Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A randomized Phase I, open-label, active-controlled study assessing the bioequivalence between single doses of 500 mg Glucophage® XR Reduced Mass tablets and 500 mg Glucophage® XR tablets under fasted and fed state in two 2-way crossover groups of healthy participants
Study Number:	MS200084_0028
Amendment Number	Amendment 6
Merck Compound Number:	200084
Short Title:	GXR RM 500 mg Korea BE study
Principal Investigator:	PPD
Sponsor Name and Legal Registered Address:	Merck Ltd. Korea 508 Teheran-ro, Gangnam-gu, Seoul, Korea PPD
Regulatory Agency Identifying Numbers:	Not Applicable
Protocol Version	15 September 2021 / Version 6.1
Replaces Version:	08 July 2021 / Version 6.0
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Medical Monitor Name and Contact Information:	Medical Responsible: PPD

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	02-May-2020
2.0	Revised Protocol	05-October-2020
3.0	Revised Protocol	01-December-2020
4.0	Revised Protocol	08-December-2020
5.0	Revised Protocol	04-January-2021
6.0	Revised Protocol	08-July-2021
6.1	Revised Protocol	15-September-2021

Protocol Version 6.1 (XX-September-2021)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

Rationale Statement

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Addition of "Physical Examination" on Day 2	To clarify the activity to be implemented on Day 2, and to correct discrepancy in description of Day 2 activity(i.e., Interview and Physical Examination).
8.2.2 Physical Examinations	Addition of "Physical Examination" on Day 2	
8.10.4 Clinic Day 2 (Period 1 and Period 2)	"Interview" was changed to "Physical Examination".	
6.3.1 Study Intervention Assignment	Change in Screening Number	To differentiate subjects to be screened from the screened subjects in 2020 & beginning of 2021.

- Confidential –

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1 Protocol Summary

1.1 Synopsis

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

Short Title: GXR RM 500 mg Korea BE study

Rationale: The aim of this clinical study is to investigate the bioequivalence of a new Glucophage® XR formulation, i.e., Glucophage® XR Reduced Mass (RM) tablet (= test drug), which contains less excipients, is easier to swallow and might therefore improve patient compliance and efficacy of the product compared to the current marketed formulation (Glucophage® XR tablet = reference drug). For this purpose, and according to the "Regulation on Standard for Drug Equivalence Test" from the Ministry of Food and Drug Safety (MFDS), a 2-way crossover bioequivalence study under fasted and fed condition will be conducted.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)
Primary	
To demonstrate the bioequivalence of the newly developed "Glucophage® XR Reduced Mass tablet" (containing metformin hydrochloride 500 mg) and the current marketed "Glucophage® XR tablet" (containing metformin hydrochloride 500 mg) after single oral administration under fasted and fed conditions.	Pharmacokinetic (PK) profile of metformin in terms of AUC_{last} (area under the plasma concentration-time curve from time zero to time of last measurable concentration) and C_{max} (Maximum observed concentration)
Secondary	
To evaluate the safety and tolerability of the metformin formulations after single dose treatment under fasted and fed conditions.	• Treatment-emergent adverse events (TEAEs) • Concomitant Medication • Laboratory safety tests, including blood glucose safety determination • Cardiac safety monitoring by 12-lead ECGs (Vent. rate, PR interval, QRS duration, QT and QTc) • Vital signs (body temperature [tympanic], Blood Pressure and pulse rate) • Physical examination

Objectives	Endpoints (Outcome Measures)
To characterize other PK parameters of the metformin formulations under fasted and fed conditions.	AUC_{inf} (if data allows to calculate), AUC_{last}/AUC_{inf} (if data allows to calculate), $t_{1/2}$ (if data allows to calculate) and T_{max} of metformin

Overall Design: This bioequivalence study is divided into two parts according to the method of administration of the study interventions: Part 1 (Fasted state) and Part 2 (Fed state).

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

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

In the case of fasted group (Part 1), the sample size is 19 participants per sequence and in total, 38 participants thus meeting the 2-period 2-sequence crossover study design that has a significance level of 0.05 and a power of 90%. Considering the drop-out rate of about 20% during the study, 24 participants per sequence, hence 48 participants in total will be recruited.

In the case of fed group (Part 2), the sample size is 11 participants per sequence and in total, 22 participants thus meeting the 2-period 2-sequence crossover study design that has a significance level of 0.05 and a power of 90%. Considering the drop-out rate of about 35% during the study, 17 participants per sequence, hence 34 participants in total will be recruited.

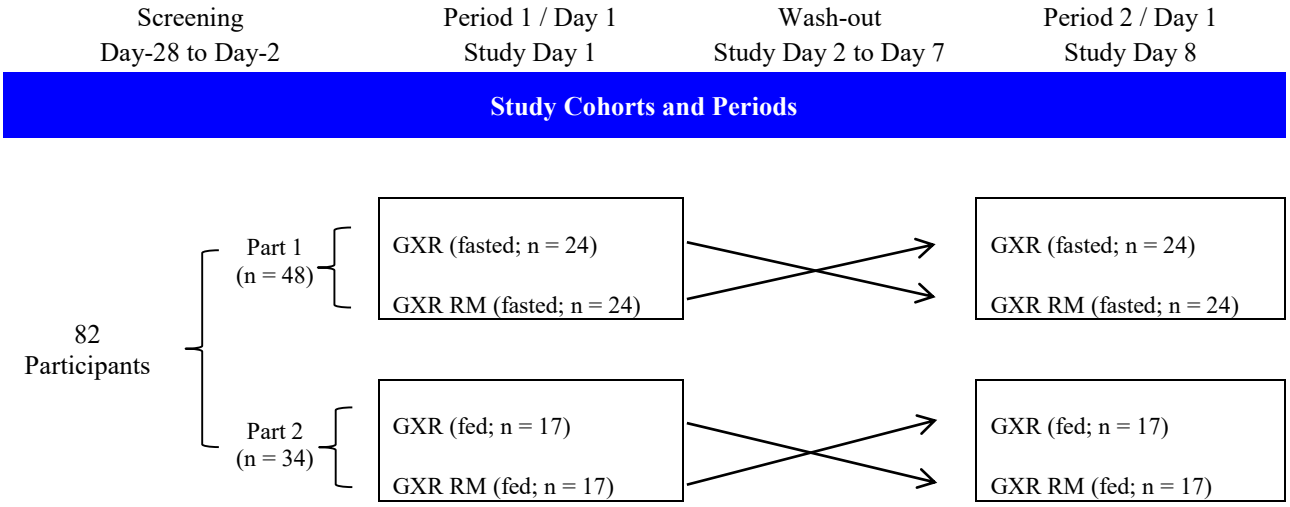
When BE study was performed in Korea, it was found the drop-out rate of fed study was higher than that of fasted study. Therefore, a higher drop-out rate for the fed study is considered.

Please see Section 9.2.2 (Sample Size Justification), also.

Study Intervention Groups and Duration: A single oral dose of Test Drug, “Glucophage® XR Reduced Mass tablet” (containing metformin hydrochloride 500 mg) of Merck Ltd. Korea, and Reference Drug, “Glucophage® XR tablet” (containing metformin hydrochloride 500 mg) of Merck Ltd. Korea, will be administered under fasted and fed condition on Day 1 of Periods 1 and 2, in a crossover design.

Involvement of Special Committee(s): No.

1.2 Schema



GXR = Glucophage® XR tablet (Reference Drug)
GXR RM = Glucophage® XR Reduced Mass tablet (Test Drug)
n= Number of Participants

1.3 Schedule of Activities

Assessment	Screening Day-28 to Day-2	Period 1 and Period 2			End of Study Visit	Note
		Day -1	Day 1	Day 2		End of study visit is conducted 10±3 days after Day 1 of Period 2. (In the case of participant discontinuation, End of study visit is conducted 10±3 days after the last administration.)
Informed Consent	X					
Check of Inclusion/Exclusion Criteria	X	X				
Demographic Information	X					
Interview	X					
Physical Examination	X	X		X	X	A brief physical examination will be done on day -1, Day 2. See Section 8.2.2.
Medical History	X					
Clinical Laboratory Tests	X	X			X	In the case of Day-1, AST (GOT), ALT (GPT), γ-GT, UN, Cr, eGFR with MDRD, Lactic acid and pregnancy test (Serum-HCG) for female participants, only.
Drug screening	X	X				Urine sample
Alcohol breath test	X	X				

Vital Signs	X		X	X	X	Screening and end of study visit: Body temperature (tympanic), blood pressure and pulse rate. Prior to administration of each Period and before blood collection at 24 and 32 hours after administration of each Period: Blood pressure and pulse rate.
12-lead ECG	X				X	
Blood Sugar Test (BST)			X			Blood Sugar Test is performed before blood collection at 3 and 4 hours after study intervention administration of each Period.
Admission		X				
Randomization		X				Performed in Period 1 only.
Study Intervention Administration			X			Part 1 (Fasted state): On Day 1, after an overnight fast of at least 10 hours, participants will receive 1 tablet of either the Reference or the Test drug orally, starting with the first participant at around 08:00 am. Part 2 (Fed state): On Day 1, participants shall take a high-fat breakfast (over 900kcal, over 35% fat) from around 07:30 am within 20 minutes and 30 minutes after the start of the meal (around 08:00 am), participants will receive 1 tablet of either the Reference or the Test drug orally.
Pharmacokinetic Profile			X	X		Blood sample collection Part 1 (Fasted state): Before administration (just prior to administration) of study intervention and 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 24 and 32 hours thereafter (totally 16 times). Part 2 (Fed state): Before administration (just prior to administration) of study intervention and 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 24 and 32 hours thereafter (totally 16 times).
Adverse Events Monitoring	X	X	X	X	X	Signs and symptoms that occurred from the signing of informed consent to the end of the study are documented (please refer to Appendix 5).
Prior/Concomitant Medication	X	X	X	X	X	For prior medication, the medications administered from 30 days prior to screening up to the administration of study intervention of Period 1 are documented. For concomitant drug, the medications administered from Period 1 to the end of the observation are documented.
Discharge				X		Participants can stay at the Study Center at the discretion of the Principal Investigator (or delegated investigator).
Outpatient Visit					X	

2 Introduction

Glucophage Extended Release (GXR) tablet contains metformin hydrochloride (metformin HCl), an active pharmaceutical ingredient that belongs to the biguanide group antihyperglycemic drugs used in the management of Type 2 Diabetes Mellitus (T2DM). Metformin has been used for clinical management of diet-failed T2DM patients since 1959 and is presently marketed in several forms and strengths in more than 130 countries.

Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with T2DM, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, delays intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin, when used alone, does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may decrease.

Complete information on the chemistry, pharmacology, efficacy and safety of metformin is in the Investigator's Brochure.

2.1 Study Rationale

The aim of this clinical study is to investigate the bioequivalence of a new Glucophage XR formulation, i.e., Glucophage XR Reduced Mass (RM), which contains less excipients, is smaller and thus easier to swallow and might therefore improve patient compliance and efficacy of the product. For this purpose, and according to the "Regulation on Standard for Drug Equivalence Test" from the Ministry of Food and Drug Safety, a 2-way crossover bioequivalence study under fasted and fed condition will be conducted.

2.2 Background

Glucophage and Glucophage XR (metformin HCl Extended Release tablets) are antihyperglycemic drugs used in the management of T2DM. Metformin HCl (N,N-dimethylimidodicarbonimidic diamide hydrochloride; 1,1-dimethylbiguanide hydrochloride; N,N-dimethyldiguanide hydrochloride; N'-dimethylguanylguanidine hydrochloride) is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents.

