PPD

Compound: Metformin

Research Protocol

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

Merck Protocol Number: MS200084_0015

PPD *Project Code:* PPD

Author :
PPD

Principal Investigator :
PPD

Change History:

Version number	*Date*
Final Version 1.0	*19 March 2018*
Final Version 1.1	*22 May 2018*

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STATEMENT OF COMPLIANCE

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

Principal Investigator:	PPD
PPD	PPD
Study Center (Clinical and Analytical Laboratory Site):	PPD
Telephone No.:	PPD

We, the undersigned, have reviewed this protocol, including Appendices. We will adhere to the Ethical and Regulatory considerations stated and will perform the study in compliance with PPD SOPs and according to the relevant versions of the Declaration of Helsinki and the International Conference on Harmonisation, GCP (CPMP/ICH/135/95).

PPD

Principal Investigator

PPD

Date

PPD

PPD

Date

[redacted]

PROTOCOL AGREEMENT PAGE

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

Approved:

PPD

PPD

Medical Director / Local Medical Responsible

PPD — Date

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Principal Investigator

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Study Physician

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Study Director

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LIST OF ABBREVIATIONS

TERM	DEFINITION
°C	degree Celcius
µL	microlitre
μ_R	average score of bioavailability parameters for the comparator drug
μ_T	average score of bioavailability parameters for the test drug
α	significance level (5%)
β	power (20%)
$\overline{X}_T$, $\overline{X}_R$	the means of the ln transformed values for the test drug (T) and the comparator drug (R)
ACE	angiotensin-converting-enzyme
ad lib	ad libitum, at pleasure
AE	adverse event
ALT	alanine aminotransferase
ANOVA	Analysis of Variance
AP	serum alkaline phosphatase
ASEAN	Association of Southeast Asian Nations
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-inf}	area under plasma concentration vs 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
BE	bioequivalence
bpm	beats per minute
BPOM	*Badan Pengawasan Obat dan Makanan* (the Indonesian National Agency of Drug and Food Control, NA-DFC)
BQL	below quantification limit
C_{max}	maximum observed plasma concentration
CIs	confidence intervals
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CV	Coefficient of Variation
dL	decilitre

[redacted]

TERM	DEFINITION
ECG	electrocardiogram
e.g	example
EMA	European Medicines Agency
g	relative centrifugal force
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
h, hr, hrs	hour(s)
K_3EDTA	tripotassium ethylenediaminetetraacetic acid
Hb	hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPLC-UV	high performance liquid chromatography with ultraviolet detector
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
kg	kilogram
KGaA	Kommanditgesellschaft auf Aktien (limited partnership on shares)
kg/m^2	kilogram / square meter
L	litre
LLOQ	Lower Limit of Quantification
ln	natural logarithm with e constant
m, min, min(s)	minute(s)
mg	milligram
ms	millisecond(s)
mL	millilitre
mL/min	milliliter / minute(s)
mm	millimeter
mmHg	millimeter mercury column
n	number of subject

[redacted]

TERM	DEFINITION
ng	nanogram
ng/mL	nanogram / millilitre
NSAID	non-steroidal anti-inflammatory drug
PK	Pharmacokinetics
PT	*Perseroan Terbatas* (limited liability company)
QC	Quality Control
QTc	corrected QT interval
R	Comparator (Reference) drug
RBC	red blood cells
s, sec	second(s)
S^2	the error variance obtained from the ANOVA
SAE	Serious Adverse Event
SD	standard deviation
SOP	Standard Operating Procedure
SUSARs	suspected unexpected serious adverse reactions
T	Test drug
$t_{0.1}$	the t value for 90% CI
$t_{½}$	elimination half-life in plasma
Tbk	*terbuka* (public company)
t_{max}	time taken to reach maximum observed plasma concentration
ULN	upper limit of normal
USA	United States of America
v	the degree of freedom of the error variance from the ANOVA
Vd	volume of distribution
WBC	white blood cell (count)
WMA	World Medical Association
WOCBP	Women of Childbrearing Potential
XR	extended release

[redacted]

1 SYNOPSIS

Study 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

Protocol Number

- PPD project code : PPD
- Merck protocol number : MS200084_0015

Compound under investigation

Metformin

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 Santé, 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 drugs.
- To examine the safety and tolerability of metformin after single dose administrations of test and comparator 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, with at least 20% for each gender.

Dosing Regimen

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

[redacted]

Duration of the Clinical Phase

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

Inclusion Criteria:

1. Subject has provided written informed consent prior to the conduct of any study-related activities.
2. Male and female subjects.
3. Aged between 18 and 55 years, inclusive.
4. Body mass index of 18 to 25 kg/m^2.
5. Good physical and mental health status, determined on the basis of medical history and physical examination.
6. 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.
7. 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.
8. No clinically significant abnormality on 12-lead electrocardiogram (ECG) recording as judged by the Investigator; QTc (Bazett) should be ≤ 450 ms.
9. Non-smoker or smoker less than 10 cigarettes per day.
10. 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.
11. WOCBP must have a negative urine pregnancy test at Screening and on each admission (Day 1 of each dosing period).
12. Negative screen for alcohol and drugs abuse (opiate class, barbiturates, cocaine and metabolites, amphetamines, cannabinoids and benzodiazepines) at Screening and on each Study Check-In (Day -1 of each dosing period).
13. Negative screen for Hepatitis B surface antigen (HBsAg), HCV antibodies and/or HIV antibodies.

Exclusion Criteria:

1. Participation in a clinical trial/study within 90 days prior to Screening.
2. Blood donation (equal or more than 300 mL) or significant blood loss within 90 days prior to first drug administration.
3. 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

[redacted]

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.

4. History of malignant diseases, except in-situ basal cell skin tumors treated with curative intent.
5. History of surgery of the gastrointestinal tract which could influence the gastrointestinal absorption and/or motility per the Investigator's opinion.
6. History or presence of relevant liver diseases or hepatic dysfunction (laboratory result for liver function test ≥ 1.5 ULN).
7. History or presence of renal failure or renal dysfunction based on clinical symptoms and finding (serum creatinine concentration >1.4 mg/mL).
8. 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.
9. 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).
10. Consumption of large quantities of methylxanthine-containing beverages (> 5 cups of coffee/day or equivalent).
11. Consumption of grapefruit, orange, cranberry or juices of these three fruits, 24 hours prior to drug administration.
12. 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 pre-dose, 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™, Milford, MA, USA) 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 $t_{½}$

[redacted]

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.*

Study Timeframe (TENTATIVE):

Apr – Jun 2018	Application for ethical clearance, BPOM approval, and analytical method verification
Jul 2018 – Aug 2018	Subject recruitment and blood sampling
Aug 2018 – Oct 2018	Analysis of drug concentrations and data management
Oct 2018 – Feb 2019	Statistical analysis and final study report

[redacted]

2 PRODUCT BACKGROUND

2.1 Indication and Usage

Metformin hydrochloride extended release tablet is indicated for treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Glucophage XR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin. [14]

2.2 Dosing Information

The usual starting dose of metformin hydrochloride extended release tablet is 500 mg once daily. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 2000 mg XR once daily with the evening meal. If glycaemic control is not achieved on 2000 mg once daily, Glucophage XR 1000 mg twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to metformin IR tablets to a maximum dose of 3000 mg daily. In patients already treated with metformin tablets, the starting dose of Glucophage XR should be equivalent to the daily dose of metformin IR tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to Glucophage XR is not recommended. [14]

2.3 Pharmacokinetics

2.3.1 Absorption

After an oral dose of Glucophage XR 500, metformin absorption is significantly delayed compared to the immediate-release tablet (t_{max} at 2.5 hours) with a t_{max} at 7 hours. Following a single oral administration of 1500 mg of Glucophage XR 750, a mean peak plasma concentration of 1193 ng/mL is achieved with a median value of 5 hours and a range of 4 to 12 hours. Glucophage XR 750 was shown to be bioequivalent to Glucophage XR 500 at a 1500 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects. [14]

Following a single oral administration in the fed state of one tablet of Glucophage XR 1000, a mean peak plasma concentration of 1214 ng/mL is achieved with a median time of 5 hours (range of 4 to 10 hours). Glucophage XR 1000 was shown to be bioequivalent to Glucophage XR 500 at a 1000 mg dose with respect to C_{max} and AUC in healthy fed and fasted subject. [14]

At steady state, similar to the immediate-release formulation, C_{max} and AUC are not proportionally increased to the administrative dose. The AUC after a single oral administration of 2000 mg metformin prolonged-release is similar to that observed after administration of 1000 mg metformin immediate-release twice daily. [14]

When two tablets of 500 mg metformin prolonged-release are administered in fed conditions the AUC is increased by approximately 70% (both C_{max} and t_{max} are only slightly increased). When the 1000 mg prolonged-release tablet are administered in fed conditions the AUC is increased by 77% (C_{max} is increased by 26% and t_{max} is slightly prolonged by about 1 hour). Metformin absorption from the prolonged-release formulation is not altered by meal composition. [14]

No accumulation is observed after repeated administration of up to 2000 mg metformin prolonged-release. [14]

[redacted]

2.3.2 Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 L. [14]

2.3.3 Metabolism

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans. [14]

2.3.4 Elimination

Renal clearance of metformin is >400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma. [14]

2.4 Adverse Reactions

Common adverse reactions that reported in ≥ 1% are gastrointestinal disorders (such as nausea, vomiting, diarrhoea, abdominal pain, and loss of appetite) and taste disturbance. [14]

2.5 Contraindications

Metformin is contraindicated in patients with [14]:

- Hypersensitivity to metformin or to any of the excipients
- Diabetic ketoacidosis, diabetic pre-coma
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/min)
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see section Warning and Precaution)
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock
- Elective major surgery (see section Warning and Precaution)
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

2.6 Warning and Precaution

- Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia. The risk of lactic acidosis must be considered in the

[redacted]

event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia.

