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Keyword: hydrogel, metformin, diabetes, pharmacokinetics, overweight
Effect of a non-systemic, orally-administered hydrogel, GS100, on metformin pharmacokinetics

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Abstract:

Overweight and obesity are major health concerns worldwide, and are major predisposing factors for type 2 diabetes. This single centre, Phase I, randomised, open-label, single-dose, four-arm crossover, device-drug interaction study on 24 healthy volunteers with a body mass index of 25–40 kg/m$^2$ tested the effect of a novel, non-systemic, orally administered hydrogel (GS100) on the pharmacokinetics of the oral antidiabetic drug, metformin. When administered in both the fed and fasted states, the effect of GS100 on metformin pharmacokinetic characteristics was found to be similar to that of food. The type, frequency, and intensity of adverse events observed when GS100 was co-administered with metformin were similar to those observed with metformin alone. This study demonstrates that GS100 can be taken by patients receiving metformin, without altering the administration of metformin.

Key words: diabetes, hydrogel, metformin, novel, obesity, overweight, pharmacokinetics, safety.

Clinical trial: The Effect of Gelesis100 on the Pharmacokinetics of Metformin;
https://clinicaltrials.gov/ct2/show/NCT02524821; NCT02524821
Introduction

Overweight and obesity are major predisposing factors for prediabetes and type 2 diabetes (T2D) and are responsible for increased morbidity and all-cause mortality worldwide (Di Angelantonio et al. 2016). Weight loss of 5–10% is known to lower the risk of weight-related comorbidities such as T2D, hypertension, and cardiovascular disease (Goldstein 1992; Magkos et al. 2016). In a study of 12 patients with recently diagnosed T2D, patients achieved a mean weight loss of 9.7 kg (−9% body weight) following a 6-month intensive exercise and weight loss programme. Eight patients (67%) achieved partial remission of T2D (defined as HbA1c 5.7–6.5%) and all patients had a reduced HbA1c following weight loss. The study also reported significant reductions in inflammation markers, triglycerides, cardiovascular risk, insulin resistance, and fasting insulin levels (Ades et al. 2015).

Recently, we described the results of the First Loss Of Weight (FLOW) study, in which significant weight loss and improved glycaemic control were achieved following twice-daily administration of a novel, non-systemic, orally-administered hydrogel (GSP3, a predecessor of GS100) over 12 weeks (Astrup et al. 2014a, 2014b; Astrup et al. 2015). GS100 is synthesized through a multi-step process that crosslinks carboxymethylcellulose sodium salt (99.7% w/w, E466, GRAS status under FDA 21CFR182.1745 in the USA) with citric acid (0.3% w/w, E330, GRAS under FDA 21CFR184.1033 in the USA), and is designed to mimic the viscoelastic properties of naturally occurring dietary fibres in vegetables (Demitri et al. 2017). Upon ingestion, individual GSP3/GS100 particles absorb water and hydrate to approximately 100 times their original size, mix homogeneously with food (Heshmati et al. 2011), and alter the viscoelastic profile of the gastrointestinal milieu (Demitri et al. 2017). A key observation in the FLOW study was that weight loss was more pronounced in subjects who had elevated or impaired fasting glucose at baseline, compared with the global intention-to-treat population. This supports further study and development of GS100 for patients with prediabetes or T2D.
Metformin hydrochloride, is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with T2D, and is the most widely prescribed first line oral antidiabetic agent (Agarwal et al. 2014). The absolute bioavailability of a single metformin 500 mg tablet under fasting conditions is approximately 50–60% (Bristol Myers Squibb, 2017). Intravenous single-dose studies demonstrate that metformin is excreted unchanged in the urine, and does not undergo first-pass hepatic metabolism or biliary excretion (Bristol Myers Squibb, 2017). While patients are advised to administer metformin with meals to reduce potential gastrointestinal symptoms, administration with food delays time to peak plasma concentration ($T_{\text{max}}$) from 1.5–3 hours to 2–4 hours, reduces peak plasma concentration ($C_{\text{max}}$) by ~40%, and total drug exposure over time (area under the curve; AUC) by ~25% (Bristol Myers Squibb, 2017). Consumption of soluble, fibre-rich agents such as guar gum in the fed state delays metformin $T_{\text{max}}$, reduces AUC by an additional ~40%, and suppresses $C_{\text{max}}$ for at least 6 hours beyond the effects of food (Gin et al. 1989). The clinical relevance of these pharmacokinetic (PK) changes are unknown. However, given these observations with fibre-rich agents, the objectives of this study were to assess whether single-dose, co-administration of GS100 and metformin has any effect on the PK parameters or safety of metformin beyond that of food.
Methods

