Title: Oral bioavailability study comparing OXEMET™ 1000 mg coated tablets containing metformin hydrochloride with 1000 mg of the reference product (GLAFORNIL™) administered as two 500 mg tablets, through a randomized, single-dose, open label, balanced, 2-way crossover study in healthy volunteers under fasting conditions.

Description: This is an open-label, single-center, randomized, 2-way crossover study to evaluate the bioequivalence of OXEMET™ 1000 mg coated tablets, relative to 1000 mg of the reference product administered as two 500 mg tablets, under fasting conditions, in 24 healthy adult subjects. Each subject will receive two treatments (Treatment A and Treatment B). In Period 1, subjects will be dosed with either one OXEMET™ 1000 mg tablet (Treatment A, Test) or two 500 mg tablets of reference product (GLAFORNIL™ 500 mg) (Treatment B, Reference). Following a washout of at least 7 days, subjects will be crossed over in Period 2 to receive the treatment that they did not receive in Period 1.

Subject: Bioequivalence, Metformin hydrochloride.

Author(s): [Redacted] MD Medical Director GSK Chile
SPONSOR SIGNATORY:

Name: [Redacted]
Title: MD Medical Affairs GSK Chile

Date: 26 Feb 2014
SPONSOR/MEDICAL MONITOR INFORMATION PAGE

Medical Monitor and Sponsor Contact Information:

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<th>Role</th>
<th>Name</th>
<th>Day Time Phone Number</th>
<th>After-hours Phone/Cell/Pager Number</th>
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<td>GSK Chile Medical Director</td>
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<td></td>
<td></td>
<td>Avda. Andrés Bello 2687, Piso 18, Las Condes, Santiago, Chile</td>
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<tr>
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<td>MD Medical Manager</td>
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<td></td>
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Sponsor Legal Registered Address:

GlaxoSmithKline Chile Farmacéutica Ltda.

Andrés Bello 2687, Las Condes

Santiago de Chile

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s):
INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

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<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>ALT</td>
<td>Alanine aminotransferase (SGPT)</td>
</tr>
<tr>
<td>ANMAT</td>
<td>Argentine Regulatory Authority</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>AST</td>
<td>Aspartate aminotransferase (SGOT)</td>
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<tr>
<td>AUC</td>
<td>Area under the concentration-time curve</td>
</tr>
<tr>
<td>AUC(_{(0-\infty)})</td>
<td>Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time</td>
</tr>
<tr>
<td>AUC(_{(0-t)})</td>
<td>Area under the concentration-time curve from time zero (pre-dose) to the time of the last quantifiable concentration</td>
</tr>
<tr>
<td>BE</td>
<td>Bioequivalence</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BPM</td>
<td>Beats Per Minute</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIB</td>
<td>Clinical Investigator’s Brochure</td>
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<tr>
<td>C(_{\text{max}})</td>
<td>Maximum observed concentration</td>
</tr>
<tr>
<td>C(_{t})</td>
<td>Last observed quantifiable concentration</td>
</tr>
<tr>
<td>CO(_{2})</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CPK</td>
<td>Creatine phosphokinase</td>
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<tr>
<td>CPMS</td>
<td>Clinical Pharmacokinetics Modelling &amp; Simulation</td>
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<td>CPSR</td>
<td>Clinical Pharmacology Study Report</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variance</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DRE</td>
<td>Disease Related Event</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EISR</td>
<td>Expedited Investigator Safety Report</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma glutamyltransferase</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GLS</td>
<td>Geometric Least-Squares</td>
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<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>H</td>
<td>Hour(s)</td>
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<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<tr>
<td>IP</td>
<td>Investigational Product</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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</tr>
<tr>
<td>ISP</td>
<td>Institute of Public Health (Chilean Regulatory Authority)</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>L</td>
<td>Liter</td>
</tr>
<tr>
<td>LFTs</td>
<td>Liver function tests</td>
</tr>
<tr>
<td>Ln</td>
<td>Naperian (natural) logarithm</td>
</tr>
<tr>
<td>µg</td>
<td>Microgram</td>
</tr>
<tr>
<td>µL</td>
<td>Microliter</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean corpuscular hemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean corpuscular hemoglobin concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean corpuscular volume</td>
</tr>
<tr>
<td>mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>MSDS</td>
<td>Material Safety Data Sheet</td>
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<tr>
<td>msec</td>
<td>Milliseconds</td>
</tr>
<tr>
<td>NQ</td>
<td>Non-quantifiable concentration measured as below LLQ</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetic(s)</td>
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<tr>
<td>QC</td>
<td>Quality control</td>
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<td>QTcB</td>
<td>QT duration corrected for heart rate by Bazett’s formula</td>
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<tr>
<td>QTcF</td>
<td>QT duration corrected for heart rate by Fridericia’s formula</td>
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<tr>
<td>RAP</td>
<td>Reporting and Analysis Plan</td>
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<tr>
<td>RBC</td>
<td>Red blood cells</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event(s)</td>
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<tr>
<td>SAS</td>
<td>Statistical Analysis Software</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SGOT</td>
<td>Serum glutamic-oxaloacetic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SPM</td>
<td>Study Procedures Manual</td>
</tr>
<tr>
<td>t(_{1/2})</td>
<td>Terminal phase half-life</td>
</tr>
<tr>
<td>t(_{max})</td>
<td>Time of occurrence of Cmax</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>WBC</td>
<td>White blood cells</td>
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### Trademark Information

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1. INTRODUCTION

1.1. Background

Different studies carried out in healthy volunteers provide relevant information for this bioequivalence study:

Pharmacokinetics and comparative Bioavailability of Two Metformin Formulations after Single-Dose Administration in Healthy Subjects: it consisted of a single-dose, open-label, two-period, two-treatments, crossover study under fasting conditions. 20 healthy volunteers (10 men and 10 women) took part in this study; each volunteer received a single dose of 850 mg of either the test (NIHFI, Sofia, Bulgaria) or the reference formulation: Siofor™ (Berlin Chemie, Berlin, Germany) with a 7-day washout period. Drugs were administered after a 12 h fasting and blood samples were collected according to the following time schedule: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 36 h after administration. Samples were centrifuged and plasma separated for analysis. To assess bioequivalence direct and indirect measures of exposures were determined: area under the concentration curve from time zero to infinity (AUC$_{(0-\infty)}$), to the last sampling time (AUC$_{(0-36)}$), peak plasma concentrations (C$_{\text{max}}$) among others. The 90% CIs of the ratios of geometric means of pharmacokinetic parameters AUC$_{(0-36)}$, AUC$_{(0-\infty)}$, C$_{\text{max}}$ and the rest were in the bioequivalence range of 0.80 - 1.25, the nonparametric analysis of tmax revealed no significant difference between test and reference products.