- As metformin is excreted by the kidney, it is recommended that creatinine clearance and/or serum creatinin levels be determined before initiating treatment and regularly thereafter.
- Decreased renal function in elderly subject is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).
- The intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Therefore, depending on the renal function, metformin bust be discontinued 48 hours before the test or from the time of the test and may be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.
- Metformin must be discontinued 48 hours before elective major surgery. Therepy may be restarted no earlier than 48 hours following surgery and only after renal function has been re-evaluated and found to be normal.
- All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g., sulfonylureas or meglitinides).

2.7 Drug Interaction

- Depending on the renal function, metformin must be discontinued 48 hours before the test or from the time of the test and may not be reinstituted until 48 hours afterward.
- The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition, hepatic insufficiency. Avoid consumption of alcohol and alcohol-containing medicinal product.
- More frequent blood glucose monitoring may be required when administered with medicinal product with intrinsic hyperglycaemic activity (e.g., glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonists, danazol, chlorpromazine at high dosages of 100 mg per day and diuretics), especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon discontinuation.
- Co-administration with loop diuretics may increase the risk of lactic acidosis due to their potential to decrease renal function.
- Co-administration with ACE inhibitors may decrease the blood glucose levels. Therefore, dose adjustment of metformin may be necessary during and after addition or discontinuation of such medicinal products.

3 OBJECTIVE

The primary objective of this study:

[redacted]

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

The secondary objective of this study:

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

4 STUDY DESIGN

- Open-label, randomized, single-dose, two-period, two-sequence crossover study under fasting conditions (bioequivalence study design for metformin in accordance to *Indonesian guidelines, Pedoman Metodologi Uji Bioekivalensi Spesifik Zat Aktif, Badan Pengawas Obat dan Makanan (BPOM), Jakarta, 2015, page 39*). [4]
- Total subjects: Forty-eight (48) healthy adult male and female subjects, with at least 20% each gender.
- Total duration of the study (from Screening through Follow-Up Visit): approximately 6 weeks.
- Washout period: at least 7 days between doses.
- At Study Check-In, the subjects will report to the clinical site at least 12 hours prior to Day 1 dosing.
- Subjects will be required to stay for 32 hours after Day 1 dosing.

5 SUBJECT SELECTION

5.1 Number of Subjects

For this study, the total sample size will be 48 subjects.

5.2 Inclusion Criteria for Study Subjects

1. Subject has provided written informed consent prior to the conduct of any study-related activities.
2. Male and female subjects.
3. Aged between 18 and 55 years, inclusive.
4. Body mass index of 18 to 25 kg/m^2.
5. Good physical and mental health status, determined on the basis of medical history and physical examination.
6. 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.

[redacted]

7. 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.
8. No clinically significant abnormality on 12-lead electrocardiogram (ECG) recording as judged by the Investigator; QTc (Bazett) should be ≤ 450 ms.
9. Non-smoker or smoker less than 10 cigarettes per day.
10. 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 volunteers 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..
11. WOCBP must have a negative urine pregnancy test at Screening and on each Study Check-In (Day 1 of each dosing period).
12. 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).
13. Negative screen for Hepatitis B surface antigen (HBsAg), HCV antibodies and/or HIV antibodies.

5.3 Exclusion and Restriction Criteria for Study Subjects

5.3.1 Exclusion Criteria

Any of the following criteria will exclude the subject from the study:

1. Participation in a clinical trial/study within 90 days prior to Screening.
2. Blood donation (equal or more than 300 mL) or significant blood loss within 90 days prior to first drug administration.
3. 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.
4. History of malignant diseases, except in-situ basal cell skin tumors treated with curative intent.
5. History of surgery of the gastrointestinal tract which could influence the gastrointestinal absorption and/or motility per the Investigator's opinion.
6. History or presence of relevant liver diseases or hepatic dysfunction (laboratory result for liver function test ≥ 1.5 ULN).
7. History or presence of renal failure or renal dysfunction based on clinical symptoms and finding (serum creatinine concentration >1.4 mg/mL).
8. 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.

[redacted]

9. 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).
10. Consumption of large quantities of methylxanthine-containing beverages (> 5 cups of coffee/day or equivalent).
11. Consumption of grapefruit, orange, cranberry or juices of these three fruits, 24 hours prior to drug administration.
12. Known lack of subject compliance or inability to communicate or cooperate with the Investigator (e.g., language problem, poor mental status).

This study will be carried out in accordance to the Good Clinical Practice (GCP) standards. Approval from the Ethics Committee will be sought prior to the conduct of the study.

5.3.2 Restrictions

Subjects will be administered the drug products in sitting posture. Subjects will avoid severe physical exertion during sampling hours.

Methylxanthine-containing food or beverages and grapefruit, orange, cranberry or juices of these three fruits are not allowed for 24 hours before and during the entire sampling days. Consumption of alcohol-based products is restricted for 24 hours before and during the entire sampling days.

Any concomitant medications (including non-prescription medication, multi-vitamin preparations or herbal medications) are prohibited during the whole study (from Screening Visit to the Follow-Up Visit).

5.3.3 Criteria for Subjects' Withdrawal from the Study

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

1. Withdrawal of subject's consent;
2. Significant protocol violation, such as non-compliance with restriction regarding alcohol and drug use, and non-adherence to the the fasting condition;
3. Adverse events, as assessed by the Investigator to affect the subject safety or the outcome of the study endpoints;
4. Difficulties with blood collection;
5. Subject who vomits anytime during PK blood sampling periods 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;
6. 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;
7. Subject is uncooperative during the study;
8. 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

[redacted]

the first dose of the study drug, the 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 final study report.

6 STUDY PRODUCTS AND RANDOMIZATION

6.1 Product

TEST DRUG INFORMATION

Each extended release tablet produced by PT Merck Tbk, Jakarta, Indonesia (Glucophage® XR 750 mg Tablet) contains metformin hydrochloride 750 mg.

Batch No. : 2050201
Mfg. Date : 23 April 2017
Exp. Date : 22 April 2019
Batch size : 100,000 tablets

Name and address of manufacturer:
PT Merck Tbk
Jl. TB Simatupang No.8 Pasar Rebo
Jakarta Timur 13760
INDONESIA

COMPARATOR (REFERENCE) DRUG INFORMATION

Each extended release tablet produced by Merck Santé, Semoy, France (Glucophage® XR 750 mg Tablet) contains metformin hydrochloride 750 mg.

Batch No. : Y02170
Mfg. Date : 09 November 2016
Exp. Date : October 2019
Reg. No. : DKI1401600214B1

Name and address of manufacturer:
Merck Santé
2 Rue du Pressoir Vert
45400 Semoy
FRANCE

Name and address of importer:
PT Merck Tbk
Jl. TB Simatupang No.8 Pasar Rebo
Jakarta Timur 13760
INDONESIA

All drug supplies will be kept in an appropriate locked cupboard which can only be accessed by the Investigator or designated study personnel. Drug accountability records, including study drug storage, handling, dispensing, documentation of administration, return and the return/destruction of the drug will be maintained.

A designated study personnel will record the actual date and time of drug administration to the subjects. In case the study has to be discontinued, the exact date, time and the reason for discontinuation will be documented in the CRF.

[redacted]

6.2 Randomization

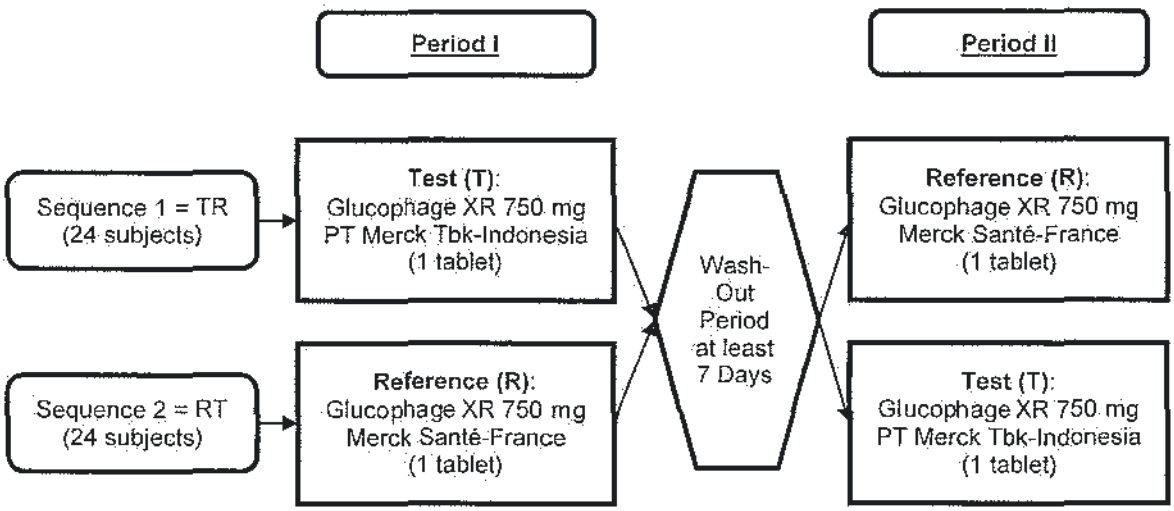

Figure 1 Flow Chart / Study Design Diagram

The randomization code is tabulated for all subjects according to block randomization with a block size of 4. [6] 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 labelled 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 analysis of all blood samples have been completed but prior to statistical analysis; the Sponsor's green light will be obtained prior to code breaking, upon satisfying pre-defined conditions.

