Adv Ther (2012) 29(10):889–899.
DOI 10.1007/s12325-012-0055-3

ORIGINAL RESEARCH

Pharmacokinetics of Empagliflozin, a Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitor, Coadministered with Sitagliptin in Healthy Volunteers

Tobias Brand · Sreeraj Macha · Michaela Mattheus · Sabine Pinnetti · Hans J. Woerle

To view enhanced content go to www.advancesintherapy.com
Received: July 5, 2012 / Published online: October 1, 2012

ABSTRACT

Introduction: This randomized, open-label, crossover study investigated potential drug–drug interactions between the sodium glucose cotransporter-2 (SGLT-2) inhibitor empagliflozin and the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin. Empagliflozin is a potent and selective SGLT-2 inhibitor that lowers blood glucose levels by inhibiting renal glucose reabsorption, leading to an increase in urinary glucose excretion. Sitagliptin lowers blood glucose through an insulin-dependent mechanism of action.

Methods: Sixteen healthy male volunteers received three treatments (A, B, C) in one of two treatment sequences (AB then C, or C then AB). In treatment AB, 50 mg empagliflozin was administered once daily (q.d.) for 5 days (treatment A), immediately followed by coadministration of 50 mg empagliflozin q.d. and 100 mg sitagliptin q.d. over 5 days (treatment B). In treatment C, 100 mg sitagliptin was administered q.d. for 5 days. A washout period of ≥7 days separated treatments AB and C.

Results: Coadministration of sitagliptin with empagliflozin did not have a clinically relevant effect on the area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ ($AUC_{\tau,ss}$) (geometric mean ratio [GMR] 110.4; 90% confidence interval [CI] 103.9, 117.3) or maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ ($C_{max,ss}$) (GMR 107.6; 90% CI 97.0, 119.4) of empagliflozin. Coadministration of empagliflozin with sitagliptin did not have a clinically meaningful

EudraCT registration number: 2008-006088-35

T. Brand (✉) · S. Pinnetti
Department of Translational Medicine, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, Biberach 88397, Germany
e-mail: tobias.brand@boehringer-ingelheim.com

S. Macha
Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, CT 06877, USA

M. Mattheus · H. J. Woerle
Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Strasse 173, Ingelheim 55216, Germany

Enhanced content for Advances in Therapy articles is available on the journal web site: www.advancesintherapy.com

effect on the $AUC_{\tau,ss}$ (GMR 103.1; 90% CI 98.9, 107.3) or $C_{max,ss}$ (GMR 108.5; 90% CI 100.7, 116.9) of sitagliptin. Empagliflozin and sitagliptin were well tolerated when given alone or in combination. Five subjects (31.3%) reported at least one adverse event (AE): three (18.8%) experienced an AE while receiving empagliflozin monotherapy and three (18.8%) while receiving sitagliptin monotherapy. No adverse events were reported during the coadministration period. No AEs were regarded as drug-related by the investigator.

Conclusion: These results indicate that empagliflozin and sitagliptin can be coadministered without dose adjustments.

Keywords: BI 10773; Diabetes; Dipeptidyl peptidase-4 inhibitor; Drug–drug interaction; Empagliflozin; Sitagliptin; Sodium glucose cotransporter-2 inhibitor

INTRODUCTION

The kidney plays an important role in glucose homeostasis [1]. In healthy individuals, glucose is filtered through the glomeruli and almost completely reabsorbed from the proximal tubule back into the blood [2]. Approximately 90% of this reabsorption is facilitated by the sodium glucose cotransporter-2 (SGLT-2) [2]. A potential new strategy for the treatment of type 2 diabetes involves the inhibition of this glucose transporter. SGLT-2 inhibition blocks glucose reabsorption in the kidney, which increases urinary glucose excretion and results in a reduction in plasma glucose levels. As this reduction in plasma glucose occurs through an insulin-independent mechanism of action, SGLT-2 inhibition is associated with a low risk of hypoglycemia. SGLT-2 inhibition has also been associated with weight loss [3].

In a phase 1 clinical study in healthy volunteers, empagliflozin (a potent and selective SGLT-2 inhibitor [4]) exhibited linear pharmacokinetics following single oral doses over the dose range of 0.5 mg to 800 mg; approximately 11–19% of the administered dose was excreted unchanged in urine over a 72-h period [5]. In this study, doses of up to 800 mg were well tolerated, with no reports of drug-related hypoglycemia. In another study, 8 days' treatment with multiple oral doses of up to 100 mg empagliflozin once daily (q.d.) in patients with type 2 diabetes was shown to be well tolerated, resulting in increases in urinary glucose excretion, and decreases in fasting plasma glucose, compared with placebo [6].