Bioequivalence Evaluation of two brands of Metformin 500 mg Tablets (Dialon™ & Glucophage™) - in Healthy Human volunteers: randomized, two treatments, two periods, crossover study under fasting conditions and 7 days washout period. 24 healthy volunteers were given a single dose of either formulation: reference: Glucophage™ (Lipha Pharmaceutical Industries, France) or test: Dialon™ (Gulf Pharmaceutical Industries, Julphar, United Arab Emirates) with 240 mL of water. Following drug administration, 100 mL of glucose 10% solution was administered at 0.5, 1.5, 2, 2.5, 3.0 and 5.0 h. Lunch and dinner were served at 5 and 12 h, respectively, after drug administration. Blood samples for metformin assay were collected at 0.33, 0.66, 1.0, 1.33, 1.66, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, and 30.0 h after dose administration. Samples were centrifuged and plasma was separated and kept frozen at -20°C. After 7 days the study was repeated in the same manner to complete the crossover design. The ratio (test product/ reference product) of the pharmacokinetic parameters: AUC$_{(0-t)}$, AUC$_{(0-\infty)}$ and C$_{\text{max}}$ with a 90% CI was analyzed, results were: (897.9-110.8)%, (97.4-110.7)% and (95.3-110.5)% respectively. These values were within the bioequivalence acceptance range of 80-125% (using log transformed data). It was concluded that Dialon™ and Glucophage™ were bioequivalents.

1.2. Rationale

1.2.1. Study Rationale

The purpose of this study is to assess the bioequivalence of OXEMET™ 1000 mg coated tablets compared to 1000 mg of reference product, administered as two 500 mg tablets.
Bioequivalence will be tested following a single dose under fasting conditions, in healthy adult subjects.

1.2.2. Dose Rationale

The 1000 mg dose of Metformin was selected for this study as it is the highest approved clinical dose.

Subjects will remain under medical supervision in the institute at least until completion of 36 h assessments, which is considered to be sufficient to detect safety issues related to singles doses of the IP.

1.3. Summary of Risk Management

Metformin has an established safety profile and has been extensively studied in both patients and healthy volunteers at the dose (1000 mg) to be used in the current study. Routine monitoring, as described in Section 4.5.2 Stopping Safety Criteria, Section 7.4 Safety, and Section 12 Adverse Events and Serious Adverse Events, is considered sufficient risk management.

Refer to the metformin labels (Annexe 2) for more information on the warnings, precautions, contraindications, adverse events, and other pertinent information on the study treatment.

2. OBJECTIVE(S)

2.1. Primary

To compare the oral bioavailability of OXEMET™ 1000 mg coated tablets containing metformin hydrochloride relative to 1000 mg of the reference product (GLAFORNIL™), administered as two 500 mg coated tablets, through a randomized, single-dose, open label, balanced, 2-way crossover study in healthy volunteers under fasting conditions.

3. ENDPOINT(S)

According to the local regulations (Disposición 3185/99, 5040/06 and 1746/07 from ANMAT and Resolución Exenta 727/05 from Ministerio de Salud de Chile), the following parameters will be calculated from metformin plasma concentration determined in serial samples, using a non compartmental method (WinNonlin v.6.02 - Pharsight Corporation, St. Louis, MO, USA).

3.1. Primary

Plasma Metformin AUC\(_{(0-t)}\), AUC\(_{(0-\infty)}\), C\(_{\text{max}}\) and t\(_{\text{max}}\).

AUC\(_{(0-t)}\): Area under the concentration-time curve from time zero (pre-dose) to the time of the last quantifiable concentration for Test product and Reference product.

AUC\(_{(0-\infty)}\): Area under the curve of plasma concentration of metformin between time 0 and infinity for Test product and Reference product.
C_{\text{max}}: Maximum plasma concentration of metformin for Test product and Reference Product.

t_{\text{max}}: Time at which maximum plasma concentration of metformin is obtained, for Test product and Reference product.

3.2. Secondary

The elimination constant (kel) and terminal plasma half-life (t_{1/2}) of Metformin will be determined for each subject, both for Test and Reference products.

4. INVESTIGATIONAL PLAN

4.1. Study Design

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This is a single-center, randomized, open-label, single-dose, two-period, crossover study in healthy adult volunteers to assess the bioequivalence of OXEMET™ to reference product. Both formulations will be administered in the fasting state. 24 subjects will be randomized to receive a single dose of OXEMET™ and the reference product separately in each treatment period. There will be two treatment sequences (AB, BA) and a 7 day washout between administrations of the two doses as shown in the following table:

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>Sequence</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

1. Treatment A = OXEMET™ one 1000 mg tablet/dose
2. Treatment B = GLAFORNIL™ two 500 mg tablets/dose

Subjects will have a screening visit within 30 days prior to the first dose of study drug, two treatment periods with each containing a single dose of study drug, followed by 36 h of serial PK sample collection. Subjects will check-in at the unit on Day-1 of each treatment period, at 20 h Serial PK sample collection will be performed on Day 1 of each treatment period, starting at 8 am. Subjects will check out of the unit on Day 2 of each treatment period, at least 2 h after finishing the 36 PK sample. The subject should be instructed to return for the next treatment period or for the follow-up visit, as appropriate. The follow-up visit will occur 7 days after the last dose of study drug. Study periods will
be separated by a 7 day washout between doses and subjects will be assigned each of the two treatments randomly as per the randomization schedule.

4.2. Discussion of Design

This open-label, two-period, randomized sequence, single-dose, crossover study is an appropriate design for evaluating the bioequivalence of OXEMET™ to reference product.

The primary PK endpoints selected for this study are the $C_{\text{max}}$, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and $t_{\text{max}}$.

4.3. Treatment Assignment

Subjects will be assigned to one of the sequences (Sequence 1 or Sequence 2) in accordance with the randomization schedule generated by the entity conducting the study (DominguezLab), prior to the start of the study, using Random, version 3.01™ JH Abramson 1993-2000 PEPI, a validated software. Once a randomization number is assigned to a subject, it cannot be re-assigned to any other subject in the study.

A description of each regimen is provided below:

Table 2 Treatment Assignment

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Treatment A²</td>
<td>Treatment B³</td>
</tr>
<tr>
<td>2</td>
<td>Treatment B</td>
<td>Treatment A</td>
</tr>
</tbody>
</table>

1. There will be a washout of 7 days between doses of study drug
2. Treatment A = OXEMET™ 1000 mg
3. Treatment B = GLAFORNIL™ two 500 mg tablets/dose

4.4. Washout interval

The minimum time interval between the two treatment periods has to be equal to 5 to 7 terminal half-lives of the study drug or higher, and this interval is called washout interval. Since terminal half-life for metformin is 4 h, a 7 days washout interval is planned between the two treatment periods.

