Statistical Analysis Plan

Bioequivalence Protocol Identification No.	PPD Project Code : PPD Merck Protocol Number : MS200084_0015
Title:	A randomized, open-label, two-way crossover study assessing the bioequivalence (BE) between single dose of 750 mg Glucophage® XR Tablets (PT Merck Tbk, Jakarta, Indonesia-Manufactured) and 750 mg Glucophage® XR Tablets (Merck Santé, Semoy, France-Manufactured) under fasted state in healthy subjects
Study Phase	Phase I (Bioequivalence Study)
Investigational Medicinal Product(s)	Glucophage XR® 750 mg
Clinical Study Protocol Version	Version 1.1, 22-May-2018
Statistical Analysis Plan Author	PPD
Statistical Analysis Plan Date and Version	Version 1.0, 06-Sep-2018
Statistical Analysis Plan Reviewers	PPD, PPD PPD, Clinical Pharmacologist PPD, Clinical Pharmacologist PPD, Local Medical Responsible

1 Signature Page

Statistical Analysis Plan: MS200084_0015

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2 Table of Contents

List of Tables

3 List of Abbreviations and Definition of Terms

µL	Microlitre
AE	Adverse Event
ALT	Alanine minotransferase
ANOVA	Analysis of Variance
AP	Alkaline Phosphatase
ASEAN	Association of Southeast Asian Nations
AST	Aspartate aminotransferase
AUC_{0-inf}	Area under plasma concentration versus time curve extrapolated to infinite time
AUC_{0-t}	Area under plasma concentration versus time curve from administration to last observed concentration at time t
BPOM	*Badan Pengawasan Obat dan Makanan* (the Indonesian National Agency of Drug and Food Control, NA-DFC)
BE	Bioequivalence
BMI	Body mass index
BP	Blood pressure
BQL	Below the quantification limit
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CRF	Case Report Form
CV	Coefficient of variation
CSR	Clinical Study Report
dL	Decilitre
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	Ehrlich units (corresponding to one milligram of urobilinogen per deciliter of sample)
F	Female
FDA	Food and Drug Administration
FU	Follow-up
g	Gram
GCP	Good Clinical Practice

h	Hour
Hb	Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPF	High Power Field
HPLC-UV	High Performance Liquid Chromatography with Ultraviolet Detector
ICH	International Conference on Harmonization
ID	Identification
IU	International Unit
kg	Kilogram
L	Litre
ln	Natural logarithm
M	Male
m	Metre
Max	Maximum
Mean	Arithmetic mean
mg	Milligram
ms	Milliseconds
Min	Minimum
min	Minute(s)
mL	Millilitre
mmHg	Millimetre mercury column
N	Number of non-missing observations
Neg.	Negative
PK	Pharmacokinetics
Pos.	Positive
QTc	Corrected QT interval
R	Comparator drug
RBC	Red Blood Cells

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
T	Test drug
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum plasma concentration
ULN	Upper limit of normal
WBC	White Blood Cells
WHO-ART	World Health Organization Adverse Reaction Terminology
WOCBP	Women of childbearing potential
XR	Extended Release
yr	Year

4 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
1.0	06-Sep-2018	PPD	Not applicable

5 Purpose of the Statistical Analysis Plan

The purpose of this SAP is to document technical and detailed specifications for the final analysis of data collected for study protocol MS200084_0015. Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). 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 the study protocol (version 1.1 dated 22 May 2018) and is prepared in compliance with ICH E9.

6 Summary of Clinical Study Features

Objective

Primary objective:

- To assess bioequivalence between metformin hydrochloride (Glucophage® XR) manufactured in PT Merck Tbk, Indonesia (test drug) and metformin hydrochloride (Glucophage® XR) manufactured in Merck Sante, France (comparator drug) following single oral dose administration under fasting condition.

Secondary objective:

- To compare pharmacokinetic parameters of metformin after single dose administrations of test and comparator (reference) drugs.
- To examine the safety and tolerability of metformin after single dose administrations of test and comparator (reference) drugs.

