Statistical Analysis Plan

Clinical Trial Protocol Identification No.	MS200084_0013
Title:	A Randomized, Open-label, 2-way-crossover Study Assessing the Bioequivalence between Single Doses of 500 mg Glucophage Extended Release (GXR) Tablets (Merck/China Nantong-Manufactured) and 500 mg GXR Tablets (Merck/Germany Darmstadt-Manufactured) under Fed and Fasted State in Two Groups of Healthy Volunteers
Trial Phase	I
Investigational Medicinal Product(s)	Glucophage Extended Release (GXR)
Clinical Trial Protocol Version	19 Apr 2018 /Version1.0
Statistical Analysis Plan Author	PPD Biostatistician PPD Biostatistician PPD Pharmacokineticist
Statistical Analysis Plan Date and Version	20 December 2018/Version 2.0
Statistical Analysis Plan Reviewers	PPD

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Electronic Signature Manifestation

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Signer Full Name	Meaning of Signature	Date and Time
PPD	Document Approval	20 Dec 2018 16:31:46 UTC
PPD	Document Approval	20 Dec 2018 17:08:13 UTC
PPD	Document Approval	20 Dec 2018 17:22:16 UTC

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3 List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration-Time Curve
$AUC_{0\rightarrow\infty}$	The AUC from time zero (= dosing time) extrapolated to infinity
$AUC_{0\rightarrow t}$	The AUC from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0\rightarrow\infty}$
BE	Bioequivalence
BMI	Body Mass Index
CI	Confidence Interval
$CL_{/f}$	The apparent total body clearance of drug following extravascular administration.
C_{max}	The Maximum Plasma Concentration Observed
CRO	Contract Research Organization
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CTP	Clinical Trial Protocol
CV	Coefficient of Variation (%)
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GeoCV%	Geometric Coefficient of Variation
GeoMean	Geometric Mean
GXR	Glucophage Extended Release

HAV	Hepatitis A Virus
HbA_{1C}	Glycosylated Hemoglobin Type A_{1C}
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
LCI	Lower Confidence Interval
IMP	Investigational Medicinal Product
LC/MS/MS	Liquid Chromatography-tandem Mass Spectrometry
LC/MS	Liquid Chromatography-Mass Spectrometry
LLOQ	Lower Level of Quantification
Max	Maximum
Mean	Arithmetic Mean
Min	Minimum
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MSS	Merck Santé s.a.s. in Semoy
N	Number of non-missing observations
N.R.	No result or result not valid
PK	Pharmacokinetic(s)
PR	Partial Response
PT	Preferred team
Q1	The First Quartile
Q3	The Third Quartile
Rsq	Goodness-of-fit statistic
SAE	Serious Adverse Event
PPD	
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation

SDTM	Study Data Tabulation Model
SEM	Standard Error of the Mean
SOC	System Organ Class
$t_{1/2}$	Apparent terminal half-life
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification
t_{max}	Time of Maximum Plasma Concentration Observed
TP	Treponema Pallidum
UCI	Upper Confidence Interval
$V_{z/f}$	Apparent volume of distribution during the terminal phase following extravascular administration
λ_z	Terminal Elimination Rate Constant
WHO DDE	World Health Organization Drug Dictionary Enhanced

4 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
Draft V0.1	26 June 2018	PPD	Not Applicable –First Version
Draft V0.2	02 July 2018	PPD	Updated based on Sponsor comments
Draft V0.3	10 July 2018	PPD	Updated based on Sponsor comments through email
Draft V0.4	21 August 2018	PPD	Updated based on Sponsor comments
Final V1.0	07 September 2018	PPD	Updated based on Sponsor comments
Final V2.0	20 December 2018	PPD	Updated based on Medical Writer's comments according to CFDA BE CSR template

5 Purpose of the Statistical Analysis Plan

The purpose of this Statistical Analysis Plan (SAP) is to document technical and detailed specifications for the final analysis of data collected for protocol MS200084_0013, Version 1.0. Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this SAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective SAP will be clearly identified in the CSR.

The SAP is based upon Section 8 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with ICH E9.

6 Summary of Clinical Trial Features

Trial Objectives	**Primary Objective:** To assess bioequivalence (BE) between the GXR tablet manufactured in Merck Nantong China (test) and that manufactured in Merck Darmstadt Germany (reference product) following single oral dose administrations under fasting and fed conditions. **Secondary Objectives:** • To compare additional pharmacokinetic (PK) parameters of GXR after single dose administrations of test and reference products. • To examine the safety and tolerability of GXR after single dose administrations of test and reference products.

Trial Endpoints	**Primary Endpoints:**
	• The following PK parameters calculated from metformin plasma concentrations:
	  • C_{max}: maximum plasma concentration observed of metformin
	  • $AUC_{0\rightarrow t}$: area under the (plasma) concentration-time curve from time 0 (dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification (LLOQ)
	Secondary Endpoints:
	• Pharmacokinetic endpoints: additional PK parameters: $AUC_{0\rightarrow\infty}$, $AUC_{extra\%}$, λ_z, t_{max}, $t_{1/2}$, $CL_{/f}$, $V_{z/f}$.
	• Safety Endpoints**:** Safety assessments including:
	  • Adverse events
	  • Vital signs
	  • Clinical laboratory tests (Biochemistry, hematology, and urinalysis)
	  • 12-lead ECG
	  • Physical examination
	  • Concomitant medications.

Trial Design	This study is designed as a Phase I, open-label, randomized, 2-period, 2-sequence, crossover study to assess BE between a single oral dose of GXR from 2 different manufacturing facilities, each given as a single dose in fasting or fed state. Participants will be randomized within each food consumption group (fasting or fed) to receive, in each period, either: • 1 tablet of 500 mg test GXR (manufactured in Merck Nantong China), or • 1 tablet of 500 mg reference GXR (manufactured in Merck Darmstadt Germany). • Drug administration will be done with or without food depending on group allocation to either fed or fasted condition.

