Clinical Trial Protocol

Clinical Trial Protocol Number	MS200084_0009
Title	A Randomized, Open-label, 2-Way-Crossover Study Assessing the Bioequivalence between Single Doses of 500 mg Glucophage Immediate Release (GIR) Tablets (Sino-American Shanghai Squibb Pharmaceuticals Ltd./ Manufactured in China) and 500 mg GIR Tablets (Merck Santé s.a.s. in Semoy/ Manufactured in France) under Fed and Fasted State in Two Groups of Healthy Subjects
Phase	I
IND Number	Not applicable
EudraCT Number	Not applicable
Principal Investigator	PPD
Sponsor	Sino-American Shanghai Squibb Pharmaceuticals Ltd. 1315 Jianchuan Road, Minhang District Shanghai 200240 P. R. China Protocol Lead: PPD PPD Merck Serono Co., Ltd. 25F, NUO Center Office No. 2A, Jiangtai Road, Chaoyang District Beijing 100016 P. R. China Medical Responsible: PPD Merck Serono Co., Ltd.

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Clinical Trial Protocol Version	20 Nov 2017/ Version 2.0 including amendment 1.0
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- [redacted] –

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List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
$AUC_{0\rightarrow\infty}$	Area Under The Plasma Concentration-Time Curve From Time 0 To Infinity
$AUC_{0\rightarrow t}$	Area Under The Plasma Concentration-Time Curve From Time 0 To Time t
AUC_{extra}	Extrapolated Part Of $AUC_{0\rightarrow\infty}$ Calculated By C_{last}/λ_z, Expressed In Percent
BE	Bioequivalence
BMI	Body Mass Index
CI	Confidence Interval
CL/f	Total Clearance Following Extravascular Administration
C_{max}	The Maximum Plasma Concentration Observed
CRU	Clinical Research Unit
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GIR	Glucophage Immediate Release
GMP	Good Manufacturing Practice
HAV	Hepatitis A Virus
HbA_{1C}	Glycosylated Hemoglobin Type A_{1C}
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
Max	Maximum
MDRD	Modification of Diet in Renal Disease
MSS	Merck Santé s.a.s. in Semoy
PK	Pharmacokinetic(s)
SAE	Serious Adverse Event
SASS	Sino-American Shanghai Squibb Pharmaceuticals Ltd
SBP	Systolic Blood Pressure
SD	Standard Deviation
SEM	Standard Error of The Mean
SOP	Standard Operating Procedure
$t_{1/2}$	Half-Life
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-emergent Adverse Event
t_{max}	Time of Maximum Plasma Concentration Observed
TP	Treponema Pallidum

V_{ss}/f	Apparent Volume of Distribution At Steady-State After Extravascular Administration
WOCBP	Woman of Childbearing Potential
λ_z	Terminal Elimination Rate Constant

1 Synopsis

Clinical Trial Protocol Number	MS200084_0009
Title	A Randomized, Open-label, 2-Way-Crossover Study Assessing the Bioequivalence between Single Doses of 500 mg Glucophage Immediate Release (GIR) Tablets (Sino-American Shanghai Squibb Pharmaceuticals Ltd./ Manufactured in China) and 500 mg GIR Tablets (Merck Santé s.a.s. in Semoy/ Manufactured in France) under Fed and Fasted State in Two Groups of Healthy Subjects
Trial Phase	I
IND Number	Not applicable
FDA covered trial	No
EudraCT Number	Not applicable
Principal Investigator	PPD
Sponsor	Sino-American Shanghai Squibb Pharmaceuticals Ltd.
Trial centers/countries	PPD
Planned trial period (first subject in-last subject out)	Fourth quarter 2017- Second quarter 2018
Trial Registry	Chinadrugtrials.org.cn

Objectives:

Primary Objective:

To assess bioequivalence (BE) between the GIR formulation manufactured in China (test investigational medicinal product [IMP]) and that manufactured in France (reference IMP) following single oral dose administrations under fasting and fed conditions.

Secondary Objectives:

1. To compare additional pharmacokinetic (PK) parameters of GIR after single dose administrations of test and reference products.
2. To examine the safety and tolerability of GIR after single dose administrations of test and reference products.

Methodology:

This trial is designed as a Phase I, open-label, randomized, 2-period, 2-sequence, crossover trial to assess BE between single oral doses of GIR from different manufacturing facilities, each given concomitantly as a single dose in fasting or fed state. Subjects will be randomized to receive, in each period, either:

- 1 tablet of 500 mg test GIR (manufactured in Sino-American Shanghai Squibb Pharmaceuticals Ltd. [SASS]/China) or
- 1 tablet of 500 mg reference GIR (manufactured in Merck Santé s.a.s. in Semoy [MSS]/ France).
- Drug administration will be done with or without food depending on group allocation to either fed or fasted condition.

The trial has a duration for each subject of approximately 4 weeks including:

- A screening period within 2 weeks before the first GIR administration
- First dosing/sampling period up to 2 days (48 hours) after dosing
- A washout period of approximately 7 days after the first GIR administration
- Second dosing/sampling period up to 2 days (48 hours) after dosing
- A conditional follow-up examination period (only for subjects who has AE during the trial and ongoing at discharge) up to 7 days following the last GIR administration.

Planned number of subjects:

A total of 44 healthy male and female Chinese subjects will be enrolled in the trial, with at least 7 subjects of each gender in the fasted group, and at least 5 subjects of each gender in the fed group, representing 1/4 of the total number. The sample size provides sufficient power to demonstrate BE.

Primary Endpoints:

Primary Endpoints will be the PK parameters area under the (plasma) concentration-time curve from time 0 to time t ($AUC_{0\rightarrow t}$) and maximum plasma concentration observed (C_{max}) of metformin, the active ingredient of GIR tablet.

Secondary Endpoints:

Secondary Endpoints include time of maximum plasma concentration observed (t_{max}), half-life ($t_{1/2}$), area under the plasma concentration curve from time 0 to infinity ($AUC_{0\rightarrow\infty}$), the extrapolated part of area under the plasma concentration curve (AUC_{extra}), terminal elimination rate constant (λ_z), total clearance following extravascular administration (CL/f), and apparent volume of distribution at steady-state after extravascular administration (V_{ss}/f) for metformin, as well as safety and tolerability.

The safety assessments comprise adverse events, vital signs (blood pressure, pulse rate, temperature and respiration), laboratory tests (biochemistry, hematology, and urinalysis), electrocardiogram (ECG), physical examination, and concomitant medications.

Pharmacokinetics:

The plasma concentrations of metformin will be determined by a validated LC/MS analytical method. Pharmacokinetic parameters (Primary and Secondary Endpoints) will be calculated according to noncompartmental analysis methods. The mixed trapezoidal rule will be used to calculate the area under the plasma concentration curve.

Diagnosis and key inclusion and exclusion criteria:

Subjects meeting all of the following criteria will be considered for enrollment in the trial:

1. Subject has given written informed consent before any trial-related activities
2. Gender: Chinese male and female subjects (at least 1/4 of each gender per trial group)
3. Age: between 18 and 55 years, inclusive
4. Weight: 50 to 80 kg; Body mass index (BMI): 18 to 30 kg/m^2
5. Nonsmoker since at least 3 months
6. Good physical and mental health status, determined on the basis of the medical history and a physical examination
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. Vital signs (blood pressure, pulse, body temperature, and respiration) in sitting position within the normal range or showing no clinically relevant deviation as judged by the Investigator (The blood pressure normal range is considered $\geq$ 90 mmHg and $\leq$ 139 mmHg for systolic blood pressure [SBP]; $\geq$ 60 mmHg and $\leq$ 90 mmHg for diastolic blood pressure [DBP])
10. All women of childbearing potential (WOCBP) are not nursing, are not pregnant, and are using highly effective methods of birth control (defined as those, alone or in combination, that result in a low failure rate (ie, less than 1 percent per year) when used consistently and correctly) for a period of at least 1 month before and after last dosing. Standard birth control methods are considered to be implanted contraceptive therapy and intrauterine devices (oral contraceptive excluded). Female subjects may also be enrolled if they are postmenopausal (ie, at least 12 consecutive months of amenorrhea after the last menstrual period) or surgically sterilized/ hysterectomized at least 6 months prior to trial participation; WOCBP must have negative serum pregnancy tests at screening and on admission (Day -1)
11. Negative screen for alcohol and drugs of abuse (cannabis, benzodiazepines, barbiturates, opiates, cocaine, and methyl amphetamine) at screening and on admission
12. 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.

Subjects presenting with any of the following will not be included in the trial:

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 pretrial 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 trial or that could interfere with the trial 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 trial
7. Receipt of any prescription or nonprescription medication within 2 weeks before the first IMP administration, including multivitamins and herbal products (eg, St John's Wort, or traditional Chinese medicines), except paracetamol
8. Renal failure or renal dysfunction (creatinine clearance < 80 mL/min) as assessed by using the estimated measure with the Modification of Diet in Renal Disease (MDRD) equation
9. Known lack of subject compliance or inability to communicate or cooperate with the Investigator (eg, language problem and poor mental status)
10. Nonacceptance of trial high-fat breakfast (eg, vegetarians, vegans, and subjects who follow special diets)
11. Consumption of large quantities of methyl xanthine-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

Investigational Medicinal Product: dose/mode of administration/dosing schedule:

500 mg GIR tablet (manufactured in SASS/China): oral administration, single dose on Day 1 or a single dose on Day 8 of the trial.

Reference therapy: dose/mode of administration/dosing schedule:

500 mg GIR tablet (manufactured in MSS/France): oral administration, single dose on Day 1 or a single dose on Day 8 of the trial.

Planned trial and treatment duration per subject:

The planned treatment consists of initial screening assessments (within 14 days prior to the first IMP administration on Day 1) followed by 2 trial periods (consisting of IMP administration following 2 days of blood sampling) in a crossover trial design. Each trial period includes a single dose of IMP administration and the doses are separated by approximately a 7-day Washout period. A conditional follow-up visit (Day 15) will be conducted 7 days after administration in Period 2 (only for subjects who has AE during the trial and ongoing at discharge). The overall trial duration for each subject is approximately 4 weeks (or approximately 28 days) including the screening and conditional follow-up visit.

Statistical methods:

Based on the results of the previously conducted BE trial, a within-subject Coefficient of Variation (CV) for $AUC_{0\rightarrow t}$ and C_{max} has been calculated. In previous studies, GIR formulation has shown relatively low intra-individual CV. With 20 evaluable subjects in the fasting and 12 subjects in the fed group will provide at least 90% power and 99.7% power to show BE in the fasting group and in the fed group respectively, resulting in nearly 90% power to get both. For a compensation of possible drop-outs, a total of 26 subjects will be included in the fasting group and 18 subjects in the fed group, corresponding to a drop-out rate of around 25%. In total, 44 subjects should be included in the trial.

Primary Endpoint analysis

The analysis of Primary Endpoints will be based on PK Population The primary variable, C_{max} and $AUC_{0\rightarrow t}$ in 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. Subject within sequence will be included as random effect. Bioequivalence will be assessed separately, in the fed and in the fasted group, and the trial 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%.

Secondary Endpoint analysis

For t_{max}, the Hodges-Lehmann estimates 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. Summaries using descriptive analyses will be applied for the remaining PK parameters.

For safety endpoints, all data recorded during the trial will be presented in individual data listings performed on the Safety Population. All safety variables will be analyzed using descriptive statistics. 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.

Blood pressures, pulse rate measurements and ECG recordings will be individually listed by treatment, subject 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, period, and time point on observed values. Urinalysis will be summarized in frequency tables.

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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[c] medications	X	X								
Laboratory tests including blood test and urinalysis	X	X							X	X
Pregnancy test[d] (females 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; TP = Treponema pallidum

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

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

c. Prior medications within 30 days before the date of first signature of informed consent will be collected at screening visit. Medications administered before first IMP dosing 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. Refer to Table 8 for detail schedule of sampling during inpatient at research center. There will be an extra PK sampling for subjects with premature withdrawal; for subjects 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 subject has rested comfortably for at least 5 minutes(The blood pressure normal range is considered ≥ 90 mmHg and ≤ 139 mmHg for SBP; ≥ 60 mmHg and ≤ 90 mmHg for DBP). At Day 1and Day 8: Vital signs will be repeated prior to dosing and at 4 hours postdose. Vital signs will also be assessed at Day 10.

h. Electrocardiogram (12-lead ECG, including QTc evaluation) will be performed 4 hours postdose at Day 1 and Day 8. Electrocardiogram will also be performed at Day 10 before discharge from research unit.
i. Adverse events will be collected starting from Day -1, the AEs since the date of first signature of informed consent will be recorded. The following visits will record any AEs since the last visit.
j. Subjects will be discharged on Day 10, after final sample collection and safety examinations are completed (final examination).
k. If subject has AE during trial and ongoing at discharge, the subject has to come back for the conditional follow-up visit.

2 Sponsor, Investigators, and Trial Administrative Structure

2.1 Trial Structure

The Sponsor's legal representative is Sino-American Shanghai Squibb Pharmaceuticals Ltd. (SASS). The study will be conducted by Contract research organization (PPD and PPD).

The Sponsor will supply the medication used in the trial. The investigational medicinal products (IMPs), Glucophage Immediate Release (GIR) 500 mg tablets, will be produced under Good Manufacturing Practice (GMP) conditions by SASS in China and by Merck Santé s.a.s. in Semoy (MSS) in France as test and reference IMPs respectively.

2.2 Trial Center/Country

The trial will be conducted in single center in China.

3 Background Information

3.1 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 [1]. The disease has a long asymptomatic pre-clinical phase, but complications are usually present at the time of diagnosis [2].

Type 2 diabetes mellitus (T2DM) accounts for 90 to 95% of patients with diabetes [1]. It is usually acquired secondarily and during adulthood, with a tendency to earlier onset, especially in connection with obesity, even in adolescence and childhood [3]. The T2DM is a worldwide health concern, with the global prevalence estimated to be as high as 9% amongst adults aged 18+ years [4]. 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 $\geq$ 200mg/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 [1,2,4,5].