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor [7] approved for the treatment of type 2 diabetes [8], which enhances the duration of incretin action by inhibiting the enzymatic degradation of incretins [9]. The primary route of elimination of sitagliptin is via renal excretion of the intact drug, with approximately 70–80% of the sitagliptin dose excreted unchanged in urine [10, 11].

Despite the availability of a large number of treatments for type 2 diabetes, many patients do not meet targets for glycemic control [12]. New oral antidiabetic agents that can be combined with existing treatment options to improve glycemic control without negative side effects are warranted, and combination therapy with two or more classes of antidiabetic agents is more likely to achieve long-term glycemic control in patients with type 2 diabetes than monotherapy [13]. The complementary modes of action of SGLT-2 inhibitors and DPP-4 inhibitors suggest that empagliflozin has the potential to be combined with a DPP-4 inhibitor in a clinical setting.

The aim of this study was to investigate potential drug–drug interactions between empagliflozin and sitagliptin when coadministered as multiple oral doses in healthy volunteers.

MATERIALS AND METHODS

Subjects

Male subjects aged between 18 and 50 years with a body mass index (BMI) of 18.5–29.9 kg/m², who were in good general health according to a complete medical history and physical examination, were eligible to enter the study. Exclusion criteria included evidence or history of a clinically relevant concomitant disease, the use of any drugs that might influence the results of the trial, and participation in another trial with an investigational drug within the previous 2 months. All subjects gave written informed consent. The protocol was reviewed and approved by the local ethics committee (Ethik-Kommission der Landesärztekammer Baden-Württemberg) and by the Federal Institute for Drugs and Medical Devices of Germany (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). The study was conducted in compliance with the Good Clinical Practice guidelines and the ethical standards for human experimentation established by the Declaration of Helsinki (1996 version), as well as other applicable regulatory requirements. This trial was registered with the European Union Drug Regulating Authorities Clinical Trials database (EudraCT registration number 2008-006088-35).

Study Design

The study was conducted according to an open-label, randomized, multiple-dose, crossover design with three treatments (A, B, C) and two treatment sequences (AB then C, or C then AB) (Fig. 1). In treatment AB, 50 mg empagliflozin was administered q.d. for 5 days (treatment A), immediately followed by coadministration of 50 mg empagliflozin q.d. and 100 mg sitagliptin q.d. over 5 days (treatment B). In treatment C, 100 mg sitagliptin alone was administered q.d. for 5 days. Treatments AB and C were separated by a washout period of at least 7 days (Fig. 1). Subjects were assigned to treatment sequences based on their chronological registration to the study, which occurred at random. The randomization list was generated using a validated system, involving a pseudorandom number generator and a supplied seed number.

Subjects were admitted to the trial center on days 1 and 5 of treatments A and C and on days 1, 2, 3, and 5 of treatment B. The subjects stayed overnight at the trial center on these days

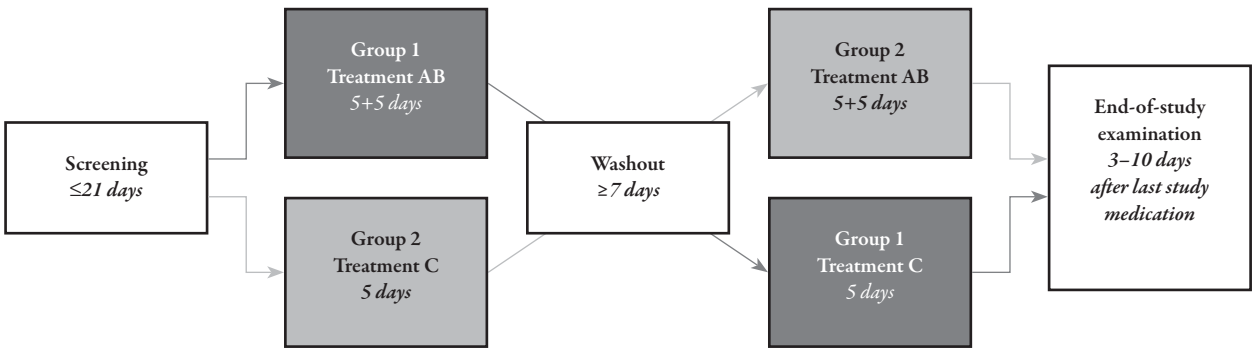

Fig. 1 Study design. Treatment A: administration of 50 mg empagliflozin q.d. for 5 days; treatment B: coadministration of 50 mg empagliflozin q.d. and 100 mg sitagliptin q.d. for 5 days; treatment C: administration of 100 mg sitagliptin q.d. for 5 days. *q.d.*, once daily

except day 1 of treatments A and C, where they were admitted from morning until midday. On day 5 of each treatment, the study medication was administered after the subject had fasted for at least 10 h and with 240 mL water whilst the subject was standing. For standardization, subjects were not allowed to lie down for 2 h following drug administration and water was allowed *ad libitum* except for 1 h before and 1 h after drug administration. Dosing on other days was performed at the trial center but subjects were allowed to leave immediately after drug administration. Medical examinations were performed at screening (within 21 days before administration of any study medication) and at the end-of-study examination visit (3–10 days after last study medication administration).

