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Pharmacokinetics of Empagliflozin, a Sodium Glucose Cotransporter 2 Inhibitor, and Glimepiride Following Co-administration in Healthy Volunteers: A Randomised, Open-label, Crossover Study

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Abstract

Background: Empagliflozin is a potent and selective sodium glucose cotransporter 2 inhibitor in development for the treatment of type 2 diabetes mellitus. This randomised open-label crossover study investigated potential drug–drug interactions between empagliflozin and the sulphonylurea glimepiride.

Methods: Sixteen healthy male volunteers received 3 treatments (A: 50 mg qd empagliflozin for 5 days, B: 50 mg empagliflozin and 1 mg glimepiride for 1 day, C: 1 mg glimepiride for 1 day) in one of two treatment sequences (AB then C, or C then AB). A washout period of ≥7 days separated treatments AB and C.

Results: Co-administration of glimepiride with empagliflozin had no clinically relevant effects on the area under the plasma concentration-time curve ($AUC_{\tau,ss}$ geometric mean ratio [GMR] 95.2; 90% CI: 92.0, 98.5) or the maximum plasma concentration ($C_{max,ss}$ GMR 95.6; 90% CI: 88.2, 103.5) for empagliflozin or for glimepiride ($AUC_{0-\infty}$ GMR 93.3; 90% CI: 86.1, 101.0; C_{max} GMR 104.2; 90% CI: 89.5, 121.3). Five subjects (31.3%) reported at least one adverse event (AE). Headache (18.8%) was the most frequently reported AE (1 subject while taking empagliflozin and 2 subjects while taking glimepiride). No hypoglycaemia was reported. All AEs were mild or moderate.

Conclusions: Co-administration of empagliflozin and glimepiride did not alter the pharmacokinetics of either drug and was well tolerated. These data suggest that empagliflozin can be co-administered with glimepiride without dose adjustment of either drug.

Trial registration: European Union Drug Regulating Authorities Clinical Trials Eudra CT2008-006060-11

Keywords: Type 2 diabetes, empagliflozin, BI 10773, SGL T2 inhibitor, glimepiride, drug–drug interaction

Background

Although the understanding of type 2 diabetes pathogenesis continues to evolve, the disease is known to be characterised by beta-cell dysfunction and progressive insulin resistance [1]. This progressive nature of the disease is known to cause the gradual loss of efficacy in existing therapies [2]. Side effects associated with existing therapies include hypoglycaemia, weight gain, oedema and gastrointestinal problems [3,4]. As such, there is a need for new medications for the treatment of type 2 diabetes, especially those with novel mechanisms of action, that can be used alone or in combination therapy to help patients achieve and maintain glycaemic targets, without the limiting side effects of current therapies [4].

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of medications being developed as treatments for type 2 diabetes [1]. In healthy individuals, approximately 180 g of glucose per day is filtered by the kidney and this is almost completely reabsorbed back into the bloodstream [5]. SGLT2 is located in the proximal tubule and is estimated to facilitate about 90% of this reabsorption, whilst the remaining 10% is mediated by SGLT1 [5]. The inhibition of SGLT2 reduces glucose reabsorption in the kidney, leading to an increase in urinary glucose excretion and a reduction in plasma glucose levels [6].