During such washout interval, volunteers should not take any medication without previous consultation to the Study Principal Investigator, unless it is deemed necessary due to an arising life-threatening condition.

4.5. Investigational Product Dosage/Administration

Active Moiety, International Common Denomination—Chemical Name and/or Code: The active moiety to be studied is Metformin; its chemical name is 1,1-dimethyl-biguanide and is available as a hydrochloride.

CAS register for Metformin is 657-24-9 and 1115-70-4 for the hydrochloride; ATC code is A10BA02.
Molar mass for Metformin is 129.16 g/mol; its chemical formula is $\text{C}_4\text{H}_{11}\text{N}_5$; its chemical structure is shown below (Fig. 1).

![Chemical structure for metformin](image)

Figure 1  Chemical structure for metformin.

<table>
<thead>
<tr>
<th>Study Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product name:</strong></td>
</tr>
<tr>
<td><strong>Formulation description:</strong></td>
</tr>
<tr>
<td><strong>Dosage form:</strong></td>
</tr>
<tr>
<td><strong>Unit dose strength(s)/Dosage level(s):</strong></td>
</tr>
<tr>
<td><strong>Route/ Administration/ Duration:</strong></td>
</tr>
<tr>
<td><strong>Dosing instructions:</strong></td>
</tr>
<tr>
<td><strong>Physical description:</strong></td>
</tr>
</tbody>
</table>

As per the randomization schedule, either 1 tablet of Test product or 2 tablets of Reference product will be administered orally to each subject in each period after an overnight fast of at least 10 h with 240 mL of 10% glucose solution.

Subjects will be instructed not to chew or crush the formulation which should be swallowed whole. Administration of the investigational products will be carried out while the subjects are in a sitting posture. Compliance for dosing will be assessed by identification of subjects, identification of the label on investigational product to confirm correct allocation of treatment and checking the subject’s oral cavity immediately after dosing.

The subjects will remain leaning with 45° inclination or sitting for 4 h after dosing in each period.

The subjects will receive a standardized meal 4 h post-dose. Water will be permitted *ad libitum* except for 1 h before and until 1 h after dosing.
4.5.1. Time and Schedule for study drug and meals administration

Volunteers will check-in at 20 h on the day before the study drug administration day (Day 1 of each treatment period) at the unit where they will remain hospitalized for at least 36 h for each treatment period.

The next day (Day 1 of each treatment period), approximately at 8 am the Test drug or Reference product will be administered.

Time-schedule for meals is described in Section 8.2.

4.5.2. Stopping Safety Criteria

4.5.2.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Study treatment will be stopped if the following liver chemistry stopping criteria is met:

- ALT ≥ 3xULN

Refer to Section 13, Liver Chemistry Follow-up Procedures, for details of the required assessments if a subject meets the above criteria.

4.5.2.2. QTc Withdrawal Criteria

A subject that meets either criteria below will be withdrawn from the study. The QT correction formula used to determine discontinuation should be the same one used throughout the study.

- QTc > 500 msec

Withdrawal decisions are to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.
### 4.6. Time and Events Table

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Periods 1-2</th>
<th>FU (36 hours after visit 3 study drug intake)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window Relative to Day 1</td>
<td>-30 to -1 days</td>
<td>+ 7 days</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Complete Physical Exam</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Brief Physical Exam</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height, Weight and BMI</td>
<td>X</td>
<td>X&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Inclusion/Exclusion</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medical/ Medication/ Drug/ Alcohol Histories</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vital Signs&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>12 lead ECG</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Dose with Investigational Product</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Clinical Laboratory Tests (Chemistry &amp; hematology)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Drug/alcohol screen</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HbsAg, HCV, HIV testing</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Admit Subject</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Adverse event assessment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant medication use</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Plasma PK sampling&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Discharge subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out Patient Visit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Weight only.
2. BP, HR at screening, on Day 1 of each period, pre-dose and at the follow-up visit.
3. Plasma PK samples will be collected pre-dose (within 15 minutes prior to dosing) and 36 h post-dose.
5. STUDY POPULATION

5.1. Number of Subjects

Approximately 24 subjects will be enrolled such that approximately 24 subjects complete dosing and critical assessments. Replacement subjects may be added if any subject does not complete both treatment periods.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on OXEMET™ or the reference product that may impact subject eligibility is provided in the product labels, attached in the annexes to this protocol.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. ALT, alkaline phosphatase and bilirubin $\leq 1.5 \times$ ULN (isolated bilirubin $> 1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin $< 35\%$).

2. Single QTc $< 450$ msec.

3. Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the Investigator and the GSK Medical Monitor agree that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

4. Male or female between 21 and 55 years of age inclusive, at the time of signing the informed consent.

5. A female subject is eligible to participate if she is of:

   - Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea.

   - Child-bearing potential and is abstinent\(^1\) or agrees to use one of the contraception methods listed in Section 8.1.1. for an appropriate period of time

---

\(^1\) Abstinence from penile-vaginal intercourse must be consistent with the preferred and usual lifestyle of the subject.
(as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until 7 days post-last dose.

6. Body weight ≥ 50 kg and BMI within the range 19 - 27 kg/m² (inclusive).

7. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

5.2.2. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

8. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening.

9. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

10. A positive pre-study drug/alcohol screen. A minimum list of drugs that will be screened for include amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines.

11. A positive test for HIV antibody.

12. History of regular alcohol consumption within 6 months of the study defined as:

   • an average weekly intake of > 14 drinks for males or > 7 drinks for females. One drink is equivalent to 12 g of alcohol: 360 mL of beer, 150 mL of wine or 45 mL of 40% abv distilled spirits.

13. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

14. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

15. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John’s Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

16. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.
17. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period.

18. Subjects whose sitting blood pressure is less than 110/60 mmHg at screening or prior to dosing, or greater than 140/90 mmHg at screening.

19. Subjects whose pulse is lower than 50 beats per minute or higher than 99 beats per minute at screening or prior to dosing.

20. Subjects whose ECG PR interval is > 220 msec at screening or prior to dosing.

21. Pregnant females as determined by positive serum or urine hCG test at screening or prior to dosing.

22. Lactating females.

23. Unwillingness or inability to follow the procedures outlined in the protocol.

24. Subject is mentally or legally incapacitated.

25. Urinary cotinine levels indicative of smoking or history of regular use of tobacco- or nicotine-containing products within 6 months prior to screening.