A prospective study in T2DM patients revealed that lacking 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 [6]. The primary effectiveness of T2DM treatment therapy in present time is determined by a surrogate outcome, ie, change in HbA_{1C} [7,8]. The IDF recommends a general HbA_{1C} target of 7% [2]. 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 [9], 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 [10].

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 [11]. Metformin was established as first-line oral antidiabetic therapy in patients with T2DM by findings of the UKPDS study in 1998 and further confirmed in all internationally accepted guidelines [12,13] unless contraindicated or not tolerated.

3.2 Glucophage Immediate 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 Immediate Release (GIR) 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 Investigator's Brochure (IB) [14] for further information about the nonclinical and clinical programs of GIR and Guidance for the Investigator.

3.3 Study Rationale

A bioequivalence (BE) study is proposed to support "Generics Quality Consistency Evaluation" in China, a campaign started by Chinese health authority since 2015 with the aim to improve the overall quality of generics-manufacture pharmaceutical industry.

The aim of a clinical BE trial is to investigate the BE of GIR 500 mg tablets manufactured by SASS in China (test product) and GIR 500 mg tablets manufactured by MSS in France (as reference product) as a key demonstration of quality of the test product being equal to the reference. The clinical BE result serves also 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.

This clinical trial will be conducted in compliance with the clinical trial protocol, International Council for Harmonisation (ICH) good clinical practice (GCP), and any additional applicable regulatory requirements.

4 Trial Objectives

4.1 Primary Objectives

The primary objective of this trial is:

To assess BE between the GIR formulation manufactured in China (test IMP) and that manufactured in France (reference IMP) following single oral dose administrations under fasting and fed conditions.

4.2 Secondary Objectives

The secondary objectives of this trial are:

1. To compare additional pharmacokinetic (PK) parameters of GIR after single dose administrations of test and reference products.
2. To examine the safety and tolerability of GIR after single dose administrations of test and reference products.

5 Investigational Plan

5.1 Overall Trial Design and Plan

This trial is designed as a Phase I, open-label, randomized, 2-period, 2-sequence, crossover trial to assess BE between single oral doses of GIR from different manufacturing facilities, each given concomitantly as a single dose in fasting or fed state. Subjects will be randomized to receive, in each period, either:

- 1 tablet of 500 mg test GIR (manufactured in SASS/China) or
- 1 tablet of 500 mg reference GIR (manufactured in MSS/France)
- Drug administration will be done with or without food depending on group allocation to either fed or fasted condition.

The trial has a duration for each subject of approximately 4 weeks (as shown in Table 2), including:

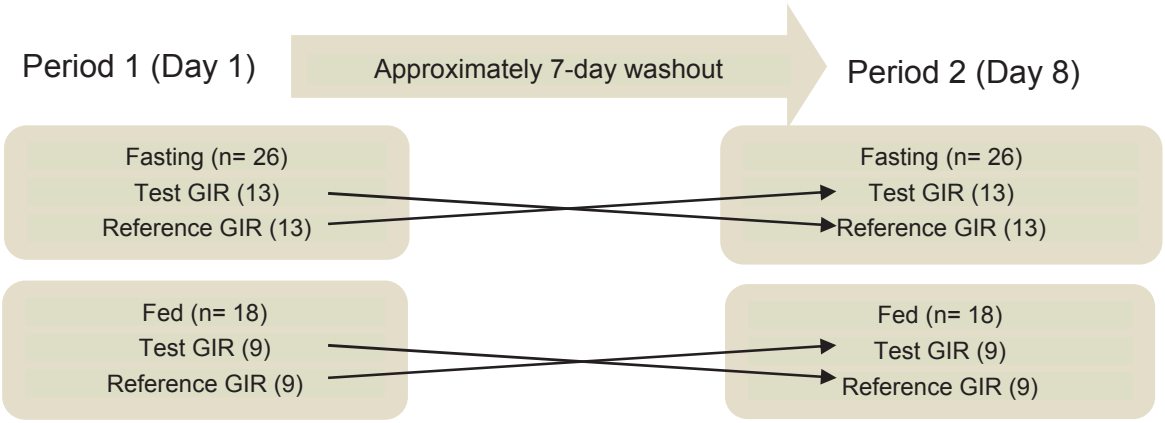
- A screening period within 2 weeks before the first GIR administration
- First dosing/sampling period up to 2 days (48 hours) after dosing
- A washout period of at least 7 days after the first GIR administration
- Second dosing/sampling period up to 2 days (48 hours) after dosing
- A conditional follow-up examination period (only for subjects who has AE during the trial and ongoing at discharge) up to 7 days following the last drug administration.

Table 2 Instruction of Trial Periods

Screening Period	Treatment Period 1	Washout Period	Treatment Period 2	Conditional follow-up visit (only for subject who has AE)
Day -14 – Day -1	Day 1 – Day 3 (inpatient)	7 days (inpatient)	Day 8 – Day 10 (inpatient)	Day 15

Given local health authority guidance and Investigator recommendation, a total of 44 healthy male or female Chinese subjects will be enrolled in the trial, with at least 7 subjects of each gender in the fasted group, and at least 5 subjects of each gender in the fed group, representing 1/4 of the total number. Subjects will be allocated to fasting vs. fed sub-group, ie, 26 subjects will be enrolled into the fasting group and 18 subjects in the fed group, respectively (Figure 1). The sample size provides sufficient power to demonstrate BE. Each subject will be administered both the test and reference products in this 2 × 2 crossover BE trial to minimize the effect of the individual difference and periodic difference of the testing results.

Figure 1 Schematic Chart of Trial Design



GIR= glucophage immediate release

5.2 Discussion of Trial Design

This is a single-center, open-label, 2-way crossover design. This trial 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 trial in a crossover design, allowing for each subject to serve as his/her own control. The trial will be performed in an open-label manner, which will not influence the outcome as the primary objectives and endpoints are related to 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 26 subjects in the fasting group and 18 subjects 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). The treatment

schedule and dose of metformin has been chosen according to the standard treatment regimen applied for subjects suffering from T2DM. In China, the recommended daily dose prescribed for metformin is 2000 mg, whereas the average daily dose is approximately 1500 mg. There are 3 selections of strength for GIR tablets, 500, 850 and 1000 mg. Base on ethical consideration for the trial will be conducted on healthy subjects, and that the 500 mg GIR tablet is a commonly prescribed dose strength in China, the GIR 500 mg tablet is selected for this trial.

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

5.3.1 Inclusion Criteria

Subjects meeting all of the following criteria will be considered for enrollment in the trial:

1. Subject has given written informed consent before any trial-related activities
2. Gender: Chinese male and female (at least 1/4 of each gender per trial group)
3. Age: between 18 and 55 years, inclusive
4. Weight: 50 to 80 kg; BMI: 18 to 30 kg/m^2
5. Nonsmoker since at least 3 months
6. Good physical and mental health status, determined on the basis of the medical history and a physical examination
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. Vital signs (blood pressure, pulse, body temperature, and respiration) in sitting position within the normal range or showing no clinically relevant deviation as judged by the Investigator (The blood pressure normal range is considered ≥ 90 mmHg and ≤ 139 mmHg for systolic blood pressure [SBP]; ≥ 60 mmHg and ≤ 90 mmHg for diastolic blood pressure [DBP])
10. All women of childbearing potential (WOCBP) are not nursing, are not pregnant, and are using highly effective methods of birth control (defined as those, alone or in combination, that result in a low failure rate [ie, less than 1 percent per year] when used consistently and correctly) for a period of at least 1 month before and after last dosing. Standard birth control methods are considered to be implanted contraceptive therapy and intrauterine devices (oral contraceptive excluded). Female subjects may also be enrolled if they are postmenopausal (ie, at least 12 consecutive months of amenorrhea after the last menstrual period) or surgically sterilized/hysterectomized at least 6 months prior to trial participation; WOCBP must have negative serum pregnancy tests at screening and on admission (Day -1) (see Appendix I for details)

11. Negative screen for alcohol and drugs of abuse (cannabis, benzodiazepines, barbiturates, opiates, cocaine, and methyl amphetamine) at screening and on admission
12. 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.

5.3.2 Exclusion Criteria

Subjects presenting with any of the following will not be included in the trial:

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 pretrial 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 trial or that could interfere with the trial 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 trial
7. Receipt of any prescription or nonprescription medication within 2 weeks before the first IMP administration, including multivitamins and herbal products (eg, St John's Wort, or traditional Chinese medicines), except paracetamol
8. Renal failure or renal dysfunction (creatinine clearance < 80 mL/min) as assessed by using the estimated measure with the Modification of Diet in Renal Disease (MDRD) equation
9. Known lack of subject compliance or inability to communicate or cooperate with the Investigator (eg, language problem and poor mental status)
10. Nonacceptance of trial high-fat breakfast (eg, vegetarians, vegans and subjects who follow special diets)
11. Consumption of large quantities of methyl xanthine-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

5.4 Criteria for Initiation of Trial Treatment

Not applicable.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Therapy

Subjects who withdraw from the trial will also be withdrawn from the IMP. A subject who drops out will not be replaced for this trial as long as the minimum sample size of evaluable subjects is met. The minimum requirement is 20 evaluable subjects in the fasting and 12 subjects in the fed group, which will provide adequate power to show BE in both groups.

5.5.2 Withdrawal from the Trial

Subjects are free to discontinue the trial at any time without giving their reasons. A subject must be withdrawn in the event of withdrawal of the subject's consent. Furthermore, participation in this clinical trial can be discontinued by the Investigator for one of the following reasons:

1. Adverse events(AEs), as assessed by the Investigator to affect the subject safety or the outcome of the trial endpoints
2. Significant protocol violation such as noncompliance with restrictions regarding alcohol and drug use, and nonadherence to the fasting or fed conditions
3. Difficulties with blood collection
4. Emesis experienced within 4 hours following drug administration because of possibly incomplete absorption (this period of time corresponds also to 2 times the median time of maximum plasma concentration [t_{max}] of GIR). Subjects experiencing vomiting later than 4 hours postdose will not be withdrawn unless otherwise decided by the Investigator in light of subject's safety or trial integrity
5. Subject is uncooperative during the trial
6. Use of any ongoing or concomitant medication that is prohibited

Concomitant medication of any drug except pain relief medication (paracetamol) is prohibited, the administration of paracetamol should not exceed 1 g per day and not more than 3 consecutive days. Details of reasons for premature withdrawal of subjects will be recorded and documented in the final report.

5.6 Premature Termination of the Trial

This trial is to be conducted in healthy subjects using products in which the safety profile is well known and also proven in the population with the target disease. The conduct of this trial 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 6.13).

In addition, the clinical trial 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 GIR. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of GIR or withdrawal of GIR 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 trial in accordance with applicable regulations.

5.7 Definition of End-of-Trial

The End-of-Trail is defined as the last contact of the last subject (Day 10 or the conditional follow-up visit/ [Day 15]/or any special day for Premature Withdrawal visit).

6 Investigational Medicinal Product and Other Drugs Used in the Trial

6.1 Description of the Investigational Medicinal Products

All IMPs will be sourced from respective manufacturer as listed below (Table 3). The IMPs manufacturing process compliant with GMP requirements. The transportation and storage are to be tracked by temperature monitor to insure the medication quality and compliance to China regulation requirements.

Table 3 Information of Investigational Medicinal Products

Drug Treatment	Test IMP	Reference IMP
Formulation:	GIR 500 mg Tablet	GIR 500 mg Tablet
Manufacturer:	SASS., China	MSS, France
Expiry Date:	Refer to the label content	Refer to the label content
Storage Condition	According to medication label	According to medication label

GIR 500 mg = Glucophage 500 mg Immediate Release; IMP = Investigational Medicinal Product; MSS = Merck Santé s.a.s. in Semoy; SASS = Sino-American Shanghai Squibb Pharmaceuticals Ltd.

6.2 Dosage and Administration

Potential trial subjects 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 trial administration (first IMP given on Day 1, Period 1).

On the evening before the dosing day in the first period, subjects will be admitted to the Clinical Research Unit (CRU) to fast prior to Day 1 dosing (administered the next morning). During the fast, subjects 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.

On Day 1 before IMP administration, ECG and vital signs will be assessed. If the subject does not meet all eligibility requirements, the subject cannot be randomized to the trial.

Eligible subjects will be randomly assigned to 1 of 2 sequences. Each subject will receive single dose GIR 500 mg (SASS/China manufactured) or single dose of GIR 500 mg (MSS/France manufactured) separated by a Washout period of 7 days.

The subjects in the fasting group will have fasted for at least 10 hours by the time of predose blood sample collected after 07:00 on Day 1.

For the fed group, subjects will consume a standard breakfast around 30 minutes before dosing, the breakfast should be finished by 10 minutes before dosing and subjects should have predose blood sample collected. The single dose of trial drug administration will occur 10 minutes after blood collection around 07:00 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 [16].

6.3 Assignment to Treatment Groups

Each eligible subject will receive his allocated treatment according to a computer-generated randomization schedule (Table 4).

Sequence A to B:

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

Sequence B to A:

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

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

Table 4 Assignment to Administration Sequences

	Day 1 of Period 1	Day 1 of Period 2
Sequence A to B	GIR 500 mg (SASS/China manufactured) (Test IMP)	GIR 500 mg (MSS/France manufactured) (Reference IMP)
Sequence B to A	GIR 500 mg (MSS/France manufactured) (Reference IMP)	GIR 500 mg (SASS/China manufactured) (Test IMP)

GIR = Glucophage Immediate Release; IMP = Investigational Medicinal Product; MSS = Merck Santé s.a.s. in Semoy; SASS = Sino-American Shanghai Squibb Pharmaceuticals Ltd.

This 2 × 2 crossover design for comparison of 2 treatments complies with the Chinese guideline for BE trials [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.

6.4 Noninvestigational Medicinal Products to be Used

No other drugs are required by the protocol.

6.5 Concomitant Medications and Therapies

Concurrent administration of any medication including herbal medications and traditional Chinese medicines are prohibited during the trial (except paracetamol, see Section 6.5.1).

Any additional concomitant therapy that becomes necessary during the trial must be recorded in the corresponding section of the eCRF noting the name, dose, duration and indication of each drug. Upon use of any prohibited concomitant medication the subject shall then discontinue his/her participation in the trial treatment and be withdrawn from trial as described in Section 5.5.2.