Glucophage XR consists of a dual hydrophilic polymer matrix system. Metformin is released slowly from the extended release (XR) dosage form via diffusion through the gel matrix that is essentially independent of pH.

2.3 Benefit/Risk Assessment

Healthy participants participating in this bioequivalence study will not gain direct clinical benefit from their participation in the study. However, this study will help to evaluate the bioequivalence of the new Glucophage XR formulation.

Metformin is used for clinical management of diet-failed T2DM patients since 1959 and marketed in more than 100 countries. Based on clinical experience, Glucophage® XR is well tolerated and the most frequently reported adverse events (AEs) are nausea, vomiting, diarrhea, abdominal pain, and loss of appetite (reported in >1/10 patient receiving metformin). These symptoms are almost always transient, occur early during therapy initiation, and spontaneously resolve in most cases. Even more, this study will investigate single doses so that the likelihood of AEs is further reduced compared to chronic use in clinical practice.

Based on the favorable safety profile of metformin, the risks in participating in this single dose study are considered low.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of metformin may be found in Section 4.2 (Scientific Rationale for Study Design) and the Investigator's Brochure.

Based on the available clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

3 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
Primary	
To demonstrate the bioequivalence of the newly developed "Glucophage® XR Reduced Mass tablet" (containing metformin hydrochloride 500 mg) and the current marketed "Glucophage® XR tablet" (containing metformin hydrochloride 500 mg) after single oral administration under fasted and fed conditions.	AUC_{last} and C_{max} for metformin in plasma.
Secondary	
To evaluate the safety and tolerability of the metformin formulations after single dose treatment under fasted and fed conditions.	• Treatment-emergent adverse events (TEAEs) • Concomitant Medication • Laboratory safety tests, including blood glucose safety determination • Cardiac safety monitoring by 12-lead ECGs (Vent. Rate, PR interval, QRS duration, QT and QTc) • Vital signs (body temperature [tympanic], Blood Pressure and pulse rate) • Physical examination
To characterize other pharmacokinetic (PK) parameters of the metformin formulations under fasted and fed conditions.	AUC_{inf} (if data allows to calculate), AUC_{last}/AUC_{inf} (if data allows to calculate), $t_{1/2}$ (if data allows to calculate) and T_{max} of metformin

4 Study Design

4.1 Overall Design

This bioequivalence study is divided into two parts according to the method of administration of the study interventions: Part 1 (Fasted state) and Part 2 (Fed state). More detailed information about overall design can be found in Sections 1.2 (Schema), 1.3 (Schedule of Activities) and 6.7 (Study Intervention after the End of the Study).

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

Metformin will be administered as a single dose of 500 mg either as a Glucophage XR RM tablet (Test drug) or Glucophage XR tablet (marketed formulation = Reference drug) under fasted or fed condition in a crossover design.

The study duration for the individual participant will be approximately 7 weeks, including a screening period of maximum 27 days before Day 1 of Period 1, two 1-day hospitalization periods separated by a wash-out period of at least 7 days between Day 1 of each period, and an End of Study Visit at 10 days ± 3 days after the last drug administration. Part 1 and Part 2 of the study will have a staggered start, therefore the total study duration (from the First Participant Screened to the Last Participant Last Visit) is approximately 3 months.

The metformin single oral administration will be performed on Day 1 of each period either as Glucophage XR or Glucophage XR RM formulation. For logistical reasons, in the case of failure of enrollment of targeted number of participants per each part (Fasted/ Fed) as specified in the protocol, enrollment may be staggered within each study part. In this case, participants will be included in the relevant study part in two or more groups. All conditions will be identical for the groups.

4.1.1 Treatment Method per Period

Total number of participants: 82 (Part 1: 48 participants, Part 2: 34 participants)

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

Sequence	Period		
	1	Wash-out period	2
1(n=24): RT	R	At least7 days	T
2(n=24): TR	T		R

R (Reference Drug): Glucophage® XR tablet

T (Test Drug): Glucophage® XR Reduced Mass tablet

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

Sequence	Period		
	1	Wash-out period	2
1(n=17): RT	R	At least 7 days	T
2(n=17): TR	T		R

R (Reference Drug): Glucophage® XR tablet

T (Test Drug): Glucophage® XR Reduced Mass tablet

The wash-out period is set to be at least 7 days, which is considerably more than 5 times the half-life of metformin (about 3.27 hours) (referred from the Article 15 (2) of the "Standard on Pharmaceutical Equivalence Study"), so that the administered study interventions can be completely excreted from body.

4.1.2 Rationale for determination of Pharmacokinetics Time Points

Idkaidek et al (1) provided the following pharmacokinetic parameters of oral metformin 750 mg XR in healthy adults:

Formulation / Pharmacokinetic parameter	XR-Fasted	XR-Fed
C_{max} (ng/mL)	832 (300)	794 (143)
T_{max} (h)	4.3 (1.0)	6.35 (1.1)
$t_{1/2}$ (h)	3.8 (1.2)	3.66 (0.8)

Metformin mean (SD) plasma pharmacokinetic parameters after 750 mg XR (Extended Release) oral doses to healthy volunteers

In the Article 15 (2) of the Korean guideline "Standard on Pharmaceutical Equivalence Study"[2], it is mentioned that "Blood collection shall be conducted with sufficient time period of more than 3 times the elimination half-life or AUC_{0-t} to reach at least 80% of AUC_{∞}.". It is recommended that blood sampling needs more than 12 times and more than twice blood collection before reaching to the highest blood concentration (C_{max})."

To reflect this requirements, the blood collection time period shall be 32 hours which is more than 3 times the elimination half-life, and totally 16 blood samples will be collected as in below.

1) Part 1 (Fasted state)

- Number of samples: 16 times (once just before administration of study intervention, 15 times thereafter)
- Sampling time: Before administration (just prior to administration) of study

intervention and 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 24 and 32 hours thereafter

2) Part 2 (Fed state)

- Number of samples: 16 times (once just before administration of study intervention, 15 times thereafter)
- Sampling time: Before administration (just prior to administration) of study intervention and 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 24 and 32 hours thereafter

4.2 Scientific Rationale for Study Design

This is a single-center, open-label, two-way crossover design. This clinical study will be conducted in compliance with the "Regulation on Pharmaceuticals Approval, Notification and Review" (MFDS Notification No. 2020-36, 04 May 2020), Annex 4 Good Clinical Practice "Regulation on Safety of Medicinal Products, etc." (Ordinance of the Prime Minister No. 1650, 14 October 2020) and "Standard on Pharmaceutical Equivalence Study" (MFDS Notification No. 2020-91, 22 September 2020). According to these, it is justified to conduct the study in a crossover design allowing that each participant serves as its own control. The study will be performed in an open-label manner, which will not have influence on the outcome as the primary objectives and endpoints are related to PK parameters, which will be evaluated with validated methods. Bioanalytical assessments will also be done with validated methods not influenced by the respective treatment.

Based on previous PK experience and the regulations, the sample size of 48 participants in fasted group (Part 1) and 34 participants in fed group (Part 2) will provide sufficient PK information as well as safety and tolerability data without exposing too many participants. Both sexes will be included in each group. Details on sample size justification can be found in Section 9.2.2 (Sample Size Justification).

4.3 Justification for Dose

The usual starting dose of Glucophage XR to treat T2DM patients is 500 mg once daily with the evening meal and the maximum recommended daily dose is 2,000 mg.

In this study, the starting dose of 500 mg will be used. Multiple dosing is not required as no accumulation is observed after repeated administration of metformin XR tablets in healthy volunteers.

Metformin will be administered as a single dose of 500 mg either as a Glucophage XR Reduced Mass tablet (Test drug) or Glucophage XR tablet (marketed formulation = Reference drug) separated by an at least 7-days wash-out period.

4.4 End of Study Definition

The end of the study is defined as the date of the last contact with the last participant who participated in the study (last participant last observation).

A participant has completed the study if he/she has completed all study parts, including all study visits, including admission/discharge and outpatient visit. However, in the event blood

collection for PK is completed but safety confirmation test is not performed, the completion of the study by a particular participant will be determined at the discretion of the Principal Investigator.

5 Study Population

For this bioequivalence study, healthy adult volunteers aged over 19 and below 55 years shall be recruited through announcement of applicants for bioequivalence study for each of fasted and fed state part of the study. Only volunteer recruitment announcements for bioequivalence study approved by the Institutional Review Board (IRB) will be used. Volunteers are also recruited through the website of the Clinical Trials Center of Chungnam National University Hospital & web site of an external recruiting company. Participants enrolled in the Clinical Trials Center can obtain detailed information regarding the bioequivalence study by telephone or visit prior to participating in the study.

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are designed to enroll only participants who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in Appendix 2 (Study Governance).

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are between 19 and 55 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. All values for hematology and biochemistry tests of blood and urinalysis (especially eGFR > 80 mL/min/1.73m^2 and normal Creatinine) within the normal range or showing no clinically relevant deviation as judged by the Investigator.

3. Are not having congenital or chronic diseases, nor pathological symptoms based on the screening.

4. Have no history of gastrointestinal resection that may affect drug absorption.

5. Have no history of psychiatric disorder within 5 years prior to screening.

6. Vital signs (body temperature [tympanic], blood pressure [BP], and pulse rate in sitting position) within the normal range or showing no clinically relevant deviation as judged by the Investigator.

7. Electrocardiogram recording (12-lead) without signs of clinically relevant pathology in particular QTc (Bazett) ≤ 450 ms.

8. Non-smoker (i.e. zero cigarettes, pipes, cigars or others) at least three months before study entry.

9. Negative screen for HBsAg, anti-HBc, HCV Ab, anti-HIV1&2 and RPR Ab.

Weight

10. Have a body weight within the range 55~95 kg and a Body Mass Index (BMI) within the range 18.5~29.9kg/m^2 (inclusive).

Sex

11. Are female or male.

Contraceptive use by males or females will be consistent with local regulations on contraception methods for those participating in clinical studies.

a Female Participants

- Are not pregnant or breastfeeding, and at least one of the following conditions applies:
  - **Not** a WOCBP

  OR

  - If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 4 for the following time periods:
    - Before the first dose of the study intervention(s), if using hormonal contraception:
      - Has completed at least one 4-week cycle of an oral contraception pill and either has begun or finished her menses

      OR
      - Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a serum pregnancy test.
    - During the intervention period
    - After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 7 days plus 30 days (a menstrual

cycle) after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.

- Have a negative serum pregnancy test, as required by local regulations within 7 days before the first dose of study intervention. The participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are in Section 8.2.5 (Clinical Safety Laboratory Assessment) and Section 8.10 (Study Schedule).
- The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

b Male Participants

- When having sexual intercourse with a WOCBP, who is not currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 4 (Contraception) since a condom may break or leak.