7 STUDY PROCEDURES

7.1 Screening

All assessments previously performed (within 21 days of the first study drug administration) may be used for enrollment purposes as long as a study-specific consent is signed prior to any other study-specific study procedure or assessment. During the Screening Visit the following will be completed:

- Informed consent for study
- Medical history (commencement of safety surveillance)
- Vital signs (blood pressure, pulse rate, respiratory rate, temperature)
- Physical examination and body measurements (height, weight)

[redacted]

- Clinical laboratory tests
  - Liver function : AP, ALT, AST, total protein, albumin and total/direct bilirubin
  - Renal function : serum creatinine and ureum
  - Hematology : hemoglobin, hematocrit, erythrocyte count, leucocyte count, and platelet count
  - Urinalysis : urine chemistry and urine sediment
  - Serology test : HBsAg, anti-HCV, and anti-HIV
  - Blood glucose
- Alcohol breath test and urine test for drug abuse (opiate class, barbiturates, cocaine and metabolites, amphetamines, cannabinoids and benzodiazepines)
- Pregnancy screening (female subjects only)
- 12-lead ECG (remain in a supine position)
- Eligibility (inclusion/exclusion criteria)

7.2 Study Check-In (Day 1)

At Study Check-In, the subjects will report to the clinical site at least 12 hours prior to Day 1 dosing, and will be required to stay for approximately 32 hours after Day 1 dosing. The following will be completed at check-in:

- Alcohol breath test and urine test for drug abuse (opiate class, barbiturates, cocaine and metabolites, amphetamines, cannabinoids and benzodiazepines) will be performed. A urine sample will be collected for a pregnancy screen (female only). Subjects with a positive result will be excluded from the study.
- Subjects will begin fasting at least 10 hours prior to dosing on Day 1.
- Water will be allowed ad lib during fasting till 1 hour prior to dose administration. Throughout the study, standardized meals and beverages will be served. Meals will be the same in content and quantity during each dosing period.

7.3 Treatment Phase

Prior to dosing, the following activities will be completed:

- Vital signs will be measured.
- Pharmacokinetic (PK) sampling will be performed within 60 minutes prior to each subject's scheduled dose time (0-hour blood sample).
- No fluid allowed at least from 1 hour prior to dose administration until 2 hours after dosing except that given at drug administration.

Dosing: each subject will be instructed to take either one tablet of test drug (Glucophage® XR 750 mg Tablet produced by PT Merck Tbk, Indonesia) or one tablet of comparator drug (Glucophage® XR 750 mg Tablet, Merck Sante, France) with 200 mL of water during each dosing period, for a total of 2 doses per subject in the entire study. The actual clock time for each dosing will be recorded in the CRF.

[redacted]

After dosing, the following activities will be completed:

- A fast will be maintained until at least 4 hours after dosing. Water intake will be allowed from 2 hours after drug administration.
- Blood sample collections will be obtained 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 dosing (± 2 minutes for post-dose blood draw).
- Blood pressure, pulse rate, respiration rate, and adverse events will be monitored at pre-dose, 2, 4, 6, 8, 12, 24, and 32 hours after dosing (± 30 minutes from the scheduled time point for post-dose vital signs measurements).
- Adverse Event (AE) / Concomitant Medication Query: each subject's well-being will be evaluated.
- Subjects will undergo clinical observation by qualified study personnel for 4 hours after receiving study drug. The Investigator, study physician, and study nurse will be on-site during drug dosing and will stay at the site until all study procedures required in each period is completed, thereafter the study nurse(s) will remain at the site during the subjects' overnight stay.
- Subjects will be instructed not to engage in excessive physical activity during the entire period of the study.
- Lunch will be provided at approximately study hour 4.
- Dinner will be provided at approximately study hour 10.
- Meals/snacks served after study hour 10 will be scheduled by the clinic.
- Subjects who experience vomiting will be treated at the Investigator's discretion.

7.3.1 Study Meals

- Food intake is standardized during the sampling days. Meals will be the same in composition and quantity during each dosing period.
- Methylxanthine-containing food or beverages and grapefruit, orange, cranberry or juices of these three fruits are not allowed for 24 hours before and during the entire sampling day.

7.4 Follow-Up Visit

Follow-up procedures will be performed after the last study activity in the second dosing period, and completed within 7 days after the last blood sampling. Procedures will include physical examination, assessment of vital signs (blood pressure, pulse rate, respiratory rate and temperature), body measurements (height and weight), ECG, clinical laboratory tests (liver function, renal function, blood glucose, hematology, urinalysis), and adverse event evaluation.

If a subject who has received at least one dose of the study drug withdraws prematurely, the Follow-Up Visit will need to be completed within 7 days after his/her last blood sampling.

8 SAFETY ASSESSMENTS

The safety profile of the study drug will be assessed for all enrolled subjects through the recording, reporting and analyzing of baseline medical conditions, physical examination

findings, vital signs (i.e. systolic and diastolic blood pressure, pulse rate, and respiration rate), 12-lead ECG, hematology and biochemistry laboratory tests including urinalysis, and AEs. See section 12.1.2 Clinical Laboratory Assessments, and section 12.1.3 Vital Signs, Physical Examination, ECG and Other Assessments for details.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the study, from the time the subject signs on the informed consent form. Study site personnel will report any AE to the Sponsor, whether observed by the Investigator or reported by the subject.

9 PK SAMPLE COLLECTION AND HANDLING PROCEDURES

9.1 PK Sample Collection Schedule

- A 10 mL blood sample (control) will be drawn by venepuncture immediately before drug administration.
- Subsequent blood samples will be 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 (±2 minutes for post-dose blood draws).
- 18 blood samples will be collected in each dosing period for pharmacokinetic analysis.
- Blood sampling will be conducted according to Blood Sampling Collection Form. The actual time of sample collection will be documented in the CRF.

9.2 PK Sample Collection and Processing

- For each sampling time point, 5 mL of blood will be collected in vaccum polypropylene tubes containing K_3EDTA using 22G needle.
- The labels for all biological sample collection and storage containers will contain, at a minimum, the subject's number, study number, dosing period, scheduled collection time point.
- Samples will be sequentially collected by direct venepuncture and placed into the centrifuge within 60 minutes of blood sampling at room temperature.
- After collection, samples will be centrifuged at approximately 1538 g (radius of rotor = 86 mm) at room temperature for 15 minutes.
- Plasma will be divided and transferred into two polypropylene tubes.
- Samples will then be stored in a freezer, at approximately -20°C ± 5°C until transferred to the bio-analytical laboratory.
- In cases where the volume of plasma harvested from the blood sample is insufficient to meet the minimum volume requirement for bioanalysis, the first polypropylene tube will be filled to meet the minimum volume requirement, and any remaining plasma will be transferred to the second polypropylene tube.

9.3 Criteria for Recording and Reporting PK Blood Sampling Deviation

- A window period of ±2 minutes from the scheduled time point is allowed for all blood draws.

[redacted]

- The actual sampling time will be recorded in the Blood Sampling Form and also in the CRF. Any sampling time deviation will be recorded in the "Blood Sampling Form" and attached to the CRF.
- Time corrections will be done in the dataset prior to performing PK calculations for any deviations to the post-dose blood sampling time points beyond the specified window period.

9.4 Transport of PK Samples

The separated plasma will be stored in pre-labelled polypropylene tubes during each dosing period. These tubes will be stored in the -20°C ±5°C freezer located in the clinical site's sample storage room till the end of each period, after which they will be transferred to another -20°C ±5°C freezer at the bio-analytical facility during the sample processing and bio-analysis phase, and until long-term stability tests are performed. Stability tests have been conducted to ensure that the analyte in plasma is stable during storage.

10 BIOANALYTICAL SAMPLE ANALYSES

10.1 Analytical Method Validation

Metformin concentrations will be assayed using a validated high-pressure liquid chromatography with ultraviolet detection (HPLC-UV; Waters™, Milford, MA, USA) method with respect to adequate sensitivity, specificity, linearity, recovery, and accuracy and precision (both within and between run). The Lower Limit of Quantification (LLOQ) of metformin obtained from method validation was 10 ng/mL. Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles has also been determined.

The study will start when the analytical method validation has been completed. Validation will be in accordance to the EMA Guideline on Bioanalytical Method Validation, 2011.

10.2 Assay Method

For analysis of drug concentrations, validated high pressure liquid chromatography with ultraviolet detection (HPLC-UV; Waters™, PPD) method will be used.

An aliquot of human plasma sample will be extracted using protein precipitation with an appropriate solvent, then an appropriate volume of sample will be injected to the HPLC-UV system using methylparaben as an internal standard. Calibration standards, controls, and samples will be processed in batches, where each batch consists of two subjects.

All chromatograms in the same batch will be processed automatically by the software using the same processing parameters such as integration, peak to peak amplitude and peak detection. Manual integration will be performed when the automatic integration performed by the data system has an error:

- Software integration limitations
- Complicated chromatography
- Poor resolution or response

[redacted]

10.3 Quantification

Calibration curve is prepared for metformin by least square linear regression (Y = aX + b; where X is the concentration of metformin and Y is the peak area ratio of metformin to internal standard).

The concentration of metformin in plasma sample is determined by entering the peak area ratio of metformin to internal standard into the regression line equation of the standard calibration curve of each substance.

10.4 Quality Control

QC samples in duplicate at three concentrations [within 3x of the LLOQ (low QC), in the mid-range (medium QC), and approaching the high end of the range (high QC)] will be incorporated into each run. At least 67% of the QC samples and at least 50% of the QC samples at each concentration level should be within 15% of their respective nominal (theoretical) concentrations.

Incurred sample reanalysis will be conduct according to the EMA Guideline on Bioanalytical Method Validation, 2011.

11 STUDY ANALYSES

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

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 the study evaluations.

11.1 Parameters of Bioavailability

The following PK parameters will be estimated according to non-compartmental standard methods using the PK software program Pharsight Phoenix WinNonlin (Version 8.0 or higher):

C_{max}	maximum observed plasma concentration
t_{max}	time to reach C_{max}
AUC_{0-t}	area under plasma concentration versus time curve from administration to last observed concentration at time t
AUC_{0-inf}	area under plasma concentration vs time curve extrapolated to infinite time
$t_{½}$	terminal phase half-life time

C_{max} and t_{max} will be obtained in directly from the observed data.

11.2 Statistical Analysis

Safety data will be evaluated for all subjects who received at least one dose of study medication. The data from subject(s) who received concomitant medication(s) or experienced diarrhea or vomiting during PK blood sampling periods, which could render the plasma concentration-time profile unreliable as stated on section 5.3.3, may be excluded

[redacted]

for that period from the pharmacokinetic analysis and statistical evaluation. The decision to exclude is made before bioanalysis.

Statistical analyses will include data from all subjects who have valid primary endpointsavailable for both periods of the study. The plasma concentrations obtained from the bioanalytical laboratory for subjects who have been withdrawn from the study due to adverse events or as list on section 5.3.3 will not be used for statistical evaluation.