Planned number of subjects	A total of 54 healthy male and female Chinese participants (28 evaluable participants in the fasted group and 12 evaluable participants in the fed group) will be enrolled in the study, with each gender representing no less than 1/4 of the total number and also adequately allocated to fasting versus. fed group (i.e., no less than 10 participants of each gender in the fasting group and no less than 4 participants of each gender in the fed group), and are statistically powered to provide adequate sample size for BE testing.
Treatment and Trial Duration	The trial has a duration for each subject of approximately 4 weeks (or approximately 29 days), including: • A screening period within 2 weeks before the first GXR administration • First dosing/sampling period up to 2 days (48 hours) after dosing • A washout period of at least 7 days after the first GXR administration • Second dosing/sampling period up to 2 days (48 hours) after dosing • End-of-Study examinations and discharge on Day 10 • A conditional follow-up examination period (only for participants with any ongoing AEs at discharge) up to 7 days following the last drug administration.
Pharmacokinetics	The plasma concentrations of metformin will be determined by a validated liquid chromatography-mass spectrometry (LC/MS) analytical method. Pharmacokinetic parameters (Primary and Secondary Endpoints) will be calculated according to noncompartmental analysis methods. The mixed log linear trapezoidal rule will be used to calculate the AUC.
Randomization and Blinding	A total of 54 eligible healthy male and female Chinese subjects (38 in fasting state and 16 in fed state) who meet the eligibility criteria will be randomized (with each gender representing no less than 1/4 of the total number within each group) on Day 1, in a 1:1 ratio to 1 of 2 treatment sequences: Sequence A-B or Sequence B-A. As this is an open-label trial, no method of blinding was used.

7 Sample Size/Randomization

7.1 Sample Size

The BE is declared if all comparisons in primary hypothesis achieve the criteria - the 90% confidence intervals (CI) for the ratios between test and reference of geometric means of both $AUC_{0\rightarrow t}$ and C_{max} for metformin in plasma are within 80.00% to 125.00% in both the fasted and fed group.

Based on the results of previously conducted BE trial PK data, (EMR200084-108 [1]), GXR formulation showed intra-individual coefficient of variations (CVs) as below (Table 1 and Table 2).

- Test: Single dose (Day 1) of GXR 500 mg tablets of manufactured at Merck Darmstadt (Germany) under fed/fast condition
- Reference: Single dose (Day 1) of GXR 500 mg tablets of manufactured at Bristol-Myers Squibb (USA) under fed/fast condition

Table 1 Results from EMR200084-108 Fed CCI

CCI

$AUC_{0\rightarrow t}$ = area under the plasma concentration-time curve from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification; C_{max}= the maximum plasma concentration observed; CV= Coefficient of Variation; LS=least squares

Table 2 Results from EMR200084-108 Fasting CCI

CCI

$AUC_{0\rightarrow t}$ = area under the plasma concentration-time curve from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification; C_{max}= the maximum plasma concentration observed; CV= Coefficient of Variation; LS=least squares

CCI

CCI

[redacted]

7.2 Randomization

Each eligible participant will be allocated to a treatment sequence according to a computer-generated randomization schedule. Subjects will be identified only by their assigned participant number. The participants will receive consecutive participant numbers in the order of their enrollment into the study.

A total of 54 eligible healthy male and female Chinese participants (38 in fasting group and 16 in fed group, Table) who meet the eligibility criteria will be randomized (with each gender representing no less than 1/4 of the total number within each group, i.e., no less than 10 participants

of each gender in the fasting group and no less than 4 in the fed group) on Day 1, in a 1:1 ratio to 1 of 2 treatment sequences: Sequence A-B or Sequence B-A as presented in Table .

Sequence A to B:

- Day 1 (Period 1), Treatment A: the administration of a single dose of test GXR
- Day 8 (Period 2), Treatment B: the administration of a single dose of reference GXR

Sequence B to A:

- Day 1 (Period 1), Treatment B: the administration of a single dose of reference GXR
- Day 8 (Period 2), Treatment A: the administration of a single dose of test GXR

The 2 doses will be separated by a Washout period of approximately 7 days (Table 7).

Table 5 Randomization Allocation

	Day 1	Day 8
Fasting group (n= 38)	Treatment A (n= 19)	Treatment B (n= 19)
	Treatment B (n= 19)	Treatment A (n= 19)
Fed group (n= 16)	Treatment A (n= 8)	Treatment B (n= 8)
	Treatment B (n= 8)	Treatment A (n= 8)

Table 6 Assignment to Administration Sequences

	Day 1	Day 8
Sequence A to B	GXR 500 mg (Merck Nantong manufactured) (Test Product)	GXR 500 mg (Merck Darmstadt manufactured) (Reference Product)
Sequence B to A	GXR 500 mg (Merck Darmstadt manufactured) (Reference Product)	GXR 500 mg (Merck Nantong manufactured) (Test Product)

GXR=Glucophage® Extended Release.

Table 7 Instruction of Study Periods

Screening Period	Randomization	Treatment Period 1	Washout Period	Treatment Period 2	End-of-Study Discharge	Conditional Follow-up

Day -14 to Day -1	Day -1	Day 1 to Day 3 Inpatient	7 days Inpatient	Day 8 to Day 10 Inpatient	Day 10	Day 15

This 2 x 2 crossover design for comparison of 2 treatments complies with the Chinese guideline for BE studies [2]. The guideline recommends 2 sequences in order to minimize the effect of individual and periodic differences. The guideline suggests that the duration of a Washout Period should be at least 7 times $t_{1/2}$. Therefore, 7 days have been assigned as the Washout Period duration to assure that the main collection times in Period 2 can occur on a weekday.