Informed Consent

12. Can give signed informed consent, as indicated in Appendix 2 (Study Governance), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participants determined ineligible to participate in this study at the discretion of the Principal Investigator (or delegated investigators).
2. Hypersensitivity to venous puncture
3. Known hypersensitivity to ingredients of study interventions or Biguanides, or having other clinically relevant hypersensitivities
4. Type I diabetes mellitus, lactic acidosis, acute or chronic metabolic acidosis including diabetic ketoacidosis, with or without coma; diabetic pre-coma, pre-diabetes
5. Patients with renal impairment (eGFR with MDRD < 80 mL/min/1.73m^2 – calculations according to Modification of Diet in Renal Disease (MDRD) formula). Patient presenting with acute conditions with the potential to alter renal function such as dehydration, severe infection, cardiovascular collapse (shock), acute myocardial infarction, and septicemia

6. Participants with acute and unstable heart failure

7. Participants with severe infection or severe traumatic general disorder

8. Participants who are scheduled to undergo surgical procedures

9. Participants with malnutrition, inanition, pituitary dysfunction or adrenal function failure

10. Participants with hepatic dysfunction, acute or chronic disease which may cause tissue hypoxia such as respiratory failure, acute myocardial infarction, shock and GI disorder such as excessive alcohol intake, hydration, diarrhea, vomiting etc.

11. Participants undergoing intravascular administration of iodinated contrast materials in radio diagnostic examinations (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials etc.)

Prior/Concomitant Therapy

12. Participants who took drugs that significantly induce (e.g., barbiturate) or inhibit drug metabolism enzymes, and those drugs that may alter metformin pK, most importantly OCT1/2 inhibitors and inducers, within 30 days prior to screening.

13. Use of a concomitant drug. However, any medications that are considered necessary for participant's welfare and will not interfere with the trial medication may be given at the discretion of the Investigator. For the detail of prohibited medicines, see Section 6.5.3 (Prohibited Medicines).

14. Use of any medication that may affect the outcome of the study within 10 days prior to screening and during study conduct

Prior/Concurrent Clinical Study Experience

15. Participation in another bioequivalence or other clinical studies where the last administration of previous study medication was within 6 months, before the first drug administration in this study

Other Exclusions

16. Donation of whole blood or loss (≥ 400 mL) within 2 months, plasma donation or apheresis within 2 weeks prior to first drug administration

17. History of regular alcohol drinking within 6 months prior to screening as shown below
    - For females, > 14 cups/week
    - For males, > 21 cups/week
    (1 cup: Soju 50 mL, Liquor 30 mL, Beer 250 mL)

18. Excessive consumption of xanthine-containing food or beverages (>5 cups of coffee a day or equivalent) or inability to stop consuming caffeine, from 48 hours prior to drug administration until collection of last PK sample in each period (hour 32 [H32]).

19. Intake of grapefruit, orange, cranberry or juices of these three fruits, from 48 hours prior to drug administration until collection of last PK sample in each period (hour 32 [H32]).
20. Inability to communicate or cooperate with the Investigator (e.g., language problem, illiterates, poor mental status) or to comply with the requirement of the entire trial, including dietary restrictions.
21. Non-acceptance of study high-fat breakfast for participant included in the fed group (e.g., vegetarians, vegans and participants who follow special diets).
22. Legal incapacity or limited legal capacity.
23. Participants kept in detention.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

(1) Part 1: Fasted state (both periods)

- Refrain from all food and beverages (except water) for at least 4 hours prior to clinical laboratory tests (except for tests on Day-1).
- Refrain from all food and beverages (except water) for at least 10 hours before and 4 hours after dosing.
- Refrain from water for 1 hour before and after dosing except 150 mL water for administration.
- Lunch is served after blood collection at 4 hours after dosing.
- Dinner is served around 06:00 pm on Day -1 after blood collection, and at 10 hours after dosing.

(2) Part 2: Fed state (both periods)

- Refrain from all food and beverages (except water) for at least 4 hours prior to clinical laboratory tests (except for tests on Day-1).
- Refrain from all food and beverages (except water and milk or juice in the course of high-fat meal) for at least 10 hours before high-fat meal intake and 4 hours after dosing.
- Refrain from water for 1 hour before and after dosing.
- From around 7:30 am on the day of the study, take all of breakfast (more than 900 Kcal, more than 35% fat) without leaving any food at 1-minute interval in the order of random assignment number, and the meal time should be completed within 20 minutes.
- Lunch is served after blood collection at 4 hours after dosing.
- Dinner is served around 06:00 pm on Day -1 after blood collection, and at 10 hours after dosing.

5.3.2 Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting xanthine-containing beverages (e.g., coffee, tea, cola drinks, and chocolate) from 48 hours before the start of dosing until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- Use of tobacco products will not be allowed from at least three months before study entry until after the final follow-up visit.

5.3.3 Activity

- Participants will abstain from strenuous exercise for 48 hours before admission to the Clinical Facility for each Period. Participants may participate in light recreational activities (e.g., watching television or reading).
- Participants should not lie down for at least 2 hours post administration of study interventions in a sitting position and should maintain similar posture and behavior to minimize the effect on blood flow velocity and motility of gastro intestines.
- Because metformin may cause very rarely severe lactic acidosis, participants have to stay at clinical site for 32h after each administration though it is for pharmacokinetic samplings. Additionally, if any of the following symptoms or signs comes out, it should be notified to the investigators immediately, and the investigators should check for the abnormalities through careful monitoring. Hypoglycemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is hemodialysis.

- Lactic acidosis: Unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened for Clinical laboratory test, 12-lead ECG, etc.. If clinical laboratory test results are out of reference range, additional visits may be requested to conduct a re-test or further examination at the discretion of the Principal Investigator (or the delegated investigators). If the test result is judged to be a transient change due to lifestyle (specific diet, drinking, exercise, night shift, etc.), it is possible to re-test participants once after correction of lifestyle

at the discretion of the Principal Investigator (or delegated investigators). If re-test is performed, the inclusion criteria are confirmed based on the last result value. Re-screened participants will retain their initially assigned screening numbers.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

	Study Interventions	
	Test Drug	Reference Drug
Study Intervention Name:	500 mg Glucophage® XR Reduced Mass tablet	500 mg Glucophage® XR tablet
Dose Formulation:	Tablet	Tablet
Unit Dose Strength(s)/Dosage Level(s):	Metformin hydrochloride 500 mg	Metformin hydrochloride 500 mg
Physical Description	White to off-white, round, biconvex tablet debossed with "500" on one side	White to off-white, capsule-shaped, biconvex tablet engraved "500" on one side and "XR" on the other
Route of Administration:	p.o.	p.o.
Dosing Instructions:	Metformin tablets will be administered as a single dose of 500 mg either as a Glucophage XR Reduced Mass tablet (Test drug) or Glucophage XR tablet (Reference drug) in fasted or fed condition as described in Section 5.3.1 (Meals and Dietary Restrictions).	
Supplier/Manufacturer:	Manufacturer of (commercial) drug product: Merck Sante s.a.s – Semoy (France) Manufacturer of Study Intervention: Merck Healthcare KGaA, Darmstadt (Germany) Both the finished product of Test drug and Reference drug are manufactured at the same manufacturing site (Merck Sante s.a.s – Semoy (France))	

Storage Condition:	In airtight container not above 30℃
Packaging and Labeling	The study interventions shall be manufactured by the Sponsor in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines and will be supplied to Clinical Facility as QP (Qualified Person) released and labeled study intervention (unblinded labeled blister containing 15 tablets each). Labeling will be done on the blister in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.
GCP Dispensing	Upon study intervention delivery, the PI delegated Clinical Trial Pharmacist for study intervention (hereinafter referred to as "the Clinical Trial Pharmacist") checks the information (quantity and storage condition of study interventions) provided in the receipt form and enclosed documents. He/she then records the information in the study intervention logbook. The unopened carton is kept in the storage room as indicated. The Clinical Trial Pharmacist will generate the study intervention prescription codes so that the Investigator can prescribe the study intervention via the Electronic Medical Record (EMR). Detailed GCP Dispensing follows SOP of the Clinical Facility.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). For this study, the PI will delegate these responsibilities to the Clinical Trial Pharmacist for study intervention (hereinafter referred to as "the Clinical Trial Pharmacist").

- Upon receipt of the study intervention(s), the Investigator or designee (i.e., Clinical Trial Pharmacist) must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may dispense it. All study intervention(s) must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in accordance

with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.

- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, container numbers, expiry dates and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the SOP of Clinical Facility.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Block Randomization Method at the Clinical Facility	The Principal Investigator (or delegated investigators) uses a block randomization method in accordance with the Clinical Facility SOP to determine which product, Test Drug or Reference Drug, would be administered in Part 1 and Part 2 respectively, and based on this, prescribes the study interventions for bioequivalence study. According to the prescription, the Clinical Trial Pharmacist prepares the study interventions for Part 1 and Part 2 in accordance with the Clinical Facility SOP. The Principal Investigator (or delegated investigators) keeps records of the prescription.

Participant identifier & Assignment to treatment sequence	For Part 1 (Fasted state) and Part 2 (Fed state), screening number in the form of SXXX (e.g. 'S301, S302, S303 …' if it is for Part 1 and 'S401, S402, S403 …' if it is for Part 2) is given to the applicants who visited the Clinical Facility and agreed the informed consent in writing. The screening number will be used to identify the participants for the whole duration of the bioequivalence study. One day (Day -1) prior to administration of study intervention of Period 1, each participant is given a participant number according to the order of obtainment of the Informed Consent and the Sequence is randomly assigned to each of Part 1 (Fasted state) and Part 2 (Fed state). Randomization is done using Excel or SAS programs, and a total of 82 participants (Part 1: 48 participants, Part 2: 34 participants) are randomly assigned to 2 Sequences (1 or 2) with 24 participants per Sequence in Part 1 and 2 Sequences (1 or 2) with 17 participants per Sequence in Part 2 in a 1:1 ratio. Randomization number is given to the 48 participants if it is Part 1 (Fasted state) and to the 34 participants if it is Part 2, excluding the stand-by participants (waiting list), who satisfied the screening, inclusion/exclusion criteria and clinical laboratory tests. The randomization number is the number of the administration order of participants and its form is R1YY (e.g., R101, R102, R103, ..., R148) if it is Part 1 (Fasted state) and R2YY (e.g., R201, R202, R203, ..., R234) if it is Part 2 (Fed state). Participants who have been assigned a randomization number but dropped out before the first administration of Period 1 can be replaced with stand-by participants. When the participant is replaced, the stand-by participant will be assigned the drop-out's randomization number. However, participants will not be replaced after the first administration of Period 1.

6.3.2 Blinding

Blinding Method

Not applicable, this is an open-label study.

Assignment Method Retention

Not applicable, this is an open-label study.

Unblinding Clinical Studies for Sample Analysis of Special Data

This is an open-label study. However, the Analytical Facility will initially be blinded to prevent biases that might affect the result of sample analysis. The randomized sample code will be unblinded to the Analytical Facility only following the completion of sample analysis. Analytical Facility initiates statistical analysis after receiving the unblinded sample code from the Clinical Facility.

The samples from Part 1 (Fasted state) and Part 2 (Fed state) that are delivered to the Analytical Facility are blinded so that Information on administration of study intervention (Test or Reference, blood collection time, Period) are not known. Samples are randomized according to the SOP of Clinical Facility to assign sample codes to the samples.

- The blinded sample code should be indicated only on the sample or source data (Eppendorf tube, Box, Sample transfer related documents, etc.). Example of Eppendorf tube label is as follows.

Protocol No. CCI Part 1 or CCI
Sampling time point, period and Participant number / PPD
For Analysis or Back-up / AN or BU

Information on blinded sample is not disclosed to the Analytical Facility until the concentration measurement is completed. Once the concentration analysis at the Analytical Facility is completed, the concentration of each sample from Part 1 (Fasted state) and Part 2 (Fed state) is informed to the Clinical Facility. After the Principal Investigator of Clinical Facility receives the concentration of each sample from Part 1 (Fasted state) and Part 2 (Fed state) from the Analytical Facility, he/she provides the blinded information on the sampling time and period to the Analytical Facility. After the Analytical Facility confirms the blinded information on the sampling time and period, the Analytical Facility performs Incurred Sample Reanalysis (ISR). After the Principal Investigator of Clinical Facility receives the ISR result from the Analytical Facility, he/she provides the blinded information on the sample code. After the Analytical Facility confirms the blinded information on the sample code, the sample code is unblinded.