Medications administered between dates of informed consent form (ICF) signed to first IMP dosing (Day 1) will be recognized as prior medication and used for eligibility check. After IMP dosing, any medication will be recorded as concomitant medication. The medication taken, if any, shall be documented in the eCRF stating the international nonproprietary name and trade name of the medication, its dose, duration, galenic form, route of administration, date and time of all administrations and indication. The data recorded up to the time at which the subject in question was withdrawn shall be taken for the evaluation of the trial substance's safety and tolerability.

6.5.1 Permitted Medicines

No concomitant medication except pain relief medication (paracetamol) is allowed during the trial. The administration of paracetamol should not exceed 1 g per day and not more than 3 consecutive days, and should be documented in eCRF.

6.5.2 Prohibited Medicines

Concurrent administration of any medication except paracetamol is prohibited during the trial.

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

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

6.5.3 Other Interventions

Not applicable.

6.5.4 Special Precautions

6.5.4.1 Alcohol Prohibition

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

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

6.5.4.2 Smoking Prohibition

Smoking is included as an exclusion criterion barring eligibility into the trial and smoking is also prohibited during the trial.

6.5.4.3 Food Restriction

Fluids

Subjects are not allowed to excessively consume beverages containing xanthine derivate (> 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. Subjects 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

Subjects included in the fed group must agree to consume the trial 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 trial center. During the hospitalization periods, subjects will receive breakfast, lunch, and dinner at regular times (as applicable).

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

All subjects 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 subjects. The subjects should drink approximately 2 L of water during the first 24 hours after each drug administration.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

Not applicable.

6.6 Packaging and Labeling of the Investigational Medicinal Product

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and to be GMP compliance, so that it shall be possible to retrace the composition and pharmaceutical quality.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

All IMP treatment boxes supplied to the trial center must be stored carefully, safely, and separately from other drugs. The handling and storage of IMPs should follow the regulatory requirements from authorities. Sponsor must provide trial center enough drugs, including subject treatment and in additional at least 5 times full testing sample size for any requested testing in the inspection in the future. In terms of study IMP as well as reference IMP, the subject treatment using part and the extra 5 times of full testing samples will be from one identical batch and to be labeled equally without any difference to fulfill the randomized treatment IMPs/retention sample selection requirement at trial center. This requirement is appropriate for both study drugs and reference drugs.

Trial medication must not be used for any purpose other than the trial. The administration of trial medication to subjects who have not been enrolled into the trial is not covered by the subject's trial insurance.

Upon receipt of trial treatment boxes at the trial center, the following must be performed by the trial staff:

- Check and insure the IMPs shipment period is under the controlled temperature by referring the temperature logger data.

The Investigator (or the pharmacist or another person who is designated by the Investigator) will maintain the following records for the trial medication:

- Inventory at the center
- Administration to each subject
- Destruction of unused medication.

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

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

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

The drugs for the subjects must be random drawing from all the study drugs and reference drugs provided by the 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 occurred during the trial center storage should report to CRA immediately. The responsible CRA report it to Merck immediately as well to collect Merck written decision to use or block the impacted IMPs.

6.8 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring accountability for IMPs, including reconciliation of drugs and maintenance of drug records. The details are:

- Upon receipt of IMP, the Investigator (or designee) will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained for the Investigator File
- The dispensing of the IMP will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Sponsor Monitor at each monitoring visit
- The IMP accountability records will include:
    - Confirmation of IMP receipt, in good condition and in the defined temperature range
    - The inventory of IMP provided for the clinical trial and prepared at the site
    - The use of each dose by each subject
    - The disposition (including return, if applicable) of any unused IMP
    - Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMP prepared at the site), and the individual subject trial numbers.
- The Investigator should maintain records that adequately document:
    - That the subjects were provided the doses specified by the clinical trial protocol/amendment(s), and
    - That all IMP provided by the Sponsor was fully reconciled.

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

6.9 Assessment of Investigational Medicinal Product Compliance

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

Investigational medicinal product administration and any reason for noncompliance should be recorded in the eCRF.

6.10 Blinding

Not applicable as this is an open-label trial.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

This is a trial where GIR (test or reference) will be administered once per period by the Investigator/Clinical Trial Coordinator. Therefore, the risk of overdose will be 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.

6.13 Medical Care of Subjects after End-of-Trial

After a subject has completed the trial and has AE during the trial and ongoing at discharge or has withdrawn prematurely, a conditional follow-up visit (Day 15, if subject completed the trial on Day 10, or any specific day for premature withdrawal) will be conducted and safety assessments will be performed.

Upon the careful screening for healthy subjects such as detailed in the eligibility criteria for this trial, no serious AEs related to study treatment are expected during this trial. 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.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

The schedule of assessments will include:

- Screening (determining eligibility to the trial, including assessments during admission to CRU; Day -14 to Day -2)
- Admission to the CRU before Period 1 (Day -1)
- Period 1 (Day 1 to Day 3)
- Washout Period
- Period 2 (Day 8 to Day 10 Discharge Day)
- Conditional follow-up (Day 15) only for subject who has AE during the trial and ongoing at discharge (Table 1).

Subject will participate in the clinical trial on an inpatient basis during Day -1 to Day 10.

The description of these trial intervals are as follow.

7.1.1 Screening (Day -14 to Day -2)

The following assessments will be conducted during screening (between Day -14 and Day -2) to determine eligibility of the subject for randomization to the trial.

Informed Consent

Prior to performing any trial assessments, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent according to the procedure described in Section 9.2. The ICF will be signed by the subject prior to the subject's inclusion into the trial.

Inclusion/exclusion Criteria

Potential trial subjects will be examined at screening to determine their eligibility for clinical trial participation. The inclusion and exclusion criteria will be reviewed to determine eligibility for the trial while collecting the necessary information. All screening assessments are to be conducted within 14 days before the first trial administration (first IMP given on Day 1, Period 1). Renal failure will be assessed by using the estimated measure with MDRD equation [17].

Demographic Information

Demographic information will consist of data collected for date of birth, sex, race (Chinese, non-Chinese), height and weight. The BMI (kg/m^2) will be calculated.

Other Baseline Information

Other Baseline information will include inquiry for the history of alcohol and nicotine consumption plus the Baseline assessments described in more detail below: physical examination, vital signs, ECG recordings, medical history, and laboratory tests.

Medical history will include screening for past illnesses associated with allergic disorders; eyes, ears, nose, and throat; and past illnesses describing the cardiac, vascular, pulmonary, musculoskeletal, gastrointestinal, genitourinary, neurological, endocrine, psychiatric, dermatological, hematological systems of the body, and previous treatments.

Prior medications within 30 days before the date of first signature of informed consent will be collected.

Physical Examination

A detailed physical examination will be performed. This examination includes assessments of the general appearance, skin and mucosa, superficial lymph nodes, head and neck, chest, abdomen, musculoskeletal, and neurological systems.

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 subject has rested comfortably for at least 5 minutes.

Electrocardiogram Recording

A 12-lead ECG (including QTc evaluation) will be performed. Results of the ECG recordings will be included in the subject's eCRF. Printouts for each ECG will include date, time, initials of the technician/nurse, and initials of the Investigator who reviewed the printout. (see Section 7.4.4 for specific ECG determinations and procedures).

Chest X-ray

A chest X-ray imaging will be performed to check for any clinical significant abnormalities.

Laboratory Tests

Laboratory tests include blood tests and urinalysis. Parameters of hematology assessments are tabulated in Table 5 and Table 6, biochemistry assessment parameters are tabulated in Table 7. All laboratory test sample should be collected under fasted condition if possible. There will also be serum pregnancy test for WOCBP.

Table 5 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 6 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 7 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 (eg, cannabis, benzodiazepines, barbiturates, opiates, cocaine, and methyl amphetamine).

Breath test of alcohol

Concentration of alcohol in breath will be tested.

Urine nicotine

Concentration of nicotine in urine will be tested.

7.1.2 Admission to Clinical Research Unit (Day -1)

In the evening before the dosing day, subjects will be admitted in an inpatient status to the CRU at least 12 hours prior to Day 1 dosing for an overnight fast. Subjects will refrain from all food and drinks except water from the evening after dinner of Day -1. They will have fasted for at least 10 hours by the time of drug administration (fasting group) or standard breakfast (fed group) next morning.

Trial eligibility assessments will be performed including: physical examination, vital signs, ECG, laboratory tests, and prior medications since screening visit, treatments and diseases (medical

history) as well as testing for alcohol and drug abuse. Female subjects with childbearing potential will have a serum pregnancy test.

If the subject is determined to be ineligible for the trial due to any of the above assessments, the subject will be considered a screening failure and will not continue to randomization to the trial.

Adverse events will be collected and recorded on the eCRF, AEs since the date of first signature of informed consent will be recorded.

Randomization

Eligible subjects will then be randomly assigned to 1 of 2 sequences (Table 4).

7.1.3 Period 1 (Day 1 administration to 48 hours post administration)

Day 1, IMP Administration

On Day 1, the following assessments will be conducted and/or collected and recorded on the eCRF.

Trial Eligibility Assessments

Subjects will be assessed for vital signs (blood pressure, pulse rate, temperature and respiration). Blood pressure assessments determine eligibility to be randomized to the trial. The blood pressure (measured in sitting position after at least 5 minutes rest) normal range is considered ≥ 90 mmHg and ≤ 139 mmHg for SBP; ≥ 60 mmHg and ≤ 90 mmHg for DBP.

Any concomitant medications, diseases and treatments should be documented. Concurrent administration of any medication will be prohibited during the trial (Section 6.5.2).

If the subject is determined to be ineligible for any of the above assessments, the subject will not receive randomized treatment.

Any AEs and serious adverse events (SAEs) should also be recorded.

Baseline Sampling

Eligible subjects will have their Baseline blood sample collected at 10 minutes before GIR administration in Period 1 for both the fasting and fed group subjects.

Administration of IMP

As per randomization, each subject will receive a single dose of test GIR (Sequence A-B) or reference GIR (Sequence B-A) accordingly.

The single dose of GIR administration will occur after 07:00 in the morning of the first day of each period. A total volume of 240 mL water will be consumed with the medication. Following the administration of the drug, hands and mouth will be checked in order to

confirm the consumption of the medication. All subjects will refrain from drinking water during the first 2 hour after drug administration and 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 inpatient period for all subjects. The subjects should drink approximately 2 L of water during the first 24 hours after drug administration.

Fasting condition and Meal Information Recording

The subjects will have their meals at the research unit on Day 1. The fasting condition; time of breakfast uptake and corresponding time to IMP administration; the scheduled time and exact time of lunch and dinner, will be recorded.

Blood Sampling (Postdose)

Blood samples for the determination of metformin (active ingredient of GIR) will be taken at the specified times (Table 8). The complete schedule for each trial period is presented in the table. The clock time of all blood draws will be recorded and reported for each subject in the eCRF. The actual sampling times, if available, will always be used for calculation.

Pharmacokinetic Sampling procedure

For plasma metformin detection, 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. 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. Plasma samples will be prepared, divided into 2 aliquots and stored at maximum (max) -20°C. Plasma concentration of metformin will be analyzed by validated bioanalytical method.

Table 8 Sampling Collection Schedule

Trial Day	Period Day	Time of Blood Sample (hour)	Window Allowance (minute)
1	1 – Predose in Period 1	Baseline blood draw (10 minutes prior to drug administration)	±2
1	1 – Single dose administration and Washout begins	0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14	±2
2	2	24, 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 and Washout begins	0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14	±2
9	2	24, 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 2000g) or otherwise should be kept in an ice water bath pending processing. There will be an extra PK sampling for subjects who has premature withdrawal. For subjects having conditional follow-up visit for safety, no PK sampling is required.

Safety Monitoring

Vital signs will be repeated prior to dosing and at 4 hours postdose.

A 12-lead ECG (including QTc evaluation) will be performed 4 hours postdose.

Any concomitant diseases and treatments should be documented. Any AEs and SAEs should also be recorded. Concurrent administration of any medication will be prohibited during the trial.

Day 2 to Day 3, Period 1

Pharmacokinetic Blood Sampling (Postdose, continued)

During the 2 days following Day 1, blood samples will be taken according to the trial schedule (Table 8). On Day 2, sampling will be conducted at 24 and 36 hours; on Day 3, sampling will be conducted at 48 hours after GIR administration.

Safety Monitoring

Any concomitant diseases and treatments have to be documented. Concurrent administration of any medication will be prohibited during the trial. Any AEs and SAEs should also be recorded. Physical examination will be performed on Day 3.

7.1.4 Washout Period

The 2 administrations of IMP are separated by a Washout of 7 days (inpatient). Washout begins postdose on Day 1 and continues for approximately 7 days.

7.1.5 Day 7

Subjects 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.

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

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

Any AEs will be collected and recorded on the eCRF.

7.1.6 Period 2 (Day 8 administration to 48 hours post administration)

Day 8, IMP Administration

Procedures outlined on Day 1 in Period 1 will be repeated on Day 8 for continuing trial eligibility into Period 2.

Baseline Sampling

Eligible subjects will have their Baseline blood sample collected 10 minutes before IMP administration in Period 2.

Administration of IMP

Each subject will receive the IMP according to the randomization plan (sequence of test and reference GIR).

The single dose of GIR administration will occur after 07:00 in the morning of Day 8 following the procedures described for Day 1 in Section 7.1.3.

Pharmacokinetic Blood Sampling (Postdose)

Blood samples for the determination of plasma metformin will be taken at the specified times: as shown in Table 8.

Safety Monitoring

Any AEs and SAEs are also to be recorded. Any concomitant diseases and treatments have to be documented.

Vital signs will be taken prior to dosing and also at 4 hours postdose.

A 12-lead ECG (including QTc evaluation) will be performed 4 hours postdose.

Day 9 to Day 10

Pharmacokinetic Blood Sampling (Postdose, continued)

Blood samples for the determination of GIR will be taken at the specified times (Table 8).

On Day 9, sampling will be conducted at 24 and 36 hours; on Day 10, sampling will be conducted at 48 hours after GIR administration. The subject is allowed to leave the CRU on Day 10 after the morning blood sampling (48 hours sample).