26. Consumption of red wine, seville oranges, grapefruit or grapefruit juice from 7 days prior to the first dose of study medication.

27. History of sensitivity to heparin or heparin-induced thrombocytopenia.

6. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

6.1. Hypotheses and Treatment Comparisons

Bioequivalence

This study is designed to test the bioequivalence of OXEMET™ 1000 mg relative to reference product. The null hypothesis is that the true ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, \( \mu(\text{test})/\mu(\text{reference}) \), for each primary PK endpoint, is either less than or equal to 0.80 or greater than or equal to 1.25. The alternate hypothesis is that the true ratio of the test treatment geometric mean to the reference treatment geometric mean is greater than 0.80 and less than 1.25. Symbolically, this is expressed as follows:

\[
H(0): \mu(\text{test})/\mu(\text{reference}) \leq 0.80 \, \text{or} \, \mu(\text{test})/\mu(\text{reference}) \geq 1.25,
\]

i.e., treatments are not bioequivalent.

Versus

\[
H(1): 0.80 < \mu(\text{test})/\mu(\text{reference}) < 1.25,
\]

i.e., treatments are bioequivalent.

For each PK parameter designated as a primary endpoint, a two one-sided t-test (TOST) procedure [Schuirmann, 1987] with \( \alpha = 0.05 \) for each one-sided test will be used to test
this set of hypotheses. This is equivalent to requiring that a 90% interval for the true ratio of test to reference geometric means falls entirely within the range of 0.80 to 1.25.

In this study, national and international guidelines will be followed to determine bioequivalence of OXEMET™ to the reference product, by presenting Concentration against Time profiles and ratios of PK parameters ($\frac{AUC_{\text{Test}}}{AUC_{\text{Ref}}}$ and $\frac{C_{\text{maxTest}}}{C_{\text{maxRef}}}$).

Geometric means ratios for PK parameters will be assessed according to the bioequivalence ranges set by “Disposición 3185/99, 5040/06 and 1746/07” by ANMAT; “Resolución 727/05” by Ministerio de Salud de Chile and other international rules as follows:

$AUC_{\text{Test}} / AUC_{\text{Ref}}$: geometric means ratios for areas under the curve of Test product and Reference product. AUCs ratios will be determined from time zero (pre-dose) to the time of the last quantifiable concentration after study drug administration and from time zero (pre-dose) extrapolated to infinite time after study drug administration. The 90% confidence interval for AUCs geometric means ratio must be within bioequivalence range of 0.8 – 1.25. The 90% confidence interval for logarithmic transformation of the parameter will be assessed.

$C_{\text{maxTest}} / C_{\text{maxRef}}$: geometric means ratio for $C_{\text{max}}$ of Test product and Reference product. The 90% confidence interval for $C_{\text{max}}$ geometric means ratio must be within bioequivalence range of 0.8 – 1.25. The 90% confidence interval for logarithmic transformation of the parameter will be assessed.

An analysis of variance will be performed to assess the effect of sequences and individual on the different PK parameters $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $C_{\text{max}}$.

Descriptive statistics will include mean values (± standard deviation) and geometric means. Individual results will be presented for each volunteer and each formulation, as well as mean values.

Statistical analysis will be performed using WinNonlin v.6.02 (Pharsight Corporation, St. Louis, MO, USA).

6.2. Sample Size Considerations

6.2.1. Sample Size Assumptions

Primarily, up to 24 subjects will be recruited into the study to ensure completion of 24 evaluable subjects. Additional subjects may be enrolled as replacement subjects to attain the 24 evaluable subjects.

Assuming the largest within-subject variability (CVw%) of 25 % and the true ratio of 1, a sample size of 24 should provide 80% power to demonstrate bioequivalence for Oxemet™ under the bioequivalence limit of 0.8 to 1.25.
6.2.2. Sample Size Sensitivity

If the intra-subject CV% is 10% higher than stated above (i.e., equal to 28%) then a sample size of 24 would provide 77% power to demonstrate bioequivalence.

6.2.3. Sample Size Re-estimation

No sample size re-estimation will be performed.

6.3. Data Analysis Considerations

Safety Population

All subjects who enrolled into the study and receive at least one dose of study drug will be included in the Safety Population. This will be the population for the safety analyses, and for summarization of baseline/demographic characteristics.

Pharmacokinetic Parameters Population

The AUC\(_{(0-t)}\), AUC\(_{(0-\infty)}\) populations will include all subjects who undergo plasma PK sampling and have evaluable AUC\(_{(0-t)}\), AUC\(_{(0-\infty)}\) assay results.

The C\(_{\text{max}}\) Populations will include all subjects who undergo plasma PK sampling and have evaluable C\(_{\text{max}}\) parameters.

These populations will be used for PK parameter listing.

6.3.1. Interim Analysis

No interim analysis will be performed.

6.3.2. Final Analyses

Final analysis will be performed after the completion of the study and final datasets authorization.

Data will be listed and summarized with listings being sorted by subject, period, day, and time, noting treatment; summaries will be presented by treatment, day, and time.

WinNonlin v.6.02 (Pharsight Corporation, St. Louis, MO, USA) will be used to analyze the data.

6.3.2.1. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively.
6.3.2.2. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the entity conducting the study (DominguezLab). Plasma metformin concentration-time data will be analyzed by non-compartmental methods with WinNonlin v.6.02 (Pharsight Corporation, St. Louis, MO, USA). Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration ($C_{\text{max}}$), time to $C_{\text{max}}$ ($t_{\text{max}}$), area under the plasma concentration-time curve [AUC$_{(0-t)}$ and AUC$_{(0-\infty)}$], and apparent terminal phase half-life ($t_{1/2}$). Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively.

Descriptive summaries will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and the between-subject CV (% CVb) for continuous variables, whereas n and percent will be used as summary statistics for categorical variables.

Statistical Analysis of Pharmacokinetic Data

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of the entity conducting the study (DominguezLab).

Following log-transformation, $C_{\text{max}}$, AUC$_{(0-t)}$ and AUC$_{(0-\infty)}$ will be separately analyzed using a mixed effects model with fixed effect terms for Period and Treatment. Subject will be treated as a random effect in the model. Point estimates and their associated 90% confidence intervals will be constructed for the differences, A-B. The point estimates and their associated 90% confidence intervals from the log-transformed analysis will then be back-transformed to provide point estimates and 90% confidence intervals for the ratios, A/B, on the original scale.

Bioequivalence will be demonstrated in the adjusted 90% confidence intervals for AUC and $C_{\text{max}}$ of OXEMET™ are completely contained within the equivalence range of (0.80 - 1.25).

