Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Randomized, Open-label, 2-Way-Crossover Study Assessing the Bioequivalence between Single Doses of 500 mg Glucophage Extended Release (GXR) Tablets (Merck/China Nantong-Manufactured) and 500 mg GXR Tablets (Merck/Germany Darmstadt-Manufactured) under Fed and Fasted State in Two Groups of Healthy Volunteers
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Principal Investigator:	PPD [redacted]
Sponsor Name and Legal Registered Address:	Merck Pharmaceutical Manufacturing (Jiangsu) Co., Ltd. No. 168 Hexing Road, NETDA, Nantong, Jiangsu, China 226010 Protocol Lead: PPD [redacted] Merck Serono (Beijing) Pharmaceutical R&D Co., Ltd. 25F, NUO Center Office No. 2A, Jiangtai Road, Chaoyang District Beijing 100016 P. R. China
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Protocol History

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Table of Contents

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Randomized, Open-label, 2-Way-Crossover Study Assessing the Bioequivalence between Single Doses of 500 mg Glucophage Extended Release (GXR) Tablets (Merck/China Nantong-Manufactured) and 500 mg GXR Tablets (Merck/Germany Darmstadt-Manufactured) under Fed and Fasted State in Two Groups of Healthy Volunteers

Short Title: GXR China Bioequivalence Study (Nantong – Darmstadt)

Rationale: A bioequivalence (BE) study is proposed to investigate the GXR tablet manufactured by 2 different sites, Merck Darmstadt (Germany) and Merck Nantong (China). While the Merck Darmstadt-manufactured GXR tablet has been approved in multiple countries including China, Merck Nantong is a new manufacturing site with production of GXR expected to start in 2020.

The aim of this clinical BE study is to investigate the BE of GXR 500 mg tablets manufactured by Merck Nantong (test product) and GXR 500 mg tablets manufactured by Merck Darmstadt (as reference) as a key demonstration of quality of the test product being equal to the reference. The clinical BE result also serves as part of the supporting package along with additional necessary testing including Chemistry, Manufacturing, and Controls, in vitro dissolution, etc., to substantiate regulatory filing upon request.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
Primary		
To assess BE between the GXR manufactured in Merck Nantong China (test) and that manufactured in Merck Darmstadt Germany (reference product) following single oral dose administrations under fasting and fed conditions.	The following PK parameters calculated from metformin plasma concentrations: • $AUC_{0\rightarrow t}$ • C_{max}.	Time from predose (Baseline) to 48 hours after each dosing.
Secondary		
1. To compare additional PK parameters of GXR after single dose administrations of test and reference products. 2. To examine the safety and tolerability of GXR after single dose administrations of test and reference products.	1. Additional PK parameters: t_{max}, $t_{1/2}$, $AUC_{0\rightarrow\infty}$, $AUC_{\%extra}$, λ_z, CL/f, V_z/f. 2. Safety assessments including: • Adverse events • Vital signs • Clinical laboratory tests (biochemistry, hematology, and urinalysis) • 12-lead ECG • Physical examination • Concomitant medications	PK: Time from predose (Baseline) to 48 hours after each dosing. Safety: Time from informed consent to End-of-Study assessment at Day 10 (or the conditional follow-up visit at Day 15)

$AUC_{0\rightarrow\infty}$ = area under the plasma concentration-time curve from time zero to infinity; $AUC_{0\rightarrow t}$ = area under the plasma concentration-time curve from time zero to the last sampling time at which the concentration is at or above the lower limit of

quantification; $AUC_{\%extra}$ = extrapolated part of $AUC_{0\rightarrow\infty}$ calculated by $C_{last\ calc}/\lambda_z$, expressed in percent; BE = bioequivalence; CL/f = total body clearance of drug from plasma following extravascular administration; C_{max} = the maximum plasma concentration observed; ECG = electrocardiogram; GXR = Glucophage Extended Release; λ_z = terminal elimination rate constant; PK = pharmacokinetics; $t_{1/2}$ = apparent terminal half-life; t_{max} = time to reach the maximum plasma concentration; V_z/f = apparent volume of distribution during the terminal phase following extravascular administration.

Overall Design: This study is designed as a Phase I, open-label, randomized, 2-period, 2-sequence, crossover study to assess BE between a single oral dose of GXR from 2 different manufacturing facilities, each given as a single dose in a fasting or fed state.

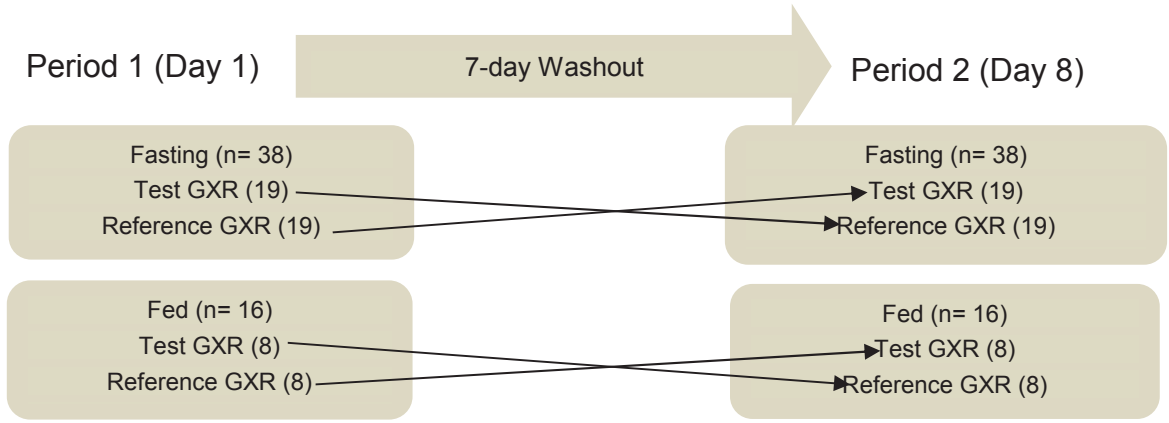
Number of Participants: A total of 54 healthy male and female Chinese participants will be enrolled in the study, with each gender representing no less than 1/4 of the total number and also adequately allocated to fasting vs. fed group (i.e., no less than 10 participants of each gender in the fasting group and no less than 4 participants of each gender in the fed group), and are statistically powered to provide adequate sample size for BE evaluation.

Study Intervention Groups and Duration: The planned study duration consists of initial screening assessments (within 14 days prior to the first GXR administration) followed by 2 treatment periods (consisting of GXR administration followed by 2 days of blood sampling) in a crossover study design. Participants will be randomized to receive, in each period, either 1 tablet of 500 mg GXR (manufactured in Merck Nantong China), or 1 tablet of 500 mg GXR (manufactured in Merck Darmstadt Germany). The treatment periods are separated by a 7-day Washout period. Participants will be discharged at End-of-Study visit on Day 10. A conditional follow-up visit (Day 15) will be conducted 7 days after administration in Period 2 (only for participants who have any ongoing adverse events at the End-of-Study visit). The overall study duration for each participant is approximately 4 weeks (or approximately 29 days) including the screening and conditional follow-up visit.

Involvement of Special Committee(s): Not applicable.

1.2 Schema

Figure 1 Schematic Chart of Study Design



GXR = Glucophage Extended Release

1.3 Schedule of Activities

Table 1 Schedule of Assessments

Assessments	Screening (Baseline)		Period 1				Period 2			Conditional Follow-up Visit or Premature Withdrawal[k]
Day[a]	**-14 to -2**	**-1**	**1**	**2**	**3**	**7**	**8**	**9**	**10[j]**	**15 (or specific day)**
Informed consent form signed	X									
Inclusion/exclusion criteria	X	X								
Demographic information[b]	X									
History of alcohol and nicotine consumption	X									
Medical history	X	X								
Prior medications[c]	X	X								
Laboratory tests (including blood and urine tests)	X	X							X	X
Pregnancy test[d] (women of childbearing potential)	X	X								
HAV antibody, HBsAg, HCV antibody, HIV antibody, and TP antibody tests	X									
Urine drug abuse test and breath test of alcohol	X	X								
Urine nicotine	X									
Randomization		X								
Drug administration			X				X			
Meal recording			X				X			
Blood sampling for pharmacokinetics[e]			X	X	X		X	X	X	X[e]
Physical examination[f]	X	X			X	X			X	X
Vital signs[g]	X	X	X[g]				X[g]		X[g]	X
Electrocardiogram	X	X	X[h]				X[h]		X[h]	X
Chest X-ray	X									
AE recording[i]		X	X	X	X	X	X	X	X	X
Concomitant therapy recording			X	X	X	X	X	X	X	X