6.3.3 Emergency Unblinding

Not applicable, this is an open-label study.

6.4 Study Intervention Compliance

- A mouth check will be performed by Principal Investigator (or delegated investigators) or Clinical Trial Pharmacist to ensure that the participants have swallowed the study interventions.
- This study shall be processed as two parts: Part 1 (Fasted state) and Part 2 (Fed state).

- In the event of failure of enrollment of targeted number of participants as stated in the protocol, for each study of Part 1 (Fasted state) and Part 2 (Fed state), a separate hospitalization, that is, a separate administration to 2 groups can be arranged for the quality assurance and performance convenience of this study. The clinical trials of the divided participants will follow the same performance methods and procedures described in this protocol. The separate hospitalizations should be made in two groups. If from the first dose of the first hospitalization group to the first dose of the second hospitalization group is completed within 6 weeks, the effect of separate hospitalization would not considered and for the situation where it exceeds 6 weeks, interaction due to separate hospitalization must be checked.

1) Part 1: Fasted state

After an overnight fast of at least 10 hours, participants will receive 1 tablet (metformin hydrochloride 500 mg) of either the Reference or the Test drug orally with 150 mL of room-temperature water, starting with the first participant at around 08:00 am. Participants should swallow the entire study intervention with water, without chewing or crushing.

The difference of administration time between participants has to be about 1-minute interval considering the blood sampling time.

2) Part 2: Fed state

After an overnight fast of at least 10 hours, participants shall take a high-fat breakfast (over 900 kcal, over 35% fat) from around 07:30 am within 20 minutes according to the randomized number sequence on the day of the study. The difference of taking breakfast time between participants has to be about 1-minute interval considering the administration time. 30 minutes after the start of the meal (around 08:00 am), participants will receive 1 tablet (metformin hydrochloride 500 mg) of either the Reference or the Test drug orally with 150 mL of room-temperature water. Participants should swallow the entire study intervention with water, without chewing or crushing.

6.5 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name (preferably INN name), reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

Participants are prohibited from taking any of concomitant medications during the entire period of the bioequivalence study. If taking of a concomitant medication is confirmed, the participant will be dropped out. Participants who have been dropped out by taking concomitant medication for the treatment of adverse events shall be subject to appropriate medical treatment in accordance with 'Measures to Protect Safety of Participants' in Appendix 2 (Study Governance).

Medications administered from 30 days before screening to prior to administration of study interventions on Day 1 of Period 1 shall be recorded as prior medications. Medications administered from the 1st administration of study interventions to the end of observation shall be recorded as concomitant medications. For prior medications/ concomitant medication, name of the medications, the dosage per administration, the frequency of administration, the route of administration, the purpose of administration, the beginning/ ending date of administration, and whether the administration was continued or not shall be recorded.

6.5.1 Rescue Medicine

Not applicable.

6.5.2 Permitted Medicines

Participants enrolled in this study should be in good general health and therefore, should not be taking or using any other medication.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

6.5.3 Prohibited Medicines

No concomitant medication (with the exception of contraceptive in females) or over-the-counter medication intake, including multivitamins, nutritional supplements and herbal products (e.g. St. John's wort) will be permitted within 2 weeks or 5 half-lives, whatever is longer, prior to first study intervention administration and during the study until last PK sampling.

If the administration of a non-permitted concomitant drug becomes necessary during the study, e.g. because of AEs, the Investigator and the Sponsor will decide if the participant's withdrawal is necessary.

Use of any investigational agent is not permitted within 6 months or prior to screening and during the whole study duration.

6.5.4 Other Interventions

Not applicable.

6.6 Dose Selection and Modification

Not applicable. See Section 4.3 (Justification for Dose).

6.7 Study Intervention after the End of the Study

In this study of healthy participants, no further treatment is planned or required after the end of the study.

6.8 Special Precautions

Medical emergency and resuscitation equipment as well as agents (such as epinephrine, prednisolone equivalents, etc.) are to be available at the study site in case of severe allergic reactions.

6.9 Management of Adverse Events of Interest

Healthy participants may be exposed to diarrhea, decreased appetite, nausea, vomiting and abdominal pain. These symptoms are almost always transient and occur early during therapy initiation and spontaneously resolve in most cases. If any of these AEs are observed, their severity should be defined based on clinical judgment of the Investigator and defined according to the Qualitative Toxicity Scale (See Appendix 5 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting)).

- If adverse events (such as nausea, vomiting, diarrhea, abdominal pain, rash, etc.) occur after administration of metformin, it should be notified to the investigators immediately and the investigators should check for abnormalities through careful monitoring.

- After administration of metformin, the shell of the tablets may come out through the stool, and this should be notified to participant that it is a normal phenomenon.

- If blood glucose is lower than 60 mg/dL or hypoglycemic symptoms occur after administration of metformin, participants should take the sugar water containing 15g of sugar in 100 mL of water according to the judgment of the Principal Investigator (or delegated investigators). And if Principal Investigator (or delegated investigators) believes that the symptoms are severe, participants should receive an immediate treatment and have to move to emergency room to receive inpatient treatment. Blood Sugar Test is performed before blood collection at 3 and 4 hours after administration of each Period.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

If a clinically significant finding is identified (including changes from baseline in QT/QTc interval corrected using Bazett's formula [QTcB]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

The Section 1.3 (Schedule of Activities) specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Not applicable.

7.1.2 Rechallenge

Not applicable.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his/her own request (i.e. withdrawal of consent), and without giving a reason.
- The participant may be withdrawn by the Investigator due to participation in another clinical study.
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If Principal Investigator (or delegated investigators) decides that the study cannot be continued by occurrence of Adverse Events/ Adverse Drug Reaction/ Serious AE
- If the participant arbitrarily takes any medication that is expected to affect the evaluation of safety and pharmacokinetic characteristics of the study intervention
- If a serious violation of the protocol is found during the study that belongs to inclusion/exclusion criteria
- If the Sponsor, MFDS or IRB requests suspension of the study
- If protocol non-compliance is found during the study
- The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed
- The participant may be withdrawn if the participant has difficulties in collecting blood samples
- The participant may be withdrawn if the participant vomits or has diarrhea during PK sampling periods
- The participant will be withdrawn if the participant is pregnant
- If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated. Any biological samples collected until withdrawal shall be archived for a certain period, and pharmacokinetic analysis sample treatment of the withdrawn participants and other details regarding the disposal will follow SOP of the Analytical Facility.
- A participant has the right at any time to request destruction of any biological samples taken. The investigator must document this in the site study records.

Details such as participant discontinuation date and specific reasons should be recorded in the source document and the electronic Case Report Form (eCRF).

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant. 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the Section 1.3 (Schedule of Activities).
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2 (Study Governance).
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- A maximum of 203 mL of blood will be collected from each participant in the study. Repeat or unscheduled additional samples may be taken for any extra assessments that may be required or for safety reasons or for technical issues with the samples.

The total blood sample amount collected for each participant is as follows.

Assay	Volume per sample (mL)	Total number of samples	Total blood volume (mL)
Screening (Clinical laboratory tests)	16 mL	1 time	16 mL
Admission day check	8 mL	2 times	16 mL
Safety confirmation test (including end of study) check)	11 mL	1 time	11 mL
Pharmacokinetics	5 mL*	32 times	160 mL
Total	-	36 times	203 mL

* Excludes the discarding 1 mL per each blood collection to completely remove the saline that is left in the collection set.

8.1 Efficacy Assessments and Procedures

Not applicable.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, adverse events (AEs), physical examination findings, vital signs, electrocardiograms, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information).

8.2.1 Adverse Events

Principal Investigator (or delegated investigators) will assess all adverse events that occur during the bioequivalence study (from the obtainment of Informed Consent to the end of observation. See Section 8.3 (Adverse Events and Serious Adverse Events) and Appendix 5 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting) for details of AE.

8.2.2 Physical Examinations

During screening and at the End of Study Visit, a complete physical examination is performed for all participants. Subsequently, participants will be interviewed, and a brief physical examination will be performed on admission day (Day-1) & Day 2:

- A complete physical examination will include, at a minimum, assessments of the general condition, nutritional status, skin/ mucous membrane, eye (except decreased eyesight), nasopharyngeal system, thyroid, lung/ respiratory system, cardiovascular system, abdomen and digestive system, kidney/ genitourinary system, neuropsychiatric system, spine/ limbs/ tumor, peripheral circulation, lymphatic system and others. During screening, height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, abdomen (liver and spleen), and the symptoms reported by the participant.
- Investigators should pay special attention to clinical signs related to previous serious illnesses, particularly renal impairment and/or dehydration, vomiting, diarrhea.
- Physical examination is assessed as normal, abnormal/ no clinical significance (Abnormal/ NCS) and abnormal/ clinical significance (Abnormal/ CS).

8.2.3 Vital Signs

- Vital signs will be measured in a sitting position after 5 minutes of rest and will include tympanic temperature, systolic and diastolic blood pressure and pulse rate.
- Measurement of tympanic temperature is performed only during the Screening and at the End of Study Visit or if deemed necessary by the Investigator or delegated Investigator. Preferably, automated device has to be used however, manual device can be used if necessary. The measurement results are evaluated by Principal Investigator (or delegated investigators).

8.2.4 Electrocardiograms

12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

The 12-lead ECG measurement will be performed while maintaining the lying posture without any sudden changes of body position. By combining the readings indicated by the algorithm within the examination instrument and the clinical findings from the reading physician, the examination outcome will be assessed as normal (Normal ECG), borderline, no clinical significance (Abnormal ECG / NCS) and clinical significance (Abnormal ECG / CS).

8.2.5 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6 (Clinical Laboratory Tests), at the time points listed in the SoA. All samples should be clearly identified.

- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- Clinical laboratory tests will be performed in the Department of Diagnostic Laboratory Medicine, Chungnam National University Hospital, which is a registered lab in the Korean Association of External Quality Assessment Service (Registered number: 0055) and is regularly certified for quality control.
- The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Sponsor.
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.
- Clinical laboratory tests are assessed as normal, abnormal/ no clinical significance (Abnormal/ NCS) and abnormal/ clinical significance (Abnormal/ CS) depending on the deviation from the reference value.
- Additional serum or highly sensitive urine pregnancy tests may be conducted, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.

8.2.6 Suicidal Risk Monitoring

Not applicable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an Adverse Event (AE) and a Serious Adverse Event (SAE) are in Appendix 5.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of first informed consent) and continues until the end of the observation. Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.

Any SAE assessed as related to the study intervention must be recorded and reported, as indicated in Appendix 5, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 5. All SAEs will

be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 5 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.

Investigators are not obligated to actively solicit AEs or SAEs after the end of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate report form as specified in Appendix 5 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Adverse events collected from the time of receipt of the Informed Consent Form to the end of participant observation shall be recorded in the "Adverse Events" sheet of the eCRF regardless of causal relationship with study intervention.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the End of Study Visit. All AE/SAEs ongoing at the End of Study Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant 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. Further information on follow-up procedures is given in Appendix 5 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

If an adverse event due to the participation in the bioequivalence study has not recovered at the End of Study Visit, Principal Investigator (or delegated investigators) shall provide the required examinations and treatments, and the Principal Investigator shall follow-up until symptoms disappear. If all detrimental and unintended signs or symptoms have not disappeared, appropriate medical interventions such as first aid, outpatient records (additional

examination and medication) and consultation and referral to medical specialists, may be performed at the discretion of the Principal Investigator (or delegated investigators).

