

Bioequivalence of Glucophage® (Metformin) Tablets from Europe and the United States Tested in Healthy Volunteers

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Abstract

Objectives: To investigate whether Glucophage® (metformin) tablets from Europe are bioequivalent to Glucophage tablets from the United States (US) despite *in vitro* dissolution differences. Bioequivalence would indicate that global Phase III data collected with either product is valid for the registration of fixed-dose combinations with metformin in both regions.

Research design and methods: This study included two parts, both of which were conducted according to a randomised, open-label, single-dose, two-period crossover design. The subjects of Part I (N=28) received the 1000 mg Glucophage products, and the subjects of Part II (N=28) received the 500 mg Glucophage products.

Results: At both dose levels (1000 mg and 500 mg), administration of single doses of Glucophage from Europe and the US resulted in comparable exposures, as determined by AUC_{0-inf} and C_{max} of metformin. The geometric mean ratios of AUC_{0-inf} and C_{max} were close to 100%, and the 90% confidence intervals of AUC_{0-inf} and C_{max} were contained within the bioequivalence acceptance limits of 80% to 125%. Incidence of adverse events was low and randomly distributed between treatment groups.

Conclusions: Glucophage tablets from Europe and the US were shown to be bioequivalent at doses of 1000 mg and 500 mg. Glucophage tablets from both markets were well tolerated by healthy male and female subjects.

Keywords: Bioequivalence; Bioavailability pharmacokinetics; Metformin; Glucophage; Type 2 diabetes

Introduction

Metformin has been used as an oral antihyperglycaemic therapy in type 2 diabetes mellitus (T2DM) for over 50 years. Together with lifestyle modification, it is recommended by the American Diabetes Association and the European Association for the Study of Diabetes as first-line treatment for T2DM [1].

A member of the biguanide class of drugs, metformin has a variety of metabolic effects, and its full spectrum of molecular mechanisms has not yet been fully elucidated. Its primary mechanism of action is to decrease hepatic glucose output by inhibiting gluconeogenesis through activation of adenosine monophosphate-activated protein kinase in the liver [2-5]. Although metformin does not stimulate direct insulin secretion from the pancreas, it improves the insulin sensitivity of peripheral tissues and decelerates glucose absorption from the gastrointestinal tract [6,7]. As a result, metformin therapy leads to substantial reductions in glycated haemoglobin A1c (HbA1c) without weight gain or increased risk of hypoglycaemia [8].

Metformin is used at maximum daily doses of 3000 mg in Europe and 2550 mg in the United States (US). Immediate-release tablets (IR) are available at doses of 500 mg, 850 mg and 1000 mg. It is marketed under several trade names. Absorption of metformin is incomplete with a dose-dependent absolute bioavailability that decreases with increasing doses. This effect is most probably attributable to a relatively slow absorption rate together with an effective absorption window that is confined to the small intestine [9].

Since metformin shows good solubility over the entire pH range of 1 to 7.5, it is considered a Biopharmaceutics Classification System (BCS) Class III compound [10]. Metformin is not bound to plasma proteins

to a significant extent [9]. Its volume of distribution (V_d) ranges from 63 to 276 L after intravenous administration [11]. The drug partitions into erythrocytes, most likely as a function of time. Renal excretion of unchanged parent drug in urine is the major mode of elimination of metformin [9]. It does not undergo significant hepatic metabolism or biliary excretion. Metformin shows a high renal clearance that far exceeds creatinine clearance, indicating active tubular secretion as a major contributing factor of metformin elimination. The estimated population mean (± SD) of clearance is 507 ± 129 mL/min in subjects with normal renal function [12].

As the recommended first-line treatment for T2DM, metformin is the most widely used oral antidiabetes drug [13]. Therefore, new antidiabetes drugs are regularly used with metformin, either as a free combination or as a fixed-dose combination (FDC). Phase III studies conducted in support of FDC registrations are typically conducted with the free combination and then bridged to the final FDC product with a bioequivalence trial. In these Phase III and bioequivalence trials, either a European or a US metformin product is used. However, regulators in each region require evidence of bioequivalence between the FDC and the free combination using the respective local reference product.