AE= adverse event; BMI= body mass index; HAV= hepatitis A virus; HBsAg= hepatitis B surface antigen; HCV= hepatitis C virus; HIV= human immunodeficiency virus; IMP = investigational medicinal product; PK = pharmacokinetic; TP = Treponema pallidum.

a. Participant will participate in the clinical study on an inpatient basis during Day -1 to Day 10.

b. Demographic data include: date of birth, sex, race, height, and weight. The BMI (kg/m^2) will be calculated automatically.

c. Prior medications within 30 days before the date of first signature of informed consent will be collected at the screening visit. Medications administered before the first IMP dose will also be recognized as prior medication and used for eligibility check.

d. Serum pregnancy test will be done at screening and at Day -1.

e. See Table 6 for a detailed schedule of sampling during the inpatient at the research center. There will be an extra PK sampling for participants with premature withdrawal; for participants having conditional follow-up visit for safety, no PK sampling is required.
f. Physical examination includes assessments of the general appearance, skin and mucosa, superficial lymph nodes, head and neck, chest, abdomen, musculoskeletal, and neurological systems.
g. Vital signs including blood pressure (systolic and diastolic pressures), pulse rate, body temperature, and respiration (frequency per minute) will be measured and recorded. Blood pressure and pulse rate will be recorded in a sitting position after the participant has rested comfortably for at least 5 minutes (The blood pressure normal range is considered ≥ 90 mmHg and ≤ 139 mmHg for systolic blood pressure; ≥ 60 mmHg and ≤ 90 mmHg for diastolic blood pressure])). At Day 1 and Day 8, vital signs will be measured 1 hour (±30 minutes) prior to dosing and at 4 hours (±30 minutes) postdose. Vital signs will also be assessed at Day 10.
h. Electrocardiogram (12-lead electrocardiogram, including QTc evaluation) will be performed 4 hours (±30 minutes) postdose at Day 1 and Day 8. Electrocardiogram will also be performed at Day 10 before discharge from the research unit.
i. Adverse events will be collected starting from Day -1. At Day -1, the AEs since the date of signing of informed consent will be recorded; the subsequent visits will record any AEs since the last visit.
j. Participants will be discharged on Day 10, after final sample collection and safety examinations are completed (final examination).
k. If a participant has ongoing AE at End-of-Study discharge on Day 10, the participant must come back for the follow-up visit.

1.4 Estimated Blood Sample Volumes per Participant

The blood sample volumes of each participant are estimated in Table 2.

Table 2 Estimated Blood Sample Volumes per Participant

Time Points	Evaluation Indexes	Total Blood Volume (mL)
Screening (including Randomization)	Serum virology	4
	Hematology	2*2
	Biochemistry	4*2
	Serum Pregnancy Test (if applicable)	4*2
	Subtotal	***24 (16 for male)***
Period 1	Pharmacokinetics	3*17
	Subtotal	***51***
Period 2	Hematology	2
	Biochemistry	4
	Pharmacokinetics	3*17
	Subtotal	***57***
Conditional follow-up Or Premature withdrawal	Hematology	2
	Biochemistry	4
	Subtotal	***6***
	Pharmacokinetics (only for premature withdrawal)	***3***
Approximate Total Amount of Blood for Each Participant		***132 (124 for male)*** ***With conditional follow-up:*** ***138 (130 for male)***

2 Introduction

Glucophage® Extended Release (GXR) tablet contains metformin hydrochloride, 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 authorized in 140 countries and marketed in 127 of them. Complete information on the chemistry, pharmacology, efficacy, and safety of GXR tablet is in the Investigator's Brochure (IB) [1].

2.1 Study Rationale

A bioequivalence (BE) study is proposed to investigate GXR tablet manufactured by 2 different sites, Merck Darmstadt (Germany) and Merck Nantong (China). While Merck Darmstadt-manufactured GXR tablet has been approved in multiple countries including China, Merck Nantong is a new manufacturing site with production of GXR expected to start in 2020.

The aim of this clinical BE study is to investigate the BE of GXR 500 mg tablets manufactured by Merck Nantong (test product) and GXR 500 mg tablets manufactured by Merck Darmstadt (as reference) as a key demonstration of quality of the test product being equal to the reference. The clinical BE result also serves as part of the supporting package along with additional necessary testing including Chemistry, Manufacturing, and Controls, in vitro dissolution, etc., to substantiate regulatory filing upon request.

2.2 Background

2.2.1 Diabetes Mellitus and Treatment

Diabetes mellitus is a metabolic disorder categorized by chronic hyperglycemia resulting from insufficient insulin secretion, insulin resistance, or both. This in turn leads to disturbances of the carbohydrate, lipid, and protein metabolism. Diabetes mellitus is therefore often associated with hypertension, dyslipidemia and central obesity, and is part of the metabolic syndrome [2]. The disease has a long asymptomatic preclinical phase, but complications are usually present at the time of diagnosis [3].

Type 2 diabetes mellitus (T2DM) accounts for 90% to 95% of patients with diabetes [2]. It is usually acquired secondarily and during adulthood, with a tendency to earlier onset, especially in connection with obesity, even in adolescence and childhood [4]. The T2DM is a worldwide health concern, with the global prevalence estimated to be as high as 9% amongst adults aged 18+ years [5]. According to World Health Organization, the diagnosis of T2DM is based on a glycosylated hemoglobin type A_{1C} (HbA_{1C}) $\geq$ 6.5%; or fasting plasma glucose (FPG) $\geq$ 126 mg/dL (7.0 mmol/L); or 2-hour plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) in a 75 g oral glucose tolerance testing; or a random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis [2,3,5,6].

A prospective study in T2DM patients revealed the lack of glycemic control is correlated with the development of diabetic complications, even a small rise above the normal plasma glucose concentration range increases the risk of macrovascular and microvascular complications [7]. The primary effectiveness of T2DM treatment therapy in present time is determined by a surrogate outcome, i.e., change in HbA_{1C} [8,9]. The IDF recommends a general HbA_{1C} target of 7% [3]. In patients with renal impairment, the HbA_{1C} should be targeted between 7.0% and 8.5%, depending on patient characteristics, in order to delay or prevent progression of the microvascular complications, including diabetic kidney disease [10], but also not to risk hypoglycemia. Increasingly, additional surrogate parameters, such as the body mass index (BMI), are taken into account in order to apply a more patient-tailored approach [11].

To date, the first intervention in newly diagnosed diabetes is still a change in lifestyle together with weight loss and physical activity. Until 2015, there were 9 distinct oral pharmacologic classes and a variety of insulin and noninsulin injectable medications available for the treatment of T2DM [12]. Metformin was established as first-line oral antidiabetic therapy in patients with T2DM by findings of the United Kingdom Prospective Diabetes Study in 1998 and further confirmed in all internationally accepted guidelines [13,14] unless contraindicated or not tolerated.

2.2.2 Glucophage Extended Release

Glucophage (metformin hydrochloride: N,N-dimethylimidodicarbonimidic diamide hydrochloride; 1,1-dimethylbiguanide hydrochloride; N,N-dimethyldiguanide hydrochloride; N'- dimethylguanylguanidine hydrochloride) is an oral antihyperglycemic drug belonging to the class of biguanides and is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents. The active ingredient, metformin, is the main representative of the biguanide class antihyperglycemic drugs.

Glucophage Extended Release tablet contains metformin hydrochloride, a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \bullet HCl$ and a molecular weight of 165.62. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. It is an antihyperglycemic agent, which improves glycemic control in patients with T2DM. It does not stimulate insulin secretion and therefore does not produce clinically significant hypoglycemia. Metformin targets insulin resistance at the liver by decreasing hepatic glucose production and in muscle by enhancing peripheral glucose uptake and utilization, furthermore, it also delays intestinal glucose absorption. Metformin has been used for clinical management of diet failed T2DM patients since 1959. Over this time, extensive experience has been gathered relating to the clinical use and safety of metformin. Currently, there are different approved pharmaceutical forms of Glucophage, which have been developed to offer patients options that may fit their lifestyle and thereby improve compliance. Refer to the IB [1] for further information about the nonclinical and clinical programs of GXR and guidance for the Investigator.

2.3 Benefit/Risk Assessment

Metformin has been demonstrated by extensive clinical experience to be well tolerated in diabetic and prediabetic individuals with an acceptable safety profile. The most common side-effects observed in association with metformin are mild to moderate gastrointestinal events, which occur mainly during initiation of therapy and resolve spontaneously in most cases. Serious side-effects under treatment with metformin are very rare and generally limited to the condition of lactic acidosis, which is very rare and occurs primarily in patients with diabetes with acute deterioration of renal function or severe renal failure.