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met. The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the IEC/IRB that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (e.g., resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) must be recorded in the AE page/section of the eCRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 5 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting), section on Reporting Serious Adverse Events.

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

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Event Information), while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from the study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

8.4 Treatment of Overdose

For this study, any dose of study intervention greater than the highest daily dose included in the clinical study protocol within a 24-hour time period will be considered an overdose.

Hypoglycemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is hemodialysis and may be used for an overdose.

Even if it not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 5 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting), section on Reporting Serious Adverse Events.

In this study, metformin will be administered under medical supervision as 2 oral single doses of 500 mg separated by a 7-day wash-out. Overdosage is accordingly unlikely, however in case of overdose, close monitoring will be performed, and adequate medical care will be provided based on the clinical judgment of the Investigator.

8.5 Pharmacokinetics

- The following PK parameters will be calculated, when appropriate:

  Parameters will be calculated from the metformin blood concentrations.

Symbol	Definition	Measuring method

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

- The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration.

  Blood sample amount and aliquots per time points of pharmacokinetics are as follows.

Part 1: Fasted state

Collection time (h)	0	0.5	1	2	2.5	3	3.5	4	5	6	7	8	10	12	24	32
Sample amount (mL)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Aliquots	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Part 2: Fed state

Collection time (h)	0	1	2	3	4	5	5.5	6	6.5	7	8	9	10	12	24	32
Sample amount (mL)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Aliquots	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

- The quantification of metformin in plasma will be performed using a validated analytical method (UPLC-MS/MS; LLOQ 20 ng/mL). Concentrations will be used to evaluate the PK of metformin.
- Remaining samples collected for analyses of metformin concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Details on processes for collection and shipment of these samples are in the SOP of Clinical Facility. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

1) Blood Collection Method

A normal saline-locked catheter will be inserted into the vein of arm or hand of the participants before dosing on Day 1 of each Period. 1 mL of the collected blood will be discarded to remove the saline left in the collection set and after that, collect blood into the EDTA(K2) treated collection tube. About 1 mL of physiological saline is injected into the catheter to prevent blood coagulation.

2) Place and Person for Blood Collection

The collection site should be a place where about 60 people can be active, taking into consideration the space required for blood collection management and blood collection of 48 participants for Part 1 and 34 participants for Part 2. It is conducted within the Clinical Trial Center (PPD) of Chungnam National University Hospital, which is separated from general patients.

Blood collection and management personnel include a Principal Investigator (or delegated investigator), a Clinical Trial Pharmacist, nurse(s), an assistant for the blood collection and a participant management personnel who is responsible for checking the randomization number of each participant and to arrange the order of blood samples collection. A total of more than 7 people are expected to be involved.

3) Measures to Prevent Infections When Collect Blood Sample

The collection of blood samples from participants will be done in a room with limited access to the public. Single use sterilized apparatus will be used to collect blood samples. The disposable blood collection apparatus will be disposed in a biohazard box. Needle-

stick injury will be managed according to the Infection Management Procedure of Chungnam National University Hospital.

4) Allowable Pharmacokinetics Blood Collection Time

Every effort should be made to ensure that the pharmacokinetics blood sample is collected at nominal time following administration of the study interventions. The exact time of sample collection must be recorded in the source document and eCRF. The actual time of blood collection may be different from the nominal time, but the number of samples should remain the same.

In the case of deviation of the blood sampling from the planned time point specified in this protocol, details such as the actual blood sampling time should be recorded in the eCRF. The acceptance range according to each sampling time point is as follows.

Part 1: Fasted state

Day (per period)	Time (h)	Deviation
1	0	-1 h
	0.5	±5 min
	1	
	2	
	2.5	
	3	
	3.5	
	4	
	5	
	6	
	7	
	8	
	10	
	12	±10 min
2	24	
	32	±30 min

Part 2: Fed state

Day (per period)	Time (h)	Deviation
1	0	-1 h

	1	±5 min
	2	
	3	
	4	
	5	
	5.5	
	6	
	6.5	
	7	
	8	
	9	
	10	
	12	±10 min
2	24	
	32	±30 min

Refer to '9. Statistical Considerations' for details when performing statistical processing on primary variables.

5) Plasma Storage for Pharmacokinetic Analysis

Blood for pharmacokinetic analysis will be stored in an ice bath immediately after collection and centrifuged (CCI) within 30 minutes from the collection time to isolate the upper plasma. About 0.6 mL of the separated plasma will be transferred into 2 polypropylene tubes (one for analysis, one as back-up) and stored in a freezer set at CCI until they are ready to be transferred to the Analytical Facility.

6) Transportation of Pharmacokinetic Samples

Samples stored at CCI or below are transferred from the Clinical Facility to the Analytical Facility. At the Analytical Facility, continue to store the samples at CCI until the date of product approval by MFDS. Details of blood sample preparation, aliquot dispensing, sample storage and transportation shall be in accordance with Sample Treatment and Transfer Manual. The sample shall not be used for any purpose other than for this bioequivalence study and shall be discarded in consultation with the Sponsor after product approval.

7) Analysis of Concentration of Metformin in Plasma

Analysis of metformin in plasma is done by using ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) (LLOQ: 20 ng/mL). After

validation of the analytical method is completed, the analytical method will be applied to the sample analysis.

Method validation is performed in accordance with the "Guideline on Bioanalytical Method Validation" (MFDS, December 2013).

Reanalysis should be completed before the pharmacokinetic analysis or statistical analysis. Sample reanalysis is performed only when the sample analysis result falls in the criteria specified in the PPD SOP titled "Reanalysis, Reinjection Analysis and Reintegration".

After the sample analysis is completed, Incurred Sample Reanalysis (ISR) is performed in accordance with '5. Incurred Sample Reanalysis' of the "Guideline on Bioanalytical Method Validation" (MFDS, December 2013) and Standard Operating Procedure of PPD

8.6 Pharmacodynamics

Not applicable.

CCI [redacted]

8.10.1 Screening

- Written informed consent is obtained from the participant.
- Demographic information (gender, age, height, weight and BMI)

  Height and weight will be measured to one decimal place, and BMI shall be rounded to 1 decimal from 2 decimal places..
- Vital signs: Blood pressure (sitting position), pulse rate (measured after taking rest for more than 5 minutes), body temperature (eardrum)
- Interview: Drinking and smoking history, caffeine consumption, allergy, hypersensitivity, blood donation, etc.
- Previous medication
- Medical history:

  Liver biliary system, kidneys, digestive system, respiratory system, blood/ tumor

system, endocrine system, genitourinary system, neuropsychiatric system, musculoskeletal system, skin/ mucous membrane, immune system, nasopharyngeal system, ophthalmology system, cardiovascular system, operation, others, etc. are investigated.

- 12-lead ECG
- Physical examination
- Clinical laboratory tests: blood and urine collection for clinical laboratory tests as listed in Appendix 6 after at least 4 hours of fasting
- Drug Screening (urine sample)
- Alcohol test (breath test)
- For female participants, pregnancy test (serum)
- Confirmation of inclusion and exclusion criteria

8.10.2 Clinic Day -1 (Period 1 and Period 2)

Participants should admit to the Clinical Facility until about 3 to 5 pm on Day -1 of administration of study interventions and remain in the Clinical Facility until they are discharged at 32 hours post administration of each Period. After the admission of participants, the following activities are performed.

- Introduction of activities and schedule
- Recheck of inclusion and exclusion criteria
- Confirmation of prior medication use (Period 1), concomitant medication (Period 2) and adverse events
- A brief physical examination
- Blood sample collection for admission day assessment (Clinical chemistry: AST(GOT), ALT(GPT), γ-GT, UN, Cr, eGFR with MDRD, Lactic acid). Based on the result of admission day assessments, participants that the Principal Investigator (or delegated investigators) considers to be ineligible for participation in the study are excluded from the study
- For female participants, serum sample collection for pregnancy test
- Drug Screening(urine sample)
- Alcohol test (breath test)

  Based on the results of the pregnancy, drug and alcohol tests, participants who do not fulfill eligibility criteria are excluded from the study
- Dinner at around 6 pm
- Randomization of Part 1 and 2 respectively according to admission day assessment result (only in Period 1)
- The fasting status is maintained for at least 10 hours before drug administration

to 4 hours after administration on the next day. (Part 1: Fasted state only)

- The fasting status is maintained for at least 10 hours before taking high-fat diet to 4 hours after drug administration on the next day. (Part 2: Fed state only)
  - During admission period in the Clinical Facility, intake of food and beverages is limited except food and beverages provided by the Clinical Facility
  - Intake of xanthine-containing beverages (coffee, green tea, cola, black tea, chocolate, etc.) and grapefruit juice is restricted until the final blood sample collection of each Period is completed
  - Intake of alcohol is restricted until Period 2 has been completed
  - Strenuous physical activity (weight training, aerobics, long distance running, etc.) is to be avoided from 48 hours before admission for each Period to the final pharmacokinetics blood sample collection
  - Restrict smoking and the use of nicotine-containing products during admission period
- Sleep at around 10:00 pm

8.10.3 Clinic Day 1 (Period 1 and Period 2)

After participants wakes up in the morning, the following procedures are carried out.

- Measure blood pressure and pulse rate
- Principal Investigator (or delegated investigators) interviews participants and if the participant is determined ineligible to participate in the study, the participant will be excluded from the study
- Confirmation of prior medications (prior to administration of Period 1), concomitant medication (after administration of Period 1 and Period 2) and adverse events
- Intravenous catheter insertion for blood sample collection
- Blood sample collection for pre-dose pharmacokinetics analysis
- Limit intake of water for 1 hour before and after administration.
- In the case of Part 2 Fed state, participants should take all of the high-fat breakfast of over 900 kcal and over 35% fat from around 07:30 am within 20 minutes. If a participant did not take all of diet within 20 minutes, the participant shall be dropped out at the discretion of the Principal Investigator (or delegated investigators). The difference of taking breakfast time between participants has to be about 1-minute interval considering the administration time
- Drug administration at about 08:00 am and in accordance to the description in '6.4 Study Intervention Compliance'
- Blood sample collection for pharmacokinetics analysis after drug administration

- Part 1 (Fasted state): 0 (before administration), 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8,

10 and 12 hrs after administration

- Part 2 (Fed state): 0 (before administration), 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 8, 9, 10 and 12 hrs after drug administration

- Blood Sugar Test (BST): Before blood collection at 3 and 4 hours after drug administration
- Confirmation of adverse events
- Lunch after blood sample collection at 4 hours after drug administration
- Dinner after blood sample collection at 10 hours after drug administration
- Sleep at around 10:00 pm

8.10.4 Clinic Day 2 (Period 1 and Period 2)

After participants get up in the morning, the following procedures will be carried out.