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To avoid multiple bioequivalence studies for each new molecular entity, we have sought to establish bioequivalence between the European and US reference products for Glucophage® (metformin), as marketed by Merck Pharma (Darmstadt, Germany) and Bristol-Myers Squibb (Princeton, NJ, USA), respectively [11,14]. With this approach, it is hoped that a single bioequivalence study between an FDC and free combination would suffice for approval of new metformin FDC products in both the EU and the US. An *in vitro* approach was considered but determined to be non-feasible since the two products showed different dissolution characteristics. Metformin has non-linear pharmacokinetics, and different tablet strength compositions are not a homologous row. Therefore, we chose to investigate the highest and lowest doses and bracket the intermediate dose.

Methods

Subjects

The study enrolled 56 healthy male and female adult volunteers, 28 for each of two study parts that investigated the bioequivalence of Glucophage 1000 mg and 500 mg tablets. Participants were aged 18-55 years with a body mass index of 18.5-29.9 kg/m². Pre-enrolment health assessments for each participant included complete medical histories, physical examinations, vital signs, 12-lead electrocardiograms (ECGs) and clinical laboratory tests.

Potential participants were excluded based on clinically relevant findings or disorders at screening, hypertension, history of allergies or hypersensitivity, recent blood donations or participation in other clinical trials, and recent treatment with any prescription or non-prescription drugs with half-life >24 hours. Subjects who abused alcohol, drugs or tobacco were also excluded, as were women of child-bearing age who were unwilling or unable to use appropriate contraception until 1 month after study completion. All subjects gave written informed consent.

The protocol was reviewed and approved by the Ethik-Kommission der Landesärztekammer Baden-Württemberg (local ethics committee) and by the Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices) in Germany. The study was conducted in compliance with the guidelines on good clinical practice and with ethical standards for human experimentation established by the Declaration of Helsinki and in accordance with applicable regulatory requirements.

Study design

The two study parts shared a randomised, open-label, single-dose, two-period cross-over design. Study Part I investigated the bioequivalence of two Glucophage tablets at a dose strength of 1000 mg, and Part II investigated the bioequivalence of two Glucophage tablets at a dose strength of 500 mg. Glucophage tablets containing metformin hydrochloride (1000 mg and 500 mg) were obtained from Merck Pharma GmbH, Darmstadt, Germany, and Bristol-Myers Squibb Company (BMS), Princeton, New Jersey, USA. In both study parts, subjects were randomised in a 1:1 ratio to either test (Glucophage Merck)-reference (Glucophage BMS) or reference-test sequences. Treatment sequences were separated by a wash-out period of at least 6 days.

After an overnight fast, the participants received single oral doses of study medication in a standing position with approximately 240 mL water. A physician or a designee administered study medication between

08:00 and 09:00 hours on both study days, and subjects remained under medical surveillance for 24 hours. During both treatment periods a light breakfast was served 2 hours after study drug administration, and standardised meals were served at 4 hours (lunch), 7.5 hours (snack) and 11 hours (dinner) following dosing. Examinations were performed at screening (≤ 21 days before administration of any study medication) and 3-10 days after the last study drug administration. Water was allowed *ad libitum* up to 2.5 L per day except for 1 hour before and 2 hours after drug administration.

Blood sampling

For quantification of metformin plasma concentrations, 4.9 mL of blood was collected from a forearm vein in an ethylenediaminetetraacetic acid anticoagulant blood-drawing tube at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24 and 48 hours after drug administration. Sampling times were based on prior information on the pharmacokinetics of metformin from published literature and in-house studies, which showed that this sampling schedule adequately covered the absorption, distribution and elimination phases for the drug. Blood samples were centrifuged within 60 minutes of collection at 2500 x g for 10 minutes at +4°C. Plasma was collected in two aliquots (each containing at least 1.0 mL plasma) and frozen immediately at or below -18°C.

Bioanalytical methods

Plasma concentrations of metformin were determined using high-performance liquid chromatography coupled to a previously described tandem mass spectrometry method [15]. Assay performance during the study was assessed by back-calculation of calibration standard, tabulation of the standard curve fit function parameters, and measurement of quality control samples.

Pharmacokinetic analysis

Pharmacokinetic analyses were carried out using non-compartmental analysis methods as recommended by the European Medicines Agency's guidance for the investigation of bioequivalence [16]. Maximum concentration (C_{max}) and time to maximum concentration (t_{max}) values were directly obtained from the plasma concentration profiles.