This BE study will only enroll healthy participants. Only a single dose of the investigational medicinal product (IMP) will be administered per period. Since metformin does not act by stimulating insulin secretion, single dose of metformin does not significantly influence the average fasting or 6-hour postprandial plasma insulin levels in either patients with T2DM or healthy subjects. During the study participants will be closely monitored by means of adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), clinical safety laboratory assessments, and physical examinations.

More detailed information about the known and expected risks and reasonably expected AE of the IMP may be found in Section 4.2 and the IB.

Based on the available nonclinical and 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)	Endpoints (Outcome Measures) Timeframe
Primary		
To assess BE between the GXR manufactured in Merck Nantong China (test) and that manufactured in Merck Darmstadt Germany (reference product) following single oral dose administrations under fasting and fed conditions.	The following PK parameters calculated from metformin plasma concentrations: • $AUC_{0\rightarrow t}$ • C_{max}.	Time from predose (Baseline) to 48 hours after each dosing.
Secondary		
1. To compare additional PK parameters of GXR after single dose administrations of test and reference products. 2. To examine the safety and tolerability of GXR after single dose administrations of test and reference products.	1. Additional PK parameters: t_{max}, $t_{1/2}$, $AUC_{0\rightarrow\infty}$, $AUC_{\%extra}$, λ_z, CL/f, V_z/f. 2. Safety assessments including: • Adverse events • Vital signs • Clinical laboratory tests (Biochemistry, hematology, and urinalysis) • 12-lead ECG • Physical examination • Concomitant medications	PK: Time from predose (Baseline) to 48 hours after each dosing. Safety: Time from informed consent to End-of-Study assessment at Day 10 (or the conditional follow-up visit at Day 15)

$AUC_{0\rightarrow\infty}$ = area under the plasma concentration-time curve from time zero to infinity; $AUC_{0\rightarrow t}$ = area under the plasma concentration-time curve from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification; $AUC_{\%extra}$ = extrapolated part of $AUC_{0\rightarrow\infty}$ calculated by $C_{last\ calc}/\lambda_z$, expressed in percent; BE = bioequivalence; CL/f = total body clearance of drug from plasma following extravascular administration; C_{max} = the maximum plasma concentration observed; ECG = electrocardiogram; GXR = Glucophage Extended Release; λ_z = terminal elimination rate constant; PK = pharmacokinetics; $t_{1/2}$ = apparent terminal half-life; t_{max} = time to reach the maximum plasma concentration; V_z/f = apparent volume of distribution during the terminal phase following extravascular administration.

4 Study Design

4.1 Overall Design

This study is designed as a Phase I, open-label, randomized, 2-period, 2-sequence, crossover study to assess BE between a single oral dose of GXR from 2 different manufacturing facilities, each given as a single dose in fasting or fed state. Participants will be randomized within each food consumption group (fasting or fed) to receive, in each period, either:

- 1 tablet of 500 mg test GXR (manufactured in Merck Nantong China), or
- 1 tablet of 500 mg reference GXR (manufactured in Merck Darmstadt Germany).
- Drug administration will be done with or without food depending on group allocation to either fed or fasted condition.

The study has a duration of approximately 4 weeks (or approximately 29 days, as shown in Table 3), including:

- A screening period within 2 weeks before the first GXR administration
- First dosing/sampling period up to 2 days (48 hours) after dosing
- A Wash-out period of 7 days after the first GXR administration
- Second dosing/sampling period up to 2 days (48 hours) after dosing
- End-of-Study examinations and discharge on Day 10
- A conditional follow-up examination period (only for participants with any ongoing AEs at discharge) up to 7 days following the last drug administration.

Table 3 Instruction of Study Periods

Screening Period	Randomization	Treatment Period 1	Washout Period	Treatment Period 2	End-of-Study Discharge	Conditional Follow-up
Day -14 – Day -1	Day -1	Day 1 – Day 3 Inpatient	7 days Inpatient	Day 8 – Day 10 Inpatient	Day 10	Day 15

A total of 54 healthy male or female Chinese participants will be enrolled in the study. Participants will be allocated to a fasting or fed group, i.e., 38 participants will be enrolled into the fasting group and 16 participants in the fed group, respectively (Figure 1). Based on local regulations and Investigator's opinion, each gender should represent no less than 1/4 of the total number (i.e., no less than 10 participants of each gender in the fasting group and no less than 4 participants of each gender in the fed group). Each participant will be administered both the

test and reference products in this 2 × 2 crossover BE study to minimize the effect of the individual difference and periodic difference of the testing results.

4.2 Scientific Rationale for Study Design

This is a single-center, open-label, 2-way crossover design. This study has been designed considering the latest regulatory guidelines on BE design issued by Chinese Food and Drug Administration in March 2016 [15]. In this new guideline, it is recommended to design a clinical BE study in accordance with the intended clinical practice and label of the test and reference product.

According to these guidelines, it is justified to conduct the study in a crossover design, allowing for each participant to serve as his/her own control. The study will be performed in an open-label manner, which will not influence the outcome as the primary objectives and endpoints are related to pharmacokinetic (PK) parameters, which will be evaluated with validated methods. Bioanalysis will also be done with validated methods. Based on previous PK experience, the sample size of 38 participants in the fasting group and 16 participants in the fed group will provide sufficient PK information as well as safety and tolerability data without exposing too many subjects. Study healthy subject demographics will represent a broader population of age (18 to 55 years old) and BMI (18 to 30 kg/m^2). In a BE study conducted in 2014 in France (Study EMR200084-108) [16], it was shown that a 500 mg GXR tablet manufactured by Merck Darmstadt Germany met the BE criteria with the respective reference product of GXR manufactured in USA (Bristol-Myers Squibb, Mount Vernon).

4.3 Justification for Dose

The treatment schedule and dose of metformin has been chosen according to the standard treatment regimen applied for patients suffering from T2DM. The 500 mg dose of GXR is one of the intended clinical doses and one of the most commonly supplied tablet strengths of Merck Darmstadt and Merck Nantong sites.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the End-of-Study visit (Day 10)/or the conditional follow-up visit (Day 15)/or any special day for premature withdrawal visit.

The end of the study is defined as the date of the last contact of the last participant (End-of-Study visit [Day 10]/or the conditional follow-up visit [Day 15]/or any special day for premature withdrawal visit).

5 Study Population

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are chosen to enroll only participants who are appropriate for the study; thereby, ensuring that the study objectives are met. All relevant medical and nonmedical conditions are to be taken into consideration when deciding whether a potential 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:

1. Are 18 to 55 years of age inclusive, at the time of signing the informed consent.
2. Are overtly healthy as determined by medical evaluation, including medical history and a physical examination.
3. Have a body weight within 50 to 90 kg and BMI within the range 18 to 30 kg/m^2 (inclusive).
4. Are Chinese male and female (at least 1/4 of each gender per study group)
   - A male participant must agree to use and to have their female partners use a highly effective contraception (i.e., methods with a failure rate of less than 1 % per year) as detailed in Appendix 3 of this protocol for a period of at least 1 month before and after dosing.
   - A female is eligible if she is not pregnant (i.e., after a confirmed menstrual period and a negative serum pregnancy test), not breastfeeding, and at least one of the following conditions applies:

     a. Is **not** a woman of childbearing potential (WOCBP), as defined in Appendix 3.

     OR

     b. Is a WOCBP who agrees to use a highly effective contraceptive method (i.e., has a failure rate of less than 1 % per year), as listed in Appendix 3, for a period of at least 1 month before and after dosing.
5. 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.
6. Non-smoker (0 cigarettes, pipes, cigars, or others) since at least 3 months.
7. All values for biochemistry and hematology tests of blood and urine within the normal range or showing no clinically relevant deviation as judged by the Investigator.
8. Electrocardiogram recording (12 lead ECG) without signs of clinically relevant pathology as judged by the Investigator.
9. Pulse, body temperature, and respiration in sitting position within the normal range or showing no clinically relevant deviation as judged by the Investigator. Blood pressure in sitting position within normal range: ≥ 90 mmHg and ≤ 139 mmHg for systolic blood pressure; ≥ 60 mmHg and ≤ 90 mmHg for diastolic blood pressure.

10. Negative screen for alcohol and drugs of abuse (cannabis, benzodiazepines, barbiturates, opiates, cocaine, and methyl amphetamine) at screening and on admission.
11. Negative screen for hepatitis A virus (HAV) antibodies, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibodies, human immunodeficiency virus (HIV) antibodies, and *Treponema pallidum* (TP) antibodies.