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 logarithmic (ln) transformation of the original values. The terms to be used in the ANOVA model are sequence, subject within sequence, period, and formulation.

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.*

Non-compartmental standard methods computation of PK parameters will be performed. Details will be provided in the final study report. Phoenix® WinNonlin (Version 8.0 or higher) (PPD) will be used to perform the statistical analyses of AUC_{0-t} and C_{max} using analysis of variance (ANOVA) 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.

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.

Descriptive Statistic

Arithmetic means, standard deviations, minimum, maximum, median, and coefficients of variation will be calculated for the parameters listed in section 11.1.

Plasma concentration-time profile will be provided in linear and log scale for mean curves with standard deviation and individual curve in each subject.

Demographic data will be provided as summary tables with information of mean, minimum value and maximum value presented.

11.3 Sample Size Justification

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

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

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

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 (reference) drug

[redacted]

CV : intra-subject CV

CCI

CCI 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. To achieve the targeted number of eligible subjects, the number of potential subjects screened will be around two times of the sample size.

12 ADVERSE EVENTS/TOXICITY

12.1 Definition of an Adverse Event

An AE 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.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

Subjects will be instructed by the Investigator/study physician to report the occurrence of any adverse event. The Investigator is required to grade the severity or toxicity of each AE.

Investigators must assess the severity of AEs according to the Qualitative Toxicity Scale, as follows:

Mild:	The subject is aware of the event or symptom, but the event or symptom is easily tolerated.
Moderate:	The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
Severe:	Significant impairment of functioning: the subject is unable to carry out his or her usual activities.

Investigators must also systematically assess the causal relationship of AEs to the study drugs (including any other non-study drugs, study procedures, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to metformin hydrochloride (Glucophage® XR) include, but may not be limited to, temporal relationship between the AE and metformin hydrochloride (Glucophage® XR), known side effects of metformin hydrochloride (Glucophage® XR), medical history, concomitant medication, course of the underlying disease, study procedures.

Unrelated: Not reasonably related to the study drugs. AE could not medically (pharmacologically/clinically) be attributed to the drugs under study in this study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study drugs. AE could medically (pharmacologically/clinically) be attributed to the drugs under study in this study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

For the purposes of reporting, any suspected transmission of an infectious agent via a study drug is also considered an SAE, as described in Section 12.1.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study procedures (for example, an overnight stay to facilitate pre-drug administration procedures) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an

[redacted]

elective hospitalization (for example, undesirable effects of any administered study drugs and/or procedures) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the Screening visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions, and are not to be considered AEs.

Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature on the informed consent form [ICF]) and continues until the last post-treatment safety visit, which in this case is completion of the Follow-Up Visit.

Any SAE assessed as related to metformin hydrochloride (Glucophage® XR) must be reported whenever occurs, irrespective of the time elapsed since the last administration of metformin hydrochloride (Glucophage® XR).

Procedure for Reporting Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 hours after becoming aware of the event) inform the Sponsor in writing. All written reports should be transmitted using Merck SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by e-mail to icsr_gds@merckgroup.com.

Relevant pages from the CRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the CRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor to allow the Sponsor to meet strict regulatory timelines associated with expedited safety and tolerability endpoints reporting obligations.

Merck Global Drug Safety department may contact the Investigator to obtain further information or to discuss the event.

Safety Reporting to Local Health Authority, Ethics Committee and Investigator

The Sponsor will send appropriate safety notifications to the local Health Authority, *Badan Pengawas Obat dan Makanan* (BPOM) in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the Ethics Committee that approved the study.

In accordance with ICH GCP, the Sponsor will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious

[redacted]

and unexpected and are considered to be related to the administered drugs ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. BPOM regulations with regard to Safety Report notifications to Investigators will be taken into account.

The Investigator will be responsible for promptly notifying the concerned Ethics Committee of any Safety Reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

Monitoring of Subjects with Adverse Events

AEs are recorded and assessed continuously throughout the study and are assessed for final outcome at the Follow-up Visit. All SAEs ongoing at the Follow-up Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

12.1.1 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to study drugs (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the AE reporting period must be recorded by convention in the AE page/section of the CRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor in an expedited manner of any pregnancy using Merck Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 12.1.

Investigators must actively follow-up, document and report on the outcomes of all these pregnancies, even if the subjects are withdrawn from the study.

The Investigator must notify the Sponsor of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as decribed in Section 12.1, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the study, the subject must be withdrawn from the study immediately. The Sponsor must be notified without delay and the subject must be followed as mentioned above.

12.1.2 Clinical Laboratory Assessments

At Screening Visit and Follow-Up Visit, blood samples for hematology laboratory test will be collected in vaccum polypropylene tubes containing K_3EDTA while clinical chemistry and serology laboratory tests will be collected in vacuum polypropylene tubes without anticoagulant. Serology test will be performed only at Screening Visit and any subject with a positive result will be excluded from the study. Alcohol breath test and urine test for drug abuse will be performed during Screening Visit and at each Study Check-In Visit. Urine samples for urinalysis will be collected at Screening Visit, at each Study Check-In Visit, and at the Follow-Up Visit.The total volume of blood drawn will be about 210 mL (including 10 mL for Screening Visit, 10 mL pre-dose, 85 mL during each dosing period, and 10 mL for Follow-Up Visit). Refer to section 7 and Appendix B Study Flow Chart for description of safety assessments and test schedule.

[redacted]

These blood samples will be analysed at the site's clinical laboratory. The Sponsor will be provided with a list of laboratory normal ranges before the start of the clinical phase of the study; any change in laboratory normal range during the study will additionally be forwarded to the Sponsor.

All clinical laboratory results will be recorded in the CRF and attached to the final study report.

12.1.3 Vital Signs, Physical Examinations, ECG and Other Assessments

Vital sign including blood pressure, pulse rate, and respiratory rate will be measured during Screening Visit, during blood sampling per schedule listed in Appendix B Study Flow Chart, and during the Follow-Up Visit. Physical examination, body measurement (height and weight), and ECG will be performed during Screening and Follow-Up visit.

A full standard 12-lead ECG (I, II, III, aVR, aVL, aVF, V1-V6) for about 5 seconds (at least 4 adjacent beats, calibration: 25 mm/sec 10 mm/mV) will recorded in the CRF. The 12-lead ECG will be analyzed, assessed for plausibility and clinical relevance and signed by the Investigator.

13 ADMINISTRATIVE RECORDS

13.1 Data Recording

Case Report Forms (CRFs) will be filled legibly using a black ball-point. The forms will be verified against all original records (and workbooks, if applicable). Copies of CRFs will be retained in the Investigator Site File, and the original CRFs will be returned to the Sponsor.

Screening and Follow-Up Visit data will be transcribed from the medical record and Follow-Up form into the respective CRF with a copy of the laboratory result and ECG sheet attached.

Data which are directly recorded in the CRF and where the CRF serves as the source document are:

- Pre-dose/baseline
- Dosing
- Standardization
- Blood sampling (recorded in the Blood Sampling Form and attached in the CRF)
- Monitoring (recorded in Adverse Event and Subject Monitoring Form and attached in the CRF)
- Adverse event
- Concomitant medication
- Study completion

13.2 Record Retention

Copies of all pertinent information will be retained by the Investigator for a period of at least *10 years* after the final study report. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor. Additional considerations will be made about complying with applicable local laws, guidelines, etc. A study document binder will be provided for all required study documents.

[redacted]

13.3 Subject Informed Consent

Prior to screening evaluation, subjects will be informed of the nature of the study and pertinent information as to the intended purpose, possible benefits, and possible adverse experiences. The procedures and possible hazards to which the subjects will be exposed will be explained. An approved informed consent form will then be read by each subject. Before signing the informed consent form, ample time will be provided to the subject to decide whether or not to participate in the study. The subject will receive a copy of the signed informed consent form. Subjects may withdraw from the study at any time without any reason. Verification of the signed informed consent will be noted on the CRF.

13.4 Ethics Committee

The protocol and the informed consent statement will be reviewed by the Ethics Committee of the PPD . The Ethics Committee's approval will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor. The Ethics Committee must be informed of study completion by the Investigator.

The study will commence after ethical clearance and BPOM approval have been obtained.

13.5 Modification of the Protocol

Any modification of the protocol which may have impact on the conduct of the study, potential benefit of the study, or may affect subject safety, including changes of study objective, study design, study population, sample size, study procedure, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the Sponsor, the Investigator and the Ethics Committee prior to implementation.

Minor administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These minor administrative changes will be agreed upon by the Sponsor and the Investigator and will be documented in a memorandum. The Ethics Committee may be notified of the minor administrative changes at the discretion of the Investigator.

13.6 Drug Storage and Accountability

The pharmacist will maintain accurate records of the disposition of all study drug received, administered (including date and time) and accidentally destroyed. At the end of the study all unused medication, including test drug and comparator drug, will be returned to the Sponsor minimum 3 (three) months after final study report is received by the Sponsor and it will be conducted only if the Sponsor requests to return the study drug. The remaining study drugs which are not sent back to the Sponsor will be stored until 5 years following final study report date issued or following agreement with the Sponsor.

The Investigator will be responsible for ensuring that the study drugs are stored in accordance with the instructions on the label, i.e. at room temperature below 25°C and protected from humidity.

13.7 Biological Samples

All remaining plasma samples will be destroyed one month after the final study report is received by the Sponsor.

[redacted]

13.8 Protocol Deviation

All of the protocol deviation in this study will be recorded and reported to the Sponsor, Ethics Committee, and BPOM.