Safety Monitoring

Any AEs and SAEs are also to be recorded. Any concomitant diseases and treatments have to be documented. Any AEs and SAEs are also to be recorded.

Vital signs will be assessed at Day 10.

A 12-lead ECG (including QTc evaluation) will be performed at Day 10 before discharge.

At the day of discharge (Day 10), physical examination will be performed. A blood sample for determination of hematology and biochemistry will be taken and a urinalysis will be performed. These investigations on the day of discharge represent the final examination.

On the morning of Day 10 in the clinic after the morning blood sampling collection (48-hours sample), the Investigator will decide whether or not the subject needs to stay for any additional time in the clinic. If there are no safety concerns based on the assessment by the Investigator, the subject will be allowed to leave the clinic.

7.1.7 Conditional follow-up (Day 15)/Premature Withdrawal

Conditional follow-up visit (only for subject with AE during the trial and ongoing at discharge)

At conditional follow-up (Day 15) the assessments include: physical examination, vital signs, ECG, laboratory tests (hematology, biochemistry, and urinalysis), and AEs will be assessed. Any concomitant treatments have to be documented. The case conclusion has to be filled in for every subject who has received at least one dose of the IMPs.

If AEs or pathological findings, ie, clinically relevant deviations from Baseline findings are obtained during the final examination, these findings 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.

Premature Withdrawal

The assessments at Premature Withdrawal visit include: physical examination, vital signs, ECG, laboratory tests (hematology, biochemistry, and urinalysis), AEs, and concomitant treatments (Table 1). The case conclusion has to be filled in for every subject who has received at least one dose of the IMPs.

If AEs or pathological findings, ie, clinically relevant deviations from Baseline findings are obtained during the final examination, these findings 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.

Pharmacokinetic Blood Sampling

Blood samples for the determination of GIR will be taken (Table 8).

7.1.8 Estimated Blood Sample Volumes per Subject

The blood sample volumes of each subject are estimated in Table 9.

Table 9 Estimated Blood Sample Volumes per Subject

Time Points	Evaluation Indexes	Total Blood Volume (mL)
Screening	Serum virology	4
	Hematology	2
	Biochemistry	4
	Serum Pregnancy Test (if applicable)	4
	Approximate Total	***14 (10 for male)***
Period 1	Hematology	2
	Biochemistry	4
	Serum Pregnancy Test (if applicable)	4
	Pharmacokinetics	3*17
	Approximate Total	***61 (57 for male)***
Period 2	Hematology	2
	Biochemistry	4
	Pharmacokinetics	3*17
	Approximate Total	***57***
Conditional follow-up Or Premature Withdrawal	Hematology	2
	Biochemistry	4
	Approximate Total	***6***

	Pharmacokinetics (only for premature withdrawal)	*3*
Approximate Total of Each Subject		***132(124 for male)*** ***With conditional follow-up:*** ***138 (130 for male)***

7.2 Demographic and Other Baseline Characteristics

At screening, the following demographic data will be collected: date of birth, sex, race, and height and weight. The BMI (kg/m^2) will be calculated.

7.3 Efficacy Assessments

Not applicable.

7.4 Assessment of Safety

The safety profile of GIR (test or reference) will be assessed through the recording, reporting and analyzing of baseline medical conditions, physical examination findings, vital signs (blood pressure, pulse rate, temperature and respiration), ECG, laboratory tests, and AEs.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's signature of informed consent. Trial site personnel will report any AE, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2).

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

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

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

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

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

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

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

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

Investigators must also systematically assess the causal relationship of AEs to 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, trial procedures.

Unrelated: Not reasonably related to the IMP. AE could not medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial 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 trial protocol.

Adverse Drug Reaction

In accordance with GCP, adverse drug reaction (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 (eg, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (eg, anemia, 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. (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity

- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (eg, 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 (eg, undesirable effects of any administered treatment) must be documented and reported as SAEs.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his condition. During the reporting period of the trial any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject 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 nonserious ADRs must be additionally documented and reported using an SAE Report Form as described in Section 7.4.1.4.

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 subject
2. Date/time of onset (only in relation to administration of IMP: before, during, or after)
3. Severity Grade (Section 7.4.1.1), 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 trial 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 trial 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.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues through the trial's post treatment period. The complete trial 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 trial 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 subject has AE during the trial and ongoing at discharge). In case of early termination, AEs until Premature Withdrawal visit will be collected.

Any SAE assessed as related to the IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

7.4.1.4 Procedure for Reporting Serious Adverse Events and Nonserious Adverse Drug Reactions

In the event of any SAE and nonserious ADR 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: PPD

Facsimile: PPD PPD

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 subject 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 (eg, 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.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

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 subjects to the IEC/IRB that approved the trial.

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

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

7.4.1.6 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of the clinical trial and is considered to be related to the IMP must be monitored and followed up until the outcome is known, unless the subject is documented as "lost to follow-up." Reasonable attempts to obtain this information must be made and documented. It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (eg, 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 7.4.1.3 must

be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. 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 Section 7.4.1.4.

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

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 subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

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

7.4.3 Clinical Laboratory Assessments

Safety and tolerability will be assessed by monitoring 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 trial will additionally be forwarded to the Sponsor.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Safety and tolerability will also be assessed by monitoring of vital signs, physical examinations and ECG as described in the following.

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 subject has rested comfortably for at least 5 minutes.

Physical examination

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

Electrocardiogram

A 12-lead ECG (including QTc evaluation) will be performed.

After the subject 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-V6 and all 12-leads recorded. At least 2 to 3 beats will be monitored at a speed of 25 mm/sec 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 (ie, a medical physician). Results of the ECG recordings will be included in the subject's eCRF.

The following parameters will be assessed:

- RR-Interval [ms]
- PR-Interval [ms]
- QRS-Duration [ms]
- QT-Interval [ms]
- QTc (Bazett) [ms]
- QTcF (Fridericia) [ms]
- Heart Rate [beats per minute]
- Rhythm (sinusal - other).

QT/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 ICH guidance E1.

7.5 Pharmacokinetics

For detection of metformin, the major active ingredient of GIR, blood samples will be collected as described in Section 7.1.

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

- at pre-dose (Baseline) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, 24, 36, and 48 hours after dosing.
- One sample will be collected at Premature Withdrawal if applicable.

The PK collection time is based on known single dose PK profiles of the immediate 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 max -20°C.

Subjects 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 subject in the eCRF. The actual sampling times, if available, will always be used for calculation.

The following PK parameters will be calculated from plasma concentrations of metformin by applying noncompartmental 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_{ss}/f	apparent volume of distribution at steady-state after extravascular administration

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

7.6 Biomarkers

Not applicable.

7.7 Other Assessments

Not applicable.

8 Statistics

8.1 Sample Size

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

Based on the results of previously conducted BE trial PK data, (Iran BE 2013 [fasted] and EML056023-H105 [fed]) [18,19], Glucophage/metformin IR formulation has shown relatively low intraindividual Coefficient of Variation (CV), as shown below (Table 10 and Table 11).

IRAN BE-2013

- Test: Single dose of metformin IR 500 mg tablets manufactured by PPD [redacted] (Iran) under fast condition
- Reference: Single dose of metformin IR 500 mg tablets manufactured by Merck (Darmstadt) under fast condition

Table 10 Results from IRAN Bioequivalence Study-2013 Fasting (n= 21)

Parameter	Intra-Subject CV (%)	Geometric Mean		Ratio[a] (%)	90% Confidence Limits[a] (%)	
		Test	Reference		Lower	Upper
C_{max}	17.5	1404.5	1425.5	102	92.14	110.95
$AUC_{0\rightarrow t}$	13.8	7946.5	8049.5	100	92.72	107.37

$AUC_{0\rightarrow t}$ = area under the plasma concentration-time curve from time 0 to time t; Cmax = the maximum plasma concentration observed; CV = Coefficient of Variation.
[a] Results from ANOVA Model

CCI [redacted]

As shown in Table 12 and Table 13, if applying these CVs together with applicable BE criteria for $AUC_{0\rightarrow t}$ and C_{max} [0.80 – 1.25], CCI [redacted]

CCI [redacted] In total, 44 subjects should be included in the trial.

Table 12 Sample size and power – Assuming Coefficient of Variation = 17.5% for C_{max} and 13.8% for $AUC_{0\rightarrow t}$ (Iran BE 2013 Fasting) and assume 5% variation for all ratios (95% to 105%)

Fasted Condition			
	Power (%)		
Sample Size	C_{max}	$AUC_{0\rightarrow t}$	Joint Power
18	88.2	97.4	> 85.9
20	**91.3**	**98.4**	**> 89.9**
22	93.6	99.0	> 92.7

$AUC_{0\rightarrow t}$ = area under the plasma concentration-time curve from time 0 to time t; Cmax = the maximum plasma concentration observed.

CCI [redacted]

8.2 Randomization

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

A total of 44 eligible healthy male and female Chinese subjects (26 in fasting state and 18 in fed state, Table 14) who meet the eligibility criteria will be randomized (with at least 7 subjects of each gender in the fasted group, and at least 5 subjects of each gender in the fed group, representing 1/4 of the total number within each group) on Day 1, in a 1:1 ratio to 1 of 2 treatment sequences: Sequence A-B or Sequence B-A as presented in Table 4.

In sequence A-B, subjects will receive test GIR tablets (Treatment A) in Period 1 and reference GIR tablets (Treatment B) in Period 2. In sequence B-A, subjects will receive reference GIR tablets in Period 1 and test GIR tablets in Period 2 after Washout.

Table 14 Randomization Allocation

	Day 1 of Period 1	Day 1 of Period 2
Fasting group (n= 26)	Treatment A (n= 13)	Treatment B (n= 13)
	Treatment B (n= 13)	Treatment A (n= 13)
Fed group (n= 18)	Treatment A (n= 9)	Treatment B (n= 9)
	Treatment B (n= 9)	Treatment A (n= 9)

Subjects will only be replaced if the number of subjects within each group falls below 20 (fasting) or 12 (fed). The subject who is replacing a discontinued subject will then be allocated to the treatment sequence of the subject who discontinued.

8.3 Endpoints

8.3.1 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.

8.3.2 Secondary Endpoints

The Secondary Endpoints are the following PK parameters determined from plasma concentrations of metformin

- t_{max}
- $t_{1/2}$
- $AUC_{0\rightarrow\infty}$
- AUC_{extra}
- λ_z
- CL/f
- V_{ss}/f

All PK parameters (Primary Endpoints and Secondary Endpoints) will be calculated from plasma concentrations of metformin by applying noncompartmental analysis methods according to respective Standard Operating Procedures (SOPs).

8.3.3 Safety Endpoints

Safety and tolerability will be assessed by monitoring of:

- Assessment of general safety and tolerability

- Adverse Events
- Vital signs (blood pressure, pulse rate, temperature and respiration)
- Biochemistry, hematology, and urinalysis
- Computerized 12-lead ECG recordings (including QTc evaluation)
- Physical examination.

8.4 Analysis Sets

Safety Population

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

Pharmacokinetic Population

The PK parameters will be analyzed based on PK population. The PK population may include all subjects who completed the trial with adequate trial medication compliance, without any relevant protocol deviations with respect to factors likely to affect the comparability of PK results, and with sufficient evaluable data to determine Primary Endpoints (AUC_{0-t} and C_{max}) for both treatments in both groups. If subjects would receive concomitant medication for the treatment of an AE, their inclusion in the PK population will be decided on case-by-case basis.

8.5 Description of Statistical Analyses

8.5.1 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 trial will be presented in individual data listings performed on the Safety Population. All data will be evaluated as observed values; no imputation method for missing values will be used. Methods for concentration data below the lower limit of quantification will be described in the statistical analysis plan. The consideration of covariates in the mixed effect model is not planned.

8.5.2 Analysis of Primary Endpoints

The null and alternative hypotheses are the following:

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

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

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

The analysis of Primary Endpoints will be based on PK Population (Section 8.4)

The primary variable, C_{max} and $AUC_{0\rightarrow t}$ in 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. Subject within sequence will be included as random effect. Bioequivalence will be assessed separately, in the fed and in the fasted group, and the trial 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% Confidence Interval on the ratios between test and reference of the geometric means fall within 80.00% to 125.00%.

8.5.3 Analysis of Secondary Endpoints

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.

Summaries using descriptive analyses for the remaining PK parameters and the safety variables will be performed as described in Section 8.5.4.

8.5.4 Analysis of Safety and Other Endpoints

All data recorded during the trial 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.

Blood pressures, pulse rate measurements and ECG recordings will be individually listed by treatment, subject 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, period, and time point 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 trial will be listed by treatment and subject number.

The AE listings will include the following items:

- System organ class
- Preferred term
- Investigator's description
- Whether the event is treatment-emergent
- Trial treatment at onset of event
- Date and time of onset and resolution
- Duration of the event
- Date and time of last administration before AE
- 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 subjects 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, subject, 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 subjects not in the PK population will be annotated and listed together with the data of the other subjects, 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 subjects simultaneously) and by subject (showing all treatments simultaneously).

Handling of discontinued subjects and missing data

The first 6 (fasting) or 4 (fed) discontinued subjects of each group will not be replaced. Subjects will only be replaced if the number of subjects within each group falls below 20 (fasting) or 12 (fed). The subject who is replacing a discontinued subject will then be allocated to the treatment sequence of the subject who discontinued.

8.6 Interim and Additional Planned Analyses

Not applicable

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at his/her site. The Investigator will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on GCP (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the Investigator must ensure that only subjects who have given their informed consent are included into the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on GCP (ICH Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject verbally of all

pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Depending on national regulations, a person other than the Investigator may inform the subject and sign the ICF, as above.

Where the information is provided by the Investigator, the ICF must be signed and personally dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The Investigator will explain the changes to the previous version.

9.3 Subject Identification and Privacy

Immediately after informed consent has been obtained, a unique subject number will be assigned to each subject at inclusion into the trial. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

The subject's data collected during the trial will be stored under this number. Only the Investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial.

Clinical trial Investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose and to answer any questions. Any subsequent action will follow the standard processes established for the Investigators.