Empagliflozin is an orally available, potent and selective inhibitor of SGLT2 [7] that has been shown to be effective in type 2 diabetes through an insulin-independent mode of action. Pharmacokinetic studies of empagliflozin in healthy volunteers and patients with type 2 diabetes have
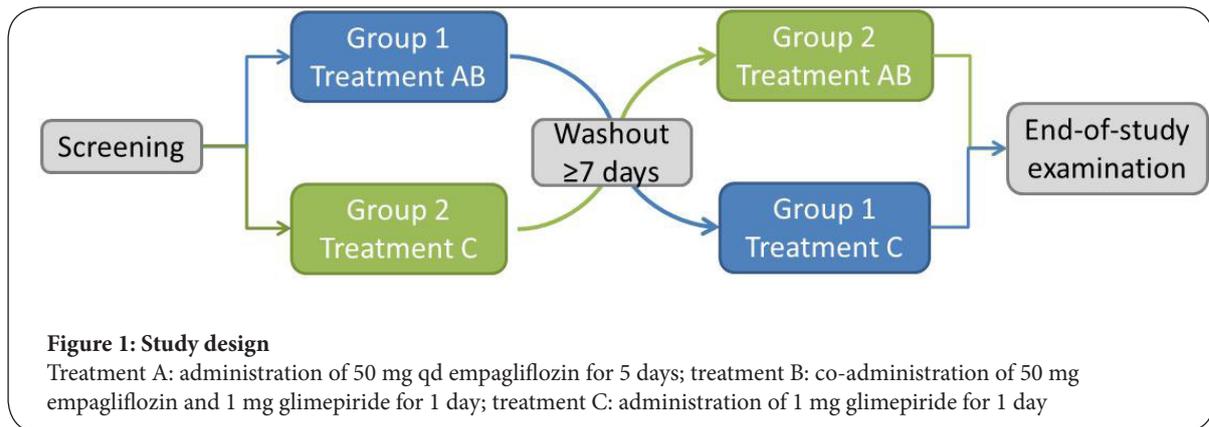
Figure 1: Study design
Treatment A: administration of 50 mg qd empagliflozin for 5 days; treatment B: co-administration of 50 mg
empagliflozin and 1 mg glimepiride for 1 day; treatment C: administration of 1 mg glimepiride for 1 day

shown that empagliflozin was rapidly absorbed following oral administration, reaching peak plasma concentrations within a median of 1 to 3 hours [8,9]. Steady state was reached by day 5 after multiple dosing, and the half-life ranged from 10 to 19 hours in patients with type 2 diabetes [9]. Early studies have shown that once daily administration of empagliflozin in patients with type 2 diabetes was well tolerated and resulted in dose-dependent, clinically meaningful reductions in HbA_{1c} and fasting plasma glucose compared with placebo [9,10].

Glimepiride (Amaryl®; Sanofi-Aventis U.S., Bridgewater, New Jersey) is a non-pancreatic-specific medium-to-long acting sulphonylurea that reduces plasma glucose levels by stimulating beta-cells to produce more insulin [11,12]. As with other sulphonylureas, the use of glimepiride in patients with type 2 diabetes is associated with an increased risk of hypoglycaemia [13]. Glimepiride is extensively metabolised in the liver, mainly by CYP2C9 [14], and concomitant administration of agents that inhibit CYP2C9, such as gemfibrozil and fluconazole, has been shown to increase the risk of hypoglycaemia [15]. Empagliflozin does not inhibit CYP450 enzymes *in vitro* (unpublished data), so the potential for CYP-mediated drug interactions is unlikely, but cannot be ruled out.

The complementary modes of action of SGLT2 inhibitors and sulphonylureas suggest that empagliflozin has the potential to be combined with glimepiride in a clinical setting. This study explored any potential drug–drug interaction between empagliflozin and glimepiride when co-administered in healthy volunteers.

Methods
Subjects
Male subjects aged between 18 and 50 years with a BMI of 18.5 to 29.9 kg/m², who were in good general health according to a complete medical history, were eligible to enter the study. Individuals were excluded if they met exclusion criteria, which included evidence or history of a clinically relevant concomitant disease, use of any drugs that might influence the results of the trial, or participation in another trial with an investigational drug within the previous 2 months. All subjects gave signed and dated informed consent prior to admission to the study. Sixteen men were enrolled and all subjects received all treatments.

Study design
The study was conducted according to an open-label, randomised, multiple-dose, crossover design with three treatments (A, B, C) and two treatment sequences (AB then C, or C then AB) (**Figure 1**). In treatment AB, 50 mg qd empagliflozin was administered for 5 days (treatment A), immediately followed by co-administration of 50 mg empagliflozin and 1 mg glimepiride once on day 6 (treatment B). In treatment C, 1 mg glimepiride alone was administered once. Treatments AB and C were separated by a washout period of at least 7 days (**Figure 1**).

In treatment A, empagliflozin was administered following an overnight fast of at least 10 hours except on day 5 (pharmacokinetic assessment day), when empagliflozin was administered within 30 minutes after breakfast. In treatments B and C, glimepiride with empagliflozin or glimepiride alone was administered within 30 minutes after breakfast. The study medication was administered with 240 mL water. Water was allowed *ad libitum* except 1 hour before and 1 hour after drug administration. In addition to breakfast, standardised meals were served after dosing at the trial centre during pharmacokinetic profile assessment days.