Participants will only be replaced if the number of participants within each group falls below 28 (fasting) or 12 (fed). The participant who is replacing a discontinued participant will then be allocated to the treatment sequence of the participant who discontinued.

8 Overview of Planned Analyses

The methods described in this document will be applied to the preparation of tables, figures and listings (TLFs). Statistical analyses will be performed using cleaned electronic case report form (eCRF) data collected.

This SAP will cover the final analysis only. The final analysis will be performed only after the last subject has completed the study with all study data in-house and all data queries resolved. The SAP will be finalized prior to database lock.

9 Changes to the Planned Analyses in the Clinical Trial Protocol

There are no changes to the planned analyses.

10 Protocol Deviations and Analysis Sets

10.1 Definition of Protocol Deviations

Protocol deviations describe how close the study has been conducted according to the protocol as expected per GCP. Some of these deviations may be significant contributors to analysis bias.

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Examples of clinically important protocol deviations or important events for PK include, but may not be limited to, the following:

- Subjects that are dosed on the study despite not satisfying the inclusion criteria
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn
- Subjects that receive the wrong treatment or an incorrect dose

- Subjects that receive an excluded concomitant medication
- Vomiting following oral dosing (each instance will be discussed in the CSR)
- Deviation from GCP
- Sample processing errors that may lead to inaccurate bioanalytical results
- Failure to fast (in fasted arm) or incomplete meal consumption (in fed arm) prior to dosing

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest. Important protocol deviations include:

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion

A data review meeting will be held to discuss and update the definition of important protocol deviations so as to determine the evaluability of the subjects prior to database lock.

All important protocol deviations should be documented in CDISC datasets whether identified through sites monitoring or medical review. Please refer to Protocol Deviation Guide for more details.

10.2 Definition of Analysis Sets and Subgroups

Screening Population

The Screening population includes all subjects who have signed the main informed consent (i.e., screening failures plus subjects enrolled).

Randomized Population

The Randomized population includes all randomized subjects.

Safety Population

The Safety Population includes all subjects who received at least 1 dose of IMP. In general, clinical data will be analyzed for the Safety Population.

Pharmacokinetic Population

The PK Population includes all participants who completed the study with adequate study medication compliance (Section 15), without any relevant protocol violations or events with respect to factors likely to affect the comparability of PK results, and with sufficient evaluable data to determine primary endpoints ($AUC_{0\rightarrow t}$ and C_{max}) for both treatments. If participants receive concomitant medication that potentially affects PK for the treatment of an AE, their inclusion in the PK Population will be decided on a case-by-case basis. Emesis occurring within 2 times of the median t_{max} for a given treatment will be considered a relevant event likely to affect the comparability of PK results. Similarly, a predose concentration for a given treatment period which

exceeds 5% of C_{max} will be considered a relevant event affecting PK results. All PK analyses will be based on the PK Population. Data for subjects excluded from the PK Population will be included in listings.

11 General Specifications for Statistical Analyses

11.1 Output Presentations

The shells provided with this SAP describe presentations for this study and therefore the format and content of the summary tables, listings and figures to be provided by PPD. Unless otherwise indicated all analyses will be presented separately for the two treatments (Treatment A and Treatment B) and/ or for two treatment sequences (Sequence A-B and Sequence B-A) under different food consumption condition (fed and fasted).

11.2 Listings

All listings will be reported separately by food consumption condition and sorted by treatment or treatment sequence (A-B or B-A), and/or scheduled time point, as appropriate. Data which are only collected before administration of study drug will be sorted by subject, food consumption condition and treatment sequence. Data which are only collected end of study (Day 10) will be sorted by subject and post-baseline timepoints are sorted under the treatment most recently received.

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory or clinical laboratory regardless of how many significant figures or decimal places the data carry. In export datasets, as well as in the Study Data Tabulation Model (SDTM) PP/XD domain, PK parameters will be provided with full precision, and will not be rounded.

Pharmacokinetic parameters and actual elapsed sample collection times will be rounded for reporting purposes in by-subject listings. Actual elapsed sample collection times will be rounded to two decimal places with units of hours. For PK parameters, the standard rounding procedure will be as follows:

- Parameters directly derived from source data (e.g., C_{max}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g., t_{max}) will be reported to two decimal places with units of hours.
- Values of AUC will be rounded to 3 significant figures.
- Percentages not derived directly from source data (e.g., $AUC_{extra\%}$) will be reported to 3 significant figures.
- Other parameters (e.g., $t_{1/2}$, λ_Z, $CL_{/f}$, $V_{z/f}$) will be reported with 3 significant figures.

11.3 Tables and Descriptive Statistics

All data will be summarized by food consumption condition, treatment or treatment sequence, and/or scheduled time point, as appropriate. Repeated and unscheduled measurements included in the listings will not be used for statistical analyses or summaries, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples.

Metformin concentration in plasma and its PK parameters will be presented in tables and descriptively summarized by food consumption condition, treatment, and/or nominal time point, as appropriate.

11.4 Presentation of PK Concentration Data

Pharmacokinetic concentration data will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), standard error of the mean (SEM), CV%, minimum (Min), median (Median), and maximum (Max).

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data, and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

Mean, Min, Median, Max:	3 significant digits
SD:	4 significant digits
CV%:	1 decimal place

Descriptive statistics of plasma concentrations below the LLOQ will be taken as zero.

11.5 Presentation of PK Parameter Data

Pharmacokinetic parameter data will be descriptively summarized using: N, Mean, SD, CV%, Min, Median, Max, geometric mean (GeoMean), the geometric CV% (GeoCV%), and the 95% CI for the GeoMean (LCI 95% GM, UCI 95% GM).