Study design

This was a single-centre, Phase I, randomised, open-label, single-dose, four-arm crossover, device-drug interaction study conducted at the inVentiv Health Clinique in Québec, Canada. This study was sponsored by Gelesis Inc. (Boston, MA, USA), approved by the Ontario Institutional Review Board, and conducted in compliance with Good Clinical Practices (International Conference of Harmonisation 2013) and guidelines established in the Declaration of Helsinki (World Medical Association 2000). The trial is registered at ClinicalTrials.gov (NCT02524821).

Interactions of metformin and GS100 in vitro

The potential for GS100 to bind metformin was assessed in vitro by dissolution of metformin hydrochloride tablets (4 x 1000 mg) in diluted simulated gastric fluid (SGF) followed by simulated intestinal fluid (SIF) in the presence or absence of GS100. A dialysis bag (Sigma-Aldrich D9402-100FT, 14 KDa cut-off) was used to collect aliquots of SGF or SIF. The dialysis bag allowed diffusion of metformin but not GS100. The quantity of metformin in these aliquots was determined by high-performance liquid chromatography. Metformin recovery – the quantity of metformin recovered from dissolution in the presence of GS100 compared with the quantity of metformin recovered from dissolution in the absence of GS100, expressed as a percentage – was then calculated.

Subjects

Twenty-four healthy, non-diabetic, non-smoking male and female volunteers between 22 and 65 years of age, and with a body mass index (BMI) between 25.0 and 40.0 kg/m² were enrolled in this study and participated following written informed consent. Exclusion criteria included clinically significant illness or surgery within the previous 4 weeks; history of neurological, endocrine, cardiopulmonary, haematological, immunologic, psychiatric, renal,
hepatic, metabolic, or gastrointestinal disease (including prior surgery or intragastric balloon); clinically significant laboratory abnormalities (including positive tests for hepatitis B, hepatitis C, or HIV); clinically significant electrocardiogram or vital sign abnormalities; history of allergic reactions to metformin, carboxymethylcellulose, citric acid, raw cane sugar, gelatin, titanium dioxide, or sodium stearyl fumarate; use of any drugs known to induce or inhibit hepatic metabolism within 30 days; significant abuse of alcohol or illicit drugs; participation in a clinical trial involving administration of an investigational or marketed drug within 30 days (90 days for biologics); use of prescription medication within 14 days or over-the-counter medication (including natural health products) within 7 days; donation of plasma within 7 days or more than 499 mL of blood within 56 days; haemoglobin concentration less than 14.0 g/dL in males and 12.5 g/dL in females; a positive pregnancy test in females; and/or an inability to consume a high-fat, high-caloric meal or drink 500–600 mL of liquid.

Treatment administration and testing

A screening visit occurred within 28 days of the first treatment, in which subjects provided written informed consent; demographic and anthropometric data and medical histories were collected; and a clinical evaluation was conducted that included a 12-lead electrocardiogram, vital signs, clinical haematology, laboratory and coagulation analysis, HIV and hepatitis B and C tests, and urinalysis of pregnancy hormones and illicit drugs.

Following a laboratory-confined 10-hour fast, subjects were provided with 1) a single tablet of 850 mg immediate-release metformin hydrochloride (Glucophage, Bristol-Myers Squibb Co, USA) with 100 mL H\textsubscript{2}O, with or without 2) 2.25 g of GS100 (administered as 3 gelatin capsules containing 0.75 g each, with a total of 600 mL H\textsubscript{2}O), and with or without 3) US Food and Drug Administration-recommended (Food and Drug Administration 2002) standard meals containing 150 kcal protein, 250 kcal carbohydrate, and 500–600 kcal fat according to the schema shown in Table 1. All subjects completed all treatment groups in a sequential, block-randomized fashion (BACD, DCAB, ADBC, or CBDA) and were allowed 7
days of washout between treatments. The total duration of the study was approximately 3 weeks.