Actual sampling times were used for all pharmacokinetic analyses. Areas under the plasma concentration-time curve (AUC) were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. Other standard pharmacokinetic parameters, such as apparent clearance (CL/F), terminal half-life ($t_{1/2}$) and apparent volume of distribution (V_z/F), were also calculated.

Safety methods

The safety evaluation included all subjects who received at least one dose of study drug. Physical examinations, vital signs, 12-lead ECGs and safety laboratory measurements were performed at screening, and at the end-of-study examination. Tolerability and adverse events (AEs) were assessed descriptively, and evaluated in terms of intensity and relationship to study drugs.

Statistical methods

The inferential analysis incorporated log transformation (natural logarithm) of the primary pharmacokinetic endpoints AUC_{0-inf} and C_{max} prior to fitting an analysis of variance. The difference between the

expected means for log (test)-log (reference) were estimated by the difference in the corresponding least square means (point estimate) between test (Glucophage Merck) and reference (Glucophage BMS). Two-sided 90% confidence intervals (CIs) based on the t-distribution were computed, then back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the median intra-subject ratio. For all other pharmacokinetic parameters, descriptive statistics were calculated.

The sample size for this trial was derived from data characterising the variability of metformin products [17-19]. The intraindividual geometric coefficient of variation (gCV) of the C_{max} of metformin is approximately 23.5%. The variability of AUC is lower than that of C_{max} and did not need to be considered in the sample size assessment. The trial was, therefore, planned to accommodate a true geometric mean ratio of the pharmacokinetic endpoints within the range of 97% to 103% with at least 88% power. These assumptions led to a sample size of 26 evaluable subjects per study part, and an enrolment of 28 subjects per study part was planned to allow for potential drop-outs.

Results

Subject characteristics

Overall, baseline characteristics were comparable between study Part I and Part II (Table 1). Of the 56 Caucasian subjects who entered this study, 15 (53.6%) subjects in Part I and 13 (46.4%) subjects in Part II were male. Mean (\pm SD) age was 36.0 ± 10.2 (range, 20-53) years in Part I and 37.2 ± 9.9 (range, 22-54) years in Part II. Mean (\pm SD) body mass index was 23.6 ± 2.6 (range, 19.4-29.9) kg/m^2 in Part I and 22.9 ± 2.8 (range, 18.5-28.4) kg/m^2 in Part II.

Assay calibration

No interference of endogenous compounds was observed in the blank plasma of humans. For metformin, the calibration curve in undiluted plasma samples was linear over the range of concentrations from 5.00 to 2500 ng/mL using a plasma volume of 50 μ L.

Assay inaccuracy (deviation) and imprecision (coefficient of variation) for the quality control samples, spiked at three concentrations of 10, 200 and 2000 ng/mL, were between 2.50%-6.00% and 3.74%-6.55%, respectively.

Pharmacokinetics of metformin

Overall, pharmacokinetic (PK) parameters of metformin were comparable after administration of Glucophage from BMS and Merck in the two study parts.

Geometric mean drug plasma concentration-time profiles of metformin (Figure 1) were nearly identical, suggesting an equal *in vivo* performance of the two products at both doses. Maximum concentrations of metformin were reached at \sim 2.5 hours after dosing (range, 0.5-4.0 hours). Following maximum concentration, bi-exponential elimination profiles of metformin were seen, with a rapid disposition phase until approximately 12 hours after drug administration followed by a slower disposition phase.

Non-compartmental pharmacokinetic parameters of metformin with Glucophage 1000 mg and 500 mg are presented in Table 2. The $t_{1/2}$ of metformin ranged from 3.5 to 30.1 hours, with means of 7.0 and 7.3 hours for the BMS and Merck 1000 mg products and 6.3 and 6.9 hours for the BMS and Merck 500 mg products. Apparent volumes of distribution were consistent within doses, with ranges of 1050-1120

	Study part I (1000 mg Glucophage)	Study part II (500 mg Glucophage)
Patients, N	28	28
Age, y (SD)	36.0 (10.2)	37.2 (9.9)
Sex, n (%)		
Female	13 (46.4)	15 (53.6)
Male	15 (53.6)	13 (46.4)
Body mass index, kg/m^2	23.6 (2.6)	22.9 (2.8)
Smoking status, n (%)		
Never smoked	14 (50.0)	13 (46.4)
Ex-smoker	9 (32.1)	10 (35.7)
Smoker	5 (17.9)	5 (17.9)
Alcohol status		
Non-drinker	9 (32.1)	5 (17.9)
Drinker – no interference*	19 (67.9)	23 (82.1)
Drinker – possible interference*	0 (0.0)	0 (0.0)

*Interference with trial participation (subjects were not allowed to consume alcoholic beverages from 7 days before drug administration until the end of the study)

Table 1: Baseline demographics and clinical characteristics of the study population.