5.2 Exclusion Criteria

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

1. Participation in a clinical trial within 90 days prior to first drug administration.
2. Blood donation (equal or more than 500 mL) or significant blood loss within 90 days prior to first drug administration.
3. Any surgical or medical condition, including findings in the medical history or in the pre-study assessments, or any other significant disease, that in the opinion of the Investigator, constitutes a risk or a contraindication for the participation of the subject in the study or that could interfere with the study objectives, conduct or evaluation.
4. History of surgery of the gastrointestinal tract which could influence the gastrointestinal absorption and/or motility according to the Investigator's opinion.
5. History or presence of relevant liver diseases or hepatic dysfunction.
6. Allergy: ascertained or presumptive hypersensitivity to the active drug substance and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study.
7. Receipt of any prescription or non-prescription medication within 2 weeks before the first IMP administration, including multivitamins and herbal products (e.g. St John's Wort, or traditional Chinese medicines), except for the permitted medications defined in Section 6.5.1.
8. Renal failure or renal dysfunction (creatinine clearance [Ccr] <80 mL/min) as assessed by using the estimated measure with the Cockcroft-Gault equation [17,18]. The equation for Ccr calculation is as follows:

$$Ccr(mL/min) = \frac{(140 - Age) \times Weight(kg)}{72 \times Blood\ creatinine(mg/dL)}\ (Male)$$

$$Ccr(mL/min) = \frac{(140 - Age) \times Weight(kg)}{85 \times Blood\ creatinine(mg/dL)}\ (Female)$$

9. Known lack of subject compliance or inability to communicate or cooperate with the Investigator (e.g., language problem, poor mental status).
10. Non-acceptance of study high-fat breakfast (e.g., vegetarians, vegans and subjects who follow special diets).
11. Consumption of large quantities of methylxanthine-containing beverages (>5 cups of coffee/day or equivalent).

12. Consumption of grapefruit, cranberry, or juices of these fruits, from 14 days prior to drug administration until collection of the last PK sample in Period 2.
13. Any contraindication to Glucophage.
14. Abnormal and clinically significant chest X-ray finding at screening.

5.3 Lifestyle Considerations

During the hospitalized period, the physical activity of the subjects should be kept to a minimum and no stress-inducing activities will be allowed. Subjects will be requested to avoid strenuous exercises outside the clinical unit from 48 hours prior to the first IMP administration.

Participants of the fed group must eat the complete breakfast.

Restrictions on food and drinks are detailed in Section 6.8.

5.4 Screen Failures

Screen failures are defined as potential participants who consent to participate in the clinical study but are not eligible according to the inclusion and exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

6 Study Interventions

6.1 Study Interventions Administration

6.1.1 Description of the Study Interventions

All IMPs will be sourced from respective manufacturer as listed below (Table 4). All IMPs will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

Table 4 Information of Study Interventions

Drug Treatment	Test Product	Reference Product
Product Name:	GXR (Metformin HCL XR)	GXR (Metformin Hydrochloride Extended-release Tablets)
Formulation:	Tablet	Tablet
Strength:	0.5 g	0.5 g

Manufacturer:	Merck Nantong, China (Merck Pharmaceutical Manufacturing (Jiangsu) Co., Ltd.)	Merck Darmstadt, Germany (Merck KGaA)
Expiry Date:	Refer to the label content	Refer to the label content
Storage Condition:	According to medication label	According to medication label

GXR = Glucophage Extended Release.

6.1.2 Dosage and Administration

Potential study participants will be examined at a screening examination to determine their eligibility for participation. These tests are to be conducted within 14 days before the first IMP administration (Day 1, Period 1).

On the evening before the dosing day in Period 1, participants will be admitted to the Clinical Research Unit (CRU) to fast prior to Day 1 dosing (administered the next morning). During the fast, participants will refrain from all food and drinks except water from the evening after dinner of Day -1. Water will be provided until 2 hours predose; the drug will be given with 240 mL (8 oz) of water at room temperature; water will then be allowed ad libitum beginning 2 hours after the administration of the IMP.

- The participants in the fasting group will have fasted for at least 10 hours by the time of predose blood sample collected after on Day 1.

- For the fed group, participants will consume a standard breakfast within 30 minutes before dosing. The single dose of study drug administration will occur immediately after breakfast completion in the morning of the first day of each period. The content of the breakfast will match the high-fat, high-calorie recommendation based on the regulatory guideline [19].

Following the administration of the drug, hands and mouth will be checked in order to confirm the consumption of the medication. All participants will refrain from drinking water during the first 2 hours after drug administration and to refrain from eating during the first 4 hours. Standard diet for lunch and dinner will be served for both fasting and fed groups. Beverages should be controlled: fluid intake will be controlled for each in-house period for all participants. The participants should drink approximately 2 L of water during the first 24 hours after drug administration. The participants will have their meals at the research unit on Day 1. The fasting condition; time of breakfast uptake and corresponding time to IMP administration, and the scheduled time and exact time of lunch and dinner, will be recorded. Participants should also be restricted from consuming any grapefruit and/or grapefruit-containing beverages during the study.

Period 1

On Day 1 before IMP administration, vital signs will be assessed. If the subject does not meet all eligibility requirements, the subject cannot participate in the study and will be considered as a screen failure.

Eligible participants will be randomly assigned to 1 of 2 sequences. Each participant will receive single dose GXR 500 mg (China manufactured) or a single dose of GXR 500 mg (Germany manufactured) separated by a Washout period of 7 days.

Period 2

Participants will refrain from all food and drinks except water from the evening after dinner of Day 7. They will have fasted for at least 10 hours at the time of drug administration (fasting group) or standard breakfast (fed group) next morning.

Study eligibility assessments will include: physical examination and concomitant medications (Table 1).

If the participant is determined to be ineligible for any of the above assessments, the participant will be dismissed from the CRU and will not continue with the study.

Eligibility assessments (vital signs measurements) outlined on Day 1 will be repeated on Day 8. Drug administration and PK blood sampling outlined on Day 1 in Period 1 will be repeated on Day 8 for participants still eligible.

6.2 Study Interventions Preparation, Handling, Storage, and Accountability

All IMP boxes supplied to the study center must be stored carefully, safely, and separately from other drugs. The handling and storage of IMPs should follow the regulatory requirements from authorities. The Sponsor must provide the study center with enough drugs, including participant treatment and, in addition, at least 5 times the full testing sample size for any requested testing for inspection in the future. In terms of the test product as well as the reference product, the supplies for clinical use and the extra 5 times of full testing samples must be from 1 identical batch and be labeled identically to fulfill the randomized IMPs / retention sample selection requirement at the study center. This requirement is appropriate for both test products and reference products.

The IMP must not be used for any purpose other than the study. The administration of the IMP to subjects who have not been enrolled into the study is not covered by the participant's study insurance.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Upon receipt of the IMP, the Investigator or designee 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 the IMP and only authorized site staff may supply or administer it. All IMP(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.

The IMP 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 IMP(s).
- Dates, quantities, batch numbers, kit numbers, expiry dates, formulation (for IMPs prepared at the site), 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 IMP(s) provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present study. No IMP that is dispensed to a participant may be redispensed to a different participant.

A Study Monitor will periodically collect the IMP(s) accountability forms.

Further guidance and information for the final disposition of unused IMP are provided in the Operation Manual.

It must be ensured that the IMP is not used at the study center:

- After the expiry date or
- After the retest date unless the study product is reanalyzed and its release date extended.
- Before to receive any written greenlight from Sponsor when temperature deviation occurred to study products during the study center storage

These procedures are to be closely monitored by the study monitor and study manager.

The drugs for the participants must be random drawing from all the study drugs and reference drugs provided by Sponsor (it can reference to randomization list from statistics), the left drugs are as the retention samples for the inspection or testing in the future. Any temperature deviation occurring during the study center storage should be reported to the responsible clinical research associate (CRA) immediately. The responsible CRA must report it to Merck immediately and obtain a written decision from Merck with regard to whether to use or block the impacted IMPs.

The retention samples should be stored at study center or a third party under appropriate condition. It is the study center to decide the retention sample storage place and the retention samples will not be returned to Sponsor. The study center must collect the Sponsor's written confirmation before to proceed any retention sample destruction activity.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

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

A total of 54 eligible healthy male and female Chinese participants (38 in fasting group and 16 in fed group) who meet the eligibility criteria will be randomized (with each gender representing no less than 1/4 of the total number within each group, i.e., no less than 10 participants of each gender in the fasting group and no less than 4 in the fed group) on Day -1, in a 1:1 ratio to 1 of 2 treatment sequences: Sequence A-B or Sequence B-A as presented below (Table 5).

Sequence A to B:

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

Sequence B to A:

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

The 2 doses will be separated by a Washout period of approximately 7 days (Table 3).