Study Design

An open-label, randomized, single-dose, two-period, two-sequence crossover study under fasting conditions

Study Subjects

Forty-eight (48) healthy adult male and female subjects

Dosing Regimen

- One (1) Glucophage® XR 750 mg Tablet produced by PT Merck Tbk, Indonesia of test drug (T) given as a single oral dose with approximately 200 mL of water at ambient temperature after an overnight fast of at least 10 hours.
- One (1) Glucophage® XR 750 mg Tablet produced by Merck Sante, France of comparator drug (R) given as a single oral dose with approximately 200 mL of water at ambient temperature after an overnight fast of at least 10 hours.

Washout

At least 7 days between doses.

Duration of the Clinical Phase

The duration of the clinical phase (from Screening through Follow-Up Study) will be approximately 6 weeks.

Inclusion criteria:

- Subject has provided written informed consent prior to the conduct of any study-related activities.
- Male and female subjects.
- Aged between 18 and 55 years, inclusive.
- Body mass index of 18 to 25 kg/m^2.
- Good physical and mental health status, determined on the basis of medical history and physical examination.
- Vital signs (blood pressure, pulse rate, respiratory rate and body temperature) in sitting position within the normal range or showing no clinically relevant deviation per the Investigator's opinion.
- All values for laboratory assessments (hematology, clinical chemistry and urinalysis) within the normal range or showing no clinically relevant deviation per the Investigator's opinion.
- No clinically significant abnormality on 12-lead electrocardiogram (ECG) recording as judged by the Investigator; QTc (Bazett) should be ≤ 450ms.
- Non-smoker or smoker less than 10 cigarettes per day.
- Women of childbearing potential (WOCBP) who are not nursing, are not pregnant, and are using highly effective methods of birth control (defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly) for a period of at least one month before and after dosing. Standard birth control methods are considered to be: oral or implanted contraceptive therapy and intra-uterine devices. Female subjects may also be enrolled if they are postmenopausal (i.e., at least

12 consecutive months of amenorrhea after the last menstrual period) or surgically sterilized/ hysterectomized at least 6 months prior to study participation.

- WOCBP must have a negative urine pregnancy test at Screening and on each admission (Day 1 of each dosing period).
- Negative screen for alcohol and drugs abuse (opiate class, barbiturates, cocaine and metabolites, amphetamines, cannabinoids and benzodiazepines) at Screening and on each admission (Day 1 of each dosing period).
- Negative screen for Hepatitis B surface antigen (HBsAg), HCV antibodies and/or HIV antibodies.

Exclusion criteria:

- Participation in a clinical study within 90 days prior to Screening.
- Blood donation (equal or more than 300 mL) or significant blood loss within 90 days prior to first drug administration.
- Any surgical or medical condition, including findings in the medical history or in the pre-study assessments, or any other significant disease, that in the opinion of the investigator, constitutes a risk or a contraindication for the participation of the subject in the study or that could interfere with the study objectives, conduct or evaluation.
- History of malignant diseases, except in-situ basal cell skin tumors treated with curative intent.
- History of surgery of the gastrointestinal tract which could influence the gastrointestinal absorption and/or motility per the Investigator's opinion.
- History or presence of relevant liver diseases or hepatic dysfunction (laboratory result for liver function test ≥ 1.5 ULN).
- History or presence of renal failure or renal dysfunction based on clinical symptoms and finding (serum creatinine concentration >1.4 mg/mL).
- Ascertained or presumptive hypersensitivity to the active drug substance and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study.
- Receipt of any prescription or non-prescription medication within 14 days before the first drug administration, except for hormonal contraceptives in female, and including multivitamins and herbal products (e.g. St John's Wort).
- Consumption of large quantities of methylxanthine-containing beverages (> 5 cups of coffee/day or equivalent).
- Consumption of grapefruit, orange, cranberry or juices of these three fruits, 24 hours prior to drug administration.
- Known lack of subject compliance or inability to communicate or cooperate with the Investigator (e.g., language problem, poor mental status).

Pharmacokinetic Sampling

- Eighteen (18) blood samples (1 x 10 mL and 17 × 5 mL) per subject in each period for drug content analysis.
- A 10-mL blood sample (control) will be drawn from fasting subjects immediately before drug administration.
- Subsequent blood samples are drawn 5 mL each at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, and 32 hours after drug administration.
- Subjects who complete both periods will have a total of 36 blood samples collected. Total blood volume collection is approximately 210 mL (including 10 mL for Screening, 10 mL for each pre-dose period, 85 mL during each dosing period, and 10 mL for Follow-Up Visit).