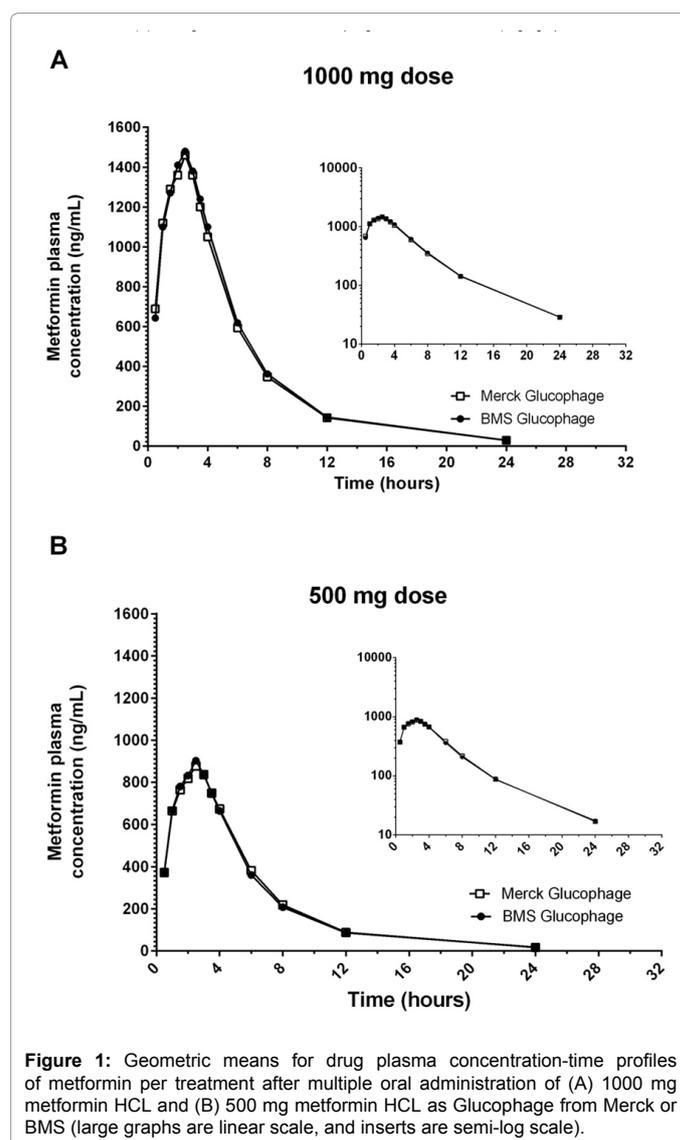


Figure 1: Geometric means for drug plasma concentration-time profiles of metformin per treatment after multiple oral administration of (A) 1000 mg metformin HCL and (B) 500 mg metformin HCL as Glucophage from Merck or BMS (large graphs are linear scale, and inserts are semi-log scale).

L and 797–862 L for the 1000 mg and 500 mg products, respectively. Apparent clearances of metformin were consistent between products at the respective doses. Metformin plasma exposures were less than proportional between the 1000 and 500 mg doses.

Geometric mean ratios and 90% CIs for the primary endpoints are shown in Table 3. For both doses, adjusted test-to-reference geometric mean ratios were close to 100 for $AUC_{0-\infty}$ and C_{max} . For the $AUC_{0-\infty}$ and C_{max} parameters, 90% CIs were contained within the bioequivalence acceptance limits of 80% to 125%. Comparisons of intraindividual values of $AUC_{0-\infty}$ and C_{max} are shown in Figures 2 and 3, respectively.