Descriptive statistics of PK parameter data will be calculated using full precision values, and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant digits
GeoMean ratio:	2 decimal places
SD:	4 significant digits
CV%, GeoCV%:	1 decimal place

11.6 Presentation of continuous and qualitative variables

Continuous variables will be summarized using the following descriptive statistics unless otherwise specified, i.e.

- Number of subjects with non-missing values (n)
- Mean
- SD
- Median
- Minimum and maximum

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated, the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of subjects still present in the trial at that visit, unless otherwise specified.

11.7 Software

Pharmacokinetic parameters will be derived using noncompartmental methods with the validated computer program Phoenix® WinNonlin® 6.4 or higher (PPD). Pharmacokinetic figures will be developed by Phoenix® WinNonlin® 6.4 or higher, or SAS® Windows Version 9.4 or higher (PPD).

All other statistical analyses will be conducted using SAS® Version 9.4 or higher.

11.8 Definition of baseline

Unless otherwise specified, baseline for end of study is defined as the last non-missing measurement taken prior to or on the day of the first IMP administration (including unscheduled assessments as applicable). However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

For vital signs, the assessment performed within 1 hour (±30 minutes) prior to IMP administration in each treatment period will be considered as baseline for the treatment period. If there is no time point, the last non-missing assessment prior to dosing in each period will be taken as baseline.

In the case where the last non-missing measurement and the dosing date/time coincide, that measurement will be considered baseline, but medications commencing on the first IMP administration date will be considered post-baseline.

11.9 Definition of End of Study

Unless otherwise specified, end of study is defined as the last measurement taken prior to or on the day of discharge (Day10 or any special day for Premature Withdrawal Visit).

11.10 Unscheduled visits

Unscheduled measurements will not be included in by-visit table summaries, but will contribute to the baseline value and best/ worst case value where required.

Descriptive statistics (mean, SD, median, minimum, maximum) by normal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

11.11 Conversion factors

The following conversion factors will be used to convert days into months or years:

1 month = 30.4375 days

1 year = 365.25 days.

11.12 Common calculations

For quantitative measurements, change from baseline will be calculated as:

Test Value at Visit X – Baseline Value

11.13 Handling of discontinued subjects.

Unless otherwise specified, data from discontinued subjects will not be replaced.

11.14 Handling of missing data

Handling of missing data for PK parameter calculations are discussed under Section 16.3.2.

In all subject data listings, imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, e.g., when they cannot be calculated, should be presented as “nd”. For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as “nd”.

For the derivation of new date variable, the following rules will apply:

Partial birth dates will be handled this way: day will be imputed as 15 if it is missing, and month imputed as June if missing. If both of day and month are missing, they will be imputed as July 1st. If year is missing then the date will not be imputed.

In case the last administration date is incomplete the date of last administration will be taken from the Treatment Termination eCRF page.

Any adverse event (AE) with incomplete start/time and or end date will be handled as described below for the classification as treatment-emergent, assignment to treatment periods, and calculation of duration.

- AE with unknown start time but known start date, will be imputed with a time of 00:00 hours, unless the start date corresponds to any given dosing date, in which case time of dosing will be used instead. However, if this results in a start time after end time of the AE, then the start time will be imputed to 00:00 hours instead.

- Any AE with completely unknown start date will be imputed with date and time of the first IMP administration, unless the end date (imputed if needed) is known and prior to first IMP administration. In the latter case, the start date will be missing.

- AE with partially missing start date but in the same year (when day and month are missing) or in the same month and year (if the day is missing) as first IMP administration then the start date will be replaced by the minimum between first IMP administration and AE resolution date. In all other cases the missing onset day or onset month will be replaced by 01.

- Adverse event with completely unknown end date will be imputed with the date of study completion (or in case of withdrawal, date of discontinuation).

Partially known end dates will be treated as follows:

- If only the day is missing, the last day of the month will be imputed or the date of study completion/discontinuation if earlier.

- If day and month are both missing, then the end date of 31 December will be imputed or the date of study completion/discontinuation if earlier.

Assignment to the different treatment periods will be performed after the imputations have been performed. An AE will be assigned to a specific treatment period if it occurs on or after the IMP administration scheduled for that period and before the IMP administration in the next period (or study completion for the last period).

11.15 Trial day

Trial day will be calculated from the reference start date, and will be used to show start/end day of assessments and events. Reference start date is defined as the day of the first IMP administration in period 1. Trial Day 1 is the day of first IMP administration in period 1. The day before is defined as Trial Day -1 (no Trial Day 0 is defined). Trial day will be calculated accordingly:

- If the date of the event is on or after the reference start date then:

Trial day = (date of event – reference start date) + 1.

- If the date of the event is prior to the reference start date then:

Trial day = (date of event – reference start date).

12 Trial Subjects

This section includes specifications for reporting subject disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided.

12.1 Disposition of Subjects and Discontinuations

All subjects who provide informed consent will be accounted into this study. Subject disposition and withdrawals will be presented for the Screening Population.

The following summaries will be produced by treatment sequence and overall for each food consumption condition group:

- Total number of subjects screened (i.e. subjects who gave informed consent)
- Number of subjects screening failures, grouped by the primary reason for study exclusion
- Numbers of randomized subjects
- Number of subjects treated in each period
- Number of subjects who complete the trial
- Number of subjects who discontinued the study treatment after administration, grouped by the main reason
- Number of subjects who terminated the study prematurely, grouped by the main reason
- Number of subjects included in Safety Population
- Number of subjects included in PK Population

Corresponding individual listings will be prepared (sorted by group, treatment sequence and subject).

Additionally, a listing of the screening failures will be produced with the reason of non-inclusion in the treatment phase.

Listings with visit dates will also be carried out by group, treatment sequence and subject.