Table 5 Assignment to Administration Sequences

	Day 1 of Period 1	Day 1 of Period 2
Sequence A to B	GXR 500 mg (Merck Nantong manufactured) (Test Product)	GXR 500 mg (Merck Darmstadt manufactured) (Reference Product)
Sequence B to A	GXR 500 mg (Merck Darmstadt manufactured) (Reference Product)	GXR 500 mg (Merck Nantong manufactured) (Test Product)

GXR= Glucophage Extended Release.

This 2 × 2 crossover design for comparison of 2 treatments complies with the Chinese guideline for BE studies [15]. The guideline recommends 2 sequences in order to minimize the effect of individual and periodic differences. The guideline suggests that the duration of Washout period should be at least 7 times $t_{1/2}$. Therefore, 7 days have been assigned as the Washout period duration to assure that the main collection times in Period 2 can occur on a weekday.

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

6.3.2 Blinding

Not applicable as this is an open label study.

6.4 Study Intervention Compliance

The study treatments will be administered either by the Investigator or under his or her direct supervision in a CRU.

Investigational medicinal product administration should be recorded in the electronic clinical report form (eCRF). Any reason for missed dose will trigger the subject's discontinuation from the study.

6.5 Concomitant Therapy

Concurrent administration of any medication including herbal medications and traditional Chinese medicines are prohibited during the study (except for the permitted medications defined in Section 6.5.1).

Medications administered between Screening (date of ICF signed) and first IMP dosing (Day 1) will be recognized as prior medication and used for eligibility check. After dosing, any medication will be recorded as concomitant medication. The medication (including prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements) taken after the signing of ICF, if any, shall be documented in the eCRF stating the international nonproprietary name and trade name of the medication, its dose, duration, unit, route of administration, date and time of all administrations and indication, including any changes. Upon use of any prohibited concomitant medication, the participant shall then discontinue his/her participation in the study treatment and be withdrawn from the study as described in Section 7. The data recorded up to the time at which the participant in question was withdrawn shall be taken for the evaluation of the study treatment's safety and tolerability.

The Medical Monitor should be contacted for any questions on concomitant or prior medication.

6.5.1 Permitted Medications

Only pain relief medication (paracetamol), and the hormone-based highly effective contraceptive methods listed in Appendix 3 are permitted medications. The administration of paracetamol should not exceed 1 g per day or exceed 3 consecutive days and should be documented in eCRF.

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.

6.5.2 Prohibited Medications

Concurrent administration of any medication except the permitted medications defined in Section 6.5.1 is prohibited during the study.

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

Upon use of any prohibited concomitant medication the participant shall then discontinue his/her participation in the study treatment.

6.6 Dose Selection and Modification

Not applicable.

6.7 Study Intervention After the End of the Study

After a participant has completed the study or has withdrawn prematurely, an End-of-Study visit (Day 10, if participant completes the study) will be conducted and safety assessments will be performed. If a participant has any ongoing AE at the End-of-Study discharge visit on Day 10, the participant must attend the conditional follow-up visit on Day 15 for safety assessments.

Upon the careful screening for healthy participants such as detailed in the eligibility criteria for this study, no serious AEs related to study treatment are expected during this study. However, in case of any ongoing AE at the last visit, these AEs must be monitored until they have either returned to normal or are no longer considered as clinically relevant or can be explained. If necessary, other medical disciplines should be consulted.

6.8 Special Precautions

6.8.1 Alcohol Prohibition

The participants must abstain from alcohol from 2.5 days (approximately 60 hours) prior to dosing and through the study period.

In case of any suspicion of alcohol consumption, a test for alcohol may be performed to confirm the Investigator's judgment.

6.8.2 Smoking Prohibition

Smoking is included as an exclusion criterion barring eligibility into the study (nonsmoker for at least 3 months before signing the ICF, Section 5.1) and smoking is also prohibited during the study.

6.8.3 Food Restriction

Fluids

Participants are not allowed to excessively consume beverages containing xanthine (> 5 cups of coffee a day or equivalent) and need to stop caffeine consumption from 48 hours prior to drug administration until collection of the last PK sample in each period. Participants also need to stop intake of grapefruit, cranberry or juices/beverages of these fruits, from 14 days prior to drug administration until collection of the last PK sample in Period 2.

Food and Fasting

Participants included in the fed group must agree to consume the high-fat breakfast. In the fed group, the breakfast should be similar in fat and caloric composition of the recommended high fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) Chinese breakfast according to the standard of the study center. During the hospitalization periods, participants will receive breakfast, lunch, and dinner at regular times (as applicable).

Prior to each drug administration (i.e., Day 1 or Day 8), participants in both groups need to fast overnight for at least 10 hours.

All participants will refrain from drinking water during the first 2 hours and fasted for the first 4 hours after drug administration. Standard diet for lunch and dinner will be served for both fasting and fed groups. Beverages should be controlled: fluid intake will be controlled for each inpatient period for all participants. The participants should drink approximately 2 L of water during the first 24 hours after each drug administration.

6.9 Management of Adverse Events of Interest

Not applicable.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Participants who withdraw from the study will also be withdrawn from the IMP. A participant who drops out will not be replaced for this study as long as the minimum sample size of evaluable participants is met.

The Schedule of Assessments (SoA, Table 1) specifies the data to collect at IMP discontinuation and follow-up, and any additional evaluations that need to be completed.

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.
- The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- Details of reasons for premature withdrawal of participants will be recorded and documented in the final report.

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; and 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address. 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.

7.4 Premature Termination of the Study

This study is to be conducted in healthy participants using products in which the safety profile is well known and also proven in the population with the target disease. The conduct of this study poses very little risk of premature withdrawal due to safety issues. However, in every case of (premature) withdrawal, the assessments scheduled for premature withdrawal visit must be conducted (Section 6.7).

In addition, the clinical study may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for GXR. The Sponsor may discontinue the study if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of GXR or withdrawal of GXR or comparator from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA (Table 1).
- **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 the IMP.
- 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 potential 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.

8.1 Efficacy Assessments and Procedures

Not applicable.

8.2 Safety Assessments and Procedures

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, ECG, 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.

8.2.1 Physical Examinations

- The examination includes assessments of the general appearance, skin and mucosa, superficial lymph nodes, head and neck, chest, abdomen, musculoskeletal, and neurological systems.

8.2.2 Vital Signs

- Blood pressure (systolic and diastolic pressures), pulse rate, body temperature, and respiration (frequency per minute) will be measured and recorded. Blood pressure and pulse rate will be recorded in a sitting position after the participant has rested comfortably for at least 5 minutes.

8.2.3 Electrocardiograms

Single 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.

After the participant has rested for at least 5 minutes in the supine position, a 12-lead ECG will be conducted by placing peripheral leads I, II, III, aVR, aVL, aVF followed by the precordial leads V1 to V6 and all 12-leads recorded. At least 2 to 3 beats will be monitored at a speed of 25 mm/s for each lead and a single lead (V2) run. Printouts for each ECG will include date, time, initials of the technician/nurse who performed the test and initials of the personnel who reviewed the printout (i.e., a medical physician). Results of the ECG recordings will be included in the participant's eCRF.

The following parameters will be assessed:

- RR interval (ms)
- PR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTcB (Bazett) (ms)
- QTcF (Fridericia) (ms)
- Heart rate (beats per minute)
- Rhythm (sinusal - other).

QTc interval will be automatically computed using the Bazett correction formula ($QTcB = QT / \sqrt{RR}$) and the Fridericia correction formula ($QTcF = QT / \sqrt[3]{RR}$) according to the recently approved International Council for Harmonisation (ICH) Guidance E1.

8.2.4 Clinical Safety Laboratory Assessments

- Safety and tolerability will be assessed by monitoring laboratory measurements. Please see Appendix 5 for the scope of laboratory measurements.
- It is essential that the Sponsor be provided with a list of laboratory normal ranges before shipment of IMP. Any change in laboratory normal ranges during the study will additionally be forwarded to the Sponsor.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.

- 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.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are in Appendix 4.

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 included into the study (date of first signature of informed consent) and continues through the study's post treatment period. The complete study duration for collecting AEs is defined as beginning with the date of the signing of the consent form (up to 14 days before Day 1 of study Period 1), continuing during the IMP administration, and collection continued until Day 10 or 7 days after the day of the last IMP administration (conditional follow-up visit, Day 15, if participant has ongoing AE at the End-of-Study visit on Day 10). In case of early termination, AEs until Premature Withdrawal visit will be collected.

Any SAE assessed as related to the IMP must be recorded and reported, as indicated in Appendix 4, whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 4.

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/her condition. During the reporting period of the study any unfavorable changes in the participant's condition will be recorded as AEs, whether reported by the participant or observed by the Investigator.