Bioanalytical Sample Analyses

The metformin plasma concentrations will be measured using a validated high-performance liquid chromatography with ultraviolet detection (HPLC-UV; Waters™, PPD) and according to the bioanalytical laboratory's standard operating procedures and applicable regulatory requirements.

Pharmacokinetic Parameters

Pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, and $t_{½}$

Statistical Methods

- Pharmacokinetic analyses will be performed using standard non-compartmental methods of Phoenix® WinNonlin (PPD).
- The statistical method for testing bioequivalence is ANOVA for two-period, two-sequence, two-treatment cross-over comparing AUC_{0-t} and C_{max} after ln transformation of the original values. The terms to be used in the ANOVA model are sequence, subject within sequence, period, and formulation. The t_{max} are compared using non-parametric test from the original data. The difference in t_{max} will be analyzed non-parametrically on the original data using Wilcoxon matched-pairs test. The $t_{½}$ difference will be analyzed using Student's paired t-test or Wilcoxon matched-pairs test depending whether the differences of the paired data were distributed normally or not.

Bioequivalence Criteria

Bioequivalence is concluded if the 90% confidence interval of the Test/Reference geometric means ratio is in the range of 80.00-125.00% for AUC_{0-t} and C_{max}. This acceptance criterion is according to the Guideline on the Investigation of Bioequivalence, EMA, London, 2010; ASEAN Guideline for the Conduct of Bioequivalence Study, Lao PDR, 2015; and *Indonesian guidelines, Pedoman Uji Bioekivalensi, Badan Pengawas Obat dan Makanan (BPOM), Jakarta, 2015, page 37-38*.

7 Sample Size/Randomization

The number of subjects needed for a bioequivalence study was calculated with the following equation:

$$N = \frac{2 \cdot s_w^2 \cdot \left(Z_{1-\beta} + Z_{1-\alpha}\right)^2}{\left(Ln\left(\mu_T / \mu_R\right) - Ln(1.25)\right)^2}$$

$$S^2_w = Ln(1 + (CV)^2)$$

α : significance level (5%)
β : power (20%)
μ_T : average score of bioavailability parameters for the test drug
μ_R : average score of bioavailability parameters for the comparator drug
CV : intra-subject CV

CCI [redacted]. If these CVs are applied together with applicable bioequivalence criteria for AUC and C_{max} (0.80-1.25), and the true treatment ratio Test/Reference is allowed to vary within 0.95 and 1.05, then 44 evaluable subjects will provide at least 90% power to show bioequivalence. Per *Indonesian guidelines, Pedoman Uji Bioekivalensi, Badan Pengawas Obat dan Makanan (BPOM), Jakarta, 2015, page 20*, only 80% power is required at the minimum.

For a compensation of possible drop-outs during the study, an additional four (4) subjects shall be included based on the site's standard practice. Subjects will not be replaced, even if there are more than four (4) drop-outs.

A total of forty-eight (48) healthy adult male and female subjects shall thus be included in this study with no reserve subjects. 48 subjects will be administered with the study drug and the blood will be taken at various time points of blood sampling procedures. The blood samples from 48 subjects will be analyzed for plasma concentrations of metformin.

Randomization Sequence

Sequence 1 = TR (24 subjects)

Sequence 2 = RT (24 subjects)

The randomization code is tabulated for all subjects according to block randomization with a block size of 4 (Dixon & Massey, 1969, page 449). Subjects will be randomly allocated to one of the 2 treatment sequences (TR or RT) based on their assigned subject number. The randomization to a treatment sequence will be performed before the first period of the study.

Each study drug (test and reference drug) will be placed in a sealed envelope indicated with the subject number and its intended period and segregated in different labeled boxes kept in a limited access drug storage room. The study drugs will be dispensed to the study subjects by an

unblinded pharmacist prior to time of dosing. The randomization will be balanced according to subject number and the randomization code will be kept under controlled access. The clinical personnel administering the study drugs and the subjects are not blinded. The randomization code will not be available to the bioanalytical personnel (blinded for bioanalytical facility) till code breaking.

Code breaking will be performed after database lock i.e. after analysis of all blood samples has been finalized, and all PK parameters have been calculated. Sponsor's green light has to be obtained prior to code breaking, upon satisfying pre-defined conditions.