- Measure blood pressure and pulse rate at 24 hours after drug administration
- Principal Investigator (or delegated investigators) performs physical examination of the participants.
- Confirmation of adverse events
- Confirmation of concomitant medication
- Pharmacokinetics blood sample collection at 24 hours post-drug administration
- Breakfast after blood sample collection at 24 hours after drug administration
- Lunch at around 12 pm
- Measure blood pressure and pulse rate at 32 hours after drug administration.
- Pharmacokinetics blood sample collection at 32 hours post-drug administration
- Return home

- Remind participants they are prohibited from strenuous physical activity, drinking, restricted food and beverages intake and medication until the end of the study. Participant may stay at the Clinical Facility at the discretion of Principal Investigator (or delegated investigators)

Observe individual participants' status throughout the study and record them in the electronic Case Report Form (eCRF).

Between Period 1 and Period 2 drug administration, wash-out period of at least 7 days is set.

Participants taking medication during the wash-out period cannot participate in the Period 2 study.

In the case of drop-outs, safety confirmation test may be conducted at a different schedule from study visits.

8.10.5 End of Study Visit

Participants will visit the Clinical Facility at 10 days ± 3 days from Day 1 of Period 2, and the following procedures is to be completed.

- Measure blood pressure, pulse rate, body temperature (eardrum)
- Physical examination
- 12-lead ECG
- Checking for adverse events, if any.
- Confirmation of concomitant medication
- Blood and urine samples collection for clinical laboratory tests listed in Appendix 6 (Clinical Laboratory Tests) as part of safety confirmation test (serum pregnancy test for woman)

9 Statistical Considerations

The detailed methodology for statistical analysis and summarization of the data collected in this study will be recorded in the Statistical Analyses Plan (SAP) that will be prepared and maintained by PPD

1) Demographic Information Analysis

Demographic information such as gender, age, height, weight, and BMI of participants participating in the bioequivalence study will be analyzed by descriptive statistical method.

2) Safety Evaluation Analysis

For the participant safety evaluation, the results of the adverse events, concomitant medications, clinical laboratory tests, 12-lead ECG, vital signs, physical examination are continuously reviewed and analyzed by descriptive statistical method.

3) 'SAS® (SAS Institute Inc. NC. USA: Ver. 9.4 or higher)' is used for the statistical processing of demographic information and safety evaluation analysis.

4) Calculation of Pharmacokinetics Variables

Using the Phoenix™ WinNonlin® 8.0 PPD or higher version software, pharmacokinetic parameters are calculated from the data obtained by non-compartmental method. However, statistical processing for primary variables is performed as follows.

- To calculate the basic statistics, arithmetic mean is used.
- Average and standard deviation shall be indicated to three decimal places.
- If the concentration prior to administration is below the lower limit of quantification (BLQ), it is indicated as “0”. All other BLQ values are considered to be “blank” when calculating the geometric mean and “0” when calculating the arithmetic mean. When calculating the pharmacokinetic parameters, the concentration of BLQ in the curve of the rising section is entered as “0” and the concentration of BLQ in the

terminal phase is treated as "blank". If the measured concentration is below the lower limit of quantitation, it is indicated as "BLQ (Below the limit of quantification)".

9.1 Statistical Hypotheses

The following null hypothesis for the ratio of the geometric means will be used to assess bioequivalence

H0: $\mu T/\mu R \leq 0.8000$ or $1.2500 \leq \mu T/\mu R$ for at least one parameter (AUC_{last} or C_{max})

H1: $0.8000 < \mu T/\mu R < 1.2500$ for all parameters (AUC_{last} and C_{max})

where μT and μR are the geometric means for the test and reference treatment respectively.

The test treatment is Glucophage® XR Reduced Mass tablet and reference is Glucophage® XR tablet both under fasting condition (Part 1) or fed condition (Part 2).

1) The comparative evaluation parameters for the bioequivalence between the Test drug and the Reference drug are the area under the plasma concentration-time curve (AUC_{last}) and maximum plasma concentration (C_{max}). In this case, C_{max} is actually measured values and AUC_{last} is a calculated value by the trapezoidal rule.
2) When log transformation and statistical evaluation on comparative parameters of the Reference and Test drug except T_{max} are performed, the 90% confidence intervals for the difference in mean values between the Test and Reference should be within log 0.8 to log 1.25.
3) In the case of drop-outs, they are excluded from statistical analysis.
4) Separate hospitalization

For each study of Part 1 (Fasted state) and Part 2 (Fed state), if from the first administration of the first group to the first administration of second group is completed within 6 weeks, the effect of separate hospitalization is not considered. However, if it exceeds 6 weeks when separate hospitalization was arranged, the interaction by separate hospitalization has to be confirmed as follows.

The interaction by separate hospitalization has to use a model that sets period, sequence, treatment, group and group*treatment as a fixed effect and sets participant nested within sequence as a random effect.

At this time, if the group*treatment is not statistically significant (if it exceeds the significance level of 5%), the bioequivalence is evaluated by adding group as a fixed effect, and if the group*treatment is statistically significant, then the bioequivalence is evaluated by adding group and group*treatment as fixed effects. The cause of the interaction and the effect of the interaction on the evaluation of bioequivalence has to be closely checked.

9.2 Sample Size Determination

9.2.1 Sample Size

82 Healthy adult participants (Part 1: 48 participants, Part 2: 34 participants)

9.2.2 Sample Size Justification

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

Variability estimates were obtained from the preliminary PK data (CCI [fasted] and CCI [fed]) and intra-participant variability of the major pharmacokinetic parameters AUC_{last} and C_{max} of metformin were about 19.1 % and 25.0%, respectively. Assuming a within-participant variability CV%=25%, and with an assumed geometric mean ratio Test/Reference (GMR T/R) of 0.95, a one-sided alpha level of 0.05, 38 evaluable participants will be needed to provide approximately 90% power to show bioequivalence. Considering the drop-out rate (about 20%) during the study, 24 participants per sequence, totally 48 participants will be recruited.

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

Variability estimates were obtained from the preliminary PK data (CCI [fasted] and CCI [fed]) and intra-participant variability of the major pharmacokinetic constants AUC_{last} and C_{max} of metformin were about 13.1% and 18.7%, respectively. Assuming a within-participant variability CV%=18.7%, and with an assumed geometric mean ratio Test/Reference (GMR T/R) of 0.95, a one-sided alpha level of 0.05, 22 evaluable participants will be needed to provide approximately 90% power to show bioequivalence. Considering the drop-out rate (about 35%) during the study, 17 participants per sequence, totally 34 participants will be recruited.

9.2.3 Replacement of Participant

To be prepared for participant drop-outs which may occur due to the withdrawal of consent prior to drug administration in Period 1, some of the volunteers who met the inclusion/ exclusion criteria will be placed on the waiting list. If a participant who is scheduled to be administered with the study intervention in Period 1 is dropped out after the assignment of a randomization number but prior to the 1st administration of the study intervention, a participant in the waiting list will replace the participant who dropped out and will have the same randomization number (assigned to the same planned treatment sequence). For replaced participants, the participant number is given according to the 'Blinding Method' described under Section 6.3.1 (Study Intervention Assignment). Participants who drop-out after drug administration will not be replaced.

9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Analysis Set	Description
All Randomized	Demographic Information is evaluated for those participants who participate in the bioequivalence study (i.e., all participants who were randomized). However, the participants who were replaced by the stand-by participants before the first administration of study interventions will be excluded from the analysis.

Analysis Set	Description
Safety	Safety is evaluated for those participants who were administered at least one dose of the study interventions.
PK	Pharmacokinetics is evaluated for those participants whose pharmacokinetics evaluation is possible by the completion of all planned pharmacokinetics blood collection schedules according to the Protocol, who do not exhibit concentrations exceeding 5% of the maximum plasma concentration (C_{max}) of the drug in the pharmacokinetics sample of prior to dosing and who have valid primary endpoints for both treatments.

9.4 Statistical Analyses

Details on the statistical analysis will be presented in the statistical analysis plan (SAP) that will be finalized prior to database lock.

The statistical analysis will not start until all data have been corrected and checked for plausibility and until all necessary coding and assessments have been completed.

All data will be evaluated as observed; no imputation method for missing values will be used.

9.4.1 Efficacy Analyses

Not applicable

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis population. Safety will be analyzed in a descriptive way.

After coding of AEs according to the Medical Dictionary for Regulatory Activities (MedDRA) classification (Version 23.0 or higher) and assignment to a system organ class (SOC), all AEs recorded during the course of the study will be listed by treatment and participant number and tabulated by MedDRA SOC and Preferred Term (PT).

9.4.3 Other Analyses

9.4.3.1 Analysis of Primary Endpoints

Primary Variables: AUC_{last} and C_{max} of metformin

- An analysis of variance (ANOVA) model will be fitted for the log-transformed PK parameters C_{max} and AUC_{last} based on the PK analysis set. The model will include treatment, period, sequence, and participant within sequence as fixed effects. Treatment differences on the log scale will be estimated for C_{max} and AUC_{last} together with their 90% CIs. Point estimates and CIs will be back-transformed to the original scale for the comparisons.

The comparison will be the test treatment (Glucophage® XR Reduced Mass tablet) vs the reference treatment (Glucophage® XR tablet) under fasting conditions in Part 1, and under fed conditions in Part 2. The null hypothesis for non-bioequivalence will be rejected if the 90% CI for the ratio of the GeoMean lies within the interval 0.8000 to 1.2500 for all primary pharmacokinetic parameters.

The primary endpoints will be descriptively analyzed and graphical displays will be prepared.

PK analyses will be specified in the Integrated Analysis Plan finalized before database lock.

In principle, analysis of variance shall be used at α (significance level) = 0.05.

9.4.3.2 Analysis of Secondary Endpoints

Secondary Variables: AUC_{inf} (if data allows to calculate), AUC_{last}/AUC_{inf} (if data allows to calculate), $t_{1/2}$ (if data allows to calculate) and T_{max} of metformin. AUC_{inf} will be analyzed in the same way as the primary PK parameters.

The secondary endpoints will be descriptively analyzed and graphical displays will be also prepared where appropriate.

9.4.3.3 Analysis of Demographic Information

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

9.4.3.4 Sequence of Analyses

Interim analysis of data is not allowed.

10 Comparative Dissolution Test Method

The comparative dissolution test between the Test drug and the Reference drug using the same lot for the bioequivalence study shall be performed in accordance with the "Standard on Pharmaceutical Equivalence Study" or ‘Specification and Test Method’ of manufacturer of test drug. The comparative evaluation is made according to the "Standard on Pharmaceutical Equivalence Study".

11 References

1) Idkaidek N, Arafat T, Melhim M, Alawneh J, Hakooz N (2011) Metformin IR versus XR Pharmacokinetics in Humans. *J Bioequiv Availab 3: 233-235*.

2) “Standard on Pharmaceutical Equivalence Study” (MFDS Notification No. 1650, 14 October 2020).

12 Appendices

Appendix 1 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT(GPT)	Alanine Transaminase
AST(GOT)	Aspartate Transaminase
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure
(B)UN	(Blood) Urea Nitrogen
CTFG	Clinical Trial Facilitation Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ECG	Electrocardiogram
γ-GT	Gamma Glutamyl Transpeptidase
HBs Ag	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropin
HCV Ab	Hepatitis C Virus Antibody
Anti-HIV	Human Immunodeficiency Virus Antibody
ICF	Informed Consent Form
ICH	International Council for Harmonization
ISR	Incurred Sample Reanalysis
IRB	Institutional Review Board
KGCP	Korea Good Clinical Practice
PEAE	Pre-Existing Adverse Event
PK	Pharmacokinetics
LEU	Leukocyte

MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
RBC	Red Blood Cell
RM	Reduces Mass
RPR Ab	Rapid Plasma Reagin Antibody
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
Vent. Rate	Ventricular Rate. The number of times the main pumping portion of the heart beats in a minute.
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential
XR	Extended Release

Appendix 2 Study Governance

Financial Disclosure

Principal Investigator and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally authorized representative will be required to sign a statement of informed consent that meets all applicable requirements.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

- Following documents will be submitted for the protection of personal information.