Sampling and Analysis

Approximately 300 mL of blood was taken from every subject for laboratory tests and pharmacokinetic assessments. For quantification of empagliflozin and sitagliptin plasma concentrations, 2.7 mL of blood was taken from a forearm vein in a tripotassium ethylenediaminetetraacetic acid (K_3-EDTA)-anticoagulant blood drawing tube. In treatment A, blood sampling for empagliflozin pharmacokinetic measurements took place at pre-dose and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, and 24 h after the last administration on day 5. In addition, pre-dose plasma samples were also collected on days 1, 3, and 4. Pre-dose samples on days 3–5 were used to investigate attainment of steady state. For treatment B, blood sampling for empagliflozin and sitagliptin pharmacokinetic measurements took place at 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 h after the last coadministration on day 5. In addition, pre-dose plasma samples were collected on days 1–4. Pre-dose samples on days 1–5 were used to investigate attainment of steady state for empagliflozin, whilst pre-dose samples on days 2–5 were used to investigate attainment of steady state for sitagliptin as plasma concentrations were expected to be below the limit of quantification on day 1 of treatment B. As treatment A was immediately followed by treatment B, only a single sample was collected at a given time point (i.e., 24 h after empagliflozin administration for treatment A and pre-dose sampling on day 1 for treatment B). For treatment C, blood sampling for sitagliptin pharmacokinetic measurements took place at 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 h after the last administration on day 5. In addition, pre-dose plasma samples were collected on days 2–4. Pre-dose samples on days 2–5 were used to investigate attainment of steady state. Urine sampling intervals were –1–0, 0–2, 2–4, 4–8, 8–12, and 12–24 h after the last dosing of the drug(s) in every treatment period (day 5). Empagliflozin and sitagliptin concentrations in plasma and urine were determined by validated high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) assays (Bioanalytical Systems, Inc., West Lafayette, Indiana, USA). The lower limit of quantification (LLOQ) for empagliflozin in plasma was 1.11 nmol/L, whilst the LLOQ for empagliflozin in urine was 4.44 nmol/L. The LLOQ for sitagliptin in plasma and urine was 1 ng/mL.

Pharmacokinetic and Pharmacodynamic Endpoints

The primary endpoints used to evaluate the pharmacokinetics of empagliflozin and sitagliptin following coadministration versus dosing alone were the area under the concentration-time curve of the analyte in

plasma at steady state over a uniform dosing interval τ ($AUC_{\tau,ss}$) and the maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ ($C_{max,ss}$) for empagliflozin and sitagliptin. Secondary pharmacokinetic endpoints included time from (last) dosing to maximum concentration of analyte in plasma at steady state ($t_{max,ss}$), terminal half-life of analyte in plasma at steady state ($t_{1/2,ss}$) and fraction (%) of the dose that was excreted unchanged in urine over 24 h at steady state ($fe_{0\text{-}24,ss}$).

Pharmacokinetic parameters were calculated using WinNonlin™ software Professional Network (v5.2, Pharsight Corporation, Mountain View, California, USA). C_{max} and t_{max} values were directly determined from the plasma concentration time profiles of each subject. The apparent terminal rate constant (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. The value of $t_{1/2}$ was calculated as the quotient of ln(2) and λ_z. The amount of drug excreted unchanged in urine in each collection interval was determined by the product of the urine concentration and the urine volume. The $fe_{0\text{-}24,ss}$ was determined by the quotient of the sum of drug excreted over all dosing intervals and the dose administered.

Urinary glucose excretion over 24 h following drug administration was a secondary endpoint. Glucose concentration was analyzed on a COBAS Integra™ 800 (Roche Diagnostics GmbH, Mannheim, Germany) using the hexokinase enzymatic method performed by AAIPharma (GmbH, Neu-Ulm, Germany).

Safety Assessments

The safety evaluation was based on physical examinations, monitoring of vital signs (blood pressure, pulse rate), 12-lead electrocardiograms (ECGs), clinical laboratory tests (hematology, clinical chemistry, urinalysis), adverse events (AEs), glucose bedside tests, and a global assessment of tolerability by the investigator. Subjects were monitored for AEs throughout the study. Vital signs were assessed at the screening visit, 1 h before first dosing in treatments A and C, and at the end-of-study examination. 12-lead ECG was assessed at the screening visit and at the end-of-study examination. Clinical laboratory tests were conducted at the screening visit, 1 h before first dosing in treatments A and C, 1 h before dosing on day 5 of treatments A and B, and at the end-of-study examination. Glucose bedside tests were performed at several time points in treatments B and C. The global assessment of tolerability was evaluated on the last day of every treatment period. AEs were coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 12.0, Chantilly, Virginia, USA) [14].