8 Overview of Planned Analyses

Pharmacokinetic and statistical analyses will be performed for metformin plasma data.

For pharmacokinetic calculations the actual sampling time will be used for any deviation in sample collection time (for post-dose blood sampling time points) from the scheduled time beyond the specified window period.

All concentration values below the quantification limit (BQL) will be set to zero for all pharmacokinetic and statistical calculations. However, it will be reported as BQL in the CSR (FDA, Bioanalytical Method Validation, May 2018, p.13).

If the pre-dose concentration is ≤ 5 percent of C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations. If there are any subjects for whom the pre-dose concentration is > 5 percent of the C_{max} value for the subject in that period, the subject will be dropped from all BE study evaluations.

Pharmacokinetic analyses will be performed using standard non-compartmental methods of Phoenix® WinNonlin® (PPD).

The statistical method for testing bioequivalence is ANOVA for 2-period, 2-sequence, 2-treatment cross-over comparing AUC_{0-t} and C_{max} after ln transformation of the original values. The t_{max} are compared using non-parametric test from the original data. The difference in t_{max} will be analyzed non-parametrically on the original data using Wilcoxon matched-pairs test. The $t_{½}$ difference will be analyzed using Student's paired t-test or Wilcoxon matched-pairs test depending whether the differences of the paired data were distributed normally or not.

9 Changes to the Planned Analyses in the Clinical Study Protocol

The statistical methods as described in the protocol were adopted. There are no changes to the planned analyses.

10 Protocol Deviations and Analysis Sets

10.1 Definition of Protocol Deviations

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.

Important protocol deviations include:

- 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;
- Deviations from scheduled sampling time points outside of the defined window period;
- Deviation from GCP.

10.2 Definition of Analysis Sets and Subgroups

Safety Analysis Set

The safety analysis will include all subjects who have received at least one dose of the investigational product and have had one subsequent safety assessment.

PK Analysis Set

The PK analysis set will include all subjects without any relevant protocol deviations with respect to PK and absence of factors likely to affect the comparability of PK results, with adequate trial medication compliance, and who have valid primary endpoints for both treatment.

11 General Specifications for Statistical Analyses

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

PK parameter data will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean, and the 90% confidence interval.

For the calculation of descriptive statistics and the statistical analysis, values as presented in the data listing will be used. Minimum and maximum will be presented to the same decimal precision as collected. Mean, median, and SD estimates will be presented to one decimal place

more than the precision of the data collected. CV will always be reported to 1 decimal place. Derived parameters will be reported using similar precision to those from which they were derived.

12 Study Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

12.1 Disposition of Subjects and Discontinuations

The Investigator may withdraw a subject from the study based on following reasons:

- Withdrawal of subject's consent;
- Significant protocol violation, such as non-compliance with restriction regarding alcohol and drug use, and non-adherence to the fasting condition;
- Adverse events, as assessed by the Investigator to affect the subject safety or the outcome of the study endpoints;
- Difficulties with blood collection;
- Subject who vomits anytime during PK blood sampling will be excluded from the remainder of the study (including the rest of the periods if the adverse event occurred in the earlier ones). The subject will be advised to remain in the clinic for the rest of the confinement period for observation and so any safety related study procedures can be carried out;
- Subject reports adverse events of diarrhea (more than three episodes of loose stools) in any PK blood sampling period, which could render the plasma concentration-time profile unreliable;
- Subject is uncooperative during the study;
- Use of any ongoing or concomitant medication.

Subject may withdraw from the study at any time without any reason. Subjects who do not attend Study Check-In or withdraw during the study will be recorded in the Log Book of Non-Conformities Work. If the subject discontinues from the study at any time after taking the first dose of the study drug, the Case Report Form (CRF) would be completed accordingly and drug concentration will be analyzed. If a subject is discontinued early, all termination evaluations will be performed at the time of discontinuation. Details of reasons for premature withdrawal of subjects will be documented in the CSR.

12.2 Protocol Deviations

12.2.1 Important Protocol Deviations

All protocol deviations will be listed in the CSR.

12.2.2 Reasons Leading to the Exclusion from an Analysis Set

All criteria/reasons leading to the exclusion of a subject from pharmacokinetic and statistical analyses will be summarized and listed in the CSR (see section 10.1).