The Sponsor will provide the appropriate information to contact a physician. This includes the provision of a 24 hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for each subject participating to the trial. Insurance conditions will meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with the ICF to the responsible IEC/IRB for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File by the Sponsor.

The trial must not start before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes (Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (eg, Investigational Medicinal Product Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

10.1 Case Report Form Handling

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee will be responsible for entering trial data in the eCRF provided by the designated Contracted Research Organization. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered into a validated database. The data management department of the designated Contracted Research Organization will be responsible for data processing, in accordance with the defined data management procedures under the supervision of the Sponsor. Database lock will occur once quality control procedure, and Quality Assurance procedures (if applicable) have been completed. Portable document format files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible:

- Subject's full name
- Date of birth
- Sex
- Height
- Weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification
- Date of subject's inclusion into the trial (ie, date of giving informed consent)
- Subject number in the trial
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All AEs observed in the subject
- Date of subject's last visit, or

- Date of premature withdrawal and reason for premature withdrawal of the subject from the trial or from IMP, if applicable.

Additionally, any other documents containing source data must be filed. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

Electronic subject files (if applicable) will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 5 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial 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.

10.6.2 Publication

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require presubmission review by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by Investigators or their representatives will require presubmission review by the Sponsor. The Sponsor is entitled to delay publication in order to obtain patent protection.

11 References

1. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014; 37 Suppl 1:S81-90.

2. International Diabetes Federation (IDF). E-Atlas of diabetes seventh edition. http://www.idf.org/diabetesatlas

3. Copeland KC, Silverstein J, Moore KR, et al. Management of newly diagnosed type 2 Diabetes Mellitus (T2DM) in children and adolescents. Pediatrics. 2013; 131(2):364-82.

4. World Health Organization (WHO). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF Consultation. 2006

5. Colagiuri S. Epidemiology of prediabetes. Med Clin North Am. 2011; 95(2):299-307, vii.

6. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000; 321(7258):405-12.

7. Stein SA, Lamos EM, Davis SN. A review of the efficacy and safety of oral antidiabetic drugs. Expert Opin Drug Saf. 2013; 12(2):153-75.

8. Singh S. Type 2 diabetes pharmacoepidemiology update 2014: safety versus efficacy. Curr Diab Rep. 2014; 14(12):563.

9. Akbari A, Clase CM, Acott P, et al. Canadian Society of Nephrology commentary on the KDIGO clinical practice guideline for CKD evaluation and management. Am J Kidney Dis. 2015; 65(2):177-205.

10. Wilke T, Groth A, Fuchs A, et al. Real life treatment of diabetes mellitus type 2 patients: an analysis based on a large sample of 394,828 German patients. Diabetes Res Clin Pract. 2014; 106(2):275-85.

11. Tran L, Zielinski A, Roach AH, et al. Pharmacologic treatment of type 2 diabetes: oral medications. Ann Pharmacother. 2015; 49(5):540-56.

12. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352(9131):854-65.

13. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009; 32(1):193-203.

14. Investigator Brochure of Glucophage Immediate Release (GIR). Version 2017.

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

16. USA Food and Drug Administration Guidance "Food-Effect Bioavailability and Fed Bioequivalence Studies". 2002.

17. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet. 2012; 379(9818):815-22.

18. Valizadeh H, Nayyeri-Maleki P, Ghanbarzadeh S, et al. Pharmacokinetics and bioequivalence of two brands of metformin 500 mg tablets in Iranian healthy volunteers. J Pharmaceutical Investigation. 2014; 44(1):61-68.

19. Clinical Study Report EML056023-H105. "Randomized, open-label, 2-way, crossover, single oral-dose, fed, bioequivalence study between 500 mg Glucophage LCM 004 and 500 mg Glucophage® in healthy subjects". 2006.

20. Lehmann, Erich L. Nonparametrics: Statistical methods based on ranks (Reprinting of 1988 revision of 1975 Holden-Day ed.). New York: Springer 2006. pp.xvi+463. ISBN978-0-387-35212-1.

12 Appendices

Appendix I: Contraceptive Guidance and Woman of Childbearing Potential

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
2. Premenarchal
3. Postmenopausal female
   - Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at screening.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraceptive Guidance

Highly Effective Contraceptive Methods That Are User Dependent Failure rate of < 1% per year when used consistently and correctly.

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • intravaginal
  • transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
• Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used).
• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. 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).
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 14 days after the last dose of study treatment

Appendix II: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Randomized, Open-label, 2-Way-Crossover Study Assessing the Bioequivalence between Single Doses of 500 mg Glucophage Immediate Release (GIR) Tablets (Sino-American Shanghai Squibb Pharmaceuticals Ltd./ Manufactured in China) and 500 mg GIR Tablets (Merck Santé s.a.s. in Semoy/ Manufactured in France) under Fed and Fasted State in Two Groups of Healthy Subjects
Clinical Trial Protocol Date/Version:	20 Nov 2017/Version 2.0

Protocol Lead:

I approve the design of the clinical trial:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	Merck Serono Co., Ltd.
Address:	25F, NUO Center Office, No. 2A Jiangtai Road, Chaoyang District, Beijing 100016, P. R. China
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Signature Page – Principal Investigator

Trial Title	A Randomized, Open-label, 2-Way-Crossover Study Assessing the Bioequivalence between Single Doses of 500 mg Glucophage Immediate Release (GIR) Tablets (Sino-American Shanghai Squibb Pharmaceuticals Ltd./ Manufactured in China) and 500 mg GIR Tablets (Merck Santé s.a.s. in Semoy/ Manufactured in France) under Fed and Fasted State in Two Groups of Healthy Subjects
Clinical Trial Protocol Date/Version	20 Nov 2017/Version 2.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial 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:	Principle Investigator
Institution:	PPD
Address:	PPD PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Signature Page – Principal Investigator

Trial Title	A Randomized, Open-label, 2-Way-Crossover Study Assessing the Bioequivalence between Single Doses of 500 mg Glucophage Immediate Release (GIR) Tablets (Sino-American Shanghai Squibb Pharmaceuticals Ltd./ Manufactured in China) and 500 mg GIR Tablets (Merck Santé s.a.s. in Semoy/ Manufactured in France) under Fed and Fasted State in Two Groups of Healthy Subjects
Clinical Trial Protocol Date/Version	20 Nov 2017/Version 2.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

PPD

Signature

Date of Signature

Name, academic degree: PPD

Function/Title: Principle Investigator

Institution: PPD

Address: PPD

Telephone number: PPD

Fax number: PPD

E-mail address: PPD

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree:	PPD
Function/Title:	Biostatistician
Institution:	Merck Serono (Beijing) Pharmaceutical R&D Co., Ltd.
Address:	Merck Serono Co., Ltd. 25F, NUO Center Office No. 2A Jiangtai Road, Chaoyang District Beijing 100016 P. R. China
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

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

Appendix III: Protocol Amendments and List of Changes

Amendment 1.0

Previous Protocol Amendments

None.

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)
1.0	Y	20 November 2017	China	Y

Rationale

The amendment of protocol version 1.0 is based on consideration from study team and study center of the feasibility of study, and additionally to simplify the study procedure in order to prevent noncompliance of subjects. The inpatient time was revised from twice to once through the study period. Instead of being hospitalized twice for each 3 days, the subjects are now staying at study center for 10 days during the study period. The demographics of subject will be adjusted to represent a population of weight that is more feasible, and also the ratio of genders are modified from 1/3 to 1/4 of total subject number. Furthermore, the blood pressure check for eligibility on Day 1 was modified to a wider range.

According to the evaluation by clinical pharmacologist, sampling time point is also adjusted.

Major Scientific Changes

The major scientific changes of this protocol amendment (Amendment No.1.0) are:

- The change of hospitalization from twice to once during the trial sampling period, subject will be hospitalized from Day -1 to Day 10
- Change descriptions regarding the inpatient period
- Revise “End-of-Trial visit” to “conditional follow-up visit, define as only for subjects who has AE during the trial and ongoing at discharge”
- Update of inclusion and exclusion criteria:
    1. Change inclusion criteria 2: proportion of subject genders from 1/3 to 1/4 of total subject number
    2. Change inclusion criteria 4: weight range from 55 – 95 kg to 50 – 80 kg
    3. Change inclusion criteria 8: revise ECG assessment result to be judged by Investigator

4. Revise inclusion criteria 9: Blood pressure normal range defined as ≥ 90 mmHg and ≤ 139 mmHg for SBP; ≥ 60 mmHg and ≤ 90 mmHg for DBP
5. Change inclusion criteria 10: reword conditions for WOCBP according to admission period change, revise all pregnancy study to be test by serum
6. Change inclusion criteria 11: revise the drug abuse list
7. Change exclusion criteria 7: revise the receipt of medication before study drug administration, remove hormonal contraceptives
8. Change exclusion criteria 12: revised wording for the time period that grapefruit, cranberry or juices of these fruits are restricted

- Update on IMP information and handling, drug accountability
- Correct the serum pregnancy test on screening
- Move randomization to Day -1
- PK sampling: remove end-of-trial sample, but keep PK sampling on Premature Withdrawal visit
- Changes on study assessments:
    1. Remove 8 hour postdose vital sign assessment on Day 1 and Day 8
    2. Remove vital sign assessments on Day 2, Day 3, Day 7 and Day 9
    3. Remove ECG on Day 3 (48 hour postdose) and Day 7
    4. Remove laboratory test on Day 3 and Day 7, recalculate blood sample requirement according to this change
    5. Remove alcohol, drug abuse test on Day 7
    6. Remove pregnancy test on Day 7 and Premature Withdrawal visit
- Recalculate sample numbers and required blood for PK and laboratory tests

Correct minor errors

Administrative and Editorial Changes

Correction of administrative (change of Investigator and manufacturer name), minor editorial changes and inconsistencies throughout the document that have been identified since the finalization of the clinical trial protocol.

Changes to the clinical trial protocol text are presented in the table below. Additions and amended text are shown in bold. If the original clinical trial protocol text was already bold, changes are shown in bold and underlined, deletions are marked using strike through.

Comparison with Clinical Trial Protocol Version 1.0, 21 July 2017

Change	Section	Page	Previous Wording	New Wording
Update the information of reference manufacturer	Title page List of abbreviation Synopsis Section 2.1 Section 6.1 Table 3 Signature page	1 8 10 17 24 67-68	Merck Santé in Semoy	Merck Santé **s.a.s.** in Semoy
Updated the information of the Principal Investigator	Title page Synopsis-Principal Investigator Signature Page-Principal Investigator	1 10 68	PPD PPD PPD.	PPD PPD
Update of protocol version and date	Title page Signature Page	1 67-68	21 Jul 2017/ Version 1.0	~~21 Jul~~**20 Nov** 2017/ Version ~~1~~**2**.0 **including amendment 1.0**
Reword secondary objective	Synopsis, Section 4.2	10 19	1. To compare pharmacokinetic (PK) parameters of GIR after single dose administrations of test and reference products.	1. To compare **additional** pharmacokinetic (PK) parameters of GIR after single dose administrations of test and reference products.
Update for methodology wording and the term of End-of-Trial examination period to conditional follow-up visit	Synopsis, Section 5.1	11 19	This trial is designed as a Phase I, open-label, randomized, 2-period, 2-sequence, crossover trial to assess BE between a single oral dose of GIR from different manufacturing facilities, each given concomitantly as a single dose in fasting or fed state. Subjects will be randomized to receive, in each period, either: • 1 tablet of 500 mg GIR (manufactured in Sino-American Shanghai Squibb Pharmaceuticals Ltd. [SASS]/China) or • 1 tablet of 500 mg GIR (manufactured in Merck Santé s.a.s. in Semoy [MSS]/ France).	This trial is designed as a Phase I, open-label, randomized, 2-period, 2-sequence, crossover trial to assess BE between ~~a~~ single oral dose**s** of GIR from different manufacturing facilities, each given concomitantly as a single dose in fasting or fed state. Subjects will be randomized to receive, in each period, either: • 1 tablet of 500 mg **test** GIR (manufactured in Sino-American Shanghai Squibb Pharmaceuticals Ltd. [SASS]/China) or • 1 tablet of 500 mg **reference** GIR (manufactured in Merck Santé s.a.s. in Semoy [MSS]/ France).