12.2 Protocol Deviations

12.2.1 Important Protocol Deviations

Important protocol deviations will be based on the Clinical Trial Management System (CTMS) data and determined by medical review process. All important protocol deviations will be included in SDTM datasets, if identified through medical review. The Analysis Data Model (ADaM) datasets will be derived from SDTM and include all important protocol deviations.

A data review meeting will be held to discuss and update the definition of important protocol deviations, so as to determine the evaluability of the subjects prior to database lock.

The following outputs will be provided by treatment sequence and overall, for each food consumption condition group:

- Summary of important protocol deviations relating to inclusion/exclusion criteria
- Summary of other important protocol deviations post inclusion criteria

All important protocol deviations will be listed. A listing presenting protocol deviations relating to inclusion/exclusion criteria and a listing presenting other deviations will be produced.

13 Demographics and Other Baseline Characteristics

Unless otherwise specified, demographic data and other baseline characteristics will be presented for the Safety Population.

Summaries of the key demographics overall and by treatment sequence for each group are to be provided. Continuous variables will be summarized using the descriptive statistics. Quantitative variables will be summarized by counts and percentages. No statistical testing will be carried out for demographic or other baseline characteristics.

13.1 Demographics

Demographic characteristics will be summarized using the following information from the Screening/Baseline Visit eCRF pages.

Demographic characteristics

- Age (years): summary statistics

  Age (years) = (date of informed consent - date of birth + 1) / 365.25

- Sex: Male, Female
- Race: Asian
- Weight (kg): summary statistics
- Height (cm): summary statistics

- BMI (kg/m^2): summary statistics

13.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using MedDRA, Version 21.0 or higher version, preferred term (PT) as event category and MedDRA system organ class (SOC) body term as Body System category.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

13.3 Other Baseline Characteristics

The following baseline characteristics will be reported overall and by treatment sequence for each food consumption group:

- Nicotine and Alcohol Consumption
- Serology: HAV antibody, HBsAg, HCV antibody, HIV antibody, TP antibody

Baseline characteristics with respect to vital signs, ECG recordings and laboratory tests will be part of Section 17 (Safety Evaluation).

Results of chest x-ray and serum pregnancy test (for women of childbearing potential) will be presented only in the listings.

13.4 Urine drug abuse test and breath test of alcohol

Urine screening of drug and breath test of alcohol will be overall and by treatment sequence and visit for each food consumption group.

14 Previous or Concomitant Medications/Procedures

Previous and concomitant medication/ procedure will be tabulated for Safety Population. All medications and procedures will be presented in the listings.

Medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) Version March 1, 2018 or higher version. Procedures will be coded using MedDRA Version 21.0or higher version.
Previous medications are medications started and ended before first IMP administration.

Concomitant medications/ procedures are medications/ procedures, other than trial medications/ procedures, which are taken by subjects any time on-trial (include medications/ procedures which started before the first IMP administration and were ongoing after first IMP administration, or started on or after the first IMP administration day).

Previous and concomitant medications will be summarized overall for both food consumption groups as well as overall and by treatment sequence for each food consumption group, and by PT

and ATC 2nd level, respectively. The listing of previous and concomitant medications/procedures will be generated.

The listing of previous and concomitant procedures will be generated.

Missing or partial dates for medication/ procedure will not be imputed. In the case where it is not possible to define a medication/ procedure as previous or concomitant, the medication/ procedure will be classified by the worst case; i.e. considered as both previous and concomitant.

15 Treatment Compliance and Exposure

Population: Safety Population

Safety Population will be used to list the IMP administration. IMP administration will be listed by group, treatment sequence and subject with treatment, date and time of administration.

Missing or partial dates or time for IMP administration will not be imputed.

The food intake information will be listed by subject, treatment sequence for each group at Day 1 and Day 8.

16 Endpoint Evaluation

16.1 Primary Endpoint Analyses

The primary endpoints are the following PK parameters calculated from metformin plasma concentrations under fasting or fed condition:

C_{max} of metformin

$AUC_{0\rightarrow t}$ of metformin

The null and alternative hypotheses are the following:

$$H_0: \begin{array}{l} for\ AUC_{0-t}\ \ \mu_T/\mu_C \le 0.8\ or\ \mu_T/\mu_C \ge 1.25 \\ for\ C_{max}\ \ \mu_T/\mu_C \le 0.8\ or\ \mu_T/\mu_C \ge 1.25 \end{array}$$, for at least 1 primary endpoint

$$H_1: \begin{array}{l} for\ AUC_{0-t}\ 0.8 < \mu_T/\mu_C < 1.25 \\ for\ C_{max}\ \ 0.8 < \mu_T/\mu_C < 1.25 \end{array}$$, for both primary endpoints and for both fasting and fed groups

where μ_T and μ_C are the means of primary endpoints following test IMP and reference IMP (Treatment A and Treatment B), respectively.

The analysis of primary endpoints will be based on PK Population.

The primary endpoints, C_{max} and $AUC_{0\rightarrow t}$ in fasting and fed group, will be log-transformed and a mixed-effects model will be applied. The model will include fixed effects for sequence, treatment, and period and a random effect of subject nested within sequence. Treatment differences on the log scale will be estimated for the parameters together with their 90% CIs. The least squares mean together with their 95% CIs by treatment will also be estimated. Point estimates and CIs will be back-transformed to the original scale for presentation, i.e., ratios of geometric means and corresponding 90% CIs for Treatment A/Treatment B, and geometric means and corresponding 95% CIs by treatment, respectively. Intra-subject CV estimated from the model will also be presented. Bioequivalence will be assessed separately in the fed and in the fasted group, and the trial will be considered successful only if BE is established for both primary parameters in both groups. The BE will be considered established if the 90% CIs for the ratios of geometric means between the investigational product and the comparator fall within 80.00% to 125.00% for all these comparisons.