13 Demographics and Other Baseline Characteristics

13.1 Demographics

Demographic characteristics will be reported (Table 1) using the following information from the Screening Visit CRF pages.

- Demographic characteristics
  - Gender: male, female
  - Race/Ethnic: Asian (Indonesia or other)
  - Age (years): summary statistics
  - Body weight
  - Body height
  - Body mass index (BMI)
  - Smoking status

Table 1 Demographic Data

Demographic Characteristic	Statistics	Treatment Test Drug (N = …)	Treatment Comparator Drug (N = …)
Age (years)	Mean ± SD	0.0 ± 0.0	0.0 ± 0.0
	Range	0 – 0	0 – 0
Gender, n (%)	Male	0 (0.0%)	0 (0.0%)
	Female	0 (0.0%)	0 (0.0%)
Race, n (%)	Indonesian	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	0 (0.0%)
Body weight (kg)	Mean ± SD	0.00 ± 0.00	0.00 ± 0.00
	Range	0.0 – 0.0	0.0 – 0.0
Body height (cm)	Mean ± SD	0.00 ± 0.00	0.00 ± 0.00
	Range	0.0 – 0.0	0.0 – 0.0
Body Mass Index	Mean ± SD	0.000 ± 0.000	0.000 ± 0.000
	Range	0.0 – 0.0	0.0 – 0.0
Smoke, n (%)	Non-smoker	0 (0.0%)	0 (0.0%)
	Smoke <10 cig./day	0 (0.0%)	0 (0.0%)

13.2 Medical History

Medical history of all subjects will be recorded in the CRF and will not be presented in the CSR.

13.3 Other Baseline Characteristics

Vital signs measurements (listed in Table 10), clinical laboratory test results, ECG findings, and physical examination during Screening will be recorded in the CRF and reported in the CSR (Table 2).

Table 2 Clinical Laboratory Test and ECG of Subjects

Parameter	Unit	Subject ID (Initials) (SUBJECT ID) (INITIAL) (GENDER)	(SUBJECT ID) (INITIAL) (GENDER)	(SUBJECT ID) (INITIAL) (GENDER)	(SUBJECT ID) (INITIAL) (GENDER)	Normal Values
Screening						
Hematology						
Leucocyte	x 10^3/µL					M :3.8 - 10.6 F: 3.6 - 11.0
Erythrocyte	x 10^6/µL					M :4.4 - 5.9 F: 3.8 - 5.2
Hb	g/dL					M:13.2 - 17.3 F: 11.7 -15.5
Hematocrit	%					M :40 - 52 F: 35 - 47
Thrombocyte	x 10^3/µL					150 - 440
Sero-immunology						
HBsAg						Neg.
Anti-HCV						Neg.
Anti-HIV						Neg.
Blood Chemistry						
Total bilirubin	mg/dL					< 1.2
Direct bilirubin	mg/dL					< 0.50
AST	IU/L					M: < 35 F: <31
ALT	IU/L					M: < 45 F:<34
AP	IU/L					M: 53 - 128 F: 42 - 98
Albumin	g/dL					3.5 - 5.2
Total protein	g/dL					6.4 - 8.3
Blood glucose	mg/dL					<140
Ureum	mg/dL					13 - 43
Creatinine	mg/dL					M: 0.67 - 1.17 F: 0.51 - 0.95
Urinalysis						
Clarity						Clear
Color						Yellow
Glucose						Neg.
Bilirubin						Neg.
Ketone						Neg.
Specific Gravity						1.015 - 1.025
Blood						Neg.
pH						5 - 8
Protein						Neg.
Urobilinogen	EU/dL					0.2 - 1.0
Nitrite						Neg.
Leucocyte						Neg.
Sediment:						
- RBC	cells/HPF					0 - 2
- WBC	cells/HPF					0 - 5
- cast						Neg.
- epithel: squamous						Neg./ Pos.
transitional						Neg./ Pos.
tubular						Neg./ Pos.
- crystal						Neg./ Pos.
- bacteria						Neg. for male