For quantification of empagliflozin and glimepiride plasma concentrations, 2.7 mL of blood was taken from a forearm vein in a tripotassium ethylenediaminetetraacetic acid (K3-EDTA)-anticoagulant blood drawing tube. For treatment A, blood sampling for empagliflozin pharmacokinetic measurements took place pre-dose on days 3 to 5, and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, and 24 hours after the last drug administration.

For treatment B, blood sampling for empagliflozin and glimepiride pharmacokinetic measurements took place pre-dose, and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 24, 36, 48 and 72 hours after co-administration. For treatment C, blood sampling for glimepiride pharmacokinetic measurements took place pre-dose and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 24, 36, 48 and 72 hours after drug administration. Urine sampling intervals (day 5 of treatment A, day 1 of treatments B and C) were -1 to 0 hour before dosing, and 0 to 2 hours, 2 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours after dosing.

Empagliflozin and glimepiride concentrations in plasma and urine were determined by validated HPLC-MS/MS assays (Bioanalytical Systems, Inc., West Lafayette, Indiana). The lower and upper limits of quantification for glimepiride were 1 ng/mL and 500 ng/mL, respectively. At the lower limit of quantification, the precision (%CV) and accuracy (% bias) of the HPLC-MS/MS were 4.2% and -7%, respectively. Selectivity was established via the evaluation of six different lots of matrix from different donor samples, which showed no peaks that interfered with the quantification of glimepiride or the internal standard. At the upper limit of quantification, the precision and accuracy was 3.3% and 2.2%, respectively. The lower and upper limits of quantification for empagliflozin were 2 ng/mL (4.4 nmol/L) and 2000 ng/mL (4440 nmol/L), respectively. At the lower limit of quantification, the precision and accuracy were 11.1% and 0.1%, respectively. At the upper limit of quantification, the precision and accuracy were 2.1% and -0.1%, respectively. Selectivity for empagliflozin was evaluated by an interference check experiment with glimepiride at a C_{max} concentration of 50000 ng/mL. No interference occurred for empagliflozin in the presence of glimepiride.

Pharmacokinetic and pharmacodynamic evaluations

The primary endpoints used to evaluate the pharmacokinetics of empagliflozin (at steady state) and glimepiride (after a single dose) following co-administration were AUC and C_{max}. Secondary endpoints included t_{max}, $t_{1/2}$, fe_{0-24} and $CL_{R,ss}$ for empagliflozin (at steady state) and glimepiride (after a single dose).

Pharmacokinetic parameters were calculated using WinNonlin™ software (v5.2, Pharsight Corporation, Mountain View, California). C_{max} and t_{max} values were directly determined from the plasma concentration time profiles of each subject. The value of $t_{1/2}$ was calculated as the quotient of ln(2) and the apparent terminal rate constant (λ_z). λ_z was estimated from a regression of ln(C) versus time over the terminal log-linear drug disposition portion of the concentration-time profiles. AUC to the last time point was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. The $AUC_{0-\infty}$ value was estimated as the sum of AUC to the last measured concentration, with the extrapolated area

given by the quotient of the last measured concentration and λ_z. The value of fe was determined by the quotient of the sum of drug excreted over all dosing intervals and the dose administered. CL_R was determined as the quotient of fe•dose over AUC.

Urinary glucose excretion over 24 hours following drug administration was a secondary endpoint. Urinary glucose concentration was analysed on a COBAS Integra™ 700 (Roche Diagnostics GmbH, Mannheim, Germany) using the hexokinase enzymatic method performed by AAIPharma GmbH, Neu-Ulm, Germany.

Safety endpoints

The safety evaluation was based on physical examinations, monitoring of vital signs (blood pressure, pulse rate), 12-lead ECG, clinical laboratory tests (haematology, clinical chemistry, urinalysis), AEs, glucose bedside tests, and a global assessment of tolerability by the investigator.

Subjects were monitored for AEs throughout the study. Vital signs and 12-lead ECG were assessed at the screening visit (days -1 to -21), on day 1 of every treatment period (prior to dosing), 2 hours after drug administration in treatments B and C, and at the end-of-study examination visit (3 to 14 days after last glimepiride administration). Clinical laboratory tests were conducted at screening, prior to dosing (treatment A and C), on day 4 (treatment A), on day 2 (treatment B) and at the end-of-study evaluation. Glucose bedside tests were performed using the One Touch® Ultra™ (LifeScan, Johnson and Johnson Company, Neckargemünd, Germany) [16], at several time points in treatments B and C. The global assessment of tolerability was made on the last day of every treatment period. AEs were coded using the Medical Dictionary for Drug Regulatory Activities (version 12.0) [17].