14 STUDY TIMEFRAME (TENTATIVE)

Apr 2018 – Jun 2018	Application for ethical clearance, BPOM approval, and analytical method verification
Jul 2018 – Aug 2018	Subject recruitment and blood sampling
Aug 2018 – Oct 2018	Analysis of drug concentrations and data management
Oct 2018 – Feb 2019	Statistical analysis and final study report

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[redacted]

APPENDIX A
ADVERSE EVENT(S) FORM AND SERIOUS ADVERSE EVENT(S) CASE REPORT FORM

[redacted]

PPD	STUDY NO. :	Subject No.: S - |__|__| Initials : |__|__|__|__|	**ADVERSE EVENT**	**D**

Are there any adverse event in this study ? Yes ☐ No ☐

Period	Adverse Event	Duration	Outcome	Intensity	Causality	Therapy/ Withdrawal	Serious Event*
	....	**Onset :** Date ________ Time ________ **End :** Date ________ Time ________	☐ Resolved ☐ Not resolved	☐ Mild ☐ Moderate ☐ Severe	☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definite	Therapy: ☐ Yes ☐ No Withdrawal: ☐ Yes ☐ No	☐ Yes ☐ No
	....	**Onset :** Date ________ Time ________ **End :** Date ________ Time ________	☐ Resolved ☐ Not resolved	☐ Mild ☐ Moderate ☐ Severe	☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definite	Therapy: ☐ Yes ☐ No Withdrawal: ☐ Yes ☐ No	☐ Yes ☐ No
	....	**Onset :** Date ________ Time ________ **End :** Date ________ Time ________	☐ Resolved ☐ Not resolved	☐ Mild ☐ Moderate ☐ Severe	☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definite	Therapy: ☐ Yes ☐ No Withdrawal: ☐ Yes ☐ No	☐ Yes ☐ No
	....	**Onset :** Date ________ Time ________ **End :** Date ________ Time ________	☐ Resolved ☐ Not resolved	☐ Mild ☐ Moderate ☐ Severe	☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definite	Therapy: ☐ Yes ☐ No Withdrawal: ☐ Yes ☐ No	☐ Yes ☐ No
	....	**Onset :** Date ________ Time ________ **End :** Date ________ Time ________	☐ Resolved ☐ Not resolved	☐ Mild ☐ Moderate ☐ Severe	☐ Unrelated ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definite	Therapy: ☐ Yes ☐ No Withdrawal: ☐ Yes ☐ No	☐ Yes ☐ No

*If needs more, this page can be copied as necessary, please fill the page number***

Please note any **SERIOUS events should not be recorded on this page, but on the Serious Adverse Event pages provided (PPD)*

**Adverse Event form; page ☐ of ☐

[redacted]

PPD	SERIOUS ADVERSE EVENTS (SAE)

Study Informations	
Project Code	
Subject Identities	Subject No. : ..... Initials : ..... Date of Birth : ..... Age : ..... years Sex : ☐ Male ☐ Female
Drug	Drug Name : ..... Batch No. : ..... Expired Date : .....

Serious Adverse Informations	
Serious Adverse Event	
Onset Date / Time	Date ☐☐ / ☐☐☐ / ☐☐☐☐ Time ☐☐ : ☐☐
End Date / Time	☐☐ / ☐☐☐ / ☐☐☐☐ ☐☐ : ☐☐
Outcome	☐ Resolved ☐ Ongoing: ☐ (1) Condition improving ☐ (2) Condition still present and unchanged (stabilized) ☐ (3) Condition deteriorated ☐ Died: ☐ (1) Death due to this AE ☐ (2) Unrelated death
Expedited Reporting Criteria:	☐ (1) Died: Day / Month / Year : ☐ (2) Involved or prolonged in hospitalization ☐ (3) Involved persistence or significant disability or incapacity ☐ (4) Life-threatning ☐ (5) Congenital anomaly ☐ (6) Criteria unspecified (other medically important condition)
Event Course	☐ Intermitent → number of episodes ☐☐ ☐ Constant

[redacted]

PPD	SERIOUS ADVERSE EVENTS (SAE)

Cont'

Intensity (maximum)	☐ Mild ☐ Moderate ☐ Severe	
Causality	☐ Not Related ☐ Possible ☐ Probable ☐ Definite ☐ Unknown If the answer "Not Related" the SAE is probably associated with: ☐ Protocol design or procedures (but not to study drug) Please specify _____ ☐ Another condition (eg. Condition under study, intercurrent illness) Please specify _____ ☐ Another drug Please specify _____	
Action taken by investigator	☐ (0) None ☐ (1) Trial drug dosage changed to _____ ☐ (2) Trial drug temporarily interrupted ☐ (3) Trial drug permanently discontinued due to this adverse event	☐ (0) Non-drug therapy ☐ (1) Concomitant drug therapy changed or discontinued ☐ (2) New drug therapy added ☐ (3) Hospitality / prolonged hospitalization
Was subject withdrawn due to this AE	☐ Yes ☐ No	

[redacted]

PPD	SERIOUS ADVERSE EVENTS (SAE)

Cont'

Relevant Laboratory Data

Test	Date DD Mon YY	Value	Units	Normal Range
	☐☐ ☐☐☐ ☐☐☐☐			
	☐☐ ☐☐☐ ☐☐☐☐			
	☐☐ ☐☐☐ ☐☐☐☐			

Remarks

If applicable, was randomization code broken at investigational site? ☐ Yes ☐ No

Study Medication : ☐ Test Drug ☐ Reference Drug

Responsible Physician	Principal Investigator
Date : _____	Date : _____

[redacted]

APPENDIX B
SPONSOR'S SERIOUS ADVERSE EVENT(S) REPORT FORM, PREGNANCY REPORT FORM, AND PARENT-CHILD/FETUS ADVERSE EVENT REPORT FORM

[redacted]

MERCK

Serious Adverse Event Report Form

Merck Protocol Number : MS200084_0015
Study Short Title : Glucophage® XR 750 mg Indonesia Bioequivalence Study

COMPANY USE ONLY
Receipt date of this report (stamp or date)

TYPE OF REPORT

☐ Initial ☐ Follow-up

A. REPORTER INFORMATION

Reporter's First Name	Reporter's Last Name
Investigator's First Name (if different from Reporter)	Investigator's Last Name (if different from Reporter)
Address	City
Country	Phone Number
E-Mail:	Fax Number

B. SUBJECT INFORMATION

Subject ID: _____ / _____ / _____ (Trial No. / Center No. / Subject No.)

Randomization Number

Subject Initials	Sex	Height	Weight
	☐ Female ☐ Male	cm	kg

Date of Birth (dd/mmm/yyyy) OR Age at Time of Adverse Event (Specify unit, e.g. years months, etc.)

/ /

Ethnicity/Race ☐ American Indian/Alaska native ☐ Asian ☐ Black or African American ☐ Caucasian/White ☐ Hispanic or Latino ☐ Native Hawaiian or other Pacific islander ☐ other _____

Assignment to treatment group or dose cohort:	Unblinded by investigator due to event? ☐ Yes ☐ No If "yes", specify the date: / /

C. RELEVANT MEDICAL HISTORY

Condition/Disorder	Start Date (dd/mmm/yyyy)	End Date (dd/mmm/yyyy)	Ongoing
	/ /	/ /	☐
	/ /	/ /	☐
	/ /	/ /	☐
	/ /	/ /	☐
	/ /	/ /	☐

[redacted]

MERCK

Subject ID: _____ / _____ / _____
Trial No. / Center No. / Subject No.

D. CONCOMITANT MEDICATIONS

Drug Trade Name	Single Dose	Frequency of Administration	Route	Start Date (dd/mmm/yyyy)	Stop Date (dd/mmm/yyyy)	Indication
				/ /	/ /	
				/ /	/ /	
				/ /	/ /	
				/ /	/ /	
				/ /	/ /	

E. INVESTIGATIONAL MEDICINAL PRODUCT(S)

Indication of Investigational Medicinal Product(s)

1	Investigational Medicinal Product Name / Route of Administration:	Kit/Batch/Lot Number
Not yet administered:		
Date and <<Time>> of first <<administration/intake>>: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Date and <<Time>> of most recent <<administration/intake>> prior to SAE: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Number of <<administrations/cycles/doses>> prior to SAE:		

ACTIONS TAKEN REGARDING THIS INVESTIGATIONAL MEDICINAL PRODUCT

☐ Temporary discontinued on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
	If "yes", how long after cessation of treatment? _____			
☐ If temporary discontinued, restarted on: ___/___/___	At previous dose?	☐ Yes	☐ No	☐ Unknown
	Event subsequently reappeared?	☐ Yes	☐ No	☐ Unknown
☐ Permanently discontinued on: ___/___/___				
☐ Dose Reduced on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
☐ Treatment Continued without Change				
☐ Not Applicable				
☐ Unknown				

[redacted]

MERCK

Subject ID: _____ / _____ / _____
Trial No. Center No. Subject No.

2 Investigational Medicinal Product Name / Route of Administration	Kit/Batch/Lot Number
Not yet administered:	
Date and <<Time>> of first <<administration/intake>>: (dd/mmm/yyyy) / / (hh:mm) /	Dose/Unit:
Date and <<Time>> of most recent <<administration/intake>> prior to SAE: (dd/mmm/yyyy) / / (hh:mm) /	Dose/Unit:
Number of <<administrations/cycles/doses>> prior to SAE:	

ACTIONS TAKEN REGARDING THIS INVESTIGATIONAL MEDICINAL PRODUCT

☐ Temporary discontinued on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
	If "yes", how long after cessation of treatment? _____			
☐ If temporary discontinued, restarted on: ___/___/___	At previous dose?	☐ Yes	☐ No	☐ Unknown
	Event subsequently reappeared?	☐ Yes	☐ No	☐ Unknown
☐ Permanently discontinued on: ___/___/___				
☐ Dose Reduced on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
☐ Treatment Continued without Change				
☐ Not Applicable				
☐ Unknown				

3 Other Study Treatment (Non-IMP/Radiotherapy)	Kit/Batch/Lot Number
Not yet administered:	
Date and <<Time>> of first <<administration/intake>>: (dd/mmm/yyyy) / /	Dose/Unit:
Date and <<Time>> of most recent <<administration/intake>> prior to SAE: (dd/mmm/yyyy) / /	Dose/Unit:
Number of <<administrations/cycles/doses>> prior to SAE:	

[redacted]

MERCK

Subject ID: _____ / _____ / _____
Trial No. / Center No. / Subject No.