7. STUDY ASSESSMENTS AND PROCEDURES

This section lists the parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 4.6). Detailed procedures for obtaining each assessment are provided in the Study Procedures Manual (SPM). Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECGs, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.

7.1. Selection and Inclusion of subjects

The selection and inclusion of patients according to eligibility criteria will be performed following DominguezLab SOP PG-005-CLI-002, attached in Annexes.
7.2. Visits

Visit I – Volunteers screening

The Principal Investigator will be responsible for explaining to the subjects about the nature and implications of participating in the study, as well as clarifying any arising doubt. Only after Informed Consent form is signed by subjects, will other visit procedures be performed, as follows:

- Collection of demographic data.
- Medical history.
- Physical exam, ECG, and laboratory tests (as listed below).
- Provision of instructions regarding hospitalization at visits 2 and 3.

All data will be recorded in the CRF. Such procedures will be conducted at DominguezLab site, Entre Ríos, Paraná, Argentina.

The Principal Investigator will check compliance with eligibility criteria and will inform the Sponsor about the inclusion of the volunteer into the study. Afterwards, the subject will be randomized into the study.

All volunteers presenting with abnormalities at the physical exam, laboratory tests or ECG which preclude their participation in the study, will be informed about the reason why they cannot participate. Additionally, such individuals will be referred to their physician or health care system so that their abnormalities are duly assessed and treated if necessary.

Visit II – Treatment Period I

Volunteers will be admitted at the unit (DominguezLab site) at 20 h, the day before of receiving the study drug. A standardized dinner will be provided to subjects on time so as to ensure 10 h of fasting before the study drug administration the following day. Thus, subjects will be under fasting conditions during 10 h for solid food, and 48 h of abstinence for alcoholic drinks or xanthine-containing drinks (coffee, tea, mate). They will be allowed to drink water *ad libitum* except for 1 h before and 1 h after the administration of the study drug.

The day after, an intravenous catheter (Abbocath, BD Saf-T-Intima or similar) will be placed in the forearm and 8 mL blood samples will be drawn according to the Schedule described in Section 7.6. If such intravenous device cannot be possibly placed, blood samples will be obtained through venipuncture. The total blood volume to be drawn during the whole study is approximately 288 mL.

Before starting with blood sampling and after blood sampling at 2, 4, 8, 12, 24 and 36 h blood pressure and heart rate will be measured; additionally, subjects will be asked about how they are feeling and about any possible adverse event.
According to their randomization number, volunteers will receive a single dose of the reference product (two 500 mg GLAFORNIL™ tablets) or a single dose of the test product (one 1000 mg OXEMET™ tablet) together with 240 mL 10% glucose solution.

Volunteers will remain hospitalized at the site for at least 36 h. Standardized meals and beverages will be provided to them during the whole stay according to the schedule described in Section 8.2.

Subjects will not be allowed to consume food until 4 h after the study drug administration. They will not be allowed to consume alcoholic drinks or xanthine-containing drinks from 48 h before the study drug intake to the completion of blood sampling.

Volunteers will be hospitalized at the DominguezLab Clinical Unit, especially designed to house healthy volunteers. Such unit is equipped with beds, bed linen, air conditioning, changing rooms and bathrooms, living, entertainment room and dining-room close to the nursery office.

Volunteers will be housed in separated rooms according to gender. Ideally, equal number of both genders volunteers will be included in the study (12 of each).

The subjects will remain leaning with 45° inclination or sitting for 4 h after dosing in each period. They will not be allowed to adopt lateral supine position for 6 h after the study drug intake. Only in case of dizziness, they will be allowed to lie on their right side. If due to hemodynamic decompensation, supine position is to be maintained, the subject will be able to remain in the study and the adverse event will be recorded in the CRF.

After blood sampling at 36 h, a general clinical assessment will be performed before discharging the subject from the unit. Instructions to be followed by the subject until the next visit will be given by the study staff.

Washout interval
After discharge, subjects will undergo a 7–day washout period. During such period they will not take any medication without previous consultation to the Principal Investigator, unless it is deemed necessary due an arising life-threatening condition.

Visit III – Treatment period II
Seven days after having received the study drug for the first time, subjects will be hospitalized again at the clinical unit. The procedures will be the same as for Visit II, but the alternate study drug will be administered according to randomization.

Final Safety Follow-up
24 h after the second study drug administration, a blood simple will be drawn for PK assessment (8 mL) and safety clinical laboratory tests (8 mL). A general clinical exam will be conducted as well.
7.3. Demographic/Medical History Assessments

The following demographic parameters will be captured: date of birth, gender, race and ethnicity.

Medical/medication/alcohol history will be assessed as related to the eligibility criteria listed in Section 5.2.

7.4. Safety

Planned timepoints for all safety assessments are listed in the Time and Events Table (Section 4.6).

Physical Exams

- A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.
- A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Vital Signs

- Vital sign measurements will include systolic and diastolic blood pressure and pulse rate.
- Vital signs will be made with the subject in a semi-supine position, having rested in this position for at least 10 minutes beforehand.
- Measurements that deviate substantially from previous readings will be repeated immediately.
- Single blood pressure (BP) and heart rate (HR) measurements will be obtained at all timepoints during the study.

Electrocardiogram (ECG)

- 12-lead ECGs will be performed with the subject in a semi-supine position having rested in this position for at least 10 minutes beforehand.
- Measurements that deviate substantially from previous readings will be repeated immediately.
- 12-lead ECGs will be obtained at 30 minutes pre-dose, 5 and 10 hours post-dosing using an ECG machine. Refer to Section 4.5.2.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

Clinical Laboratory Assessments

Subjects should fast for 8 h prior to clinical safety labs (chemistry and haematology). A 4 h fast is allowed on the day of selection (Visit 1). At the discretion of the Investigator
additional samples may be taken for safety reasons. Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

### Hematology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RBC Indices</th>
<th>Automated WBC Differential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td>RBC Count</td>
<td></td>
</tr>
<tr>
<td>RBC Count</td>
<td>MCV</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>WBC Count (absolute)</td>
<td>MCH</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Reticulocyte Count</td>
<td>MCHC</td>
<td>Monocytes</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>ESR</td>
<td>Eosinophils</td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
<td>Basophils</td>
</tr>
</tbody>
</table>

### Clinical Chemistry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>Potassium</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Chloride</td>
</tr>
<tr>
<td>Glucose, fasting</td>
<td>Total CO₂</td>
</tr>
<tr>
<td>Sodium</td>
<td>Calcium</td>
</tr>
<tr>
<td></td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td></td>
<td>LDH</td>
</tr>
</tbody>
</table>

### Routine Urinalysis

- Specific gravity.
- pH, glucose, protein, blood and ketones by dipstick.
- Urobilinogen, bilirubin.
- Microscopic examination (if blood or protein is abnormal).