Statistical analysis

All subjects who provided at least one observation for at least one primary endpoint without any protocol violations relevant to the evaluation of pharmacokinetics were included in the inferential analysis of primary endpoints (pharmacokinetic analysis set). The statistical model on log-transformed parameters used for the analysis of $AUC_{\tau,ss}$ and $C_{max,ss}$ of empagliflozin was an analysis of variance (ANOVA) model on the logarithmic scale, including effects accounting for 'subject' and 'treatment'. The model used for the analysis of $AUC_{0-\infty}$ and C_{max} of glimepiride was an ANOVA model on the logarithmic scale including effects accounting for the following sources of variation: 'sequence', 'subjects within sequences', 'period' and 'treatment'. The effect 'subject', or respectively 'subjects within sequences' were considered random, whereas the other effects were considered fixed. Pharmacokinetic parameters were log-transformed (natural logarithm) prior to fitting to the ANOVA model. The difference between the expected means was estimated by the difference in the corresponding least

Table 1: Summary of pharmacokinetic parameters of empagliflozin

Parameter	Empagliflozin	Empagliflozin+ glimepiride
$AUC_{\tau,ss}$, nmol·h/L	9370 (15.4)	8910 (14.2)
$C_{max,ss}$, nmol/L	1350 (23.0)	1280 (14.1)
$t_{max,ss}$, hours*	1.5 (1.0–4.0)	1.5 (1.0–2.5)
$t_{\frac{1}{2},ss}$, hours	8.20 (10.7)	12.8 (59.2)
$fe_{0-24,ss}$, %	20.0 (15.7)	20.5 (14.0)
$CL_{R,0-24,ss}$, mL/min	40.3 (22.6)	43.5 (21.6)

N=16. Data are mean (%CV) unless otherwise stated.

*Median (range).

$AUC_{\tau,ss}$, area under concentration-time curve of empagliflozin in plasma at steady state; $C_{max,ss}$, maximum measured concentration of empagliflozin in plasma at steady state; $t_{max,ss}$, time from last dosing to maximum concentration of empagliflozin in plasma at steady state; $t_{1/2,ss}$, terminal half-life of empagliflozin in plasma at steady state; $fe_{0-24,ss}$, fraction of empagliflozin excreted unchanged in urine at steady state over 24 hours after dosing; $CL_{R,0-24,ss}$ renal clearance of empagliflozin at steady state over 24 hours after dosing.
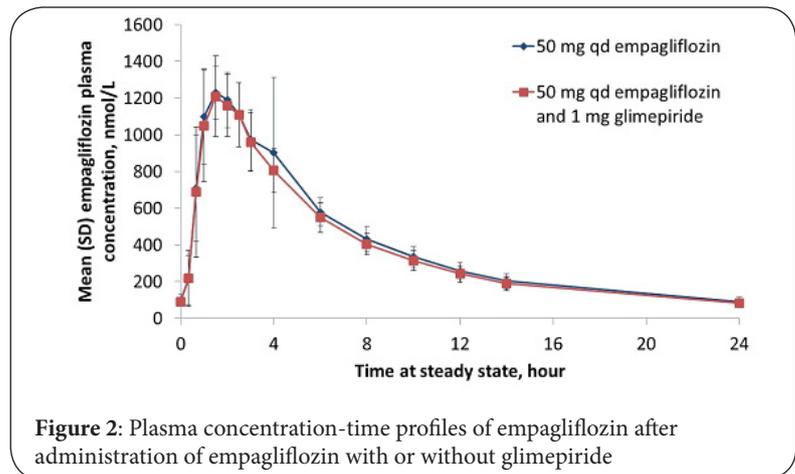