Parameter	Unit	Subject ID (Initials) (SUBJECT ID) (INITIAL) (GENDER)	(SUBJECT ID) (INITIAL) (GENDER)	(SUBJECT ID) (INITIAL) (GENDER)	(SUBJECT ID) (INITIAL) (GENDER)	Normal Values
Alcohol Test						
Urine Drug Test						
- Barbiturates						Neg.
- Cocaine						Neg.
- Amphetamine						Neg.
- Cannabinoid						Neg.
- Morphine						Neg.
- Benzodiazepine						Neg.
Urine HCG Test						
ECG Conclusion						Normal Sinus Rhythm
Period 1						
Alcohol test						Neg.
Urine Drug Test						
- Barbiturates						
- Cocaine						
- Amphetamine						Neg.
- Cannabinoid						Neg.
- Morphine						Neg.
- Benzodiazepine						Neg.
Urine HCG Test						
Period 2						
Alcohol test						Neg.
Urine Drug Test						
- Barbiturates						
- Cocaine						
- Amphetamine						Neg.
- Cannabinoid						Neg.
- Morphine						Neg.
- Benzodiazepine						Neg.
Urine HCG Test						

*deviate from normal values, but not clinically significant
° lead to screen failure

14 Previous or Concomitant Medications/Procedures

Concomitant treatments are medications, other than investigational product, which are taken by subjects any time during the study.

Previous medications are medications, other than investigational product, which started within 14 days before first drug administration.

All previous or concomitant medications, which were undertaken any time during study, will be summarized in the CRF. The Brand/Generic Name of the concomitant medications will be reported in the CRF.

15 Treatment Compliance and Exposure

This bioequivalence study is a single oral dose administration.

All dosing and treatment compliance, including the date and time of drug administration, will be recorded on "B2 Dosing" and "C2 Dosing" CRFs pages and will not be presented in the CSR.

16 Endpoint Evaluation

16.1 Primary Endpoint Analyses

The primary endpoints are C_{max} and AUC_{0-t} for metformin concentration in plasma.

The statistical method for testing bioequivalence is ANOVA for 2-period, 2-sequence, 2-treatment cross-over comparing AUC_{0-t} and C_{max} after ln transformation of the original values.

Bioequivalence is concluded if the 90% confidence interval of the Test/Reference geometric means ratio is in the range of 80.00-125.00% for AUC_{0-t} and C_{max}. This acceptance criterion is according to the Guideline on the Investigation of Bioequivalence, EMA, London, 2010; ASEAN Guideline for the Conduct of Bioequivalence Study, Lao PDR, 2015; and Indonesian guidelines, *Pedoman Uji Bioekivalensi, Badan Pengawas Obat dan Makanan (BPOM)*, Jakarta, 2015, page 37-38.

Phoenix® WinNonlin (PPD) will be used to perform the statistical analyses of AUC_{0-t} and C_{max} using analysis of variance (ANOVA) with the factors TREATMENT, PERIOD, SEQUENCE and SUBJECT(SEQUENCE) after transformation of the data to their natural logarithmic (ln) values. Mean treatment differences will be estimated using the ANOVA model above. 90% confidence intervals will be computed for the treatment differences based on the residual error term. Differences and CIs will result in ratios and corresponding CIs after back-transformation.

16.2 Secondary Endpoint Analyses

The secondary endpoints are t_{max}, AUC_{0-inf} and $t_{1/2}$ for metformin concentration in plasma.

The difference in t_{max} will be analyzed non-parametrically on the original data using Wilcoxon matched-pairs test.

The $t_{½}$ difference will be analyzed using Student's paired t-test or Wilcoxon matched-pairs test depending whether the differences of the paired data were distributed normally or not (tested with *Kolmogorov-Smirnov*).

16.3 Estimation of Individual PK Parameters

Pharmacokinetic parameters will be calculated using standard non-compartmental methods Phoenix® WinNonlin® version 8.0, or higher (PPD) as defined below

Symbol	Definition
AUC_{0-t}	area under plasma concentration curve from administration to last observed concentration at time t
AUC_{0-inf}	Area under plasma concentration from time zero (dosing time) extrapolated to infinite time. AUC_{0-inf} will be calculated as $AUC_{0-t} + C_t/k_e$, where C_t is the last observed plasma concentration; k_e is the terminal elimination rate constant and will be determined by least-squares regression analysis during the terminal log-linear phase of the concentration–time curve
C_{max}	Maximum observed plasma concentration
$t_{1/2}$	Terminal phase half-life time. $t_{1/2} = \ln(2)/ k_e$
t_{max}	The time to reach the maximum observed concentration (C_{max})

All concentration values below the quantification limit (BQL) will be set to zero for all pharmacokinetic and statistical calculations.