ACTIONS TAKEN REGARDING OTHER STUDY TREATMENT				
☐ Temporary discontinued on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
	If "yes", how long after cessation of treatment?			
☐ If temporary discontinued, restarted on: ___/___/___	At previous dose?	☐ Yes	☐ No	☐ Unknown
	Event subsequently reappeared?	☐ Yes	☐ No	☐ Unknown
☐ Permanently discontinued on: ___/___/___				
☐ Dose Reduced on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
☐ Treatment Continued without Change				
☐ Not Applicable				
☐ Unknown				

F. ADVERSE EVENT(S) *(If there are more than three adverse events, reprint this page as many times as is necessary.)*						
Report adverse event diagnosis (ses), if not available provide sign(s) and symptom(s)	AE ____:		AE ____:		AE ____:	
Onset Date and Time (dd/mmm/yyyy hh:mm)	___/___/___ :		___/___/___ :		___/___/___ :	
Resolution Date (dd/mmm/yyyy)	___/___/___		___/___/___		___/___/___	
Duration, if less than 24h	____ ☐ hr ☐ min		____ ☐ hr ☐ min		____ ☐ hr ☐ min	
SEVERITY						
Severity Grade *Use either NCI-CTC grading OR Qualitative Scale*	☐ 1	☐ Mild	☐ 1	☐ Mild	☐ 1	☐ Mild
	☐ 2	☐ Moderate	☐ 2	☐ Moderate	☐ 2	☐ Moderate
	☐ 3	☐ Severe	☐ 3	☐ Severe	☐ 3	☐ Severe
	☐ 4	☐ Life-threatening	☐ 4	☐ Life-threatening	☐ 4	☐ Life-threatening
	☐ 5	☐ Death	☐ 5	☐ Death	☐ 5	☐ Death
SERIOUSNESS						
Resulted in Death	☐		☐		☐	
Is Life-Threatening	☐		☐		☐	
Requires/Prolongs Hospitalization	☐		☐		☐	
Persistent/Significant Disability/Incapacity	☐		☐		☐	
Medically Significant	☐		☐		☐	
Is Congenital Anomaly/Birth Defect	*Parent-Child/Foetus Report Form must be completed*		*Parent-Child/Foetus Report Form must be completed*		*Parent-Child/Foetus Report Form must be completed*	
OUTCOME						
Unknown (only applicable if subject is lost to follow-up)	☐		☐		☐	
Fatal (AE resulted in death)	☐		☐		☐	
Ongoing	☐		☐		☐	
Resolved without Sequelae	☐		☐		☐	
Resolved with Sequelae	☐ Specify:		☐ Specify:		☐ Specify:	

[redacted]

MERCK

Subject ID: _____ / _____ / _____
Trial No. Center No. Subject No.

RELATION TO THE INVESTIGATIONAL MEDICINAL PRODUCT(S) / STUDY TREATMENT *If an event is unrelated, please indicate any other causality factors in the appropriate section and/or provide further details in the narrative (Description of Adverse Event(s)).*

	Related	Unrelated	Related	Unrelated	Related	Unrelated
Investigational Medicinal Product 1	☐	☐	☐	☐	☐	☐
Investigational Medicinal Product 2	☐	☐	☐	☐	☐	☐
Other Study Drug (Non-IMP)	☐	☐	☐	☐	☐	☐
Radiotherapy	☐	☐	☐	☐	☐	☐

G. DESCRIPTION OF ADVERSE EVENT(S)

Provide a detailed description of AE, i.e. clinical course of event(s), signs, symptoms, laboratory results, treatment of AE, etc.

1) In Case of Death

Cause of Death: ☐ AE ☐ Other If "other", specify: _____

Date of Death*: ___/___/___ Autopsy performed? ☐ Yes ☐ No If "yes", please attach autopsy report if available.

2) In Case of Hospitalization or Prolonged Hospitalization

Admission Date*: ___/___/___ Discharge Date*: ___/___/___ ☐ Not Discharged

H. RELEVANT TESTS/PROCEDURES/LABORATORY TESTS TO CONFIRM ADVERSE EVENT

[redacted]

MERCK

Subject ID: _____ / _____ / _____
Trial No. Center No. Subject No.

I. OTHER RELEVANT RISK FACTORS

☐ Alcohol Use	☐ Physical Therapy	☐ Contraceptive	☐ Smoking
☐ Pace Maker	☐ Drug Dependence	☐ Radiation Therapy	☐ Diet
☐ Metabolic Disorders	☐ Drug Abuse	☐ Obesity	☐ Allergy
☐ Implants	☐ Other, specify: _____		

J. CAUSALITY FACTORS OTHER THAN TRIAL TREATMENT

☐ Concomitant Medication, please specify suspected drug: _____ (record details in section D)

☐ Medical History, please specify disease: _____ (record details in section C)

☐ Disease Under Study ☐ Disease Progression; specify: _____

☐ Trial Procedure ☐ Other; specify: _____

K. INVESTIGATOR SIGNATURE

Investigator's Signature _____ Date of Report*: _____

[redacted]

MERCK

Pregnancy Report Form

(Clinical Trial / Observational Study)

MS200084_0015
Glucophage® XR 750 mg
Bioequivalence Study

COMPANY USE ONLY

Receipt date of this report (stamp or date)

TYPE OF REPORT

☐ Initial ☐ Follow-up

A. REPORTER INFORMATION

Reporter's First Name	Reporter's Last Name
Investigator's First Name (if different from Reporter)	Investigator's Last Name (if different from Reporter)
Address	City
Country	Phone Number
E-Mail:	Fax Number

B. SUBJECT INFORMATION

Subject ID: _____ / _____ / _____
(Trial/Study No. / Center No. / Subject No.)

Randomization Number

Subject Initials

Relation to Fetus ☐ Mother ☐ Father

Date of Birth (dd/mmm/yyyy) OR Age at Time of Preg. (Specify unit, e.g. years, etc.)

/ /

Ethnicity/Race ☐ American Indian/Alaska native ☐ Asian ☐ Black or African American ☐ Caucasian/White ☐ Hispanic or Latino
☐ Native Hawaiian or other Pacific Islander ☐ other _____

C. CONCOMITANT DRUG INFORMATION *(Any non-Merck products)*

Drug Trade Name	Single Dose	Frequency of Administration	Route	Start Date (dd/mmm/yyyy)	Stop Date (dd/mmm/yyyy)	Indication
1)				/ /	/ /	
2)				/ /	/ /	
3)				/ /	/ /	
4)				/ /	/ /	
5)				/ /	/ /	

D. MEDICAL HISTORY *(e.g. previous history, allergies, family history, or previous drug reactions, etc.)*:

Select: Mother Father	Condition/Disorder	Start Date (dd/mmm/yyyy)	Stop Date (dd/mmm/yyyy)	Ongoing
		/ /	/ /	☐
		/ /	/ /	☐
		/ /	/ /	☐
		/ /	/ /	☐

E. OBSTETRICS HISTORY

☐ No. of Live Births: Vaginal: Caesarean; specify cause:

☐ No. of Miscarriages/Abortions: Spontaneous: Specify early ☐ or Late ☐; specify cause: Medically induced:

☐ No. of Multiple Pregnancies: Specify outcome:

☐ No. of Ectopic Pregnancies: Specify outcome:

[redacted]

MERCK

Subject ID: _____ / _____ / _____
Trial No. Center No. Subject No.

☐ Complications During Pregnancy; specify:
☐ Complications During Delivery; specify:
☐ Assisted Pregnancies: OI (please report the drugs used), ART such as IUI, IVF, ICSI, etc.: Specify past history or present pregnancy, number of cycles:

F. INVESTIGATIONAL MEDICINAL PRODUCT(S)/STUDY DRUG(S)

Indication of Investigational Medicinal Product(s) / Study Drug(s)

1	Investigational Medicinal Product / Study Drug Name /Route of Administration:	Kit/Batch/Lot Number
	Not yet administered:	
	Date and <<Time>> of first <<administration/intake>>: (dd/mmm/yyyy) / / (hh:mm) /	Dose/Unit:
	Date and <<Time>> of most recent <<administration/intake>> prior to estimated conception date: (dd/mmm/yyyy) / / (hh:mm) /	Dose/Unit:
	Number of <<administrations/cycles/doses>> prior to estimated conception date:	
2	Investigational Medicinal Product / Study Drug Name /Route of Administration:	Kit/Batch/Lot Number
	Not yet administered:	
	Date and <<Time>> of first <<administration/intake>>: (dd/mmm/yyyy) / / (hh:mm) /	Dose/Unit:
	Date and <<Time>> of most recent <<administration/intake>> prior to estimated conception date: (dd/mmm/yyyy) / / (hh:mm) /	Dose/Unit:
	Number of <<administrations/cycles/doses>> prior to estimated conception date:	
3	Other Study Treatment (Non-IMP/Radiotherapy)	Kit/Batch/Lot Number
	Not yet administered:	
	Date and <<Time>> of first <<administration/intake>>: (dd/mmm/yyyy) / / (hh:mm) /	Dose/Unit:

[redacted]

MERCK

Subject ID: _____ / _____ / _____
Trial No. / Center No. / Subject No.