Figure 2: Plasma concentration-time profiles of empagliflozin after administration of empagliflozin with or without glimepiride
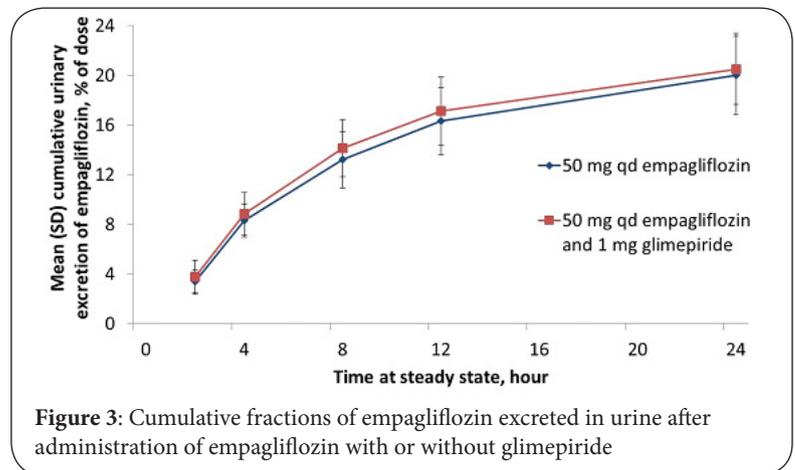

Figure 3: Cumulative fractions of empagliflozin excreted in urine after administration of empagliflozin with or without glimepiride

square means, and 2-sided 90% confidence intervals were calculated based on the t-distribution. These quantities were back-transformed to the original scale to give the point estimators (geometric mean ratios) of the primary endpoints and their 2-sided 90% confidence intervals. Descriptive statistics were also calculated.

All safety analyses were performed on the treated set, defined as subjects who took at least one dose of investigational treatment. Safety analyses were descriptive in nature.

Results
Subject disposition and demographics
All 16 randomised subjects completed the trial as planned and were included in the safety and pharmacokinetic analyses. Eight subjects were randomised to each of the treatment sequences (AB then C, or C then AB). Demographics were similar in both treatment sequences. At baseline, the median (range) age, weight and BMI were 36.0 (20–49) years, 78.5 (67–96) kg and 25.1 (21.4–28.1) kg/m², respectively.

Pharmacokinetics of empagliflozin
Following administration of multiple oral doses of 50 mg qd empagliflozin (treatment A), steady state was reached by day 5. Results of main pharmacokinetic parameters are summarised in **Table 1**. Empagliflozin was rapidly absorbed with a median $t_{max,ss}$ of 1.5 hours. Thereafter, plasma levels declined in a biphasic fashion (**Figure 2**). Empagliflozin exposure was similar after oral administration of 50 mg qd empagliflozin with 1 mg glimepiride compared with empagliflozin alone (**Table 1** and **Figure 2**). The urinary excretion of empagliflozin was not affected by co-administration of glimepiride (mean $fe_{0-24,ss}$: 20.0% when dosed alone vs. 20.5% when co-administered) (**Table 1** and **Figure 3**).

Glimepiride co-administration had no effect on the pharmacokinetics of empagliflozin with respect to the standard bioequivalence boundaries of 80% to 125% (**Table 2**). Intra-individual gCV of empagliflozin between treatments was low for both $AUC_{\tau,ss}$ and $C_{max,ss}$ (**Table 2**).

Table 2: Pharmacokinetics of empagliflozin and glimepiride when given alone and in combination in healthy male subjects

Parameter	Test	Reference	Geometric mean ratio [GMR] (%)	90% CI for GMR		gCV (%)
				Lower limit (%)	Upper limit (%)	
Empagliflozin						
$AUC_{\tau,ss}$	Empagliflozin + glimepiride	Empagliflozin	95.2	92.0	98.5	5.5
$C_{max,ss}$	Empagliflozin + glimepiride	Empagliflozin	95.6	88.2	103.5	12.9
Glimepiride						
$AUC_{0-\infty}$	Empagliflozin + glimepiride	Glimepiride	93.3	86.1	101.0	12.9
C_{max}	Empagliflozin + glimepiride	Glimepiride	104.2	89.5	121.3	24.8

Data are from the pharmacokinetic set; N=16.

CI, confidence intervals; gCV, intra-individual geometric coefficient of variation; $AUC_{\tau,ss}$, area under concentration-time curve of empagliflozin in plasma at steady state; $C_{max,ss}$, maximum measured concentration of empagliflozin in plasma at steady state; $AUC_{0-\infty}$, area under concentration-time curve of glimepiride in plasma over time interval from 0 extrapolated to infinity; C_{max}, maximum measured concentration of glimepiride in plasma.