**Blood collection and metformin pharmacokinetic analyses**

Nineteen venous blood samples (3 mL each) were collected in vacutainer tubes containing EDTA at baseline and 0.5, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 12, 16, and 24 hours following metformin dosing. Metformin concentrations were determined on aliquots of plasma by protein precipitation using acetonitrile (Omnislov, EMD, Toronto, Canada) using an API 4000 tandem mass spectrometer (Sciex, Concord, Ontario, Canada). The PK parameters $AUC_{0-24}$, $C_{max}$, and $T_{max}$ were calculated by standard non-compartmental methods and analysed using Pharsight® Knowledgebase™ Server and WinNonlin® that were validated for bioequivalence/bioavailability studies.

**Safety and adverse events**

Adverse events (AEs) were recorded and evaluated for their seriousness, intensity, and relationship to GS100 and metformin throughout the duration of the study and during a 7-day follow-up period. Serious AEs were reported to the sponsor via telephone, fax, e-mail, or in person within 24 hours.

**Data and statistical analysis**

Actual sampling time was used for the PK parameters and was calculated as the difference between the actual pre-metformin sampling time and actual post-metformin sampling time. For the evaluation of potential GS100-metformin interactions, comparisons of PK data were made for 1) co-administration of metformin and GS100 in the fasted state versus single administration of metformin in the fed state, 2) co-administration of metformin and GS100 in the fed state versus single administration of metformin in the fed state. In addition, PK data following single administration of metformin in the fed and fasted states were compared. Inferential statistics were performed using general linear models procedures.
in SAS® version 9.3 (Cary, NC, USA). Analysis of variance was performed on untransformed $T_{\text{max}}$ and on ln-transformed AUC and $C_{\text{max}}$ at an $a$ priori alpha level of 0.05. Factors incorporated in the model included: Sequence, Subject (Sequence), Period, and Treatment. Sequence was tested using Subject (Sequence) as the error term. Demographic and safety parameters were summarised descriptively.
Results

Subjects

Demographic characteristics of the 24 subjects are provided in Table 2.

Interactions of metformin and GS100 in vitro

Incubation of metformin hydrochloride with GS100 for up to 5 hours resulted in an 83–94% recovery of metformin compared with recovery of metformin alone.

Metformin pharmacokinetics

PK parameters related to metformin absorption are provided in Figure 1 and Table 3. Administration of metformin alone, with a high-calorie, high-fat meal led to expected reductions in $C_{\text{max}}$ ($-32\%, P < 0.0001$) and $AUC_{0-24}$ ($-18\%, P = 0.0012$), and a delay of $T_{\text{max}}$ by approximately 1 hour ($P = 0.0022$). Co-administration with GS100 during this fed condition had no further effect on $C_{\text{max}}$ ($-3.2\%, P = 0.4187$) or $AUC_{0-24}$ ($+0.3\%, P = 0.9701$), and $T_{\text{max}}$ was non-significantly increased from $3.4 \pm 1.3$ hours to $3.8 \pm 1.0$ hours ($P = 0.0938$).

The observed $C_{\text{max}}$ and $T_{\text{max}}$ of metformin following a single 850 mg dose under fasting conditions in this study was consistent with previously reported values for a population of generally healthy subjects who were provided the immediate-release formulation ($C_{\text{max}}$ 1938 ng/mL in this study compared with 1600 ng/mL previously reported; $T_{\text{max}}$ 2.6 hours in the current study compared with 2.64 hours previously reported) (Bristol Myers Squibb, 2017). When co-administered with GS100 under fasting conditions, $C_{\text{max}}$ and $AUC_{0-24}$ of metformin were reduced by $-37\%$ ($P < 0.0001$) and $-32\%$ ($P < 0.0001$), respectively, and $T_{\text{max}}$ was non-significantly shortened from $2.6 \pm 0.8$ to $2.3 \pm 0.9$ hours ($P = 0.3092$).

Administration of GS100 with a single dose of metformin in the fasted state had a significant effect on $AUC_{0-24}$ and $T_{\text{max}}$ compared with the administration of a single dose of
metformin in the fed state. When a single dose of metformin was co-administered with GS100 in the fasted state, AUC$_{0-24}$ was decreased by 16.7% compared with a single dose of metformin administered in the fed state (8039 ± 2909 h*ng/mL compared with 9646 ± 2339 h*ng/mL respectively, $P = 0.0003$); $T_{\text{max}}$ was also reduced when metformin was co-administered with GS100 compared with the fed state (2.3 ± 0.9 hours compared with 3.4 ± 1.3 hours respectively, $P < 0.0001$). $C_{\text{max}}$ was also reduced in metformin with GS100 compared with metformin in the fed state, but this reduction was not significant (1228 ± 384 ng/mL compared with 1312 ± 269 ng/mL, $P = 0.1593$).