All AEs must be documented in the appropriate section of the eCRF. 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. Among these AEs, all serious AEs and non-serious adverse drug reactions (ADRs) must be additionally documented and reported using an SAE Report Form as described in Appendix 4.

The following aspects must be recorded for each AE in the eCRF:

1. Description of the AE in medical terms, not as reported by the participant
2. Date/time of onset (only in relation to administration of IMP: before, during, or after)
3. Severity Grade assessed by the Investigator according to the Qualitative Toxicity Scale

4. Causal relationship to the IMP applied per protocol, assessed by the Investigator
5. Action taken with regard to study treatments
6. Concomitant medication
7. Outcome
8. Seriousness (appropriate criteria documented).

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

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

Any AE that occurs during the course of the clinical study and is considered to be related to the IMP must be monitored and followed up 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 the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

In the event of any SAE occurring during the reporting period, the Investigator must immediately (within 24 hours of becoming aware of the event) report to local regulatory authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular SAEs with outcome of death) involving his/her participants to the IEC/IRB that approved the study.

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

In accordance with ICH Good Clinical Practice (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 particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of the safety reports in the Investigator Site File. National regulations with regard to safety report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate safety reports directly to the concerned IEC/IRB and will maintain records of these notifications. When direct reporting by the Sponsor 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 and of filing copies of all related correspondence in the Investigator Site File.

8.3.5 Pregnancy

Only pregnancies considered by the Investigator to be related to study treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female participants and to 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 according to the same process as described for SAE reporting in Appendix 4.

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 must be reported in an expedited manner as described in Appendix 4, while normal outcomes must be reported within 45 days after delivery.

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

8.4 Treatment of Overdose

This is a study where GXR (test or reference) will be administered once per period by the Investigator/Clinical Study Coordinator. Therefore, the risk of overdose is negligible. In case of unexpected events, the supervising physician is responsible for diagnosis and treatment of unexpected adverse reactions according to accepted standard medical care and full documentation.

8.5 Pharmacokinetics

For metformin, blood samples will be collected by indwelling cannula (short-term peripheral catheter) for the first day and by direct venipuncture for the rest of the time. All blood samples should be processed within 30 minutes (centrifuge each tube for 10 minutes at 2000 g) or otherwise should be kept in an ice water bath pending processing.

For every participant, during each treatment period, a total of 17 samples, approximately 3 mL each whole blood, will be collected at the following times (Table 6):

- at predose (Baseline) and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 30, 36, and 48 hours after dosing.

- One sample will be collected at Premature Withdrawal if applicable.

Eligible participants will have their Baseline blood sample collected at approximately 10 minutes before GXR administration in Periods 1 and 2 for both the fasting and fed group participants.

The PK collection time is based on known single-dose PK profiles of the extended release formulation and should be frequent and long enough to characterize the peak and extent of exposure. Plasma samples will be prepared, divided into 2 aliquots and stored at -20°C or lower.

Participants who complete both treatment periods will have a total of 34 samples (approximately 3 mL whole blood each sample) collected. Total PK blood volume collection is approximately 102 mL over 2 weeks.

A validated bioanalytical method will be applied to analyze plasma concentration of metformin. The assay and all related procedure will be developed and cross-validated with previously established methods to ensure quality standard and technical specifications are met. Details of the assay will be provided in the analytical plan separately.

The clock time of all blood draws will be recorded and reported for each participant in the eCRF. The actual sampling times, if available, will always be used for calculation.

Pharmacokinetic parameters will be calculated by the PK/PD Data Processing Group of QPD, Merck, Darmstadt, Germany, or by a contract research organization selected by the Sponsor, using standard non-compartmental methods and the actual administered dose. Pharmacokinetic parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. The following PK parameters will be calculated from plasma concentrations of metformin by applying non-compartmental standard methods according respective Standard Operating Procedures.

C_{max}	the maximum plasma concentration observed
t_{max}	time to reach the maximum plasma concentration
$AUC_{0\rightarrow t}$	area under the plasma concentration-time curve from time zero to the last sampling time at which the concentration is at or above the lower limit of quantification, calculated using mixed log-linear trapezoidal rule
$AUC_{0\rightarrow\infty}$	area under the plasma concentration-time curve from time zero to infinity
$AUC_{\%extra}$	extrapolated part of $AUC_{0\rightarrow\infty}$ calculated by $C_{last\ calc}/\ \lambda z$, expressed in percent
λ_z	terminal elimination rate constant
$t_{1/2}$	apparent terminal half-life

CL/f	total body clearance of drug from plasma following extravascular administration
V_z/f	apparent volume of distribution during the terminal phase following extravascular administration

The PK parameter evaluation will be performed using the validated PK software tool Phoenix/WinNonlin.

Table 6 Sampling Collection Schedule

Study Day	Period Day	Time of Blood Sample (Hour)	Window Allowance (Minute)
1	1 - Predose in Period 1	Baseline blood draw (10 minutes prior to drug administration)	±2
1	1 – Single dose administration	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14	±2
2	2	24, 30, 36	±5
3	3	48	±5
8	1-Predose in Period 2	Baseline blood draw (10 minutes prior to drug administration)	±2
8	1 – Single dose administration	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14	±2
9	2	24, 30, 36	±5
10	3	48	±5
Premature Withdrawal		1-sample at premature withdrawal	±30

Note: All blood samples should be processed within 30 minutes (centrifuge each tube for 10 minutes at 2000 g) or otherwise should be kept in an ice water bath pending processing. There will be an extra PK sampling for participants who have premature withdrawal. For participants having a conditional follow-up visit for safety, no PK sampling is required.
PK = pharmacokinetics.

8.6 Pharmacodynamics

Not applicable.

8.7 Genetics

Not applicable.

8.8 Biomarkers

Not applicable.

8.9 Medical Resource Utilization and Health Economics

Not applicable.

8.10 Immunogenicity Assessments

Not applicable.

9 Statistical Considerations

9.1 Statistical Hypotheses

The null and alternative hypotheses for the analysis of primary endpoints are stated in Section 9.4.2.

9.2 Sample Size Determination

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

Based on the results of previously conducted BE study PK data (EMR200084-108 [16]), GXR formulation showed intra-individual coefficient of variations (CVs) as below (Table 7 and Table 8).

CCI [redacted]

Table 7 Results from EMR200084-108 Study Fed CCI

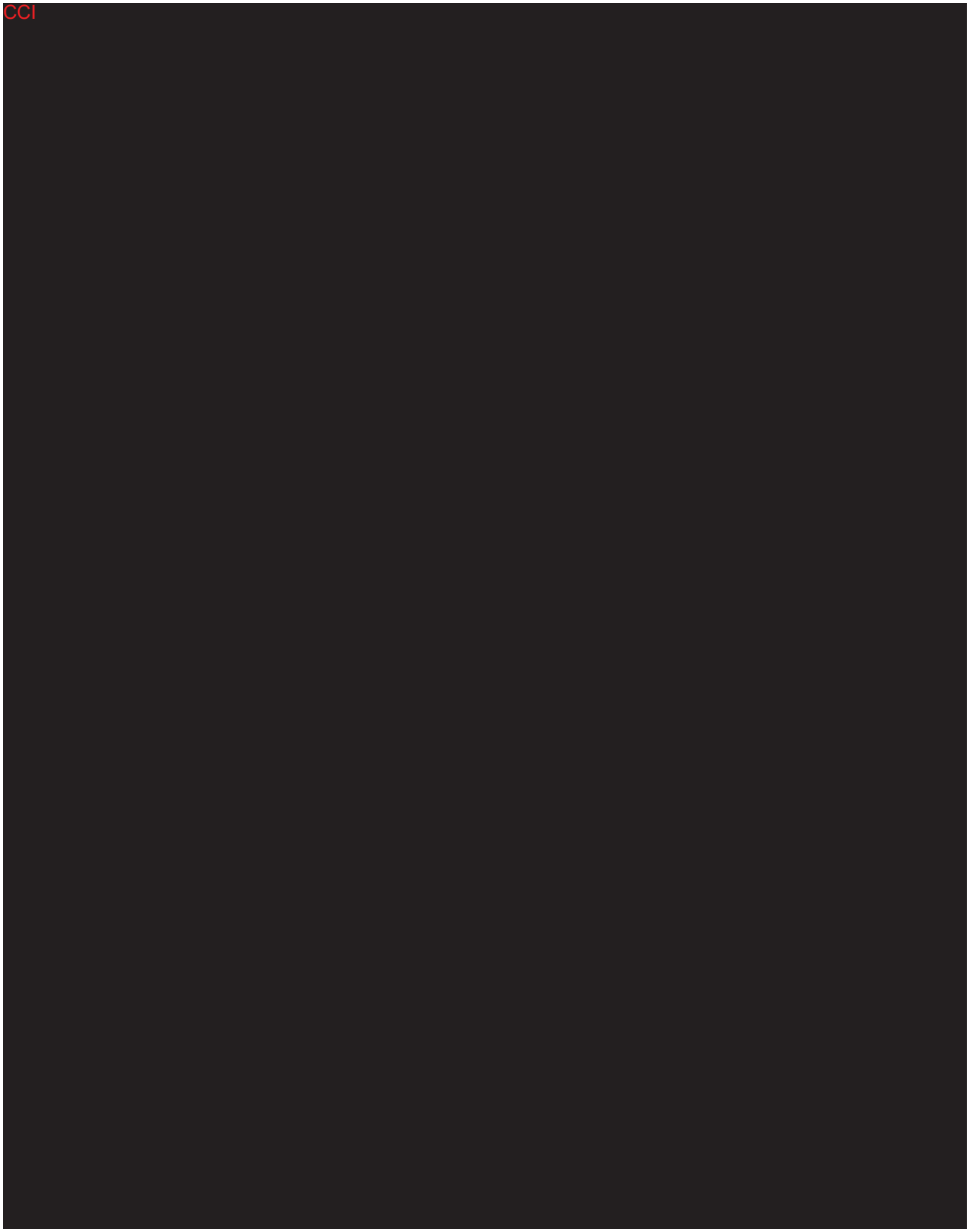
CCI [redacted]