  * Consent Form for Collection and Use of Personal Information (Fasted state)

  * Consent Form for Collection and Use of Personal Information (Fed state)

Study Administrative

- The Principal Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP and Korean Prime Minister Ordinance on GCP. The Principal Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.
- The study will appear in the following clinical studies registries:
  - Korean Drug Regulating Authority (MFDS) Clinical Trials Database
  - ClinicalTrials.gov
- Details of structures and associated procedures will be defined in a separate SOP of Clinical Facility.
- Study monitoring, pharmacokinetic analysis, design and setting of eCRF, data management, statistical analysis and medical writing (Clinical Study Protocol & Report) are responsibilities of the CRO, PPD , Ltd under the supervision of the Sponsor
- Recruiting participants, management and administration of study interventions to participants, observation/ recording/ follow-up of AEs, blood sample collection for pharmacokinetics, clinical laboratory tests, ECG measurements and entry to the eCRF are the responsibilities of the clinic site, Clinical Trials Center of Chungnam National University Hospital.
- Supply of the study interventions, drug safety reporting to Health Authorities and study oversight are responsibilities of the Sponsor.

Non-Compliance of Protocol

- Principal Investigator and sub-investigators should be fully acquainted with the protocol and implement it thoroughly enough to avoid non-compliance to the protocol. If a study protocol violation occurs inevitably, it should be reported to the IRB.
- If the occurrence of protocol non-compliance is determined to have a significant effect on the interpretation of study result, the participant is excluded from the pharmacokinetics analysis in principle. However, it is not limited to the following reasons:
  - Medical history that may affect the evaluation of the pharmacokinetics was newly found during the study
  - Concomitant administration of prohibited medication(s) that can affect the pharmacokinetics properties of the study intervention
  - Wrong type, dosage or usage of the administered study intervention

- For minor protocol non-compliance that is not expected to affect the interpretation of study result, non-compliant action and its reasons are recorded in the source document.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Annex 4 Good Clinical Practice "Regulation on Safety of Medicinal Products, etc." (Ordinance of the Prime Minister No. 1650, 14 October 2020)
  - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
  - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
  - Providing oversight of the study conduct at the site and adherence to requirements ICH guidelines, the IRB/IEC, and all other applicable local regulations, i.e. Korean regulation for clinical studies
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.
- **Measures to Protect Safety of Participants**:

The Principal Investigator (or delegated investigators) is responsible for all medical decisions related to the bioequivalence study. The Principal Investigator should ensure that participants receive appropriate medical treatment for all adverse events that occurred during the bioequivalence study including clinically significant clinical laboratory abnormalities. If medical treatment is required for the participant's disease identified during the bioequivalence study, the Principal Investigator should notify it to the participant. The investigators should be well acquainted with the adverse events and precautions specified in the study protocol beforehand and should promptly report the Serious Adverse Events to the Principal Investigator when the Serious Adverse Events occur. The Principal

Investigator reports the occurrence of the Serious Adverse Events in accordance with the 'Appendix 4 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting)'.

Emergency Medical Support

- The Sponsor or designee will provide wristband to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about the participant that may be needed to determine the course of medical treatment for the participant. The information on the wristbands may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information. When the Investigator is not available, the Phase I facility will provide the appropriate means to contact a physician. This includes the provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned. The 24-hour contact numbers of the Clinical Trials Center and PI are in the Informed Consent sheets; hence, the participants are informed of these numbers when they receive a copy of the Informed Consent.
- During clinic days, PI or an Investigator or a physician is on-duty at the Clinical Trials Center for 24-hours and hence participants can contact him or her at any emergency case. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

The Sponsor will have clinical trial compensation insurance coverage for all participants before the start of the bioequivalence study and will compensate under the 'Compensation Agreement for Victims'.

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Principal Investigator.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.

- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- A summary of data will be provided to the MFDS Clinical Trials Database and ClinicalTrials.gov.
- After completion of the study, a clinical study report will be written by the CRO under supervision of the Sponsor in consultation with the Principal Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.
- Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff who had been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.
- The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and therefore may be disclosed as required to other clinical investigators, to the US Food and Drug Administration, EMA, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study. No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the SOP of Clinical Facility.
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.

- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Project Management Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, the Korean Prime Minister ordinance on GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (i.e., the Sponsor's study number) and participant's study number.
  - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs

- Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.

- All source data must be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument/ EMR used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in Source Document Agreement.

Study and Site Start and Closure

First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment.
- The first act of recruitment is announcement of applicants for bioequivalence study and will be the study start date.

Study Closure and Site Termination

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
    - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
    - Inadequate recruitment of participants by the Investigator
    - Discontinuation of further development of the Sponsor's compound
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research

organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Data Management

Records, Archives, Quality Control and Quality Assurance of Data

To maintain the convenience and accuracy of data processing, the electronic Case Report Form (eCRF) from cubeCDMS®, the database system of CRScube Inc. will be used.

The Sub-Investigators and participating researchers who are trained on the eCRF entry guideline can access the eCRF with their unique identification number (ID) and password according to the assigned eCRF access level.

The Investigators shall accurately prepare, manage and complete the relevant documents of this study in accordance with KGCP (Korea Good Clinical Practice) and all relevant laws, regulations and rules of Korea. Bioequivalence study documents include all work logs, source documents, records by monitoring personnel and appointment schedules, correspondence between Sponsors and Investigators, and regulation documents (e.g, bioequivalence study protocol and its amendments, IRB correspondence, authorization/approval documents, signed informed consent, study interventions receipt/release records, etc.). The source document includes observational records, bioequivalence study activity record and all reports and records required for the evaluation and reconstitution of bioequivalence study. Therefore, the source document should include a record of treatments or similar records based on the bioequivalence study protocol. However, if the copy is exactly the same as the original and is clean and easy to read, if necessary, the copy can also be considered as a source document.

Information on all participants is anonymized with English initials or participant numbers, and all participating investigators involved in this study should keep confidentiality of all source data and documents related to bioequivalence study results. The Principal Investigator keeps a copy of the participant's signed consent form and maintains a personal participant identification list, participant numbers with the corresponding participant names, to enable records to be identified.

Entry to the eCRF should be conducted in accordance with the eCRF entry guideline (EDC Completion Guideline). The study data recorded in the source document are directly entered into the eCRF, with full audit trail for all inputs and modifications. For missing data, the appropriate reason should be documented.

For the quality assurance of the bioequivalence study and for the confirmation that the collection, recording, and reporting of the bioequivalence study data complies with bioequivalence study management standards and related regulations, systematic audit shall be conducted.

Details not specified in this Protocol are in accordance to PPD SOP and KGCP

Data Management Plan

A Data Management Plan (DMP) will be prepared. The DMP includes the description of the whole data management process, from the development of the eCRF, entry of bioequivalence study participant data, to query generation & resolution, and data locking.

Archive of Electronic Data

After data management activities as described in the DMP is completed, the DM personnel from PPD will convert the eCRF data into PDF file format for each participant and delivers it to the Sponsor in a CD (or USB) format. The database containing data from the eCRF is backed-up according to the standards of CRScube Inc. and can only be accessed by the administrator.

The data related to the study should be kept in the Clinical Facility by the archivist of the Clinical Facility for 15 years after the product is approved and after that, archiving and archive management is determined in consultation with the Sponsor. Data management activities in this bioequivalence study shall be conducted in accordance of the latest version of PPD SOP.

Appendix 4 Contraception

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A WOCBP is **not**:

1. Premenarchal
2. A premenopausal female with 1 of the following:
   Documented hysterectomy
   Documented bilateral salpingectomy
   Documented bilateral oophorectomy

   Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

   For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion applies to determine study entry.
3. A postmenopausal female
   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
   A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

- Oral
- Intravaginal
- Transdermal
- Injectable

Progestogen-only hormone contraception associated with inhibition of ovulation

- Oral
- Injectable

Sexual abstinence: a highly effective method **only** if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence is evaluated in relation to the duration of the study.

Acceptable Methods

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide. Male condom and female condom cannot be used together (due to risk of failure with friction)
- Cervical cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)

Contraceptive use by men or women is consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Highly effective methods have a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Acceptable methods are considered effective, but **not** highly effective (i.e., have a failure rate of ≥1% per year). Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are **not** acceptable methods of contraception.

Appendix 5 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

- **Adverse Event**

  An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the study intervention.

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

  The Investigator is required to grade the severity or toxicity of each AE.

  Adverse events that occurred from the time signed Informed Consent was obtained to prior to the administration of study interventions of Period 1 are collected as PEAE (Pre-existing Adverse Event) because there was no causal relationship with study interventions, and those that occurred after administration of study interventions are collected as TEAE (Treatment-Emergent Adverse Event). For TEAE (Treatment-Emergent Adverse Event), follow-up is performed until abnormal value of the test is normalized and symptoms are disappeared.

- Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

  Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated.

  Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

  Severe: Significant impairment of functioning: the participant is unable to carry out his or her usual activities.

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

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

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

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or 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 (Death itself is not a Serious Adverse Event, but the cause of death should be a Serious Adverse Event. The death should be recorded in the outcome.)
  - Is life-threatening. Life-threatening refers to an event in which the participant 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 (Hospitalization itself is not a serious adverse event, but the cause of hospitalization should be a serious adverse event. Hospitalization for scheduled surgery planned prior to bioequivalence study is not applicable (however, requires records of source document))
  - Results in persistent or significant disability or incapacity (It does not necessarily mean only persistent. Includes situations in which daily life is impossible, such as having problems with walking or communicating. Even though it is mild, if it interferes with normal function persistently, it can be included.)
  - Is a congenital anomaly or birth defect
  - Is otherwise considered to be medically important. 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 participant 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 an study intervention is also considered an SAE, as specified below for reporting SAEs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective

hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Following cases are excluded from "Requires inpatient hospitalization or prolongs an existing hospitalization".

- Inpatient hospitalization or prolongation of existing hospitalization for diagnosis or to receive selective surgery for underlying disease
- Inpatient hospitalization or prolongation of existing hospitalization to measure the efficacy of the bioequivalence study
- Inpatient hospitalization or prolongation of existing hospitalization to have a scheduled treatment for the target disease of the bioequivalence study
- In the case of visiting the emergency room, the case that it does not exceed 24 hours
- Hospitalization for health checkup
- Living environment related hospitalization that does not require medical/ surgical treatment

Hospitalization

Adverse event reported from the study in relation with the inpatient hospitalization or prolongation of existing hospitalization is considered to be serious. All initial hospitalization (though it is less than 24 hours) at the Clinical Facility meets this criteria. Hospitalization also includes transfer from hospital to Acute Ward/ Intensive Care Unit (e.g. from psychiatric ward to internal ward, from internal ward to cardiovascular intensive care unit, from neurology ward to tuberculosis ward).

The followings are not classified as a hospitalization.