Safety and tolerability

Overall, a single-dose administration of GS100 was safe and well tolerated. No serious, unexpected, or increased frequency of individual AEs beyond those previously reported with metformin (Bristol Myers Squibb, 2017) were observed when metformin was administered with GS100, and no individual AE frequency was increased by co-administration with GS100 (Table 4). The most common AEs reported were headache and loose/soft stools. All AEs were mild to moderate in intensity (Table 4), and no AEs were considered likely to be related to treatment, in the opinion of the investigator (Table 5).
Discussion

Weight loss resulting from a non-systemic, orally-administered hydrogel (GS100) was enhanced in subjects with elevated fasting glucose and prediabetes (Astrup et al. 2014a, 2014b; Astrup et al. 2015) which supports further study in patients with prediabetes and in patients with T2D. Given that the biguanide metformin hydrochloride is a first line oral antidiabetic agent that is widely prescribed (Agarwal et al. 2014), the objectives of this study were to determine whether acute administration of GS100 had any effect on metformin absorption, and to assess the safety and tolerability of a single dose of GS100 administered with metformin.

Absorption parameters following a single, 850 mg dose of immediate-release metformin were reduced ($C_{\text{max}}$ and $AUC_{0-24}$) or delayed ($T_{\text{max}}$) to an expected degree (Bristol Myers Squibb, 2017) when administered with a high-calorie, high-fat meal. Co-administration of metformin with GS100 under fasting conditions altered metformin $C_{\text{max}}$, $AUC_{0-24}$, and $T_{\text{max}}$ in a manner that was similar to that of the administration of metformin in the fed state. GS100 had no additive or synergistic effects on metformin absorption when metformin was administered in the fed state. In-vitro studies indicate that GS100 has a limited interaction with metformin. Furthermore, the frequency, intensity, and type of AEs observed following co-administration of metformin and GS100 were similar to those previously reported for metformin administered as a single agent (Bristol Myers Squibb, 2017).

The administration of GS100 and metformin with a high-calorie, high-fat meal was chosen to meet the recommendations of the US FDA Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence studies (Food and Drug Administration, 2002). As described in the guidance, this meal is expected to exert the greatest impact on drug absorption. However, this meal is not the generally recommended diet for obese patients who are trying to lose weight. Therefore, the actual effect of GS100 on metformin PK may be closer to that shown in the fasted state which was very similar to the fed state.
Ingestion of functional fibres and high-viscosity polysaccharides has been used as a strategy to improve glycaemic control, suppress appetite, and facilitate weight loss in patients with increased cardiometabolic risk (Wanders et al. 2011). However, previous studies reported that co-administered guar gum (Gin et al. 1989) and glucomannan (Shima et al. 1983) with oral antidiabetic agents such as biguanides and sulfonylureas resulted in marked reductions in drug absorption kinetics that were additive with food. While the precise mechanism(s) of this phenomenon are speculative, a potential explanation may be the formation of aggregate structures within the gastrointestinal system (Demitri et al. 2011; Heshmati et al. 2011) that could slow drug absorption across the intestinal mucosa (Gin et al. 1989). The hydrogel used in this study is synthesised through a multi-step process that crosslinks carboxymethylcellulose with citric acid. While the structure of cellulose consists of elongated chains of β-1,4-crosslinked D-glucosyl units that resist digestion in humans, the carboxymethylcellulose comprising the majority of GS100 represents a cellulose derivative with some hydroxyl groups that are substituted with carboxymethyl groups (-CH₂COOH) that alter the molecule’s water solubility, pH resistance, and salt compatibility. Upon ingestion, individual GS100 particles absorb water and hydrate to approximately 100 times their original size, the resulting non-caloric gel mixes homogeneously with food, does not form aggregates (Heshmati et al. 2011), and is resistant to digestion within the stomach and small intestine. The results of this human study demonstrate that metformin absorption is not affected beyond that of food. Further, given that GS100 resides exclusively within and is excreted by the gastrointestinal system, and is not metabolised by hepatic cytochrome P450 enzymes, it is unlikely that GS100 would interfere with the metabolism, pharmacodynamics, or excretion of other common antidiabetic agents that utilize this pathway.