Table 3. Summary of pharmacokinetic parameters of glimepiride

Parameter	Glimepiride	Empagliflozin+ glimepiride
$AUC_{0-\infty}$, ng·h/mL	233 (30.9)	218 (34.9)
C_{max}, ng/mL	47.4 (31.0)	47.6 (19.7)
t_{max}, hours*	2.0 (1.0–10.0)	1.5 (1.0–2.5)
$t_{\frac{1}{2}}$, hours	3.62 (44.5)	3.84 (60.7)

N=16. Data are mean (%CV) unless otherwise stated.

*Median (range).

$AUC_{0-\infty}$, area under concentration-time curve of glimepiride in plasma over time interval from 0 extrapolated to infinity; C_{max}, maximum measured concentration of glimepiride in plasma; t_{max}, time from dosing to maximum concentration of glimepiride in plasma; $t_{\frac{1}{2}}$, terminal half-life of glimepiride in plasma.
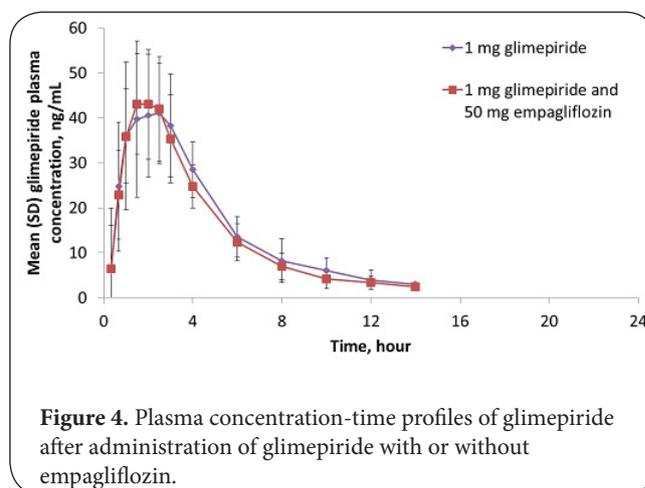

Figure 4. Plasma concentration-time profiles of glimepiride after administration of glimepiride with or without empagliflozin.

Pharmacokinetics of glimepiride

Pharmacokinetic results of glimepiride are summarised in **Table 3**. Glimepiride was rapidly absorbed with a median t_{max} of 2.0 hours. Thereafter, plasma levels declined in a biphasic fashion (**Figure 4**). Glimepiride concentration-time profiles were similar when 1 mg glimepiride was administered alone or with 50 mg empagliflozin (**Figure 4**). Glimepiride urine levels were below the limit of quantification in all subjects with or without empagliflozin co-administration.

Co-administration of empagliflozin with glimepiride had no effect on the pharmacokinetics of glimepiride with respect to the standard bioequivalence boundaries of 80% to 125% (**Table 2**). Intra-individual gCV of glimepiride between treatments was low for both $AUC_{0-\infty}$ and C_{max} (**Table 2**).

Pharmacodynamics

Consistent with the mode of action of empagliflozin and as reported in previous studies [9], increased urinary glucose excretion was observed after administration of empagliflozin alone and in combination with glimepiride. The mean (SD) cumulative urinary glucose excretion over 24 hours after oral administration of 50 mg qd empagliflozin with and without 1 mg glimepiride were 72.7 (14.4) g and 68.7 (12.3) g, respectively. Standardised meals were provided at the trial centre, however there was no control for subjects' food intake. This may be one of the reasons for the wide standard deviation of mean values in urinary glucose excretion observed, and limits the interpretability of urinary glucose excretion data as a pharmacodynamic parameter in this trial.

Safety and tolerability

A total of five subjects (31.3%) reported at least one AE during the trial. Three subjects (18.8%) reported an AE while taking empagliflozin alone, one subject (6.3%) while taking empagliflozin with glimepiride, and four subjects (25.0%) while taking glimepiride alone. All AEs were of mild or moderate intensity. No serious AEs or AEs leading to discontinuation occurred. Headache (18.8%) was the most frequently reported AE (one subject taking empagliflozin alone and two subjects taking glimepiride alone). Other AEs reported by one subject each (6.3%) were fatigue, nasopharyngitis, hordeolum, contusion and pain in extremity. Drug-related AEs (fatigue and headache) were reported by two subjects taking empagliflozin alone and by two subjects taking glimepiride alone (headache). Overall, the evaluation of laboratory parameters, glucose bedside tests, vital signs and ECG recordings revealed no trends considered to be of clinical relevance. No hypoglycaemia (blood glucose <70 mg/dL or 3.9 mmol/L) was reported. The global tolerability assessment was 'good' for all subjects in every treatment period.