Safety results

Adverse events were reported by 16 (57.1%) and 11 (39.3%) subjects in Part I and Part II, respectively. Neither AEs of severe intensity nor serious AEs were reported. The most common drug-related AE in both study parts was diarrhoea of mild intensity, experienced by 10 (35.7%) and 6 (21.4%) subjects in Part I and Part II, respectively. The incidence of drug-related diarrhoea was similar after administration of both Glucophage products. All remaining AEs reported during this study were regarded as unrelated to trial medication. All AEs resolved by the end of the study.

Overall, clinical laboratory values and all other observations related to safety (vital signs and ECG) were normal and showed no clinically relevant differences between treatments.

Discussion

This study was undertaken to establish the bioequivalence of Glucophage tablets from the European and US markets in order to

support development of upcoming FDCs with metformin. In the past, FDCs often were approved in both regions by conducting separate bioequivalence trials between the FDC and the free combination using the local reference product. Establishing bioequivalence between European and US reference products should mean that only one bioequivalence trial per FDC will be necessary in the future.

The results from this study show that Glucophage tablets manufactured by Merck (European reference product) and BMS (US reference product) at the dose strengths of 500 and 1000 mg can be considered bioequivalent. Mean plasma concentrations and times to maximum concentrations were similar within doses, and adjusted geometric mean ratios for those parameters were close to 100 with 90% CIs contained within generally accepted bioequivalence limits. These findings confirm the classification of metformin as a BCS III compound, according to which the *in vivo* performance of the drug is controlled by its permeability, and tablet dissolution differences are not relevant for *in vivo* behaviour.

When comparing the metformin plasma exposure between the 500 and 1000 mg dose strengths, a less than proportional increase was clearly observed. This was probably due to decreases in bioavailability with dose as described in the product labels. Apparent volumes of distribution and apparent clearances were consistent within doses, but were higher for the 1000 mg products than for the 500 mg products. These findings are also consistent, with a dose-dependent bioavailability explaining the differences in V/F and CL/F. Presumably there were no real differences in V or CL themselves.

Metformin products from both manufacturers are also available in 850 mg tablets. Although this study did not include the 850 mg

	Study part I		Study part II	
	Glucophage 1000 mg Merck (n=28)	Glucophage 1000 mg BMS (n=28)	Glucophage 500 mg Merck (n=28)	Glucophage 500 mg BMS (n=28)
$AUC_{0-\infty}$ (ng·h/mL)	9360 (21.3)	9620 (20.0)	5770 (24.4)	5670 (27.5)
AUC_{0-tz} (ng·h/mL)	9180 (21.7)	9410 (21.6)	5650 (25.1)	5550 (27.8)
C_{max} (ng/mL)	1560 (27.4)	1580 (25.3)	955 (29.9)	942 (28.6)
t_{max} (h)*	2.50 (0.52–3.50)	2.50 (0.98–4.03)	2.50 (1.00–4.00)	2.50 (1.50–4.00)
CL/F (mL/min)	1780 (21.3)	1730 (20.0)	1440 (24.4)	1470 (27.5)
V_z/F (L)	1120 (55.0)	1050 (71.5)	862 (62.0)	797 (59.1)
$t_{1/2}$ (h)	7.29 (49.5)	7.01 (60.0)	6.89 (54.4)	6.26 (51.8)

*Median and range are given

$AUC_{0-\infty}$ area under the concentration-time curve of the analyte in plasma from 0 to infinity; AUC_{0-tz} area under the concentration-time curve of the analyte in plasma from 0 to the last measurable concentration in plasma; C_{max} maximum measured concentration of the analyte in plasma; t_{max} time from dosing to the maximum measured concentration of the analyte in plasma; CL/F, apparent clearance of the analyte in plasma following extravascular administration; V_z/F , apparent volume of distribution during the terminal phase λ_z following an extravascular dose; $t_{1/2}$, terminal half-life of the analyte in plasma; gCV geometric coefficient of variation

Table 2: Geometric mean (%gCV) non-compartmental pharmacokinetic parameters of metformin after multiple oral administrations of 500 mg and 1000 mg metformin HCL as Glucophage from BMS and Merck.

