
C_{max}	Maximum plasma concentration	Directly observed from the analysis data.
T_{max}	Time to maximum plasma concentration	First observed time at which the maximum concentration is observed. Directly observed from the analysis data.
$t_{1/2}$	Elimination half-life	The apparent terminal half-life, calculated according to the equation $t1/2=Log_e(2)/K_{el}$ Where K_{el} is the elimination rate constant K_{el} from the linear regression analysis on the log-linear plot of the portion corresponding to the terminal phase of the blood concentration-time curve.
AUC_{last}/AUC_{inf}	The ratio of AUC_{last} to AUC_{inf}	AUC_{last}/AUC_{inf}

Type	PK Parameters
Primary endpoints	AUC_{last}, C_{max}
Secondary endpoints	AUC_{inf} (if data allows to calculate), AUC_{last}/AUC_{inf} (if data allows to calculate), $t_{1/2}$ (if data allows to calculate) and T_{max}

5.2 SAFETY ENDPOINTS

The safety profile of the Investigational Medicinal Product will be assessed through the recording, reporting and analysis of baseline medical conditions, adverse events (AEs), Physical examination, vital signs, 12-lead ECG, and Clinical laboratory tests, Blood Sugar Test(BST).

6. PRESENTATION AND EVALUATION OF PLASMA CONCENTRATION AND PHARMACOKINETIC VARIABLES

6.1 PRESENTATION OF PLASMA CONCENTRATIONS

List subject, dosing group and actual blood collection interval of the blood collection time. In addition, list blood concentrations by actual blood collection time, by dosing group and by time. And descriptive statistics for blood concentrations shall be presented.

The blood concentration-actual time curve of the drug for each subject and dosing group is presented. In addition, arithmetic and geometric mean and concentration graphs for each dosing group are presented.

If the concentration prior to administration is below the lower limit of quantification (BLQ), it is indicated as “0”.

All other BLQ values are considered to be “blank” when calculating the geometric mean and “0” when calculating the arithmetic mean.

When calculating the pharmacokinetic parameters, the concentration of BLQ in the curve of the rising section is entered as “0” and the concentration of BLQ in the terminal phase is treated as “blank”.

6.2 DEVIATIONS, MISSING CONCENTRATIONS

When performing statistical analysis to derive summary tables and mean graphs, concentration values are calculated as missing if any of the following is met:

- If actual blood collection has not been performed (Not Applicable)
- If the sample is missing (Missing Data)

6.3 PHARMACOKINETIC PARAMETERS

Pharmacokinetic parameters are calculated from the pharmacokinetic evaluation analysis group who have completed all study procedures and shall be presented up to the three decimal places.

The actual blood collection time is used to calculate pharmacokinetic parameters and to present individual blood concentration-time patterns. If it is impossible to calculate the pharmacokinetic parameters using the subject's concentration data, it is indicated as NC (i.e. not calculated). When performing statistical analysis for summary tables, NC values are calculated as missing data.

If the value of the pharmacokinetic parameter is biased due to an unexpected event (e.g., vomiting before the administered drug is completely absorbed), it is indicated as a footnote in the summary table. It is not used for the statistical analysis.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

Bioequivalence of pharmacokinetic parameters is determined by obtaining a 90% confidence interval of the mean difference between dosing groups, using the analysis of variance (ANOVA) model of log-transformed data.

For statistical analysis, the analysis of variance (ANOVA) model of SAS version 9.4 software (SAS Institute Inc.) is used, and Phoenix WinNonlin 8.0 (CERTARA USA Inc.) is used to calculate pharmacokinetic parameters from the blood concentrations.

In general, continuous data presents descriptive statistics (N, Mean, Standard Deviation, Median, Minimum, Maximum), and categorical data presents frequency (n) and percentage (%). Descriptive statistics for continuous data are presented to the second decimal place, the ratio (%) of categorical data to the first decimal place, and p-value is rounded to the fourth decimal place. At this time, if the p-value is less than 0.0001, it is presented as <0.0001. All verification is conducted at the significance level of 5%.

Blood concentration values are indicated with 3 significant digits, and basic statistics of blood concentration values are presented to the third decimal place. Pharmacokinetic parameters and their descriptive statistics are presented to the third decimal place, the geometric average ratio of the test drug to the reference drug is presented to the fourth decimal place (%Ratio is 2 decimal places), the 90% CI for the geometric mean ratio is presented up to 2 decimal places when expressed as a percentage of 4 decimal places, and Intra CV is presented to the first decimal place.