- Rehabilitation facilities
- Hospice facilities
- Temporary protection (e.g. nurse replacement)
- Skilled nursing facilities
- Sanatorium
- Regular emergency room hospitalization
- Same-day surgery (the case surgery is performed by outpatient visit/ on the same day/ in a state walking is possible)

Inpatient hospitalization or prolongation of existing hospitalization that is not related with clinical adverse events is not itself a serious adverse event. Examples include:

- Hospitalization by the development of new adverse events or for the treatment of an existing disease that is not associated with worsening of existing disease (e.g. for the close examination of abnormal clinical laboratory tests values before having ongoing treatment)

- Administrative hospitalization (e.g. annual physical examination)
- Hospitalization as specified in the protocol during the study (e.g. for the procedures required by the protocol)
- Selective hospitalization not associated with sudden clinical adverse events (e.g. the case of selective plastic surgery)
- Hospitalization for observation, without medical adverse events
- Pre-planned treatment or surgical procedures should be recorded in the protocol and/ or individual participant document.

- **Events Not to Be Considered as AEs/SAEs**

  Medical conditions present at the initial study 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.

  Diagnostic and therapeutic noninvasive and invasive procedures such as surgery are not reported as adverse events. However, the medical condition for which the procedure was performed is reported as an adverse event if the definition of adverse events is met. For example, acute appendicitis that started during the reporting period of adverse events is reported as an adverse event and the resulted appendectomy is recorded as the treatment of the adverse event.

Recording and Follow-Up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

The Principal Investigator (or delegated investigators) has to follow-up the participant who developed adverse events until the symptoms disappear or the abnormal clinical laboratory tests are recovered into the reference range or medically sufficient explanation for the observed changes can be given.

Specific guidance is in the e-CRF Completion and Monitoring Conventions provided by the Sponsor. Only the presence or absence of SAE is checked and recorded. There is no guidance for writing SAE report.

Reporting Serious Adverse Events

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 or its designee using the SAE report form (hard copy).

Reporting of SAEs using a paper report form is required as a back-up method only for an EDC system failure. Names, addresses, and telephone and fax numbers will be included on the paper form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an electronic SAE report form must be completed immediately thereafter.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee 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 or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the study monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Appendix 6 Clinical Laboratory Tests

Table 1: Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count		WBC Count with Differential: • Neutrophil (seg) (%) • Lymphocyte (%) • Monocyte (%) • Eosinophil (%) • Basophil (%)	
	RBC			
	Hemoglobin			
	Hematocrit			
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase	Total Bilirubin
	Creatinine	Sodium	Alanine Aminotransferase	Total Protein
	Glucose	Chloride	Alkaline phosphatase	Total Cholesterol
	Albumin	Phosphorus	Creatine Phosphokinase	Lactic Dehydrogenase
	Uric Acid	γ-GT	eGFR with MDRD	Lactic acid
	In the case of female, a pregnancy test of serum-HCG. (However, if menopause continued for more than 12 months or if it is infertility due to surgery, the pregnancy test can be omitted.)			
Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 (Discontinuation of Study Intervention).				
Routine Urinalysis	• Specific gravity • pH, glucose, protein, erythrocyte, ketones, bilirubin, urobilinogen, nitrite and leukocyte • Color • Turbidity and microscopic examination (if blood or protein is abnormal)			
Other Tests	• Serological tests: HBs Ag, Anti-HBc, HCV Ab, Anti-HIV 1&2 and RPR Ab • Drug screening tests: THC(Tetrahydrocannabinol), OPI(Opiate), COC(Cocaine), MET(Methamphetamine), BAR(Barbiturates), BZO(Benzodiazepines)			

- For the Screening, all of the parameters in Table 1 will be tested.
- For the Admission day check (Period 1 and Period 2), only clinical chemistry of AST(GOT), ALT(GPT), γ-GT, UN, Cr, eGFR with MDRD and Lactic acid will be tested.
- For the Safety confirmation test of Post-Study Visit, all of the parameters in Table 1 except serological tests & Drug screening tests will be tested.

Appendix 7 Pharmacokinetic Parameters

Symbol	Definition
AUC_{last}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the linear trapezoidal rule
AUC_{inf}	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last} , as estimated using the linear regression from λ_z determination. $AUC_{inf} = AUC_{last} + C_{last\ pred}/\lambda_z$
C_{max}	Maximum observed concentration
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
AUC_{last}/AUC_{inf}	The ratio of AUC_{last} to AUC_{inf}

Appendix 8 Protocol Amendment History

Protocol Version 2.0 (05-October-2020)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

Rationale Statement

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Sequence of Group 1 has been changed to RT and Group 2 to TR.	Usual practice of site is having RT for Group 1and TR for Group 2.
4.4 End of Study Definition	"last participant last visit" has been changed to " last participant last observation"	To comply with KGCP requirements of MFDS according to the opinion of Site.
5.1 Inclusion Criteria	Coagulation test has been deleted	To be consistent throughout the Protocol .
5.1 Inclusion Criteria	Added RPR Ab test.	The site needs the participant to be syphilis negative.
5.2 Exclusion Criteria	Added "… or having other clinically relevant hypersensitivities."	There can be other hypersensitivity in addition to the known hypersensitivity to ingredients of study interventions or Biguanides
5.2 Exclusion Criteria	"Diagnostic Assessments" has been moved to be located under "Medical Conditions"	The site regards it would be more appropriate to locate it under Medical Conditions.
5.3.1 Meals and Dietary Restrictions	The phrase "provided drinks during high-fat meal" has been changed to "milk or juice in the course of high-fat meal".	The type of drinks was specified and it was clearly indicated that it was in the course of high-fat meal.
6.1 Study Intervention(s) Administration	The 2nd and 3rd paragraphs in GCP Dispensing were deleted, and another sentence of "Detailed GCP Dispensing follows SOP of the Clinical Facility" was added instead.	Detailed manual of the GCP Dispensing is not necessary to be presented in the protocol.
6.3.1 Study Intervention Assignment	Combined the sections [Participant identifier] and [Assignment to treatment sequence] into one section with content of the paragraphs remains the same.	To be convenient to read.
6.5.3 Prohibited Medicines	Within 90 days has been changed to within 6 months.	To be consistent with exclusion criterion 14
7.2 Participant Discontinuation/Withdrawal from the Study	Treatment of samples from the withdrawn participant has been specified.	Treatment of samples from the withdrawn participant has not been specified.
8.2.3 Vital Signs	Combined 2 phrases into 1.	To simplify the repeated phrases.

Section # and Name	Description of Change	Brief Rationale
8.2.5 Clinical Safety Laboratory Assessments	Detail of the Clinical Laboratory has been specified.	To specify the Clinical Lab.
8.10.2 Clinic Day -1 (Period 1 and Period 2)	Recheck of inclusion and exclusion criteria	To be consistent with 1.3 Schedule of Activities.
9.4.2 Safety Analyses	From "over Version 23.0" to "Version 23.0 or higher"	Current version is 23.0 and when FSFV takes place in December-2020, MedDRA will have 23.1.
Appendix 6 Clinical Laboratory Tests	The unit of "WBC Count with Differential" of hematology tests has been simplified just to be %.	To be consistent with the unit in the "Lab Normal Range" of the diagnostic laboratory of the site.
Table 1 Protocol-Required Clinical Laboratory Assessments	2 years menopause has been revised to be more than 12 months menopause	To be consistent with Appendix 4, Contraception.
Appendix 8 Protocol Amendment History	Addition of a new Appendix 8	To follow mandatory template of the Sponsor.

Protocol Version 3.0 (01-December-2020)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

Rationale Statement

Section # and Name	Description of Change	Brief Rationale
6.3.2 Blinding	Modification according to the actual labelling method of the Site	Modification according to the actual labelling method of the Site
Appendix 6 Clinical Laboratory Tests	Addition of "except Drug screening tests" in the "Safety confirmation test of Post-Study Visit".	Addition of a phrase for clarification

Protocol Version 4.0 (08-December-2020)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

Rationale Statement

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Addition of a phrase related to separate hospitalization	Reflected the phrase for separate administration in case the recruitment of paticipants does not go smoothly.

CCI [redacted]

6.4 Study Intervention Compliance	Addition of a phrase related to participants who are subject to statistics for separate hospitalization.	Reflected the criteria for the participants to whom additional statistics for separate hospitalization would be applied.

CCI [redacted]

Protocol Version 5.0 (04-January-2021)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

Rationale Statement

Section # and Name	Description of Change	Brief Rationale
5 Study Population	Addition of a phrase of using external recruiting company by the request of the site.	For smooth recruitment of participants using external recruiting company by the request of the site.

Protocol Version 6.0 (08-July-2021)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

Rationale Statement

Section # and Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design	Correction of Error, Update of Ordinance of the Prime Minister No. and MFDS Notification No.	Error Corrected. And reflected the latest Ordinance of the Prime Minister and MFDS Notification No.

9.1 Statistical Hypotheses	Deletion of phrases due to updated "Standard on Pharmaceutical Equivalence Study" Notification	Deleted the exceptions to follow the updated "Standard on Pharmaceutical Equivalence Study" Notification.
10 Comparative Dissolution Test Method	Deletion of a phrase due to updated "Standard on Pharmaceutical Equivalence Study" Notification	Deleted the exceptions to follow the updated "Standard on Pharmaceutical Equivalence Study" Notification.
11 References	Update of MFDS Notification No.	Reflected the latest MFDS Notification No
Appendix 2 Study Governance	Update of Ordinance of the Prime Minister No. and MFDS Notification No.	Reflected the latest Ordinance of the Prime Minister and MFDS Notification No
Appendix 11 Analytical Project Manager Signature Page	Change of Analytical Project Manager & Update of Ordinance of the Prime Minister No. and MFDS Notification No.	Change according to the internal circumstances of the Analytical Facility. Reflected the latest Ordinance of the Prime Minister and MFDS Notification No

Appendix 9 Sponsor Signature Page

Study Title:	A randomized Phase I, open-label, active-controlled study assessing the bioequivalence between single doses of 500 mg Glucophage® XR Reduced Mass tablets and 500 mg Glucophage® XR tablets under fasted and fed state in two 2-way-crossover groups of healthy participants
Regulatory Agency Identifying Numbers:	Not applicable
Clinical Study Protocol Version:	15 September 2021 / Version 6.1 final

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Medical Director
Institution:	Merck Ltd. Korea
Address:	PPD
Telephone number:	
Fax number:	
E-mail address:	

Appendix 10 Principal Investigator Signature Page

Study Title:	A randomized Phase I, open-label, active-controlled study assessing the bioequivalence between single doses of 500 mg Glucophage® XR Reduced Mass tablets and 500 mg Glucophage® XR tablets under fasted and fed state in two 2-way-crossover groups of healthy participants
Regulatory Agency Identifying Numbers:	Not applicable
Clinical Study Protocol Version:	15 September 2021 / Version 6.1 final
Site Number:	Not applicable

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Principal Investigator/ PPD
Institution:	PPD
Address:	
Telephone number:	
Fax number:	
E-mail address:	

Appendix 11 Analytical Project Manager Signature Page

Study Title:	A randomized Phase I, open-label, active-controlled study assessing the bioequivalence between single doses of 500 mg Glucophage® XR Reduced Mass tablets and 500 mg Glucophage® XR tablets under fasted and fed state in two 2-way-crossover groups of healthy participants
Clinical Study Protocol Version:	15 September 2021 / Version 6.1 final
BioInfra Protocol No.:	PPD

I, the undersigned, hereby declare that the bioanalytical work will be performed by me or under my direction and that the findings will provide a true and accurate record of the results. The study will be conducted in compliance with the Protocol and BioInfra Standard Operating Procedures and in compliance with Annex 4 Good Clinical Practice "Regulation on Safety of Medicinal Products, etc." PPD and "Standard on Pharmaceutical Equivalence Study" PPD PPD

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	