Test (n=28)	Reference (n=28)	Pharmacokinetic endpoint (unit)	Adjusted gMean ratio Test/Reference [%]	Two-sided 90% confidence interval		Intra-individual gCV (%)
				Lower limit (%)	Upper limit (%)	
Glucophage Merck 1000 mg	Glucophage BMS 1000 mg	$AUC_{0-\infty}$ (nmol·h/L)	97.2	91.5	103.3	13.3
		C_{max} (nmol/L)	98.4	90.8	106.6	17.7
Glucophage Merck 500 mg†	Glucophage BMS 500 mg	$AUC_{0-\infty}$ (nmol·h/L)	102.2	95.7	109.1	14.3
		C_{max} (nmol/L)	101.6	91.6	112.8	22.9

*Pharmacokinetic parameters were log transformed prior to fitting the analysis of variance model.

†One subject vomited shortly after receiving study drug during the 500 mg phase, and the respective values of the pharmacokinetic endpoints were not included in the analyses

Table 3: Adjusted-by-treatment geometric means and relative bioavailability of metformin.*

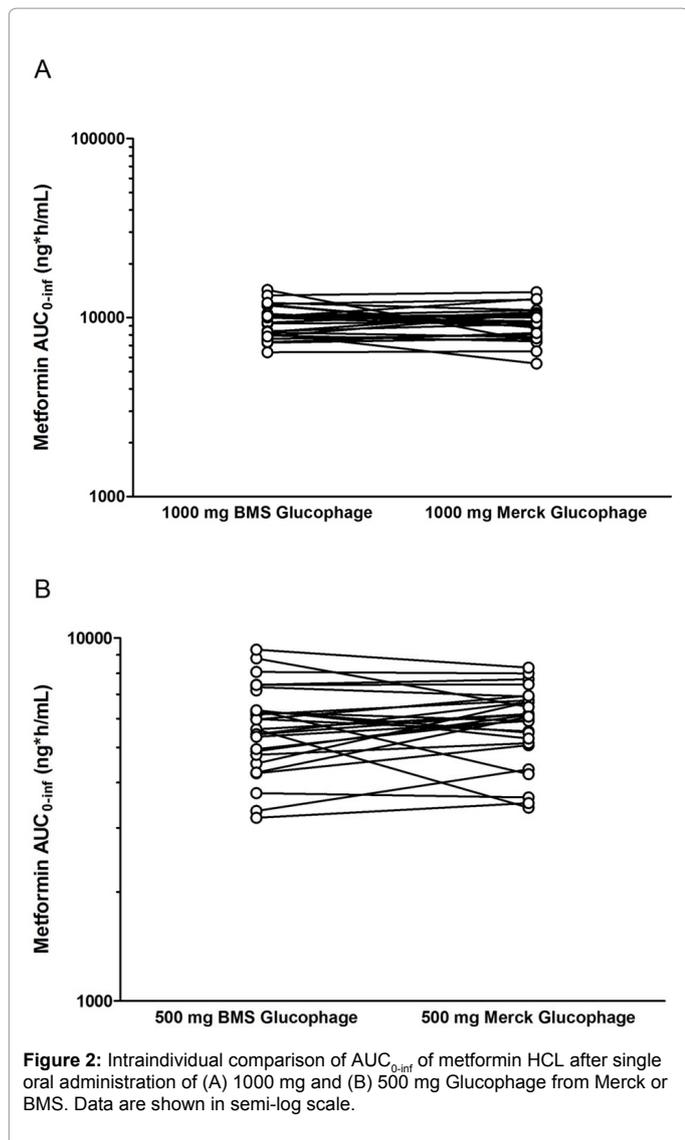


Figure 2: Intraindividual comparison of AUC_{0-inf} of metformin HCL after single oral administration of (A) 1000 mg and (B) 500 mg Glucophage from Merck or BMS. Data are shown in semi-log scale.

products, bioequivalence can be indirectly determined by the findings for the 1000 mg and 500 mg tablets. Because metformin is a BCS Class III compound, a biowaiver for bioequivalence of 850 mg products would be applicable based on the findings of this study [16].

The data from this study can also be combined with other studies to indirectly determine bioequivalence using a network meta-analysis [20]. For example, we had previously performed another trial to assess bioequivalence between a free combination and a fixed-dose combination (FDC) of the dipeptidyl peptidase (DPP)-4 inhibitor linagliptin with metformin (500 mg, 850 mg and 1000 mg) [21] [personal communication] that combines the data of both trials, using the Merck metformin data to bridge between the other two treatments (Ring A, et al. Personal Communication).