### Other screening tests

- HIV.
- Hepatitis A (IgM).
- Hepatitis B (HBsAg).
- Hepatitis C (Hep C antibody - if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA™ immunoblot assay (or other third generation immunoassay) should be reflexively performed on the same sample to confirm the result).
- β-HCG (as needed in women of non-child bearing potential only).
- Alcohol and drug screen (phencyclidine, amphetamines, barbiturates, cocaine, opiates, cannabinoids, benzodiazepines and tricyclic antidepressants).

### 7.5. Pregnancy

#### 7.5.1. Time period for collecting pregnancy information

All pregnancies in female subjects will be collected after the start of dosing and until the follow-up visit.
7.5.2. **Action to be taken if pregnancy occurs**

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.7. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

**Action to be taken if pregnancy occurs in a female partner of a male study subject**

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner’s pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

7.6. **Pharmacokinetics**

7.6.1. **Blood Sample Collection**

**Identification**

PK samples, including primary tubes (whole blood) and secondary tubes (plasma), will be identified in duplicate with Zebra Design labels that will contain the following minimum information:

- Study code.
- Subject randomization number.
- Sample unique number, correlative to total samples of the study.
• Time of extraction with respect to study drug administration time.
• Treatment period.

**Blood sampling Schedule**

Subjects will receive one of the two study medications, at random, between 8 and 9 am in the morning after being admitted to the unit, together with 240 mL of 10% glucose solution, after 10 h of fasting.

Blood sampling will be performed at the following times:

0 pre-dose; 30 min; 1 h; 1 h 30 min; 2 h; 2 h 30 min; 3 h; 3 h 30 min; 4 h; 5 h; 6 h; 8 h; 10 h; 12 h; 15 h; 24 h and 36 h post-dose, considering the moment of study drug administration as time zero. Real time of extractions will be recorded and used in the data analysis.

**Samples volume and total blood volume to be drawn**

Total blood volume to be drawn from each subject recruited in this study, is detailed as follows:

• At visits I and III, approximately 16 mL of blood will be taken to conduct the described biochemical tests, both to assess inclusion criteria and for safety assessment. In addition, urine samples will be obtained.
• At visits II y III, 17 venous blood samples of 8 mL each will be taken, corresponding to a total of 272 mL per subject in the two treatment periods.
• In total, approximately 288 mL of venous blood will be drawn from each subject during the whole study.

**Blood sampling methods**

Blood sampling corresponding to Visit I and to final Safety Follow-up will be obtained through venipuncture according to DominguezLab SOP P-004-PTG-009: “Identification and Preparation of Samples”.

Blood sampling will be performed by nurses and clinical laboratory staff, under the supervision of the Study Coordinator.

Serial blood sampling corresponding to Visits II and III, will be performed according to DominguezLab SOP P-004-PTG-009: “Identification and Preparation of Samples” as follows:

An Abbocath, BD Saf-T-Intima or similar catheter, previously heparinized will be placed at the forearm. 8 mL of venous blood will be drawn at each specified time, recording real time of extraction for consideration during data analysis. Between sampling times, the catheter will be washed with sodium heparin (5 UI/mL) and thereafter with physiologic solution.

**Other materials to be used, sample preparation and storage conditions**
Blood samples will be collected in polypropylene tubes with heparin. Afterward, they will be centrifuged at 3000 rpm. Plasma will be separated with Pasteur pipettes and divided into two polypropylene 2 mL crio-vials. These will be kept frozen at -20ºC until its posterior analysis.

**Samples transportation and storage**

Since all the study stages will be performed at the same site, DominguezLab, plasma samples will be taken to the Bio-analytical Unit which is located a few meters away from the storage area, for its immediate processing and analysis.

Staff from the analytical unit will verify samples conditions and quantity at reception. DominguezLab SOP for storage and transportation of samples is provided in Annexes.

Samples will be kept at -20°C as long as the drug remains stable in the biologic fluid and as long as deemed necessary by the regulatory authority.

DominguezLab will keep validation chromatograms, standard curves, quality controls and quantified samples controls. A copy of all the chromatograms generated through the study will be provided to the Sponsor together with the validation report including 20% of chromatograms and drug quantification results.

### 7.6.2. Sample Analysis

Plasma analysis will be performed under the management of the Clinical Unit of DominguezLab Laboratory, Entre Ríos, Paraná, Argentina. Concentrations of Metformin will be determined in plasma samples using a validated analytical methodology.

**Methods to quantify Metformin plasma concentrations:**

Metformin plasma concentrations will be determined through Liquid Chromatography with Mass Spectrometry (MS/MS) using an internal standard.

An UFLC liquid chromatography equipment composed by a binary pump (SHIMADZU, LC-20AD XR model), with automatic injector (SHIMADZU, SIL-20A XR model), oven to heat the column (SHIMADZU, CTO-10AS VP model) and MS/MS detector (AB Sciex, API 3200 model). Processing methods: protein precipitation reaction with acetonitrile.

**Validation:** The technique to quantify metformin will be validated with respect to selectivity, sensibility, specificity, linearity, accuracy and precision (intra-day and inter-day), recovery and stability, considering acceptance criteria recommended by national and international guidelines. DominguezLab interanal SOPs PG-007-FBF-001: “Validation of bio-analytical methods for HPLC-MS/MS and HPLC-UV”; PG-007-FBF-002: “Stability of drugs in the biological matrix”; and PG-007-FBF-003: “Stability of standard solutions”.
8. LIFESTYLE AND/OR DIETARY RESTRICTIONS

8.1. Contraception Requirements

8.1.1. Female Subjects

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%.

Abstinence

Abstinence from penile-vaginal intercourse must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of < 1%

- Oral contraceptive, either combined or progestogen alone.
- Injectable progestogen.
- Implants of etonogestrel or levonorgestrel.
- Estrogenic vaginal ring.
- Percutaneous contraceptive patches.
- Intrauterine device (IUD) or intrauterine system (IUS) that meets the < 1% failure rate as stated in the product label.
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records.
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, cream or suppository).

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.
8.2. Meals and Dietary Restrictions

Standardized meals provided to subjects are described in the table below. The total daily caloric intake will be between 800 and 1000 kcal, 500 to 600 of which will come from lipids, 250 from carbohydrates and 150 from proteins.

In case any exact item of the menu is not available, it will be replaced by another one but keeping a similar total energy load and proportion between carbohydrates, proteins and fat.

Subjects will not be allowed to consume any food for 4 h after the study drug administration.