Change	Section	Page	Previous Wording	New Wording
			• Drug administration will be done with or without food depending on group allocation to either fed or fasted condition. The trial has a duration of approximately 4 weeks including: • A screening period within 2 weeks before the first GIR administration • First dosing/sampling period up to 2 days (48 hours) after dosing • A washout period of approximately 7 days after the first GIR administration • Second dosing/sampling period up to 2 days (48 hours) after dosing • An End-of-Trial examination period up to 7 days following the last drug administration.	• Drug administration will be done with or without food depending on group allocation to either fed or fasted condition. The trial has a duration **for each subject** of approximately 4 weeks including: • A screening period within 2 weeks before the first GIR administration • First dosing/sampling period up to 2 days (48 hours) after dosing • A washout period of approximately 7 days after the first GIR administration • Second dosing/sampling period up to 2 days (48 hours) after dosing • ~~An End-of-Trial examination period up to 7 days following the last drug administration~~. **A conditional follow-up examination period (only for subjects who has AE during the trial and ongoing at discharge) up to 7 days following the last GIR administration**
Updated PK section description	Synopsis	11	The plasma concentrations of metformin will be determined by a validated analytical method. Pharmacokinetic parameters (Primary and Secondary Endpoints) will be calculated according to noncompartmental analysis methods. The mixed trapezoidal rule will be used to calculate the area under the plasma concentration curve.	The plasma concentrations of metformin will be determined by a validated **LC/MS** analytical method. Pharmacokinetic parameters (Primary and Secondary Endpoints) will be calculated according to noncompartmental analysis methods. The mixed trapezoidal rule will be used to calculate the area under the plasma concentration curve.
Updated the planned proportion of gender of subjects	Synopsis Section 8.2	11 50	A total of 44 healthy male and female Chinese subjects will be enrolled in the trial, with each gender representing no less than 1/3 of the total number (also evenly allocated to fasting vs. fed group), and are statistically powered to provide adequate sample size for BE testing	A total of 44 healthy male and female Chinese subjects will be enrolled in the trial, with at least 7 subjects of each gender in the fasted group, and at least 5 subjects of each gender in the fed group, representing 1/~~3~~**4** of the total number The sample size provides sufficient power to demonstrate BE.
Updated the inclusion criterion on Description of gender proportion	Synopsis Section 5.3.1	12 21	Gender: Chinese male and female (at least 1/3 of each gender per trial group)	Gender: Chinese male and female (at least 1/~~3~~**4** of each gender per trial group)

Change	Section	Page	Previous Wording	New Wording
Updated the inclusion criterion on weight	Synopsis Section 5.3.1	12 21	Weight: 50 to 80 kg; Body mass index (BMI): 18 to 30 kg/m^2	Weight: ~~55~~**50** to ~~95~~**80** kg; Body mass index (BMI): 18 to 30 kg/m^2
Updated the inclusion criterion of ECG assessment	Synopsis Section 5.3.1	12 21	Electrocardiogram recording (12-lead ECG) without signs of clinically relevant pathology in particular QTc (Bazett) < 450 ms.	Electrocardiogram recording (12-lead ECG) without signs of clinically relevant pathology **as judged by the Investigator** ~~in particular QTc (Bazett) < 450 ms.~~
Updated the inclusion criterion of blood pressure normal range	Synopsis Section 5.3.1	12 21	Vital signs (blood pressure, pulse, body temperature, and respiration) in sitting position within the normal range or showing no clinically relevant deviation as judged by the Investigator	Vital signs (blood pressure, pulse, body temperature, and respiration) in sitting position within the normal range or showing no clinically relevant deviation as judged by the Investigator **(The blood pressure normal range is considered ≥ 90 mmHg and ≤ 139 mmHg for systolic blood pressure [SBP]; ≥ 60 mmHg and ≤ 90 mmHg for diastolic blood pressure [DBP])**
Updated and corrected the inclusion criterion on women of childbearing potential condition	Synopsis Section 5.3.1	12 21	All women of childbearing potential (WOCBP) are not nursing, are not pregnant, and are using highly effective methods of birth control (defined as those, alone or in combination, that result in a low failure rate (ie, less than 1 percent per year) when used consistently and correctly) for a period of at least 1 month before and after dosing. Standard birth control methods are considered to be implanted contraceptive therapy and intrauterine devices (oral contraceptive excluded). Female subjects may also be enrolled if they are postmenopausal (ie, at least 12 consecutive months of amenorrhea after the last menstrual period) or surgically sterilized/ hysterectomized at least 6 months prior to trial participation; WOCBP must have a negative urine pregnancy test at screening and a negative serum pregnancy test on each admission (Day -1 of each treatment period)	All women of childbearing potential (WOCBP) are not nursing, are not pregnant, and are using highly effective methods of birth control (defined as those, alone or in combination, that result in a low failure rate (ie, less than 1 percent per year) when used consistently and correctly) for a period of at least 1 month before and after **last** dosing. Standard birth control methods are considered to be implanted contraceptive therapy and intrauterine devices (oral contraceptive excluded). Female subjects may also be enrolled if they are postmenopausal (ie, at least 12 consecutive months of amenorrhea after the last menstrual period) or surgically sterilized/ hysterectomized at least 6 months prior to trial participation; WOCBP must have ~~a~~ negative ~~urine~~ **serum** pregnancy test**s** at screening and ~~a negative serum pregnancy test~~ on ~~each~~ admission (Day -1 ~~of each treatment period~~)
Updated the inclusion criterion on alcohol and drug abuse	Synopsis Section 5.3.1	12 21	Negative screen for alcohol and drugs of abuse (opiate class, barbiturates, cocaine and metabolites, amphetamines, cannabinoids, benzodiazepines and tricyclic antidepressants) at screening and on each admission	Negative screen for alcohol and drugs of abuse (~~opiate class, barbiturates, cocaine and metabolites, amphetamines, cannabinoids, benzodiazepines and tricyclic antidepressants~~ **cannabis, benzodiazepines, barbiturates, opiates, cocaine, and methyl amphetamine**) at screening and on ~~each~~ admission
Updated the exclusion criterion on receipt of medications	Synopsis Section 5.3.2	13 22	Receipt of any prescription or nonprescription medication within 2 weeks before the first IMP administration, including multivitamins and herbal products (eg, St John's Wort, or traditional Chinese medicines), except hormonal contraceptives in females and/or paracetamol	Receipt of any prescription or nonprescription medication within 2 weeks before the first IMP administration, including multivitamins and herbal products (eg, St John's Wort, or traditional Chinese medicines), except ~~hormonal contraceptives in females and/or~~ paracetamol

Change	Section	Page	Previous Wording	New Wording
Updated the exclusion criterion on receipt of medications	Synopsis Section 5.3.2	13 22	Consumption of grapefruit, cranberry or juices of these fruits, 14 days prior to drug administration.	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.**
Updated the description in planned trial and treatment duration per subject	Synopsis	13	The planned treatment consists of initial screening assessments (within 14 days prior to the first IMP administration) followed by 2 trial periods (consisting of IMP administration following 2 days of blood sampling) in a crossover trial design. Each trial period includes a single dose of IMP administration and the doses are separated by approximately a 7-day Washout period. An End-of-Trial visit (Day 15) will be conducted 7 days after administration in Period 2. The overall trial duration for each subject is approximately 4 weeks (or approximately 28 days) including the screening and End-of-Trial visit.	The planned treatment consists of initial screening assessments (within 14 days prior to the first IMP administration **on Day 1**) followed by 2 trial periods (consisting of IMP administration following 2 days of blood sampling) in a crossover trial design. Each trial period includes a single dose of IMP administration and the doses are separated by approximately a 7-day Washout period. ~~An End-of-Trial~~ **conditional follow-up** visit (Day 15) will be conducted 7 days after administration in Period 2 **(only for subjects who has AE during the trial and ongoing at discharge)**. The overall trial duration for each subject is approximately 4 weeks (or approximately 28 days) including the screening and ~~End-of-Trial~~ **conditional follow-up** visit.
Update wording of background-Diabetes Mellitus and treatment	Section 3.1	17-18	A prospective study in T2DM patients revealed that lacking 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 [6]. The primary effectiveness of T2DM treatment therapy in present time is determined by a surrogate outcome, ie, change in HbA_{1C} [7,8]. The IDF recommends a general HbA_{1C} target of 7% [2]. 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 [9], 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 [10].	A prospective study in T2DM patients revealed that lacking ~~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 [6]. The primary effectiveness of T2DM treatment therapy in present time is determined by a surrogate outcome, ie, change in HbA_{1C} [7,8]. The IDF recommends a general HbA_{1C} target of 7% [2]. 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 [9], 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 [10].

Change	Section	Page	Previous Wording	New Wording
Updated the description of subject number	Section 5.1	20	A total of 44 healthy male or female Chinese subjects will be enrolled in the trial, with each gender representing no less than 1/3 of the total number (also evenly allocated to fasting vs. fed group). Subjects will also be allocated to fasting vs. fed sub-group, ie, 26 subjects will be enrolled into the fasting group and 18 subjects in the fed group, respectively (Figure 1), and are statistically powered to provide adequate sample size for BE evaluation.	**Given local health authority guidance and Investigator recommendation, ~~A~~ a** total of 44 healthy male or female Chinese subjects will be enrolled in the trial, with **at least 7 subjects of** each gender **in the fasted group, and at least 5 subjects of each gender in the fed group,** representing ~~no less than~~ 1/~~3~~**4** of the total number ~~(also evenly allocated to fasting vs. fed group)~~. Subjects will ~~also~~ be allocated to fasting vs. fed sub-group, ie, 26 subjects will be enrolled into the fasting group and 18 subjects in the fed group, respectively (Figure 1). **The sample size provides sufficient power to demonstrate BE.**~~, and are statistically powered to provide adequate sample size for BE evaluation~~.
Updated the term of End-of-Trial examination period to conditional follow-up visit	Section 5.1 Table 2 head row	**20**	**End-of-Trial**	~~End-of-Trial~~ **Conditional follow-up visit (only for subject who has AE)**
Updated the instruction of trial periods	Section 5.1 Table 2	20	Day -14 – Day -1 | Day 1 (approximately 60 hours inpatient starting from the day prior to dosing) | 7 days | Day 8 (approximately 60 hours inpatient starting from the day prior to dosing) | Day 15	Day -14 – Day -1 | Day 1 **to Day 3** (~~approximately 60 hours~~ inpatient ~~starting from the day prior to dosing~~) **(inpatient)** | 7 days **(inpatient)** | Day 8 **to Day 10** (~~approximately 60 hours~~ inpatient ~~starting from the day prior to dosing~~) **(inpatient)** | Day 15
Updated the wording of withdrawal from trial therapy	Section 5.5.1	23	Subjects who withdraw from the trial will also be withdrawn from the IMP. A subject who drops out will not be replaced for this trial as long as the minimum sample size of evaluable subjects is met.	Subjects who withdraw from the trial will also be withdrawn from the IMP. A subject who drops out will not be replaced for this trial as long as the minimum sample size of evaluable subjects is met. **The minimum requirement is 20 evaluable subjects in the fasting and 12 subjects in the fed group, which will provide adequate power to show BE in both groups.**
Updated the wording of withdrawal from trial	Section 5.5.2	23	4. Emesis experienced within 4 hours following drug administration because of incomplete absorption (this period of time corresponds also to 2 times the median time of maximum plasma concentration [t_{max}] of GIR). Subjects experiencing vomiting later than 4 hours postdose will not be withdrawn unless otherwise decided by the Investigator in light of subject's safety or trial integrity	4. Emesis experienced within 4 hours following drug administration because of **possibly** incomplete absorption (this period of time corresponds also to 2 times the median time of maximum plasma concentration [t_{max}] of GIR). Subjects experiencing vomiting later than 4 hours postdose will not be withdrawn unless otherwise decided by the Investigator in light of subject's safety or trial integrity

Change	Section	Page	Previous Wording	New Wording
Updated the wording of withdrawal from trial regarding concomitant medication	Section 5.5.2	23	Concomitant medication of any drug except pain relief medication (paracetamol) is prohibited, the administration of paracetamol should not exceed 1 g per day. Details of reasons for premature withdrawal of subjects will be recorded and documented in the final report.	Concomitant medication of any drug except pain relief medication (paracetamol) is prohibited, the administration of paracetamol should not exceed 1 g per day **and not more than 3 consecutive days**. Details of reasons for premature withdrawal of subjects will be recorded and documented in the final report.
Updated the definition of End-of-Trial	Section 5.7	24	The End-of-Trail is defined as the last contact of the last subject (usually the End-of-Trial visit [Day 15], which is scheduled for 7 days after the administration day in Period 2 [Day 8]).	The End-of-Trail is defined as the last contact of the last subject (~~usually the End-of-Trial visit [Day 15], which is scheduled for 7 days after the administration day in Period 2 [Day 8].~~**Day 10 or the conditional follow-up visit/ [Day 15]/ or any special day for Premature Withdrawal visit**).
Updated description of IMP	Section 6.1	24	All IMPs will be sourced from respective manufacturer as listed below (Table 3). GIR= glucophage immediate release; IMP= investigational medicinal product	All IMPs will be sourced from respective manufacturer as listed below (Table 3). **The IMPs manufacturing process compliant with GMP requirements. The transportation and storage are to be tracked by temperature monitor to insure the medication quality and compliance to China regulation requirements.** GIR 500 mg = Glucophage 500 mg Immediate Release; IMP = Investigational Medicinal Product; **MSS = Merck Santé s.a.s. in Semoy; SASS = Sino-American Shanghai Squibb Pharmaceuticals Ltd.**
Update dosage and administration information	Section 6.2	24	Potential trial subjects 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 trial administration (Day 1, Period 1). On the evening before the dosing day in each period, subjects will be admitted to the Clinical Research Unit (CRU) to fast prior to Day 1 dosing (administered the next morning).	Potential trial subjects 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 trial administration (**first IMP given on** Day 1, Period 1). On the evening before the dosing day in ~~each~~ **the first** period, subjects will be admitted to the Clinical Research Unit (CRU) to fast prior to Day 1 dosing (administered the next morning).
Revise Table 4 footnote	Section 6.3	25	GIR= Glucophage immediate release IMP= investigational medicinal product; SASS= Sino-American Shanghai Squibb Pharmaceuticals Ltd.	GIR= Glucophage ~~i~~**I**mmediate ~~r~~**R**eleaseImmediate Release; IMP= ~~i~~**I**nvestigational ~~m~~**M**edicinal ~~p~~**P**roduct; **MSS= Merck Santé s.a.s. in Semoy**; SASS= Sino-American Shanghai Squibb Pharmaceuticals Ltd.

Change	Section	Page	Previous Wording	New Wording
Update description regarding Concomitant Medications and Therapies	Section 6.5	26	Medications administered between enroll (date of informed consent form [ICF] signed) to first IMP dosing (Day 1) will be recognized as prior medication and used for eligibility check. After IMP dosing, any medication will be recorded as concomitant medication. The medication taken after subject enroll, if any, shall be documented in the eCRF stating the international nonproprietary name and trade name of the medication, its dose, duration, galenic form, route of administration, date and time of all administrations and indication. The data recorded up to the time at which the subject in question was withdrawn shall be taken for the evaluation of the trial substance's safety and tolerability.	Medications administered between ~~enroll (~~date of informed consent form **(**~~[~~ICF~~]~~**)** signed~~)~~ to first IMP dosing (Day 1) will be recognized as prior medication and used for eligibility check. After IMP dosing, any medication will be recorded as concomitant medication. The medication taken ~~after subject enroll~~, if any, shall be documented in the eCRF stating the international nonproprietary name and trade name of the medication, its dose, duration, galenic form, route of administration, date and time of all administrations and indication. The data recorded up to the time at which the subject in question was withdrawn shall be taken for the evaluation of the trial substance's safety and tolerability.
Updated restriction of allowed pain relief medication	Section 6.5.1	26	No concomitant medication except pain relief medication (paracetamol) is allowed during the trial. The administration of paracetamol should not exceed 1 g per day and should be documented in eCRF.	No concomitant medication except pain relief medication (paracetamol) is allowed during the trial. The administration of paracetamol should not exceed 1 g per day **and not more than 3 consecutive days,** and should be documented in eCRF.
Updated the special precaution of alcohol prohibition period	Section 6.5.4.1	26-27	The subjects have to abstain from alcohol from 2.5 days (approximately 60 hours) prior to dosing and through the End-of-Trial visit. In case of any suspicion of alcohol consumption, a test for alcohol may be performed to confirm the Investigator's judgment.	The subjects have to abstain from alcohol from 2.5 days (approximately 60 hours) prior to dosing and through the ~~End-of-Trial visit~~ **entire study period**. In case of any suspicion of alcohol consumption, a**n additional** test for alcohol may be performed to confirm the Investigator's judgment.
Updated the special precaution of food restriction	Section 6.5.4.3	27	***Fluids*** Subjects 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. Subjects 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.	***Fluids*** Subjects are not allowed to excessively consume beverages containing xanthine **derivate** (> 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. Subjects 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.