17 Safety Evaluation

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings (including body weight and height measurements), and use of concomitant medication. Adverse events, laboratory tests and vital signs will be recorded in the CRF and tabulated in the CSR.

17.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. WHO-ART will be used as coding dictionary of adverse events. All adverse events will be listed.

The following summary tables will be presented for treatment emergent AEs:

- Summary of TEAEs by SOC, PT and treatment
- Summary of TEAEs by SOC, PT, intensity and treatment

- Summary of TEAEs by SOC, PT, causality and treatment

The denominator for the percentages in the summaries will be the number of subjects in the safety population for each treatment.

17.1.1 All Adverse Events

All of adverse events occurred during the study will be listed in the CSR (Table 3). An overview of all adverse events will be presented in Table 4. Adverse reaction (from test and comparator drug) would be categorized as unrelated, unlikely, possibly related, probably, and definite related based on literature data and pharmacokinetics profile (Table 5). All adverse events, regardless of severity, will be followed up and recorded by the investigator. All adverse events will be recorded in the CRF and tabulated in the CSR.

Table 3 List of Adverse Events Occurred

Listing All Adverse Events											
Period (I or II) Treatment	**Subject No.**	**System Organ Class/ Preferred Term/ Reported Term**	**Serious criteria**	**Start Date**	**End Date (AE Duration)**	**Severity**	**Relationship to IMP**	**Action taken with study treatment**	**Other action taken**	**Outcome**	**Comment**
Period I Reference	…	…/ …/ …	No	yyyy-mm-dd, hh:mm	yyyy-mm-dd, hh mm (dd,hh,mm)	…	…	…	…	…	…
Period 2 Test											

Table 4 Overview of all Adverse Events (by Group and Overall)

	Test Drug (N=xx)	**Comparator Drug (N=xx)**	**All (N=xx)**
Subjects with any AE (%)	0 (00.0%)	0 (00.0%)	0 (00.0%)
Number of all AEs	0	0	0
Number of treatment emergent AEs	0	0	0
Drug-related AEs	0	0	0
Serious AEs	0	0	0
Withdrawal due to AEs	0	0	0

Table 5 Adverse Events: Number Observed

Adverse event	Mild					Moderate					Severe					Total
	Definite	Probably	Possibly	Unlikely	Unrelated	Definite	Probably	Possibly	Unlikely	Unrelated	Definite	Probably	Possibly	Unlikely	Unrelated	
Test Drug																
SOC 1																
…	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)
SOC 2																
…	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)
SOC 3																
…	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)
Others																
…	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)
Comparator Drug																
SOC 1																
…	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)
SOC 2																
…	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)
SOC 3																
…	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)
Others																
…	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)

17.1.2 Adverse Events Leading to Treatment Discontinuation

All adverse events leading to withdrawal of the subject will be recorded in the CRF and tabulated in the CSR (Table 6).

Table 6 Listing of Subjects Who Dropped Out from Study

Treatment	Subjects No.	Age (yr)	Last PK Sampling (date and actual time)	Duration	Dose	Concomitant Medication	Reason for Discontinuation
…	…	…	yyyy-mm-dd, hh:mm	yyyy-mm-dd, hh:mm (dd,hh,mm)	…	…	…

Test drug: Glucophage® XR (PT Merck Tbk, Indonesia)
Comparator drug: Glucophage® XR (Merck Sante, France)

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

17.2.1 Deaths

All serious adverse events that may result in death will be recorded in the SAE form and attached to the CRF. The summary of death cases will be tabulated in the CSR (Table 7).

Table 7 Listing of Deaths During the Study

Period (Treatment)	Subject No.	Serious Adverse Event	Date and Time of Death	Comments
Test drug: Glucophage® XR (PT Merck Tbk, Indonesia) Comparator drug: Glucophage® XR (Merck Sante, France)				

17.2.2 Serious Adverse Events

All serious adverse events will be recorded in the SAE form and attached to the CRF. The summary of serious adverse events will be tabulated in the CSR (Table 8).