<table>
<thead>
<tr>
<th>Meal</th>
<th>Time</th>
<th>Menu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinner</td>
<td>10 h before study drug</td>
<td>1 serving of baked beef with baked potatoes</td>
</tr>
<tr>
<td></td>
<td>administration</td>
<td>500 mL of still mineral water</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 salt sachet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 small packet of crackers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 apple</td>
</tr>
<tr>
<td>Lunch</td>
<td>4 h after study drug</td>
<td>1 chicken piece (breast or leg and thigh), without skin</td>
</tr>
<tr>
<td></td>
<td>administration</td>
<td>1 serving of boiled rice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mL of still mineral water</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 salt sachet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 small packet of crackers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 apple</td>
</tr>
<tr>
<td>Afternoon snack</td>
<td>8 h after study drug</td>
<td>1 cup of decaffeinated coffee plus 20 mL of whole milk)</td>
</tr>
<tr>
<td></td>
<td>administration</td>
<td>2 small packets of crackers or toast</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 serving of spread cheese</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 glass of whole milk</td>
</tr>
<tr>
<td>Dinner</td>
<td>12 h after study drug</td>
<td>1 serving of baked beef with baked potatoes</td>
</tr>
<tr>
<td></td>
<td>administration</td>
<td>500 mL of still mineral water</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 salt sachet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 small packet of crackers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 apple</td>
</tr>
<tr>
<td>Breakfast</td>
<td>24 h after study drug</td>
<td>1 cup of decaffeinated coffee plus 100 mL of whole milk)</td>
</tr>
<tr>
<td></td>
<td>administration</td>
<td>2 butter croissants plus 2 baked ham slices and 2 cheese slices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toast with butter(15 g) and jam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yoghurt plus 2 sugar spoonfuls</td>
</tr>
</tbody>
</table>
8.3. Caffeine, Alcohol, and Tobacco

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, guaraná drinks, chocolate) for 48 h prior to the start of dosing until collection of the final pharmacokinetic sample during each session.
- During each dosing session, subjects will abstain from alcohol for 48 h prior to the start of dosing until collection of the final pharmacokinetic sample during each session.
- Use of tobacco products is not allowed from screening and until after the final follow-up visit.

8.4. Activity

Subjects will abstain from strenuous exercise for 48 h prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

9.1. Permitted Medications

Concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

9.2. Prohibited Medications

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

9.3. Non-Drug Therapies

Subjects must abstain from taking any vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.
10. COMPLETION OR EARLY WITHDRAWAL OF SUBJECTS

10.1. Subject Completion

A completed subject is one who has completed all phases of the study including the follow-up visit. The end of the study is defined as the last subject’s last visit.

10.2. Subject Withdrawal Criteria

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at their discretion, discontinue the subject from participating in this study at any time. Subjects may be prematurely discontinued from the study for any of the following reasons:

- Consent withdrawal by the subject.
- Subject or investigator non-compliance.
- At the request of investigator, or sponsor.
- If after screening, the subject requires concurrent medications that cannot be interrupted for 2 weeks prior to administration of investigational product and until completion of the study.
- Intercurrent medical conditions or adverse events requiring medications.
- Adverse events that require interruption of the study drug.
- Medical contraindication to continue with the study drug.
- Pregnancy.
- Positive urine drug or alcohol screen.

Subjects are not obligated to state the reason for withdrawal. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the Investigator on the Completion/Withdrawal section of the CRF. Every effort should be made by the Investigator to follow up subjects who withdraw from the study.

10.3. Subject Withdrawal Procedures

If a subject is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform the following evaluations: physical examination, blood pressure and heart rate, clinical chemistry, haematology, ECG and AE assessment. These data will be recorded, as they comprise an essential evaluation that needs to be done before discharging any subject from the study.

10.4. Treatment After the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because only healthy volunteers are eligible for study participation.
10.5. **Screen and Baseline Failures**

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to GSK.

11. **STUDY TREATMENT**

Study treatment dosage and administration details are listed in Section 4.4.

11.1. **Blinding**

This will be open-label study.

11.2. **Supply, Packaging and Labeling**

Before the conduction of the study, the Sponsor (GSK Chile) will identify the product batches (authorized by the regulatory authority from the country of manufacturing source) that will be used in the study.

Comparative dissolution essays performed with the batches of the Test product and the Reference product to be used in the study will have to comply with criteria set by “Resolución 727/05 del Ministerio de Salud de Chile”, and in vitro dissolution essay according to the methods set by USP XXIV Pharmacopea. The dissolution test will be performed to 12 units of the Test product, OXEMET™ 1000 mg coated tablets, GlaxoSmithKline (ISP Register N°: Under Registration) and to 12 units of the Reference product.

The strength and contents uniformity of the Test product and the Reference Product will be assessed according to the technique described in USP XXIV Pharmacopea.

Both Test and Reference products to be used in the study will be supplied by the Sponsor. Supplies will consider the possibility of recruiting more than 24 subjects to compensate drop-outs.

**Identification of study drug and labeling**

The contents of the label will be in accordance with all applicable regulatory requirements. The label of the Test product will contain the following information:

OXEMET™, 1000 mg coated tablets containing Metformin Hydrochloride
Oral administration
Technical Director:
ISP Register N°:
Batch N°:
Expiration date:
GlaxoSmithKline

**SAMPLE FOR CLINICAL RESEARCH**

The label of the Reference Product will contain accordingly similar information.
11.3. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required. The volunteer must arrive at the clinical Unity the day previous to receiving the medication, at 20 pm, and will be admitted and remain at the Clinical Unit for at least 36 h. At 8 am of the following day the product will be administered.

Study treatment must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study treatment. Only authorized site staff may supply or administer study treatment. All study treatment will be stored in a secure area with access limited to the investigator and authorized site staff at Dominguez Lab Clinical Unit, according to DominguezLab SOP P-007-FBF-003 “Reception and Control of Study Medication”. Study treatment is to be stored at 15 - 25°C. Maintenance of a temperature log (manual or automated) is required.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance. The investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to GSK and the amount administered to subjects. Reception and accountability of study drug at the site will be documented according to DominguezLab SOP P-007-FBF-003 “Reception and Control of Study Medication”. The required accountability unit for this study will be Metformin tablets. Discrepancies are to be reconciled or resolved. At the completion of the study, both remaining study drug and empty containers will be returned to the Sponsor.

The Sponsor will keep counter samples of study medication used in the study until 2 years after expiration date.

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

11.4. Assessment of Compliance

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When subjects are dosed at the study site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each subject’s mouth to ensure that the study treatment was ingested.
11.5. Treatment of Study Treatment Overdose

For this study, any dose of Metformin > 1000 mg within a 24 h time period [+/- 1 h] will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

12. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of Study Treatment and until the follow-up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g. study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be recorded and reported to GSK within 24 h, as indicated in Section 12.7.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator would promptly notify GSK.