There were some limitations to the current study. One potential limitation was the sample size. While no formal sample size calculations were performed, 24 subjects were deemed sufficient for a crossover PK analysis. Additionally, the population was limited to a relatively homogeneous population of white or Caucasian subjects (92%) with Class I obesity, as indicated by a mean BMI of 30 ± 3 kg/m². Therefore, subgroup analysis to
determine potential influences of BMI, or race/ethnicity on metformin PK was not possible. Given the known disparity in prevalence of metabolic disorders among racial and ethnic subgroups (Beckles and Chou 2016), this represents a potential area for future research.

In conclusion, administration of GS100, a novel, non-systemic, orally-administered hydrogel was safe and well tolerated, and frequency, intensity and type of AE reported were similar to those reported when metformin is administered as a single agent. GS100 reduced metformin PK in a similar manner to a high-calorie, high-fat meal, but did not demonstrate any effect on metformin PK beyond that of food. Since it is advised that metformin should be taken with food, there would be no requirement to change the way that metformin is administered.
Abbreviation list

AUC area under the curve
BMI body mass index
C_{max} peak plasma concentration
FLOW First Loss Of Weight
PK pharmacokinetics
SGF simulated gastric fluid
SIF simulated intestinal fluid
T2D type 2 diabetes
T_{max} time to peak plasma concentration

Acknowledgements

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Figure caption

Fig.1. Metformin plasma concentrations under fed (panel A) and fasted (panel B) conditions, with or without co-administration with GS100.
### Tables

**Table 1.** Metformin, non-systemic, orally-administered hydrogel (GS100), and feeding treatment assignments.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Metformin*</th>
<th>GS100</th>
<th>High-calorie, high-fat meal†</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>D</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Note:** *Metformin was administered 30 min after GS100 in the fasted condition, and after consuming the high-calorie, high-fat meal in the fed condition; †Subjects advised to complete meals within 30 min (Food and Drug Administration, 2002).
Table 2. Subject demographics.

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Mean ± SD or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47 ± 12</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>84 ± 12</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>22 (92)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

Note: BMI, body mass index; SD, standard deviation.
Table 3. Metformin pharmacokinetics under fasted and fed conditions.

<table>
<thead>
<tr>
<th></th>
<th>Fed</th>
<th>Fasted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metformin</td>
<td>Metformin + GS100</td>
</tr>
<tr>
<td>N</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>3.4 ± 1.3</td>
<td>3.8 ± 1.0</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1312 ± 269</td>
<td>1270 ± 348</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24}$ (h*ng/mL)</td>
<td>9646 ± 2339</td>
<td>9679 ± 2615</td>
</tr>
</tbody>
</table>

**Note:** Data presented as mean values ± SD; AUC, area under the curve; $C_{\text{max}}$, peak plasma concentration; SD, standard deviation; $T_{\text{max}}$, time to peak plasma concentration.
Table 4. Adverse events in metformin and metformin + GS100-treated subjects under fasted and fed conditions.

<table>
<thead>
<tr>
<th></th>
<th>Fed (n [%])</th>
<th>Fasted (n [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metformin</td>
<td>Metformin + GS100 (2.25 g)</td>
</tr>
<tr>
<td>N</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Any AE</td>
<td>8 (31)</td>
<td>8 (31)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Most frequent AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3 (11)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Loose/soft stools</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (8)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**Note:** Data presented as number of observations and percent of subjects reporting; AE, adverse event; SAE, serious adverse event.
Table 5. Adverse event intensity distribution between metformin and metformin + GS100-treated subjects under fasted and fed conditions.

<table>
<thead>
<tr>
<th>AE intensity</th>
<th>Fed (n [%])</th>
<th>Fasted (n [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metformin</td>
<td>Metformin + GS100 (2.25 g)</td>
</tr>
<tr>
<td>N</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>Mild</td>
<td>8 (31)</td>
<td>8 (31)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Note: Data presented as number of observations and percent of subjects reporting; AE, adverse event.
Table 6. Adverse event causality distribution between metformin and metformin + GS100-treated subjects under fasted and fed conditions.

<table>
<thead>
<tr>
<th>AE causality</th>
<th>Metformin (850 mg) (n [%])</th>
<th>GS100 (2.25 g) (n [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fed Without GS100</td>
<td>Fed With GS100</td>
</tr>
<tr>
<td>Unrelated</td>
<td>2 (8)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Remote</td>
<td>2 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Possible</td>
<td>4 (15)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Probable</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Note: Data presented as number of observations and percent of subjects reporting; AE, adverse event.
Fig. 1. Metformin plasma concentrations under fed (panel A) and fasted (panel B) conditions, with or without co-administration with GS100.