All products tested in the present study were well tolerated with no severe AEs experienced. The most commonly reported AE was diarrhoea, which can be expected after administration of metformin products [11,14]. The pharmacokinetic findings of this study are consistent with the established characteristics of metformin, which

include nonlinear kinetics and decreased absorption rates at higher doses [9,11,14].

Our study is the first to demonstrate bioequivalence of European and US Glucophage products marketed by Merck and BMS, respectively. A previous European metformin study showed bioequivalence of 500 mg doses of Glucophage mite (Germany) and Diabex (Australia), and of 500 mg doses of Glucophage mite (France) and Glucophage mite (Switzerland) [18]. It is hoped that our findings will allow developers of metformin FDC products to avoid additional bioequivalence studies for European and US registrations.

Furthermore, we hope that the publication of our findings will encourage other pharmaceutical researchers to follow a similar route of publishing bioequivalence data for reference products. If regulatory authorities will acknowledge this process in their guidelines and accept indirect bioequivalence comparisons, combination drug therapies may become available to physicians and their patients more quickly. In addition, unnecessary bioequivalence studies for local products may be avoided, reducing the need to expose healthy volunteers to the drugs.

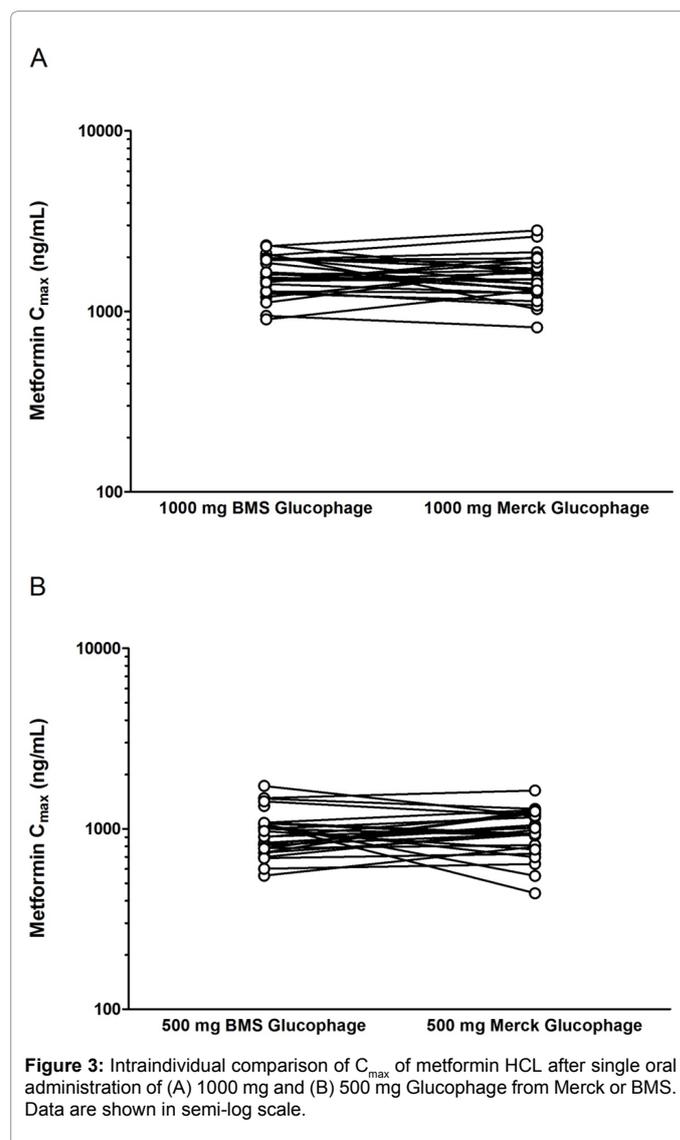


Figure 3: Intraindividual comparison of C_{max} of metformin HCL after single oral administration of (A) 1000 mg and (B) 500 mg Glucophage from Merck or BMS. Data are shown in semi-log scale.

Conclusion

Glucophage tablets from Merck (Europe) and BMS (US) were shown to be bioequivalent at doses of 500 mg and 1000 mg. Glucophage tablets from both markets were well tolerated by healthy male and female subjects.

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