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

Table 8 Results from EMR200084-108 Study Fasting CCI

CCI [redacted]

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



9.3 Populations for Analyses

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

Analysis Population	Description
Screening Population	The Screening Population includes all subjects who have signed the main informed consent (i.e., screening failures plus subjects enrolled).
Safety Population	The Safety Population includes all participants who received at least 1 dose of IMP. In general, clinical data will be analyzed for the Safety Population.
Pharmacokinetic Population	The PK Population includes all participants who completed the study with adequate study medication compliance, without any relevant protocol violations or events with respect to factors likely to affect the comparability of PK results, and with sufficient evaluable data to determine primary endpoints ($AUC_{0\rightarrow t}$ and C_{max}) for both treatments. If participants receive concomitant medication that potentially affects PK for the treatment of an AE, their inclusion in the PK Population will be decided on a case-by-case basis. Emesis occurring within 2 times of the median t_{max} for a given treatment will be considered a relevant event likely to affect the comparability of PK results. Similarly, a predose concentration for a given treatment period that exceeds 5% of C_{max} will be considered a relevant event affecting PK results. All PK analyses will be based on the PK Population. Data for subjects excluded from the PK Population will be included in listings.

PK = pharmacokinetic.

9.4 Statistical Analyses

9.4.1 General Considerations

Details of the statistical analysis will be presented in a statistical analysis plan prior to database lock.

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

All data recorded during the study will be presented in individual data listings performed on the Screening or Safety Population. All data will be evaluated as observed values; no imputation method for missing values will be used, unless otherwise stated. Methods for concentration data below the lower limit of quantification will be described in the statistical analysis plan.

9.4.2 Analysis of Primary Endpoints

The primary endpoints are the following PK parameters calculated from metformin plasma concentrations:

- $AUC_{0\rightarrow t}$ of metformin
- C_{max} of metformin

The null and alternative hypotheses for establishing BE within each group, fasted and fed, are the following:

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

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

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

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

The primary variable, C_{max} and $AUC_{0\rightarrow t}$ in the fasting and fed group will be log-transformed and mixed effect model will be applied. The model will include effects for sequence, treatment and period. Participants nested within sequence will be included as random effect. Bioequivalence will be assessed separately, in the fed and in the fasted group, and the study will be successful only, if BE has been established in both groups.

Based on the residual (within subject) variation, 90% CIs for the ratio of geometric means will be calculated. The BE can be established if the 90% CI on the ratios between test and reference of the geometric means fall within 80.00% to 125.00%.

9.4.3 Analysis of Secondary Endpoints

The secondary PK endpoints are the following parameters in plasma for metformin:

- t_{max}, $t_{1/2}$, λ_Z, $AUC_{0\rightarrow\infty}$, $AUC_{\%extra}$, CL/f, V_z/f.

For t_{max}, the Hodges-Lehmann estimates [20] for the pairwise treatment differences and the corresponding 90% CIs according to the Tukey method will be calculated.

The mixed model as described above will also be applied to $AUC_{0\rightarrow\infty}$. A 90% CI will be calculated for the ratios of geometric means of the test IMP and reference IMP.

All secondary endpoints will be summarized descriptively by group and treatment in the PK Population.

9.4.4 Analysis of Safety and Other Endpoints

All data recorded during the study will be presented in individual data listings performed on the Safety Population.

All safety variables will be analyzed using descriptive statistics.

For the evaluation of safety parameters, the continuous variables will be summarized descriptively per treatment, period, time point, and overall by N, arithmetic mean, median, standard deviation (SD), standard error of the mean (SEM), and minimum and maximum values. Categorical variables will be presented in frequency tables with the counts of observations and corresponding percentages.

Vital sign measurements and ECG recordings will be individually listed by treatment, participant number, period, and time point, and the abnormal values flagged according to reference laboratory ranges. All hematology and biochemistry parameters will be listed and summarized using descriptive statistics by treatment sequence on observed values. Urinalysis will be summarized in frequency tables.

After coding of AEs according to the Medical Dictionary for Regulatory Activity classification (current version) and assignment to a system organ class and preferred term, all AEs recorded during the course of the study will be listed by treatment and participant number.

The AE listings will include the following items:

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

Incidence of treatment-emergent adverse events (TEAEs) will be summarized using frequency of events and number of participants experiencing these events per treatment, preferred term, and system/organ class.

In addition, all TEAEs will be tabulated by intensity and relationship to drug per treatment and group. An AE will be considered "treatment-emergent" if it occurred after the first investigational product administration or if it occurred before the first investigational product administration and worsened after.

Demographic parameters (age, height, and weight) will be summarized by means of tabulated descriptive statistics (the number of observations [N], arithmetic mean, median, SD, SEM, minimum and maximum) by treatment, group, and overall.

Results of physical examination will only be listed by treatment, participant, period, time point, and body system.

Other Endpoints

Analyses described in this subsection will be performed in general for the PK population.

Plasma concentrations below lower limit of quantitation will be analyzed as zero for descriptive statistics. Plasma concentration data will be summarized by treatment, analyte and scheduled time point showing the number of observations (N), arithmetic mean, SD, SEM, CV (%), minimum, median and maximum.

Mean plasma concentrations per treatment and analyte will be plotted (linear scale with SD, and semi-logarithmic scale) using scheduled time points for metformin.

Results of participants not in the PK population will be annotated and listed together with the data of the other participants, but will not be used for descriptive statistics and mean curves. Individual plasma concentrations (linear and semi-logarithmic scales) will be plotted by treatment (showing all participants simultaneously) and by participant (showing all treatments simultaneously).

Handling of Discontinued Participants and Missing Data

Participants will only be replaced if the number of participants within the 2 groups falls below 28 (fasting) or 12 (fed). The participant who is replacing a discontinued participant will then be allocated to the treatment sequence of the participant who discontinued.

9.4.5 Sequence of Analyses

No formal interim analyses are planned.

10 References

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11 Appendices

Appendix 1 Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
$AUC_{0\rightarrow\infty}$	Area Under the Plasma Concentration-Time Curve From Time Zero to Infinity
$AUC_{0\rightarrow t}$	Area Under the Plasma Concentration-Time Curve From Time Zero to the Last Sampling Time at Which The Concentration is at or Above the Lower Limit of Quantification t
$AUC_{\%extra}$	Extrapolated Part of $AUC_{0\rightarrow\infty}$ Calculated by $C_{last\ calc}/\ \lambda_z$, Expressed in Percent
BE	Bioequivalence
BMI	Body Mass Index
Ccr	Creatinine Clearance
CI	Confidence Interval
CL/f	Total Clearance of Drug From Plasma Following Extravascular Administration
C_{max}	The Maximum Plasma Concentration Observed
CRA	Clinical Research Associate
CRU	Clinical Research Unit
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GXR	Glucophage Extended Release
HAV	Hepatitis A Virus
HbA_{1C}	Glycosylated Hemoglobin Type A1C
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

IMP	Investigational Medicinal Product
IRB	Institutional Review Board
PK	Pharmacokinetic(s)
SAE	Serious Adverse Event
SD	Standard Deviation
SEM	Standard Error of the Mean
$t_{1/2}$	Apparent Terminal Half-Life
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-emergent Adverse Event
t_{max}	Time of Maximum Plasma Concentration Observed
TP	Treponema Pallidum
V_z/f	Apparent Volume of Distribution During the Terminal Phase Following Extravascular Administration
WOCBP	Woman of Childbearing Potential
λ_z	Terminal Elimination Rate Constant

Appendix 2 Study Governance

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.
- 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.