Change	Section	Page	Previous Wording	New Wording
Added the instruction of IMP preparation	Section 6.7	28	All IMP treatment boxes supplied to the trial center must be stored carefully, safely, and separately from other drugs. The handling and storage of IMPs should follow the regulatory requirements from authorities.	All IMP treatment boxes supplied to the trial center must be stored carefully, safely, and separately from other drugs. The handling and storage of IMPs should follow the regulatory requirements from authorities. **Sponsor must provide trial center enough drugs, including subject treatment and in additional at least 5 times full testing sample size for any requested testing in the inspection in the future. In terms of study IMP as well as reference IMP, the subject treatment using part and the extra 5 times of full testing samples will be from one identical batch and to be labeled equally without any difference to fulfill the randomized treatment IMPs/retention sample selection requirement at trial center. This requirement is appropriate for both study drugs and reference drugs.**
Updated the instruction of IMP handling	Section 6.7	28	The Investigator (or the pharmacist or another person who is designated by the Investigator) will maintain the following records for the trial medication: Upon receipt of trial treatment boxes at the trial center, the following must be performed by the trial staff: • Inventory at the center • Administration to each subject • Destruction of unused medication. It must be ensured that the IMP is not used at the trial site: • After the expiry date or • After the retest date unless the IMP is reanalyzed and its release date extended.	~~The Investigator (or the pharmacist or another person who is designated by the Investigator) will maintain the following records for the trial medication:~~ Upon receipt of trial treatment boxes at the trial center, the following must be performed by the trial staff: • **Check and insure the IMPs shipment period is under the controlled temperature by referring the temperature logger data** **The Investigator (or the pharmacist or another person who is designated by the Investigator) will maintain the following records for the trial medication:** • Inventory at the center • Administration to each subject • Destruction of unused medication. It must be ensured that the IMP is not used at the trial ~~site~~ **center**: • After the expiry date~~ or~~ • After the retest date unless the IMP is reanalyzed and its release date extended • **Before to receive any written greenlight from Sponsor when temperature deviation occurred to IMPs during the trial center storage**
Removed the instruction of destroying IMP	Section 6.7	28	The unused and remained trial medication and the expired testing sample has to be destroyed under Sponsor's agreement.	~~The unused and remained trial medication and the expired testing sample has to be destroyed under Sponsor's agreement~~.

Change	Section	Page	Previous Wording	New Wording
Added the instruction of IMP dispensing	Section 6.7	28	-	**The drugs for the subjects must be random drawing from all the study drugs and reference drugs provided by the 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 occurred during the site storage should report to CRA immediately. The responsible CRA report it to Merck immediately as well to collect Merck written decision to use or block the impacted IMPs.**
Updated the instruction for drug accountability	Section 6.8	29	Unused IMP must not be discarded or used for any purpose other than the present trial. The unused IMP to be returned back or to be destroyed at site will be on sponsor's e-mail notice and greenlight to proceed. Investigational medicinal product that has been dispensed to a subject must not be re-dispensed to a different subject. The monitor will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the trial site.	~~Unused IMP must not be discarded or used for any purpose other than the present trial. The unused IMP to be returned back or to be destroyed at site will be on sponsor's e-mail notice and greenlight to proceed. Investigational medicinal product that has been dispensed to a subject must not be re-dispensed to a different subject.~~ ~~The monitor will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the trial site.~~ **The retention samples should be stored at trial center or the third party under appropriate condition. It is the trial center to decide the retention sample storage place and the retention samples will not be returned to Sponsor. The trial center must collect the Sponsor's written confirmation before to proceed any retention sample destruction activity.**
Updated the instruction for Medical Care of Subjects after End-of-Trial	Section 6.13	30	After a subject has completed the trial or has withdrawn prematurely, an End-of-Trial visit (Day 15, if subject completed the trial) will be conducted and safety assessments will be performed. Upon the careful screening for healthy subjects such as detailed in the eligibility criteria for this trial, no serious AEs related to study treatment are expected during this trial. However, in case of any ongoing AE at the End-of-Trial 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.	After a subject has completed the trial **and has AE during the trial and ongoing at discharge** or has withdrawn prematurely, a~~End-of-Trial~~ **conditional follow-up** visit (Day 15, if subject completed the trial **on Day 10, or any specific day for premature withdrawal)** will be conducted and safety assessments will be performed. Upon the careful screening for healthy subjects such as detailed in the eligibility criteria for this trial, no serious AEs related to study treatment are expected during this trial. However, in case of any ongoing AE at the ~~End-of-Trial~~ **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.

Change	Section	Page	Previous Wording	New Wording
Updated the schedule of assessments	Section 7.1	30	The schedule of assessments will include: • Screening (determining eligibility to the trial, including assessments during admission to CRU; Day -14 to Day -2) • Admission to the CRU before Period 1 (Day -1) • Period 1 (Day 1 to Day 3) • Washout Period • Admission to the CRU before Period 2 (Day 7) • Period 2 (Day 8 to Day 10) • End-of-Trial (Day 15)/Premature Withdrawal (Table 1). Subject will participate in the clinical trial on an inpatient basis during Day -1 to Day 3 and also during Days 7 to 10.	The schedule of assessments will include: • Screening (determining eligibility to the trial, including assessments during admission to CRU; Day -14 to Day -2) • Admission to the CRU before Period 1 (Day -1) • Period 1 (Day 1 to Day 3) • Washout Period • ~~Admission to the CRU before Period 2 (Day 7)~~ • Period 2 (Day 8 to Day 10 **Discharge day**) • ~~End-of-Trial~~ **Conditional follow-up** (Day 15**) only for subject who has AE during the trial and ongoing at discharge**~~/Premature Withdrawal~~ (Table 1). Subject will participate in the clinical trial on an inpatient basis during Day -1 to Day~~3 and also during Days 7 to~~ 10.
Revises Inclusion/Exclusion criteria checking statements	Section 7.1.1	31	Potential trial subjects will be examined at screening to determine their eligibility for clinical trial participation. The inclusion and exclusion criteria will be reviewed to determine eligibility for the trial while collecting the necessary information. All screening assessments are to be conducted within 14 days before the start of the trial. Renal failure will be assessed by using the estimated measure with MDRD equation	Potential trial subjects will be examined at screening to determine their eligibility for clinical trial participation. The inclusion and exclusion criteria will be reviewed to determine eligibility for the trial while collecting the necessary information. All screening assessments are to be conducted within 14 days before the ~~start of the trial~~ **first trial administration (first IMP given on Day 1, Period 1).** Renal failure will be assessed by using the estimated measure with MDRD equation
Revised ECG description due to redundant to 7.4.4	Section 7.1.1	31-32	A 12-lead ECG (including QTc evaluation) will be performed. Results of the ECG recordings will be included in the subject's eCRF. Printouts for each ECG will include date, time, initials of the technician/nurse, and initials of the Investigator who reviewed the printout. At least 5 to 7 beats will be monitored at a speed of 25 mm/sec for each lead and a single lead (V2) run (see Section 7.4.4 for specific ECG determinations and procedures).	A 12-lead ECG (including QTc evaluation) will be performed. Results of the ECG recordings will be included in the subject's eCRF. Printouts for each ECG will include date, time, initials of the technician/nurse, and initials of the Investigator who reviewed the printout. ~~At least 5 to 7 beats will be monitored at a speed of 25 mm/sec for each lead and a single lead (V2) run~~ (see Section 7.4.4 for specific ECG determinations and procedures).
Updated laboratory tests description	Section 7.1.1	34	Urinalysis Appearance, blood, glucose, ketones, nitrite, pH, protein, and leukocytes will be assessed. Microscopic examination will only be performed if dipstick test is positive for leukocytes, blood, nitrites, or proteins.	Urinalysis Appearance, blood, glucose, ketones, nitrite, pH, protein, and leukocytes will be assessed. Microscopic examination will ~~only~~ be performed if dipstick test is positive for leukocytes, blood, nitrites, or proteins.

Change	Section	Page	Previous Wording	New Wording
Updated Day 1 procedure	Section 7.1.2	34	Trial eligibility assessments will be performed including: physical examination, vital signs, ECG and prior medications since screening visit, treatments and diseases as well as testing for alcohol and drug abuse. Female subjects with childbearing potential will have a serum pregnancy test.	Trial eligibility assessments will be performed including: physical examination, vital signs, ECG**, laboratory tests**, and prior medications since screening visit, treatments and diseases **(medical history)** as well as testing for alcohol and drug abuse. Female subjects with childbearing potential will have a serum pregnancy test.
Added randomization to Day -1	Section 7.1.2	34	-	**Randomization** **Eligible subjects will then be randomly assigned to 1 of 2 sequences (Table 4).**
Updated Day 1 procedure on blood pressure check	Section 7.1.3	35	Subjects will be assessed for vital signs (blood pressure, pulse rate, temperature and respiration). Blood pressure assessments determine eligibility to be randomized to the trial. The blood pressure (measured in sitting position after at least 5 minutes rest) must not be below 100 mmHg and/or 65 mmHg or above 139 mmHg and/or 90 mmHg.	Subjects will be assessed for vital signs (blood pressure, pulse rate, temperature and respiration). Blood pressure assessments determine eligibility to be randomized to the trial. The blood pressure (measured in sitting position after at least 5 minutes rest) ~~must not be below 100 mmHg and/or 65 mmHg or above 139 mmHg and/or 90 mmHg.~~ **normal range is considered ≥ 90 mmHg and ≤ 139 mmHg for SBP; ≥ 60 mmHg and ≤ 90 mmHg for DBP.**
Updated Day 1 procedure	Section 7.1.3	35	If the subject is determined to be ineligible for any of the above assessments, the subject will not be randomized to the trial.	If the subject is determined to be ineligible for any of the above assessments, the subject will not **receive randomized treatment** ~~be randomized to the trial~~.
Removed randomization from Day 1	Section 7.1.3	35	**Randomization** Eligible subjects will then be randomly assigned to one of 2 sequences (Table 4).	~~**Randomization**~~ ~~Eligible subjects will then be randomly assigned to one of 2 sequences (Table 4).~~
Updated PK sampling procedure	Section 7.1.3	36	For plasma metformin detection, 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. Blood samples should be processed within 30 minutes or otherwise should be kept in an ice water bath pending processing. Plasma samples will be prepared, divided into 2 aliquots and stored at max -20°C. Plasma concentration of metformin will be analyzed by validated bioanalytical method.	For plasma metformin detection, 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. Blood samples should be processed within 30 minutes **(centrifuge each tube for 10 minutes at 2000g)** or otherwise should be kept in an ice water bath pending processing. Plasma samples will be prepared, divided into 2 aliquots and stored at max -20°C. Plasma concentration of metformin will be analyzed by validated bioanalytical method.
Updated PK sampling collection schedule	Section 7.1.3		End-of-Trial (Day 15)/Premature Withdrawal | | 1-sample at End-of-Trial visit | ±30	~~End-of-Trial (Day 15)~~/Premature Withdrawal | | 1-sample at ~~End-of-Trial visit~~ **premature withdrawal** | ±30

Change	Section	Page	Previous Wording	New Wording
Added note for blood sample processing	Section 7.1.3 Table 8 footnote	36	-	**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 subjects who has premature withdrawal. For subjects having conditional follow-up visit for safety, no PK sampling is required.**
Updated Vital sign assessment at Period 1	Section 7.1.3	37	Vital signs will be repeated prior to dosing and at 4 and 8 hours postdose.	Vital signs will be repeated prior to dosing and at 4 ~~and 8~~ hours postdose.
Updated assessment procedure on Day 2 to Day 3	Section 7.1.3	37	**Pharmacokinetic Blood Sampling (Postdose, continued)** During the 2 days following Day 1, blood samples will be taken according to the trial schedule (Table 8). On Day 2, sampling will be conducted at 24 and 36 hours; on Day 3, sampling will be conducted at 48 hours after GIR administration. Subjects will be allowed to leave the CRU on Day 3 after the morning blood sampling collection (48-hour sample).	**Pharmacokinetic Blood Sampling (Postdose, continued)** During the 2 days following Day 1, blood samples will be taken according to the trial schedule (Table 8). On Day 2, sampling will be conducted at 24 and 36 hours; on Day 3, sampling will be conducted at 48 hours after GIR administration. ~~Subjects will be allowed to leave the CRU on Day 3 after the morning blood sampling collection (48-hour sample).~~
Updated assessment procedure on Day 2 to Day 3	Section 7.1.3	37	**Safety Monitoring** Any concomitant diseases and treatments have to be documented. Concurrent administration of any medication will be prohibited during the trial. Any AEs and SAEs should also be recorded. Vital signs will be assessed before blood sampling from Day 2 to Day 3. A 12-lead ECG (including QTc evaluation) will be performed 48 hours postdose at Day 3. At the day of discharge, a blood sample for determination of hematology and biochemistry will be taken and a urinalysis will be performed. Physical examination will also be performed. On the morning of Day 3 in the CRU after the blood sampling collection (48-hour sample), the Investigator will decide whether or not the subject needs to stay for any additional time in the clinic. If there are no safety concerns based on the assessment by the Investigator, the subject will be allowed to leave the CRU.	**Safety Monitoring** Any concomitant diseases and treatments have to be documented. Concurrent administration of any medication will be prohibited during the trial. Any AEs and SAEs should also be recorded. **Physical examination will also be performed on Day 3.** ~~Vital signs will be assessed before blood sampling from Day 2 to Day 3.~~ ~~A 12-lead ECG (including QTc evaluation) will be performed 48 hours postdose at Day 3.~~ ~~At the day of discharge, a blood sample for determination of hematology and biochemistry will be taken and a urinalysis will be performed. Physical examination will also be performed.~~ ~~On the morning of Day 3 in the CRU after the blood sampling collection (48-hour sample), the Investigator will decide whether or not the subject needs to stay for any additional time in the clinic. If there are no safety concerns based on the assessment by the Investigator, the subject will be allowed to leave the CRU.~~
Updated description of washout period	Section 7.1.4	37	The 2 administrations of IMP are separated by a Washout of 7 days. Washout begins postdose on Day 1 and continues for approximately 7 days.	The 2 administrations of IMP are separated by a Washout of 7 days **(inpatient).** Washout begins postdose on Day 1 and continues for approximately 7 days.