Date and <<Time>> of most recent <<administration/intake>> prior to estimated conception date: (dd/mmm/yyyy) / / (hh:mm) /	Dose/Unit:
Number of <<administrations/cycles/doses>> prior to estimated conception date:	

G. OTHER RELEVANT RISK FACTORS

☐ Alcohol Use ☐ Physical Therapy ☐ Contraceptive ☐ Smoking
☐ Pace Maker ☐ Drug Dependence ☐ Radiation Therapy ☐ Diet
☐ Metabolic Disorders ☐ Drug Abuse ☐ Obesity ☐ Allergy
☐ Implants ☐ Other, specify: _____

H. PREGNANCY AND OUTCOME INFORMATION

PART A – Pregnancy Information

Date of Last Menstrual Period (dd/mmm/yyyy)
/ / ☐ Regular ☐ Irregular If "irregular", specify:

Estimated Conception Date (dd/mmm/yyyy) / /	Estimated Delivery Date (dd/mmm/yyyy) / /
☐ Positive Blood β-hCG Testing on: / /	☐ Positive Urine β-hCG Testing on: / /
☐ Positive Ultrasound on: / /	If positive, specify gestational age at time of ultrasound:

PART B – Outcome Information *(If foetus or child sustained AE(s), please use a Parent-Child/Foetus Report form. If the mother sustained AE(s) please use a Serious Adverse Event Report form.)*

☐ Normal Course of Pregnancy with Spontaneous Delivery at Week of Pregnancy on / / (date of delivery – dd/mmm/yyyy)

☐ Normal Course of Pregnancy with Caesarean Section at Week of Pregnancy on / / (date of CS – dd/mmm/yyyy)

Neonatal Evaluation

Sex	Apgar Score	Length	Weight
☐ Female ☐ Male	____ / ____ (1 min) (5 min)	_____ cm	_____ g

Any Other Important Remark

I. INVESTIGATOR SIGNATURE

Investigator's Signature _____ Date of Report*: _____

[redacted]

MERCK

Parent-Child/Fetus Adverse Event Report Form

Merck Protocol Number : MS200084_0015
Study Short Title : Glucophage® XR 750 mg Indonesia Bioequivalence Study

COMPANY USE ONLY
Receipt date of this report (stamp or date)

TYPE OF REPORT
☐ Initial ☐ Follow-up

A. REPORTER INFORMATION

Reporter's First Name	Reporter's Last Name
Investigator's First Name (if different from Reporter)	Investigator's Last Name (if different from Reporter)
Address	City
Country	Phone Number
E-Mail:	Fax Number

B. PARENT (SUBJECT) INFORMATION

Subject ID ____ / ____ / ____ (Trial/Study No. / Center No. / Subject No.) | Randomization Number

Parent (Subject) Initials | Relation to Child/Fetus ☐ Mother ☐ Father | Date of Birth (dd/mmm/yyyy)* OR Age at Time of AE (Specify unit, e.g. weeks, months, years) / /

Ethnicity/Race ☐ American Indian/Alaska native ☐ Asian ☐ Black or African American ☐ Caucasian/White ☐ Hispanic or Latino ☐ Native Hawaiian or other Pacific Islander ☐ other ____

Assignment to treatment group or dose cohort: | Unblinded by investigator due to event? ☐ Yes ☐ No If "yes", specify the date: / /

C. CHILD/FETUS INFORMATION

Initials (if applicable) | Sex ☐ Female ☐ Male ☐ Undetermined/Unknown | Age at Time of AE (Specify unit, e.g. years, etc.) ☐ Gestational ☐ Since Birth

Date of Birth or Evacuation (dd/mmm/yyyy)* / / ☐ Birth ☐ Evacuation | Gestational Age at Birth or Evacuation | Length at Birth (and unit) | Weight at Birth (and unit)

Exposure to Investigational Medical Product? ☐ Yes ☐ No ☐ Unknown | If exposed, route of exposure? ☐ Transplacental ☐ Transmammary ☐ IVF ☐ Other, specify:

D. RELEVANT MEDICAL HISTORY

Select: Mother Father	Condition/Disorder	Start Date (dd/mmm/yyyy)	End Date (dd/mmm/yyyy)	Ongoing
		/ /	/ /	☐
		/ /	/ /	☐
		/ /	/ /	☐
		/ /	/ /	☐
		/ /	/ /	☐

E. CONCOMITANT MEDICATIONS

Select: Mother Father Child	Drug Trade Name	Single Dose	Frequency of Admin-istration	Route	Start Date (dd/mmm/yyyy)	Stop Date (dd/mmm/yyyy)	Indication
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	

[redacted]

Subject ID: _____ / _____ / _____
Trial No. Center No. Subject No.

F. INVESTIGATIONAL MEDICINAL PRODUCT(S)/ STUDY TREATMENT(S)

Indication of Investigational Medicinal Product(s)

1	Investigational Medicinal Product Name /Route of Administration:	Kit/Batch/Lot Number
Not yet administered:		
Date and <<Time>> of first <<administration/intake>>: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Date and <<Time>> of most recent <<administration/intake>> prior to AE: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Number of <<administrations/cycles/doses>> prior to AE:		

ACTIONS TAKEN REGARDING THIS INVESTIGATIONAL MEDICINAL PRODUCT

☐ Temporary discontinued on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
	If "yes", how long after cessation of treatment? _____			
☐ If temporary discontinued, restarted on: ___/___/___	At previous dose?	☐ Yes	☐ No	☐ Unknown
	Event subsequently reappeared?	☐ Yes	☐ No	☐ Unknown
☐ Permanently discontinued on: ___/___/___				
☐ Dose Reduced on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
☐ Treatment Continued without Change				
☐ Not Applicable				
☐ Unknown				

2	Investigational Medicinal Product Name /Route of Administration	Kit/Batch/Lot Number
Not yet administered:		
Date and <<Time>> of first <<administration/intake>>: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Date and <<Time>> of most recent <<administration/intake>> prior to AE: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Number of <<administrations/cycles/doses>> prior to AE:		

[redacted]

Subject ID: _____ / _____ / _____
Trial No. / Center No. / Subject No.

ACTIONS TAKEN REGARDING THIS INVESTIGATIONAL MEDICINAL PRODUCT

☐ Temporary discontinued on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
	If "yes", how long after cessation of treatment?			
☐ If temporary discontinued, restarted on: ___/___/___	At previous dose?	☐ Yes	☐ No	☐ Unknown
	Event subsequently reappeared?	☐ Yes	☐ No	☐ Unknown
☐ Permanently discontinued on: ___/___/___				
☐ Dose Reduced on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
☐ Treatment Continued without Change				
☐ Not Applicable				
☐ Unknown				

3 Other Study Treatment (Non-IMP/Radiotherapy)	Kit/Batch/Lot Number
Not yet administered:	
Date and <<Time>> of first <<administration/intake>>: (dd/mmm/yyyy) / / (hh:mm) /	Dose/Unit:
Date and <<Time>> of most recent <<administration/intake>> prior to AE: (dd/mmm/yyyy) / / (hh:mm) /	Dose/Unit:
Number of <<administrations/cycles/doses>> prior to AE:	

ACTIONS TAKEN REGARDING THIS OTHER STUDY TREATMENT

☐ Temporary discontinued on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
	If "yes", how long after cessation of treatment?			
☐ If temporary discontinued, restarted on: ___/___/___	At previous dose?	☐ Yes	☐ No	☐ Unknown
	Event subsequently reappeared?	☐ Yes	☐ No	☐ Unknown
☐ Permanently discontinued on: ___/___/___				
☐ Dose Reduced on: ___/___/___	Event subsided?	☐ Yes	☐ No	☐ Unknown
☐ Treatment Continued without Change				
☐ Not Applicable				
☐ Unknown				

[redacted]

MERCK

Subject ID: _____ / _____ / _____
Trial No. / Center No. / Subject No.

G. ADVERSE EVENT(S) *(If there are more than three adverse events, reprint this page as many times as is necessary.)*

	AE ____:	AE ____:	AE ____:
Report adverse event diagnosis (ses), if not available provide sign(s) and symptom(s)			
Onset Date and Time (dd/mmm/yyyy hh:mm)	___/___/___ :	___/___/___ :	___/___/___ :
Resolution Date (dd/mmm/yyyy)	___/___/___	___/___/___	___/___/___
Duration, if less than 24h	____ ☐ hr ☐ min	____ ☐ hr ☐ min	____ ☐ hr ☐ min
SEVERITY			
Severity Grade *Use either NCI-CTC grading OR Qualitative Scale*	☐ 1 ☐ Mild ☐ 2 ☐ Moderate ☐ 3 ☐ Severe ☐ 4 ☐ Life threatening ☐ 5 ☐ Death	☐ 1 ☐ Mild ☐ 2 ☐ Moderate ☐ 3 ☐ Severe ☐ 4 ☐ Life threatening ☐ 5 ☐ Death	☐ 1 ☐ Mild ☐ 2 ☐ Moderate ☐ 3 ☐ Severe ☐ 4 ☐ Life threatening ☐ 5 ☐ Death
SERIOUSNESS			
Resulted in Death	☐	☐	☐
Is Life-Threatening	☐	☐	☐
Requires/Prolongs Hospitalization	☐	☐	☐
Persistent/Significant Disability/Incapacity	☐	☐	☐
Medically Significant	☐	☐	☐
Is Congenital Anomaly/Birth Defect	☐	☐	☐
NON-SERIOUS	☐	☐	☐
OUTCOME			
Unknown (only applicable if subject is lost to follow-up)	☐	☐	☐
Fatal (AE resulted in death)	☐	☐	☐
Ongoing	☐	☐	☐
Resolved without Sequelae	☐	☐	☐
Resolved with Sequelae	☐ Specify:	☐ Specify:	☐ Specify:

RELATION TO THE INVESTIGATIONAL MEDICINAL PRODUCT(S) / STUDY TREATMENT *If an event is unrelated, please indicate any other causality factors in the appropriate section and/or provide further details in the narrative (Description of Adverse Event(s)).*

	Related	Unrelated	Related	Unrelated	Related	Unrelated
Investigational Medical Product 1	☐	☐	☐	☐	☐	☐
Investigational Medical Product 2	☐	☐	☐	☐	☐	☐
Other Study Drug (Non-IMP)	☐	☐	☐	☐	☐	☐
Radiotherapy	☐	☐	☐	☐	☐	☐

[redacted]

MERCK

Subject ID: _____ / _____ / _____
Trial No. / Center No. / Subject No.

H. DESCRIPTION OF ADVERSE EVENT(S)

Provide a detailed description of AE, i.e. clinical course of event(s), signs, symptoms, laboratory results, treatment of AE, etc.

1) In Case of Death

Cause of Death: ☐ AE ☐ Other If "other", specify: _____

Date of Death*: ___/___/___ Autopsy performed? ☐ Yes ☐ No If "yes", please attach autopsy report if available.