Detail contents for each parameter is presented in mock-ups of the Appendix.

7.2 STATISTICAL ANALYSIS

Randomization, demographic information, medical history, physical examination, vital signs, clinical laboratory test, pregnancy test, IMP administration, 12-lead ECG , prior/ concomitant medications, adverse events, Study Conclusion , Pharmacokinetic Profile, blood concentration, pharmacokinetic parameters are presented as Listing for the demographic assessment group. Detail contents for each variable is presented in mock-ups of the Appendix.

7.2.1 Study Disposition

List the study participation status information (informed consent signed date, completion status of BE study (study completion, dropout), dropout reason) for the subjects who participated in BE study and who were assigned randomization number. In addition, for all subjects participating in BE study, the summarized number of subjects based on the progress of clinical study (screening participants, screening failed participants, stand-by participants, replaced participants, dropout participants, study completed participants, demographic set, safety set, reasons for exclusion of safety set, pharmacokinetic set, reasons for exclusion of pharmacokinetic set) are presented.

7.2.2 Demographic Characteristics

The population for demographic analysis is demographic assessment group.

- Descriptive statistics per each sequence group like mean, standard deviation, etc. are analyzed for demographic information such as gender, age, height, weight, and BMI.

7.2.3 Pharmacokinetic Analysis

The population for pharmacokinetic analysis is pharmacokinetics assessment group.

AUC_{last} and C_{max}, AUC_{inf} (if data allows to calculate), $t_{1/2}$, converted to natural logs are analyzed using an analysis of variance (ANOVA) model having sequence group, subject (sequence group), period, and dosing group effects. In principle, analysis of variance shall be used at α (significance level) = 0.05. The mean square error (MSE) is then used for the %CV calculation.

Using the ANOVA results, the point estimate of the mean difference (T-R) and the corresponding 90% confidence interval are calculated, and they are indexed to calculate the point estimate of the geometric mean ratio (T/R) and the 90% confidence interval.

T_{max} presents the median of the reference drug and the test drug, and p-value is calculated through the Wilcoxon signed-rank test.

Pharmacokinetics parameters are summarized and listed according to the dosing group.

PK parameter	Summary statistics
AUC_{last}, C_{max}, AUC_{inf}, T_{max}, $t_{1/2}$, AUC_{last}/AUC_{inf}	N, Arithmetic Mean, Standard Deviation, Median, Minimum, Maximum, Geometric Mean, Geometric Coefficient of Variation

7.2.4 Safety Analysis

The population for safety analysis is the safety assessment group.

- For all adverse events after administration, System Organ Class (SOC) and Preferred Term (PT) classified using MedDRA [V23.0 or latest] are summarized for the number of subjects per dosing group, number of occurrences, and ratio (percentage). Adverse events having causal relationship with Study Interventions and adverse events not having causal relationship with Study Interventions are also presented.
- Using the WHO ATC [2020 or latest] classification system, concomitant drugs are summarized and presented for the number of subjects per dosing group, number of occurrence, and ratio (percentage) by ATC Level 1 and Level 3. The concomitant drug dosing group is based on the start date of the concomitant drug administration, and the concomitant drug dosing group taken during the wash out period is included as a group of Study Interventions dosing taken at the prior period.
- The data of vital sign test is presented by calculating the descriptive statistics of each test item for each dosing group at each evaluation time point.
- The data of clinical laboratory test is presented by calculating the descriptive statistics of each test item for each dosing group at each evaluation time point. Depending on whether the reference value is deviated or not, the meaning is assessed as normal, abnormal/no clinical significance (Abnormal/NCS) and

abnormal/clinical significance (Abnormal/CS). Percentage per each dosing group is presented.

- The data of physical examination is assessed as normal, abnormal/no clinical significance (NCS) and abnormal/clinical significance (CS) according to the result of each test item at each evaluation time point. Percentage per each dosing group is presented.
- The data of 12-lead ECG is assessed as normal, abnormal/no clinical significance (Abnormal/NCS) and abnormal/clinical significance (Abnormal/CS) according to the result of each test item at each evaluation time point. Percentage per each dosing group is presented.
- The data of Blood Sugar Test is presented by calculating the descriptive statistics of each test item for each dosing group at each evaluation time point.

7.2.5 Interim Analysis

Interim analysis of data will not be performed.

8. LIST OF STATISTICAL APPENDICES

The numbers assigned to tables, lists and graphs were assigned during the analysis stage, and the final number will be assigned when the result report is generated. TLF is provided separately fasted and fed.

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9. REFERENCES

1) CCI

2) CCI