Table 8 Listing of Serious Adverse Events

Period (Treatment)	Subject No.	Serious Adverse Event	Start Date (yyyy,mm,dd, hh:mm)	End Date (yyyy,mm,dd, hh:mm)	Intensity	Causality	Time of drug Administration	Withdrawal/ Drop-out	Outcome (observed until FU visit)
Test drug: Glucophage® XR (PT Merck Tbk, Indonesia) Comparator drug: Glucophage® XR (Merck Sante, France)									

17.3 Clinical Laboratory Evaluation

All clinical laboratory results will be recorded in the CRF and tabulated in the CSR. Baseline clinical laboratory test results will be presented alongside vital signs measurements, ECG findings, and physical examination performed during Screening in Table 9 (see Section 13.3). Clinical laboratory test results and other characteristics during Follow-Up Visit will be presented as shown (Table 9).

Table 9 Clinical Laboratory Test and ECG of Subjects During Follow-Up Visit

Parameter	Unit	Subject ID (Initials) (SUBJECT ID) (INITIAL) (GENDER)	(SUBJECT ID) (INITIAL) (GENDER)	(SUBJECT ID) (INITIAL) (GENDER)	(SUBJECT ID) (INITIAL) (GENDER)	Normal Values
Hematology						
Leucocyte	x 10^3/µL					M :3.8 - 10.6 F: 3.6 - 11.0
Erythrocyte	x 10^6/µL					M :4.4 - 5.9 F: 3.8 - 5.2
Hb	g/dL					M:13.2 - 17.3 F: 11.7 -15.5
Hematocrit	%					M :40 - 52 F: 35 - 47
Thrombocyte	x 10^3/µL					150 - 440
Blood Chemistry						
Total bilirubin	mg/dL					< 1.2
Direct bilirubin	mg/dL					< 0.50
AST	IU/L					M: < 35 F: <31
ALT	IU/L					M: < 45 F:<34
AP	IU/L					M: 53 - 128 F: 42 - 98
Albumin	g/dL					3.5 - 5.2
Total protein	g/dL					6.4 - 8.3
Blood glucose	mg/dL					<140
Ureum	mg/dL					13 - 43
Creatinine	mg/dL					M: 0.67 - 1.17 F: 0.51 - 0.95
Urinalysis						
Clarity						Clear
Color						Yellow
Glucose						Neg.
Bilirubin						Neg.
Ketone						Neg.
Specific Gravity						1.015 - 1.025
Blood						Neg.
pH						5 - 8
Protein						Neg.
Urobilinogen	EU/dL					0.2 - 1.0
Nitrite						Neg.
Leucocyte						Neg.
Sediment:						
- RBC	cells/HPF					0 - 2
- WBC	cells/HPF					0 - 5
- cast						Neg.
- epithel: squamous						Neg./ Pos.
transitional						Neg./ Pos.
tubular						Neg./ Pos.
- crystal						Neg./ Pos.
- bacteria						Neg. for male
ECG Conclusion						Normal Sinus Rhythm

*deviate from normal values, not clinically significant ** clinically relevant deviation for repeated measurement please refer to Table 10 unscheduled measurements

17.4 Vital Signs

Vital signs will be recorded in the CRF and tabulated in the CSR (Table 10).

Table 10 Vital Signs Monitoring

Subject No.	Period	Vital Signs	Screening	Day 1						Day 2		Follow -Up
				Pre-dose	2h	4h	6h	8h	12h	24h	32h	
S1	1	Systolic BP (mmHg)										
		Diastolic BP (mmHg)										
		Pulse rate (beats/min)										
		Respiratory rate (times/min)										
	2	Systolic BP (mmHg)										
		Diastolic BP (mmHg)										
		Pulse rate (beats/min)										
		Respiratory rate (times/min)										
S2	1	Systolic BP (mmHg)										
		Diastolic BP (mmHg)										
		Pulse rate (beats/min)										
		Respiratory rate (times/min)										
	2	Systolic BP (mmHg)										
		Diastolic BP (mmHg)										
		Pulse rate (beats/min)										
		Respiratory rate (times/min)										
…	…	…										

Unscheduled measurements will be listed in Table 11.

Table 11 Unscheduled Measurement

Subject No.	Parameter	Result	Outcome

17.5 Other Safety or Tolerability Evaluations

Not applicable

18 Benefit Risk Assessment

Not applicable.

19 References

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