Study Administrative

- This study is sponsored by Merck Pharmaceutical Manufacturing (Jiangsu) Co., Ltd. The study will be conducted by a contract research organization.
- The study will be conducted in single center in China.
- The Principal Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH 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.

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 GCP Guidelines
  - 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 of ICH guidelines and the IRB/IEC for clinical studies (if applicable), and all other applicable local regulations
- 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.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards 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 this participation that may be needed to determine the course of medical treatment for the participant.
- 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 on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.
- When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes provision of a 24-hour contact number at a call

center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency.

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.

Clinical Study Report

- After completion of the study, a clinical study report according to ICH Topic E3 will be written by the Sponsor/designee in consultation with the Principal Investigator and other relevant committees or cohorts.

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.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance

- All participant study data will be recorded on electronic CRFs or transmitted to the Sponsor or designee electronically. The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information in the eCRF.
- 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.
- 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. Portable document format files of the eCRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the eCRF 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 and all applicable regulatory requirements.

- After study completion, records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a time length that is in compliance with ICH GCP and local regulatory requirements. 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.
- Monitoring will be carried out as determined by the risk assessment process conducted on the study.

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 the IMP, 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 used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on eCRFs 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, countersigned by the Monitor 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.

Study and Site Closure

- 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 sufficient 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

Appendix 3 Contraception

Woman of Childbearing Potential (WOCBP)

A woman is of childbearing potential (i.e., fertile), following menarche and until either:

1) Becoming postmenopausal; or,
2) is permanently sterile by means of a hysterectomy, bilateral salpingectomy or bilateral oophorectomy.

Postmenopausal 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 women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly Effective Contraceptive Methods

Highly effective methods are those with a failure rate of less than 1% per year when used consistently and correctly.

These methods are further classified into user-independent and user-dependent methods. Because user-independent methods do not depend on the participant's ability to use them consistently and correctly, they are preferred when contraception is introduced as a condition for study participation.

Caution should be taken for hormonal contraception, as it may be susceptible to interaction with the IMP(s), which may reduce the efficacy of the contraception method. In this case, a second highly effective method of contraception should be used during the treatment period and for at least 14 days after the last dose of study treatment.

User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable

User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD)

- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: This is a highly effective contraception method only if the partner is the sole sexual partner of the WOCBP and he has received medical assessment of the surgical success.
- Sexual abstinence: This is a highly effective method only if the WOCBP refrains from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Appendix 4 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 medicinal product.

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

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

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 the IMP using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, course of the underlying disease, and study procedures.

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

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

Adverse Drug Reaction

In accordance with GCP, ADR is an adverse event considered related to drug treatment.

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 IMP 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 alanine aminotransferase) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

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

- Results in death
- Is life-threatening. 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
- Results in persistent or significant disability or incapacity
- 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 the IMP is also considered an SAE.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify IMP administration or procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) 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.

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 IMP administration time), its severity, its causal relationship with the IMP, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Reporting Serious Adverse Events and Nonserious Adverse Drug Reactions

In the event of any SAE and non-serious ADRs occurring during the reporting period, the Investigator must immediately (within a maximum 24 HOURS after becoming aware of the event) inform Global Drug Safety by telephone, by fax or by e-mail.

To do so, the Investigator/reporter must complete a Sponsor SAE report following specific instructions (SAE report Completion Instruction) and using preferably the electronic template, and send it directly to the Sponsor's Global Drug Safety department by electronic mail or facsimile, using the dedicated e-mail address and facsimile numbers specified below.

E-mail: ICSR_GDS@merckgroup.com

Fax: +49 6151 72 6914 (Germany)

When an event (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail. All written reports should be transmitted using the SAE Report Form (Clinical Trials), which must be completed by the Investigator following specific completion instructions.

Reporting procedures and timelines are reported in the same manner as for follow-up information for any new information for a participant as was collected on a previously reported SAE.

Specific guidance can be found in SAE Report Form Instructions provided by the Sponsor.

The Investigator/reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow the Company to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible Monitor, although in exceptional circumstances the Sponsor's Drug Safety department or its designee may contact the Investigator directly to obtain clarification or to discuss a particularly critical event.

Appendix 5 Clinical Laboratory Tests

Laboratory tests include blood tests and urinalysis. Parameters of hematology assessments are tabulated in Table 11 and Table 12, biochemistry assessment parameters are tabulated in Table 13. All laboratory test sample should be collected under fasted condition if possible. There will also be serum pregnancy test for WOCBP.

Table 11 Hematology Assessments

Parameter	Dimension/Unit
Erythrocytes	$\times 10^{12}$/L
Hemoglobin	g/L
Hematocrit	%
Mean corpuscular volume	fL
Mean corpuscular hemoglobin	pg
Mean corpuscular hemoglobin concentration	g/L
Red blood cell distribution width	%
Platelets	$\times 10^{9}$/L
Mean platelet volume	fL
Thrombocytocrit	%
Platelet distribution width	%
White blood cells	$\times 10^{9}$/L

Table 12 Hematology Assessments for Differential White Blood Cell Counts

Parameter	Dimension/Unit
Neutrophils	10^{9}/L and %
Monocytes	10^{9}/L and %
Lymphocytes	10^{9}/L and %

Table 13 Biochemistry Assessments

Parameter	Dimension/Unit
Alanine aminotransferase	IU/L
Aspartate aminotransferase	IU/L
Total bilirubin	µmol/L
Direct bilirubin	µmol/L
Indirect bilirubin	µmol/L
Protein total	g/L
Albumin	g/L
Globulin	g/L
Albumin/globulin ratio	(Not applicable)
Alkaline phosphatase	IU/L
Glutamyl transpeptidase	IU/L
Urea nitrogen	mmol/L
Creatinine	µmol/L
Cholesterol	mmol/L
Triglycerides	mmol/L
Glucose	mmol/L
Creatine kinase[a]	IU/L
Lactate dehydrogenase	IU/L
Calcium	mmol/L
Phosphorus	mmol/L
α-Amylase	U/L
Sodium	mmol/L
Potassium	mmol/L
Chloride	mmol/L

a. If creatine kinase is above the upper limit of normal and evaluated as clinically relevant, a retest should be done and the creatine phosphokinase MB isoenzyme should be determined.

Urinalysis

Appearance, blood, glucose, ketones, nitrite, pH, protein, and leukocytes will be assessed. Microscopic examination will be performed if dipstick test is positive for leukocytes, blood, nitrites, or proteins.

Serum pregnancy test

Pregnancy testing for females of childbearing potential only (human chorionic gonadotropin in serum)

Other Laboratory Tests

Serology

The following test will be done for viral infection screening:

- HAV antibody
- HBsAg
- HCV antibody
- HIV antibody
- TP antibody

Urine screening of drugs of abuse

The following urine tests for drug abuse will be conducted: levels for other drugs of abuse (e.g., cannabis, benzodiazepines, barbiturates, opiates, cocaine, and methyl amphetamine).

Breath test of alcohol

Concentration of alcohol in breath will be tested.

Urine nicotine

The presence of nicotine in urine will be tested.

Appendix 6 Sponsor Signature Page

Study Title:	A Randomized, Open-label, 2-Way-Crossover Study Assessing the Bioequivalence between Single Doses of 500 mg Glucophage Extended Release (GXR) Tablets (Merck/China Nantong-Manufactured) and 500 mg GXR Tablets (Merck/Germany Darmstadt-Manufactured) under Fed and Fasted State in Two Groups of Healthy Volunteers
Clinical Study Protocol Version:	Version 1.0, 19 APR 2018

Protocol Lead:

I approve the design of the clinical study:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	Merck Serono (Beijing) Pharmaceutical R&D Co., Ltd.
Address:	25F, NUO Center Office, No. 2A, Jiangtai Road, Chaoyang District, Beijing 100016, P. R. China
Telephone number:	PPD
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Appendix 7 Principal Investigator Signature Page

Study Title:	A Randomized, Open-label, 2-Way-Crossover Study Assessing the Bioequivalence between Single Doses of 500 mg Glucophage Extended Release (GXR) Tablets (Merck/China Nantong-Manufactured) and 500 mg GXR Tablets (Merck/Germany Darmstadt-Manufactured) under Fed and Fasted State in Two Groups of Healthy Volunteers
Clinical Study Protocol Version:	Version 1.0, 19 APR 2018

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 for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

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