Discussion

Management of type 2 diabetes involves the treatment of hyperglycaemia to substantially reduce morbidity [4], and is achieved by attaining specific glycaemic targets, such as the American Diabetes Association's recommended HbA_{1c} target of <7.0% [18]. Despite a range of treatments available, only half of patients with type 2 diabetes achieve the recommended HbA_{1c} target [19]. Most anti-diabetic agents lower blood glucose levels via an insulin-dependent mechanism; however, due to the progressive nature of beta-cell dysfunction in type 2 diabetes [1], the efficacy of these agents is compromised over time [2]. A combination of two or more classes of anti-diabetic agent is more likely to achieve long-term glycaemic control in patients with type 2 diabetes compared to monotherapy [20]. SGLT2 inhibitors, such as empagliflozin, represent a new class of oral anti-diabetic agents that act via a novel insulin-independent mode of action. As glimepiride lowers plasma glucose levels through a different mechanism of action to SGLT2 inhibitors, the combination of these agents in a clinical setting may help patients with type 2 diabetes achieve and maintain glycaemic targets.

This study showed that co-administration of glimepiride had no clinically relevant effect on empagliflozin exposure, as determined by AUC and C_{max}. Similarly, co-administration of empagliflozin had no clinically relevant effect on glimepiride exposure.

Approximately 20% of the administered dose of empagliflozin was excreted in the urine. This is in line with the urinary excretion of empagliflozin shown in other pharmacokinetic studies of empagliflozin in healthy volunteers, which ranged from 17% to 20% [21-

23]. Urinary excretion of empagliflozin was not affected by co-administration with glimepiride. Glimepiride concentrations in urine were below the limit of quantification in all subjects with or without empagliflozin co-administration. This is in line with published data showing the absence of unchanged glimepiride in urine [23].

Almost a third of the 16 subjects in this trial reported at least one AE, but all the AEs were of mild or moderate intensity and none led to discontinuation. No hypoglycaemia occurred and all subjects received a 'good' global tolerability assessment by the investigator. Clinical laboratory evaluations, vital sign and ECG recording assessments revealed no clinically relevant findings.

Conclusions

Overall, empagliflozin and glimepiride were well tolerated when given alone or in combination to healthy male subjects. Based on standard bioequivalence boundaries, glimepiride co-administration had no clinically relevant effect on the pharmacokinetics of empagliflozin. Similarly, empagliflozin co-administration had no clinically relevant effect on the pharmacokinetics of glimepiride. The findings of this study support the co-administration of empagliflozin and glimepiride without dose adjustments.

List of abbreviations

AE: Adverse event

$Ae_{0-24,ss}$: Amount of empagliflozin eliminated in urine at steady state over 24 hours after dosing

ANOVA: Analysis of variance

$AUC_{0-\infty}$: Area under the concentration-time curve of glimepiride in plasma over the time interval from 0 hours extrapolated to infinity

$AUC_{\tau,ss}$: Area under the concentration-time curve of empagliflozin in plasma at steady state over a uniform dosing interval τ

BMI: Body mass index

$CL_{R,0-24,ss}$: Renal clearance of empagliflozin at steady state over 24 hours after dosing

C_{max}: Maximum measured concentration of glimepiride in plasma

$C_{max,ss}$: Maximum measured concentration of empagliflozin in plasma at steady state over a uniform dosing interval τ

CV: Coefficient of variation

ECG: Electrocardiogram

$fe_{0-24,ss}$: Fraction of empagliflozin excreted unchanged in urine at steady state over 24 hours after dosing

gCV: Geometric coefficient of variation

gMean: Geometric mean

HPLC-MS/MS: High performance liquid chromatography, tandem mass spectrometry

SGLT: Sodium glucose cotransporter

$t_{\frac{1}{2}}$: Terminal half-life of glimepiride in plasma

$t_{1/2,ss}$: Terminal half-life of empagliflozin in plasma at steady state

t_{max}: Time from dosing to maximum

concentration of glimepiride in plasma

$t_{max,ss}$: Time from last dosing to maximum concentration of empagliflozin in plasma at steady state

λ_z: Terminal rate constant

Competing interests

Authors' contributions

Acknowledgements and funding

Publication history

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