12.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events that do not meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject’s condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.2. Definition of Serious Adverse Events

If an event is not an AE per Section 12.1, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

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

a. Results in death.

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization.

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity.

NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Is associated with liver injury and impaired liver function defined as:

- ALT ≥ 3xULN, and
- Total bilirubin ≥ 2xULN (>35% direct) or INR > 1.5

NOTES:

Bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).

INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.3. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”.
- “Have you had any (other) medical problems since your last visit/contact?”.
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”.
12.4. Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the appropriate data collection tool.

It is not acceptable for the investigator to send photocopies of the subject’s medical records to GSK in lieu of completion of the GSK, AE/SAE data collection tool. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.5. Evaluating AEs and SAEs

12.5.1. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as ‘serious’ when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

12.5.2. Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

12.6. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed data collection tool. The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.7. Prompt Reporting of SAEs to GSK

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to GSK within 24 h. Any follow-up information on a previously reported SAE will also be reported to GSK within 24 h.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 12.5.2, Assessment of Causality.

Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
GSK contacts for SAE receipt can be found at this beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.8. Regulatory Reporting Requirements For SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
13. LIVER CHEMISTRY FOLLOW-UP PROCEDURES

Refer to the diagram in Appendix 1 for a visual presentation of the procedures listed below.

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 4.5.2.1:

- Immediately and permanently withdraw the subject from study treatment.
- Notify the GSK medical monitor within 24 h of learning of the abnormality to confirm the subject’s study treatment cessation and follow-up.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 12.2), the SAE data collection tool will be completed separately with the relevant details.
- Permanently withdraw the subject from the study and do not rechallenge with investigational product.
- The subject will be transferred to the “Clínica Modelo S.A., San Martin 1238, Paraná, Entre Ríos”, accompanied by the Principal Investigator (PI). Following steps will be carried out according Clinica Modelo S.A. Procedures and with the PI supervision.

14. STUDY CONDUCT CONSIDERATIONS

14.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

14.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents.
- Written informed consent (and any amendments) to be obtained for each subject before participation in the study.
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC).
Written informed consent must be obtained from each subject prior to participation in the study. No study procedure will start before the signature of the informed consent.

This study has not therapeutic purposes, therefore no health benefit for the participating subjects is expected.

As with any drug, several adverse events have been reported with metformin, as described in the label of the Test and Reference products. Most of the adverse events arise after prolonged use of metformin, while in this study, subjects will only receive a single 1000 mg dose of metformin in two occasions separated by at least seven days. There may be mild reactions at the venipuncture site like slight pain.

Subjects will be compensated with a pre-defined amount of Money for the participation in the study. The Sponsor will ensure coverage of the medical expenses incurred to treat any adverse event arising from the study medication intake or the study procedures. In case a subject prematurely withdraws from the study, the monetary compensation will be prorated according to the time dedicated to participate in the study. If a subject withdraws before the first hospitalization, there will not be any monetary compensation.

During the subjects participation in the study, DominguezLab will be responsible for the transportation of subjects from their homes to the Clinical Unit and conversely.

14.3. Confidentiality

Investigators will make clear to subjects that confidentiality regarding their personal identifiable data and their participation in the study will be preserved, and that they will not be identified as individuals in any publication of the results.

Regulatory authorities will have access to individual clinical files in order to verify study results. In addition, study monitors, Sponsor auditors and Ethics Committee members will have access to such files.

14.4. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.
The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

14.5. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

14.6. Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK procedures.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If GSK determines such action is needed, GSK will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform investigators or the head of the medical institution (where applicable) and the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

14.7. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable
back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

14.8. Provision of Study Results to Investigators, Posting to the Clinical Trials Register and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report.

Investigators are encouraged to share the summary results with the study subjects, as appropriate.

GSK aims to post a summary of results to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject’s last visit (LSLV). In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

14.9. Data Management

All personal identifiable information collected in this study will be treated and protected according to the Law 25326 (02/11/2001) of Personal Data Protection and the corresponding Ruling Decree 1558/01 (03/12/2001) current in Argentina. The data obtained in this study will not be used for purposes other than the objectives described for this study.

A copy of the CRF for each subject, together with a copy of the records of the bioanalytical assessment, will be provided to the Sponsor. Subject initials will not be collected or transmitted to GSK according to GSK policy. GSK will be provided access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Management of clinical data will undergo data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data.
15. REFERENCES


Disposición ANMAT 5040/2006. Régimen de buenas prácticas para la realización de estudios de Biodisponibilidad/Bioequivalencia.


Georgita, C; Albu, F; David, V; Medvedovicia, A. Simultaneous assay of metformin and glibenclamide in human plasma based on extraction-less sample preparation procedure and LC/(APCI)MS. J.Chromatog B. 2007, 854(1-2), 211-218.


González Cuesta, F; Holguín Martínez G; Archbold Joseph, R; Ruiz Correa, A; Restrepo Garay, M; Peña Acevedo, L; et al. Bioequivalence of Two Metformin Formulations: 850mg Tablets in Healthy Colombian volunteers. IATREIA. 2005, 18(3): 289-301.


Laosa Zafra, O; Ochoa Mazarro, D. Utilización de Medicamentos durante el Embarazo y la Lactancia. En Manual Normon (7ma edición); Laboratorios Normon S. A. Departamento de Publicaciones Científicas: Madrid, 1999, Cap 30; 400.

Najib, N; Idkaidek, N; Beshtawi, M; Bader, M; Admour, I; Mahmood Alam, S; Zaman, Q; Dham, R. Bioequivalence Evaluation of two brands of Metformin 500 mg Tablets (Dialon™ & Glucophage™) – in Healthy Human volunteers. Biopharm. Drug Dispos. 2002; 23, 301-306.


16. **APPENDICES**

16.1. **Appendix 1: Liver Safety Algorithms**

- **ALT ≥ 3xULN ?**
  - **No** → Continue investigational product (IP)
  - **Yes** →
    - Immediately and permanently withdraw the subject from study treatment.
    - Notify the GSK medical monitor within 24 h of learning of the abnormality to confirm the subject's study treatment cessation and follow-up.
    - Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 0), the SAE data collection tool will be completed separately with the relevant details.
    - Permanently withdraw the subject from the study and do not rechallenge with investigational product.
    - The subject will be transferred to the "Clinica Modelo S.A., San Martín 1238, Paraná, Entre Ríos", accompanied by the Principal Investigator (PI). Following steps will be carried out according Clinica Modelo S.A. Procedures and with the PI supervision.