The following example code could be used:

```
proc mixed data=pkparam;
 by foodconsumption param;
 class sequence period trt subjid;
 model lnest = sequence period trt /ddfm=kr;
 random subjid(sequence);
 estimate 'A vs B' trt 1 -1 /alpha=0.1 cl;
 lsmeans trt /alpha=0.05 cl;

run;
```

All primary PK endpoints will be descriptively summarized as described in Section 16.3.2. Graphs of individual values and geometric mean will be presented for primary PK parameters versus treatment and food consumption condition. Boxplots will also be created for primary PK parameters versus treatment for the fed and the fasted conditions.

16.2 Secondary Endpoint Analyses

All secondary PK endpoints will be descriptively summarized as described in Section 11. The secondary PK endpoints are the following parameters in plasma for metformin:

t_{max}, $t_{1/2}$, λ_Z, $AUC_{0\rightarrow\infty}$, $AUC_{extra\%}$, $CL_{/f}$, $V_{z/f}$.

For t_{max}, the Hodges-Lehmann estimates for the treatment differences and corresponding 90% CIs according to the Tukey method will be calculated.

The mixed-effects model for treatment comparison as described for the primary endpoints will also be applied to $AUC_{0\rightarrow\infty}$. The ratios of geometric means and corresponding 90% CIs for Treatment A/Treatment B will be estimated separately for fed and fasted treatments. Graphs of individual $AUC_{0\rightarrow\infty}$ values and geometric mean will be presented by treatment and food consumption condition.

16.3 Other Endpoint Analyses

16.3.1 Analysis of PK Endpoints

Predose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration.

Pharmacokinetic concentrations which are erroneous due to a protocol deviation (as defined in the protocol), documented handling error or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed upon prior to performing a statistical analysis. In this case, the rationale for exclusion must be provided in the Clinical Study Report (CSR). Any other PK concentrations that appear implausible to the Pharmacokineticist must not be excluded from the analysis. Any implausible data will be documented in the CSR.

All statistical analyses and descriptive summaries of PK data will be performed on the PK Population. Pharmacokinetic concentrations will be listed for all subjects by treatment and fed/fasted group; concentrations excluded from the PK analysis will be flagged within the listing.

A listing of PK blood sample collection times by individual, as well as derived actual sampling time and time deviations, will be provided.

Plasma concentration data will be summarized descriptively for metformin as described in Section 10. Values below the LLOQ will be taken as zero for descriptive statistics of PK concentrations. Missing concentrations (e.g., no sample, insufficient sample volume for analysis, no result, or result not valid) will be reported and displayed generally as “N.R.”.

Samples that are collected outside the specified time windows will be included in the PK analysis but excluded from the concentration summary. The PK sampling collection schedule is presented in Table 8 below.

Table 8 Pharmacokinetic Sample Collection Schedule

Trial Day	Period Day	Time of Blood Sample (hour)	Window Allowance (minute)
1	1 - Predose in Period 1	Baseline blood draw (10 minutes prior to drug administration)	±2
1	1 – Single dose administration	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14	±2
2	2	24, 30, 36	±5
3	3	48	±5
4 – 7 (wash-out)	NA	NA	NA
8	1-Predose in Period 2	Baseline blood draw (10 minutes prior to drug administration)	±2
8	1 – Single dose administration	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14	±2
9	2	24, 30, 36	±5
10	3	48	±5
End of Trial (Day 15)/ Premature Withdrawal		1-sample	±30

Individual concentration-time profiles showing all subjects by treatment and fed/fasted group (i.e., individual subject overlay plots), and/or showing all treatment groups by subject (i.e., by-subject plots) will be created using the actual time points and the numeric concentration data. Arithmetic mean concentration-time profiles by treatment and fed/fasted group will be provided using scheduled (nominal) time points and the numeric concentration data. All concentration-time plots for PK data will be presented both on a linear and on a semi-logarithmic scale. Mean plots will include SD error bars when plotted on a linear scale.

16.3.2 Estimation of Individual Pharmacokinetic Parameters by Noncompartmental Analysis

For the PK analysis, predose sample concentrations that are below the LLOQ or that are missing will be assigned a numerical value of zero for the calculation of AUC. Any anomalous concentration values observed at predose will be identified in the CSR, and if the anomalous predose concentration value is greater than 5.00% of the C_{max} in the profile, the profile will be included in the PK analysis, but the concentration data and the corresponding derived PK parameters will be excluded from summaries and inferential statistics as appropriate; handling of the data will be documented in the CSR.

Pharmacokinetic parameters will be calculated using standard noncompartmental methods (calculation method: linear up log down) and the actual administered dose. Pharmacokinetic parameters will be calculated and listed for all volunteers who provide sufficient concentration-time data. At least 3 valid, postdose concentration points will be required in the PK profile to obtain any PK parameter estimate.

Pharmacokinetic parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data other than for a missing predose concentration as stated above.

For each subject in the PK Population the following PK parameters will be calculated for metformin, where appropriate:

Symbol	Definition
$AUC_{0\rightarrow t}$	The AUC from time zero (= dosing time) to the time the last concentration is at or above the LLOQ (t_{last}). Calculated using the mixed log linear trapezoidal rule (linear up, log down). Units: ng*h/mL.
$AUC_{0\rightarrow\infty}$	The AUC from time zero (= dosing time) extrapolated to infinity, based on the predicted value for the concentration at $t_{last,}$ as estimated using the linear regression from λ_z determination. $AUC_{0\rightarrow\infty} = AUC_{0\rightarrow t} + C_{last\ pred} / \lambda_z$. Units: ng*h/mL. The predicted $AUC_{0\rightarrow\infty}$ will be reported.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0\rightarrow\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0\rightarrow\infty}$) *100. The predicted $AUC_{0\rightarrow\infty}$ will be used. Units: %.
$CL_{/f}$	The apparent total body clearance of drug following extravascular administration, taking into account the fraction of dose absorbed. $CL_{/f} = Dose_{p.o.}/AUC_{0\rightarrow\infty}$. The predicted $AUC_{0\rightarrow\infty}$ will be used. The dose amount to be used for this calculation is 500 mg. Units: L/h.
C_{max}	Maximum observed concentration, taken directly from the observed concentration-time profile. Units: ng/mL.
t_{max}	The time to reach the maximum observed concentration (unless otherwise defined, take the first occurrence in case of multiple/identical C_{max} values). Units: h.
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$. Units: h.
$V_{z/f}$	The apparent volume of distribution during the terminal phase following extravascular administration, based on the fraction of dose absorbed. $V_{z/f}$ = Dose/*$AUC_{0\rightarrow\infty}$*λ_z) following single dose. The predicted $AUC_{0\rightarrow\infty}$ will be used. Units: L.

λ_z	Terminal elimination rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve. Units: h^{-1}.

The predicted $AUC_{0\rightarrow\infty}$ will be reported and used in the determination of other parameter estimates, i.e., $AUC_{extra\%}$, $CL_{/f}$, and $V_{z/f}$. The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- The time interval (h) of the log-linear regression ($\lambda_{z\ lower}$, $\lambda_{z\ upper}$) to determine λ_z.
- Number of data points (N_λ) included in the log-linear regression analysis to determine λ_z.
- Goodness-of-fit statistic (Rsq) for calculation of λ_z.

The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin best fit methodology will be used as standard. The last quantifiable concentration should always be included in the regression analysis, while the concentration at t_{max} and any concentrations below the LLOQ which occur after the last quantifiable data point should not be used.

The Rsq should be ≥0.800 and the observation period over which the regression line is estimated should be at least two-fold the resulting $t_{1/2}$ itself. If these criteria are not met, then the rate constants and all derived parameters (e.g., $AUC_{0\rightarrow\infty}$, $AUC_{extra\%}$, $CL_{/f}$, $t_{1/2}$, and $V_{z/f}$.) will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. Any flags should be included in the study specific SDTM.

To ensure a reliable estimate of the extent of exposure in pivotal trials (e.g., BE), $AUC_{extra\%}$ should be less than or equal to 20.0%. If $AUC_{extra\%}$ is greater than 20.0%, all parameters derived using λ_z (i.e., $AUC_{0\rightarrow\infty}$, $AUC_{extra\%}$, λ_z, $t_{1/2}$, $V_{z/f}$, and $CL_{/f}$) will not be included in the calculation of descriptive statistics or statistical analyses.

The dose amount for IMP administered is that of the active, free drug substance only, and is synonymous with the measured analyte. No adjustment for the dose amount value of IMP will be applied when ‘dose’ is used in calculating PK parameters with formulas needing a dose value.

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

17 Safety Evaluation

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests, ECG recordings and vital signs. Safety analyses will be done on the Safety Population. All safety data will be listed in individual subject listings by group, treatment sequence and subject.

All safety variables will be analyzed using descriptive statistics. For the evaluation of safety parameters, the continuous variables will be summarized descriptively by N, mean, median, SD, Q1-Q3, and minimum and maximum values.

17.1 Adverse Events

AEs will be coded using the MedDRA Version 21.0or higher.

An AE will be considered as 'treatment emergent' if it occurred after the first IMP administration of each period or if it was present prior to first IMP administration but exacerbated after the first IMP administration of each period. All other adverse events will be considered ‘pre-treatment’.

In the case where it is not possible to define an AE as TEAE or not, the AE will be classified as TEAE as the most conservative approach.

The AE listings will include the following items:

- System organ class
- Preferred term
- Investigator’s description
- Whether the event is treatment-emergent
- Trial treatment at onset of event
- Date and time of onset and resolution
- Duration of the event
- Date and time of last administration before AE
- Study Day
- Severity
- Causality relationship to investigational product
- Outcome
- Action taken to investigational product
- Other action

- Seriousness

17.1.1 All Adverse Events

A summary table describing all the TEAEs occurring during the trial will be produced overall and by group as well as by treatment for each group using frequency of events and number and percentage of subjects experiencing these events overall and by SOC and PT.

Group/SOC terms will be sorted by decreasing total frequency. Preferred terms (PT) within each group/SOC term will likewise be sorted by decreasing total frequency.

In addition, all TEAEs will be tabulated by severity and relationship to IMP in the same manner.

The relationship to the trial treatment, as indicated by the investigator, is classified as 'unrelated' or 'related'. TEAE with a related or missing relationship to the trial treatment will be regarded as 'related'.

Multiple occurrences of the same TEAE in one subject during the same treatment in the trial will be counted as multiple events in the frequency counts for adverse events. If a subject experiences more than one occurrence of the same AE during the same treatment in the trial, the subject will only be counted once for that treatment using the worst severity and the strongest relationship. The AE will be categorized as 'unrelated' only when all relationship records are 'unrelated', otherwise it will be classed as 'related' in the corresponding relationship summaries.

In case a subject had events with missing and non-missing severities, the maximum of the non-missing severities will be displayed. In case all the TEAEs of a subject are all with missing severities then Moderate will be used unless there is any evidence that it should be Severe.

17.1.2 Adverse Events Leading to Treatment Discontinuation

AEs leading to permanent discontinuation of IMP will be identified as those records with a response of "Drug Withdrawn" to the item "Action taken with study drug" on the "Adverse Events Details" page of the eCRF.

For AEs leading to discontinuation of IMP, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

All adverse events leading to trial or treatment discontinuation will be listed by group, treatment sequence and subject including SOC, PT and investigators' verbatim.