Change	Section	Page	Previous Wording	New Wording
Updated assessment procedure on Day 7	Section 7.1.5	37-38	**7.1.5 Admission to Clinical Research Unit (Day 7)** In the evening before the dosing day, subjects will be admitted to the CRU at least 12 hours prior to Day 8 dosing for an overnight fast. Subjects 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. Trial eligibility assessments will include: physical examination, vital signs, ECG, and concomitant medications (Table 1). Testing for alcohol and drug abuse will be performed. In addition, a blood sample for determination of hematology and biochemistry will be taken and a urinalysis will be performed. Serum pregnancy test will be performed for females of childbearing potential only.	**7.1.5 ~~Admission to Clinical Research Unit (~~Day 7** ~~In the evening before the dosing day, subjects will be admitted to the CRU at least 12 hours prior to Day 8 dosing for an overnight fast.~~ Subjects 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. Trial eligibility assessments will include: physical examination~~,~~ ~~vital signs, ECG~~ and concomitant medications (Table 1).~~ Testing for alcohol and drug abuse will be performed. In addition, a blood sample for determination of hematology and biochemistry will be taken and a urinalysis will be performed. Serum pregnancy test will be performed for females of childbearing potential only.~~
Updated Day 8 procedure	Section 7.1.6	38	Procedures outlined on Day 1 in Period 1 will be repeated on Day 8 for continuing trial eligibility into Period 2 (except for randomization).	Procedures outlined on Day 1 in Period 1 will be repeated on Day 8 for continuing trial eligibility into Period 2 ~~(except for randomization)~~.
Updated Vital sign assessment at Period 2	Section 7.1.6	38	Vital signs will be repeated prior to dosing and at 4 and 8 hours postdose.	Vital signs will be repeated prior to dosing and at 4 ~~and 8~~ hours postdose.
Updated ECG procedures	Section 7.1.6	39	Day 9 to Day 10 A 12-lead ECG (including QTc evaluation) will be performed 48 hours postdose at Day 10. At the day of discharge, physical examination will be performed. A blood sample for determination of hematology and biochemistry will be taken and a urinalysis will be performed.	Day 9 to Day 10 A 12-lead ECG (including QTc evaluation) will be performed ~~48 hours postdose~~ at Day 10 **before discharge**. At the day of discharge **(Day 10)**, physical examination will be performed. A blood sample for determination of hematology and biochemistry will be taken and a urinalysis will be performed. **These investigations on the day of discharge represent the final examination.**
Update End-of-Trial visit	Section 7.1.7	39	**7.1.7 End-of-Trial (Day 15)/Premature Withdrawal** **End-of-Trial** At End-of-Trial (Day 15) the assessments include: physical examination, vital signs, ECG, laboratory tests (hematology, biochemistry, and urinalysis), and AEs will be assessed. Any concomitant treatments have to be documented. The case conclusion has to be filled in. Serum pregnancy test will be performed for females of childbearing potential only.	7.1.7 ~~End-of-Trial~~ **Conditional follow-up (Day 15)/Premature Withdrawal** **~~End-of-Trial~~** **Conditional follow-up visit (only for subject with AE during the trial and ongoing at discharge)**

Change	Section	Page	Previous Wording	New Wording
			If AEs or pathological findings, ie, clinically relevant deviations from Baseline findings are obtained during the final examination, these findings 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. **Pharmacokinetic Blood Sampling** Blood samples for the determination of GIR will be taken once (Table 8). **Premature Withdrawal** The assessments at Premature Withdrawal visit include: physical examination, vital signs, ECG, laboratory tests (hematology, biochemistry, and urinalysis), AEs, and concomitant treatments (Table 1). The case conclusion has to be filled in. Serum pregnancy test will be performed for females of childbearing potential only.	At ~~End of Trial~~ **conditional follow-up** (Day 15) the assessments include: physical examination, vital signs, ECG, laboratory tests (hematology, biochemistry, and urinalysis), and AEs will be assessed. Any concomitant treatments have to be documented. The case conclusion has to be filled **in for every subject who has received at least one dose of the IMPs**. ~~Serum pregnancy test will be performed for females of childbearing potential only.~~ If AEs or pathological findings, ie, clinically relevant deviations from Baseline findings are obtained during the final examination, these findings 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. ~~**Pharmacokinetic Blood Sampling**~~ ~~Blood samples for the determination of GIR will be taken once (Table 8).~~ **Premature Withdrawal** The assessments at Premature Withdrawal visit include: physical examination, vital signs, ECG, laboratory tests (hematology, biochemistry, and urinalysis), AEs, and concomitant treatments (Table 1). The case conclusion has to be filled in **for every subject who has received at least one dose of the IMPs**. ~~Serum pregnancy test will be performed for females of childbearing potential only.~~
Updated AE reporting period	Section 7.4.1.3	43-44	The AE reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues through the trial's post treatment period. The complete trial 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 trial Period 1), continuing during the IMP administration, and collection continued until 7 days after the day of the last IMP administration (ie, End-of-Trial visit, Day 15). In case of early termination, AEs until Premature Withdrawal visit will be collected.	The AE reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues through the trial's post treatment period. The complete trial 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 trial Period 1), continuing during the IMP administration, and collection continued until **Day 10 or** 7 days after the day of the last IMP administration (~~ie, End-of-Trial~~ **conditional follow-up** visit, Day 15**, if subject has AE during the trial and ongoing at discharge**). In case of early termination, AEs until Premature Withdrawal visit will be collected.
Updated Safety report e-mail	Section 7.4.1.4	44	E-mail:PPD	E-mail: PPD

Change	Section	Page	Previous Wording	New Wording
Updated description on ECG assessment	Section 7.4.4	47	QT/QTc interval will be automatically computed using the Bazett correction formula (QTcB = QT/√RR) and the Fridericia correction formula (QTcF = QT/3√RR) by the ECG device according to the recently approved ICH guidance E1. In case of QTc values outside of the normal range, ECGs will be manually re-evaluated by a physician.	QT/QTc interval will be automatically computed using the Bazett correction formula (QTcB = QT/√RR) and the Fridericia correction formula (**QTcF = QT/^{3}√RR**~~QTcF = QT/3√RR~~) ~~by the ECG device~~ according to the recently approved ICH guidance E1. ~~In case of QTc values outside of the normal range, ECGs will be manually re-evaluated by a physician.~~
Updated the sample collection time of PK	Section 7.5	47	One sample will be collected at End-of-Trial visit (Day 15 or Premature Withdrawal)	One sample will be collected at ~~End-of-Trial visit (Day 15 or~~ Premature Withdrawal~~)~~ **if applicable**.
Updated the total sample number for PK sample collection	Section 7.5	47	Subjects who complete both treatment periods plus an End-of-Trial PK sample will have a total of 35 samples (approximately 3 mL whole blood each sample) collected. Total PK blood volume collection is approximately 105 mL over 2 weeks.	Subjects who complete both treatment periods ~~plus an End-of-Trial PK sample~~ will have a total of ~~35~~**34** samples (approximately 3 mL whole blood each sample) collected. Total PK blood volume collection is approximately ~~105~~**102** mL over 2 weeks.
Updated the wording for subject replacement	Section 8.2	51	The first 6 (fasting) or 4 (fed) discontinued subjects of each group will not be replaced. Subjects will only be replaced if the number of subjects within each group falls below 20 (fasting) or 12 (fed). The subject who is replacing a discontinued subject will then be allocated to the treatment sequence of the subject who discontinued.	~~The first 6 (fasting) or 4 (fed) discontinued subjects of each group will not be replaced.~~ Subjects will only be replaced if the number of subjects within each group falls below 20 (fasting) or 12 (fed). The subject who is replacing a discontinued subject will then be allocated to the treatment sequence of the subject who discontinued.
Updated recording information of subject files	Section 10.2	58	• Date of subject's End-of-Trial visit, or	• Date of subject's ~~End-of-Trial~~ **last** visit, or
Updated Investigator Site File and Archiving	Section 10.3	59	The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial.	The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least ~~15~~ **5** years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial.
Updated PI affiliation	Signature page-Principal Investigator	68	Name, academic degree: PPD Function/Title: Chief pharmacist Institution: PPD Address: PPD Telephone number: PPD	Name, academic degree: ~~Chen Yu~~ **Lan** PPD Function/Title: ~~Chief pharmacist~~ **Principle Investigator** Institution: PPD PPD Address: PPD

Change	Section	Page	Previous Wording	New Wording
			Fax number: PPD E-mail address: PPD	Telephone number: PPD Fax number: PPD E-mail address: PPD PPD

Changes on Schedule of Assessment Table 1

Assessments	**Screening (Baseline)**	**Period 1**					**Period 2**			**~~End of Trial~~ Conditional follow-up visit or Premature Withdrawal[j~~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[c] medications	X	X								
Laboratory tests **including blood test and urinalysis**	X	X			~~X~~	~~X~~			X	X
Pregnancy test[d] (females of childbearing potential)	X	X				~~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				~~X~~				
Urine nicotine	X									
Randomization		**X**	~~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~~h~~]	~~X~~[i]	~~X~~[i]	~~X~~	X[g~~h~~]	~~X~~[i]	X[i]	X
Electrocardiogram	X	X	X[j~~h~~]		~~X~~[k]	~~X~~	X[j~~h~~]		X[k~~h~~]	X
Chest X-ray	X									
AE recording[l~~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; TP = Treponema pallidum

a. Subject will participate in the clinical trial on an inpatient basis during Day -1 to **Day** ~~3 and also during Days 7 to~~ 10.

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

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

d. ~~Urine~~ **Serum** pregnancy test will be done at screening~~, serum pregnancy test will be done~~ and at Day -1~~, 7, and End-of-Treatment~~.

e. Refer to Table 8Table 8 for detail schedule of sampling during inpatient at research center. **There will be an extra PK sampling for subjects with premature withdrawal, for subjects 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 subject has rested comfortably for at least 5 minutes. **(The blood pressure normal range is considered ≥ 90 mmHg and ≤ 139 mmHg for SBP; ≥ 60 mmHg and ≤ 90 mmHg for DBP)**

Day 1and Day 8: Vital signs will be repeated prior to dosing and at 4 ~~and 8~~ hours postdose.

Vital signs will be assessed ~~before blood sampling from Day 2 to Day 3 and Day 9 to~~at Day 10.

h. Electrocardiogram (12-lead ECG, including QTc evaluation) will be performed 4 hours postdose at Day 1 and Day 8. Electrocardiogram ~~(12-lead ECG, including QTc evaluation)~~ will **also** be performed **at**~~48 hours postdose at Day 3 and~~ Day 10 **before discharge from research unit**.

i. Adverse events will be collected starting from Day -1, the AEs since the date of first signature of informed consent will be recorded. The following visits will record any AEs since the last visit.

j. **Subjects will be discharged on Day 10, after final sample collection and safety examinations are completed (final examination).**

k. If subject has AE during trial and ongoing at discharge, the subject has to come back for the conditional follow-up visit.

Changes on Table 9: Estimated Blood Sample Volumes per Subject

Original Table

Time Points	Evaluation Indexes	Total Blood Volume (mL)
Screening	Serum virology	4
	Hematology	2
	Biochemistry	4
	Approximate Total	***10***
Period 1	Hematology	2*2
	Biochemistry	4*2
	Serum Pregnancy Test (if applicable)	4
	Pharmacokinetics	3*17
	Approximate Total	***67***
Period 2	Hematology	2*2
	Biochemistry	4*2
	Serum Pregnancy Test (if applicable)	4
	Pharmacokinetics	3*17
	Approximate Total	***67***
End-of-Trial Or Premature Withdrawal	Hematology	2
	Biochemistry	4
	Serum Pregnancy Test (if applicable)	4
	Pharmacokinetics	3
	Approximate Total	***13***
Approximate Total of Each Subject		***157 (145 for male)***

New Table

Time Points	Evaluation Indexes	Total Blood Volume (mL)
Screening	Serum virology	4
	Hematology	2
	Biochemistry	4
	Serum Pregnancy Test (if applicable)	**4**
	Approximate Total	***~~10~~ 14 (10 for male)***
Period 1	Hematology	2~~*2~~
	Biochemistry	4~~*2~~
	Serum Pregnancy Test (if applicable)	4

	Pharmacokinetics	3*17
	Approximate Total	***~~67~~ 61 (57 for male)***
Period 2	Hematology	2~~*2~~
	Biochemistry	4~~*2~~
	~~Serum Pregnancy Test (if applicable)~~	~~4~~
	Pharmacokinetics	3*17
	Approximate Total	***~~67~~ 57***
Conditional follow-up Or Premature Withdrawal	Hematology	2
	Biochemistry	4
	~~Serum Pregnancy Test (if applicable)~~	~~4~~
	↑***Approximate Total***	↑***~~136~~***
	↓Pharmacokinetics (only for premature withdrawal)	↓***3***
Approximate Total of Each Subject		***~~157 (145 for male)~~*** ***132(124 for male)*** ***With conditional follow-up:*** ***138 (130 for male)***