2) In Case of Hospitalization or Prolonged Hospitalization

Admission Date*: ___/___/___ Discharge Date*: ___/___/___ ☐ Not Discharged

3) In Case of Congenital Anomaly/Birth Defect

Karyotype Performed? ☐ Yes ☐ No If "yes", specify:

I. RELEVANT TESTS/PROCEDURES/LABORATORY TESTS TO CONFIRM ADVERSE EVENT

J. OTHER RELEVANT RISK FACTORS

☐ Alcohol Use	☐ Physical Therapy	☐ Contraceptive	☐ Smoking
☐ Pace Maker	☐ Drug Dependence	☐ Radiation Therapy	☐ Diet
☐ Metabolic Disorders	☐ Drug Abuse	☐ Obesity	☐ Allergy
☐ Implants	☐ Other, specify: _____		

K. CAUSALITY FACTORS OTHER THAN TRIAL TREATMENT

☐ Concomitant Medication, please specify suspected drug: _____ (record details in section D)

☐ Medical History, please specify disease: _____ (record details in section C)

☐ Disease Under Study ☐ Disease Progression; specify: _____

☐ Trial Procedure ☐ Other; specify: _____

L. INVESTIGATOR SIGNATURE

Investigator's Signature

Date of Report*:

[redacted]

APPENDIX C
STUDY FLOW CHART

Study Flow Chart

MS200084_0015 / BE. 479/EQL/2017

Study Phase	Screening	Dosing Period 1 and 2																		Follow Up
Study Day	Within 21 days before dosing	Day 1																Day 2		Within 7 days after last blood sampling
Assessment time		Pre-dose	0h	1h	1.5h	2h	2.5h	3h	3.5h	4h	4.5h	5h	6h	7h	8h	10h	12h	16h	24h	32h	
Informed consent	x																				
Inclusion/exclusion criteria	x																				
Relevant medical history/current medical conditions	x																				
Physical examination	x																				x
12-lead ECG evaluation (supine)	x																				x
Urine pregnancy test (for female)	x																				
Alcohol breath test	x	x[f]																			
Urine test for drug abuse[a]	x	x[f]																			
Serology tests for hepatitis and HIV screenings[b]	x																				
Hematology tests[c]	x																				x
Blood chemistry tests[d]	x																				x
Urinalysis[e]	x																				x
Vital signs & body measurements																					
Body height & weight	x																				x
Body temperature	x																				x
Blood pressure/pulse rate	x	x[g]				x[g]				x[g]			x[g]		x[g]		x[g]		x[g]	x[g]	x
Respiration rate	x	x[g]				x[g]				x[g]			x[g]		x[g]		x[g]		x[g]	x[g]	x
Drug administration record			x																		
Pharmacokinetics (PK) blood sampling		x[h]		x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	
Adverse events	x[i]	x[i]				x[i]				x[i]			x[i]		x[i]		x[i]		x[i]	x[i]	x[i]

[redacted]

a. Urine test for drug abuse includes opiate class, barbiturates, cocaine and metabolites, amphetamines, cannabinoids and benzodiazepines.
b. Serology tests include HBsAg, anti-HCV, and anti-HIV.
c. Hematology tests include hemoglobin, hematocrit, erythrocyte count, leucocyte count, and platelet count.
d. Blood chemistry tests include AP, ALT, AST, total protein, albumin, total/direct bilirubin, creatinine, ureum, and glucose .
e. Urinalysis tests include urine chemistry and urine sediment.
f. Alcohol breath test, and urine test for drug abuse performed at Screening and at each study Check-In (at least 12 hours prior to Day 1 of each dosing period).
g. Vital signs (blood pressure/pulse rate and respiration rate) will be measured at each study Check-In, prior to dosing and at approximately 2, 4, 6, 8, 12, 24, and 32 hours after dosing. Pre-dose vitals will be measured within 2 hours prior to dose administration. A window period of ± 30 minutes from the scheduled time point is allowed for post-dose vital signs measurements.
h. PK blood sampling will be performed within 60 minutes prior to each subject's scheduled dose time (0-hour) and after dose administration at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, and 32 hours (± 2 min window for post-dose blood draws).
i. Safety surveillance and adverse event monitoring begins when the subject is initially included in the study (date of first signature on the informed consent form [ICF]), pre-dose and throughout both PK blood sampling periods at 2, 4, 6, 8, 12, 24 and 32 hours after dosing, until the completion of the Follow-Up Visit.

[redacted]

APPENDIX D
DECLARATION OF HELSINKI

[redacted]

World Medical Association

DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, the 41st World Medical Assembly, Hong Kong, September 1989, the 48th General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, 53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added), 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added), 59th WMA General Assembly, Seoul, October 2008, 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

Preamble

The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

Medical progress is based on research that ultimately must include studies involving human subjects.

The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the

[redacted]

physician or other health care professionals and never with the research subjects, even though they have given consent.

Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

Medical research should be conducted in a manner that minimises possible harm to the environment.

Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

[redacted]

Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential

[redacted]

risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

[redacted]

Use of Placebo

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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PPD

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APPENDIX E

MS200084_001

PPD

Protocol Version 1.1, 22/05/2018

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APPENDIX E

MS200084_0015

PPD

Protocol Version 1.1, 22/05/2018

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1 PPD

3 HOW THE STUDY WILL BE CONDUCTED?

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CONDITIONS TO PARTICIPATE IN STUDY

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APPENDIX F
PROTOCOL AMENDMENT SUMMARY OF CHANGES

APPENDIX F
PROTOCOL AMENDMENT SUMMARY OF CHANGES

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

PPD , Final Version 1.1 22/05/2018

NUMBER/ PAGE(S)	SECTION(S)	INITIAL PROTOCOL WORDINGS	AMENDED PROTOCOL WORDINGS	REASON FOR CHANGE
1, 2, 4, 7, 68, 76, 79, 85	Cover Page / Study Personnel & Responsibilities / Statement of Compliance / Protocol Agreement Page / Appendix E	PPD	PPD	Change of Principal Investigator in PPD PPD
2, 5	Study Personnel & Responsibilities / Protocol Agreement Page	PPD	PPD	Change of Study Director in PPD
2, 5, 68, 74, 79, 83	Study Personnel & Responsibilities / Protocol Agreement Page / Appendix E	PPD	PPD	Change of Study Physician in PPD
3	Study Personnel & Responsibilities	-	PPD	Include name of PPD in the protocol
3	Study Personnel & Responsibilities	PPD	PPD	Changes/addition of Co-Investigators from PP PPD
3, 4, 5	Study Personnel & Responsibilities / Statement of Compliance / Protocol Agreement Page	PPD	PPD	Change of PPD PPD job title

[redacted]

NUMBER/ PAGE(S)	SECTION(S)	INITIAL PROTOCOL WORDINGS	AMENDED PROTOCOL WORDINGS	REASON FOR CHANGE
13, 19	1, 5.2: Inclusion Criteria	6. Vital signs (blood pressure, pulse and body temperature) in sitting position within the normal range or showing no clinically relevant deviation per the Investigator's opinion.	6. 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.	Inserted respiratory rate measurement during treatment phase to be consistent with study procedure described under section 7.3
15, 36	1, 14: Study Timeframe	**Oct 2017 – May 2018** Protocol development, application for ethical clearance, BPOM approval, and analytical method verification **Jun 2018 – Jul 2018** Subject recruitment and blood sampling **Jul 2018 – Sep 2018** Analysis of drug concentrations and data management **Sep 2018 – Dec 2018** Statistical analysis and final study report	**Apr – Jun 2018** Application for ethical clearance, BPOM approval, and analytical method verification **Jul 2018 – Aug 2018** Subject recruitment and blood sampling **Aug 2018 – Oct 2018** Analysis of drug concentrations and data management **Oct 2018 – Feb 2019** Statistical analysis and final study report	Adjusted based on study status at the point of protocol amendment
21	5.3.3: Criteria for Subjects' Withdrawal from the Study	-	6. 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;	BPOM's comment to add criteria "subjects have diarrhea during blood sampling" according to *Pedoman Uji Bioekivalensi*, BPOM, 2015 page 22

NUMBER/ PAGE(S)	SECTION(S)	INITIAL PROTOCOL WORDINGS	AMENDED PROTOCOL WORDINGS	REASON FOR CHANGE
34	12.1.3: Vital Signs, Physical Examinations, ECG and Other Assessments	Physical examination and ecg will be performed during screening and follow-up visit.	Physical examination, body measurement (height and weight), and ECG will be performed during screening and follow-up visit.	Inserted body measurements (height and weight) during Follow-Up Visit to be consistent with the study procedure described under section 7.4
43, 53-57	Appendix B	Sponsor's Serious Adverse Event(s) Report Form and Pregnancy Report Form	Sponsor's Serious Adverse Event(s) Report Form, Pregnancy Report Form, and Parent-Child/Fetus Adverse Event Report Form	Inserted Parent-Child/Fetus Adverse Event Report Form template under Appendix B as mentioned under section 12.1.1
59	Appendix C: Study Flow Chart	-	(Adjusted)	Inserted body height and weight during Follow-Up Visit to be consistent with the study procedure described under section 7.4
72	Appendix E: PPD	PPD	PPD	BPOM's comment to include respiratory rate measurement during treatment phase to be consistent with study procedure described under section 7.3
73	Appendix E: PPD	PPD	PPD	Inserted body measurements (height and weight) to be consistent with study procedure described under section 7.4

NUMBER/ PAGE(S)	SECTION(S)	INITIAL PROTOCOL WORDINGS	AMENDED PROTOCOL WORDINGS	REASON FOR CHANGE
75	Appendix E: 10. Perlindungan Kesehatan	PPD		BPOM's comment to revise statement regarding subject reimbursement for physical illness or injury
82	Appendix E: Drug Administration Period	...measuring your blood pressure, pulse rate, and monitor the occurrence of any adverse event...	...measuring your blood pressure, pulse rate, respiratory rate, and monitor the occurrence of any adverse event...	BPOM's comment to include respiratory rate measurement during treatment phase to be consistent with study procedure described under section 7.3
82	Appendix E: Follow-Up After The Study	...physical examination, vital signs assessments (blood pressure, pulse rate, respiratory rate and temperature), ECG...	...physical examination, vital signs assessments (blood pressure, pulse rate, respiratory rate and temperature), body measurement (height and weight), ECG...	Inserted body measurements (height and weight) to be consistent with study procedure described under section 7.4
85	Appendix E: 10. Health Protection	If you sustain physical illness or injury as a direct result of the administration of the study drug during the study...	If you sustain physical illness or injury as a direct result of participating in the study...	BPOM's comment to revise statement regarding subject reimbursement for physical illness or injury

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