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

17.2.1 Deaths

AEs leading to Death are those events which are recorded as "Fatal" to the item "Change in severity and outcome" on the "Adverse Events Details" page of the eCRF. AEs leading to deaths will be listed by group, treatment sequence and subject including SOC, PT and investigators' verbatim, if applicable.

17.2.2 Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Yes" to the item "Serious adverse event" on the "Adverse Events Details" page of the eCRF. All SAEs will be listed by group, treatment sequence and subject including SOC, PT and investigators' verbatim.

17.3 Clinical Laboratory Evaluation

Results from the central laboratory will be included in the reporting of this study for hematology, biochemistry, and urinalysis. Laboratory evaluations to be included in the outputs are as below:

Hematology: Erythrocytes, Hemoglobin, Hematocrit, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Red blood cell distribution width, Platelets, Mean platelet volume, Thrombocytocrit, Platelet distribution width, White blood cells, Neutrophils (both percentage and absolute counts), Monocytes (both percentage and absolute counts), Lymphocytes (both percentage and absolute counts).

Biochemistry: Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Total Bilirubin, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Protein total, Albumin, Globulin, Albumin/globulin ratio, Alkaline Phosphatase, Glutamyl Transpeptidase, Urea Nitrogen, Creatinine, Cholesterol, Triglycerides, Glucose, Creatine Kinase, Creatine Phosphokinase MB Isoenzyme, Lactate Dehydrogenase, Calcium, Phosphorus, α -Amylase, Sodium, Potassium, Chloride.

Urinalysis: Appearance, Blood, Nitrite, Ketone, Protein, Glucose, Leukocytes, pH, Microscopic examination (Microscopic examination will be performed if dipstick test is positive for leukocytes, blood, nitrites, or proteins).

All hematology, biochemistry and urinalysis quantitative parameters will be summarized using descriptive statistics overall and by treatment sequence for each group at baseline and at end of study visit with raw data and change from baseline.

For all hematology and biochemistry parameters, frequency tables based on the classification of values as Low, Normal, High and Missing with respect to the reference ranges will be summarized by treatment sequence at baseline and end of study for each group. Frequency tables of urinalysis will be summarized by treatment sequence at baseline and end of study for each group, based on different types of classification rules. For urinalysis parameter, pH, the classification of values as Low, Normal, High and Missing will be applied. For urinalysis parameters, Blood, Nitrite, Ketone, Protein and Glucose, the classification of values as Normal/-, +-, +, ++, +++, ++++ will be applied. For urinalysis parameters, Appearance and Microscopic Examination, the classification of values

as Normal, Abnormal, Missing, or Total will be applied. For urinalysis parameters, Leukocytes, the classification of values as Not Negative, Negative, Missing and Total will be applied.

In addition, shift tables from baseline to end of study for all hematology, biochemistry and urinalysis will be summarized and presented by treatment sequence for each group at End of Study.

All marked abnormal laboratory values will be listed by subject, treatment sequence and group.

All data will be listed by group, treatment sequence, subject, treatment, visit, and time point.

17.4 Vital Signs

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Temperature (^{0}C)
- Respiratory Rate (breaths/min)

Systolic and diastolic blood pressures (mmHg) and pulse rate (beats/min) measurements as well as body temperature (°C) and respiration (breaths/min) will be presented by descriptive statistics overall and by treatment sequence for each group at baseline and end of study visit, and by group, treatment and time point for the values obtained during the treatment periods as raw data and change from baseline in the corresponding treatment period.

Frequency tables based on the classification of values as Low, Normal, High and Missing with respect to the reference ranges will be summarized by treatment sequence at end of study for each group, and by group, treatment and time point for the values obtained during the treatment period.

All marked abnormal for vital signs values will be listed.

All data will be listed by group, treatment sequence, subject, treatment, visit, and time point.

Markedly abnormal quantitative Vital Sign measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	< 85 mmHg	> 139 mmHg
DBP	mmHg	< 50 mmHg	> 90 mmHg

Variable	Unit	Low	High
Pulse rate	bpm	< 50 Beats/min	> 100 Beats/min
Body temperature	˚C	< 36 ^{0}C	> 37.3 ^{0}C

17.5 Other Safety or Tolerability Evaluations

17.5.1 ECG Evaluation

Results from the 12-Led Electrocardiogram (ECG) be presented by descriptive statistics overall and by treatment sequence for each group at baseline and end of study visit.

The following ECG parameters will be reported for this study:

- RR Interval (ms)
- PR Interval (ms)
- QRS Duration (ms)
- QT Interval (ms)
- QTcB (Bazett) (ms)
- QTcF (Fridericia) (ms)
- Heart Rate (beats/min)
- Rhythm (sinusal – other).

Frequency tables for overall evaluation of ECG based on the classification of values as Normal, ANCS (Abnormal, Not Clinically Significant), ACS (Abnormal, Clinically Significant) and Missing will be presented by treatment sequence and overall for each group at the end of study visit.

12-lead ECG parameters and result of ECG will be listed in individual subject listing by group, treatment sequence, subject, visit, treatment and time point. All marked abnormal values of ECG evaluation will be listed by subject, treatment sequence and group.

17.5.2 Physical Examinations, and Chest X-ray

Full physical examination and chest X-ray examination will be performed, abnormal values will be marked in listing.

18 References

1. Merck Clinical Study Report (EMR200084-108) "A randomized, open-label trial assessing the bioequivalence between single doses of 500 mg Glucophage XR Tablets (Merck/ Darmstadt) and 500 mg Glucophage XR Tablets (BMS/ Mt. Vernon) under fed and fasted state in two 2-way-crossover groups in healthy volunteers".

2. Chinese Food and Drug Administration Guideline: “Technical Guidelines for Human Bioequivalence Studies with Pharmacokinetic Endpoints for Chemical Generic Drugs” Released March 2016.