Statistical Analysis

All subjects who provided at least one observation for at least one primary pharmacokinetic endpoint without any protocol violations relevant to the evaluation of pharmacokinetics were included in the analysis of primary endpoints (pharmacokinetic set). Point estimators (geometric mean ratios [GMR]) of $AUC_{\tau,ss}$ and $C_{max,ss}$ and their two-sided 90% confidence intervals (CIs) were calculated. The statistical model used for comparison of the treatments containing sitagliptin (treatments B and C) was an analysis of variance (ANOVA) model on log-transformed parameters including effects for “sequence,” “subjects within sequences,” “period,” and “treatment.” The model used for the comparison of the empagliflozin-containing treatments (treatments

A and B) was an ANOVA model on the logarithmic scale with terms for "subject" and "treatment." The values of CIs were based on the residual error from the ANOVA. The effects "subject" and "subjects within sequences" were considered random, whereas the other effects were considered fixed. Descriptive statistics were calculated for all pharmacokinetic and pharmacodynamic parameters. Safety analyses were performed on all subjects who took at least one dose of investigational treatment (treated set) and were descriptive in nature.

RESULTS

Subject Disposition and Demographics

Sixteen subjects entered the trial and were randomized to one of two 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 38.5 (20–49) years, 78.0 (60–98) kg and 24.2 (20.8–28.1) kg/m², respectively. All randomized subjects completed the trial and were included in the treated set as well as the pharmacokinetic set.

Pharmacokinetics of Empagliflozin

Following administration of multiple oral doses of 50 mg empagliflozin q.d. (treatment A), steady state was reached by day 5. Pharmacokinetic data are summarized in Table 1. Empagliflozin was rapidly absorbed with a median $t_{max,ss}$ of 2.5 h. Thereafter, plasma levels declined in a biphasic fashion (Fig. 2a, 2b). Empagliflozin exposure was slightly higher after oral administration of 50 mg empagliflozin q.d. with 100 mg sitagliptin q.d. (treatment B) compared with empagliflozin alone (Table 1,

Table 1 Summary of pharmacokinetic parameters of empagliflozin and sitagliptin (n = 16)

	Pharmacokinetics of empagliflozin		Pharmacokinetics of sitagliptin	
	50 mg empagliflozin q.d. administered alone	50 mg empagliflozin q.d. coadministered with 100 mg sitagliptin q.d.	100 mg sitagliptin q.d. administered alone	100 mg sitagliptin q.d. coadministered with 50 mg empagliflozin q.d.
$AUC_{\tau,ss}$ [a]	8,430 (20.9)	9,280 (19.3)	2,600 (18.7)	2,680 (21.3)
$C_{max,ss}$ [b]	1,180 (23.8)	1,260 (20.0)	341 (26.5)	370 (27.1)
$t_{max,ss}$ (h)[c]	2.5 (1.0–4.0)	2.2 (0.7–4.0)	3.0 (0.7–6.0)	3.0 (0.7–4.0)
$t_{½,ss}$ (h)	8.5 (19.0)	10.7 (26.8)	12.7 (15.0)	13.2 (19.1)
$fe_{0\text{-}24,ss}$ (% of dose)	17.1 (18.0)	19.3 (16.8)	60.3 (17.3)	62.8 (14.0)

Data are mean (%CV) unless otherwise stated

$AUC_{\tau,ss}$ area under concentration-time curve of analyte in plasma at steady state over a uniform dosing interval τ, $C_{max,ss}$ maximum concentration of analyte in plasma at steady state, $fe_{0\text{-}24,ss}$ fraction of the dose that was excreted unchanged in urine over 24 h at steady state, *q.d.* once daily, $t_{max,ss}$ time from (last) dosing to maximum concentration of analyte in plasma at steady state, $t_{1/2,ss}$ terminal half-life of analyte in plasma at steady state

[a] nmol·h/L for empagliflozin; ng.h/mL for sitagliptin

[b] nmol/L for empagliflozin; ng/mL for sitagliptin

[c] Median (range)

Fig. 2a, 2b). Based on standard bioequivalence boundaries of 80–125%, sitagliptin coadministration had no clinically relevant effect on either AUC or C_{max} of empagliflozin (Table 2). Intra-individual geometric coefficient of variation (gCV) between the treatments was low for the $AUC_{\tau,ss}$ and $C_{max,ss}$ of empagliflozin (Table 2). There were no major changes in the urinary excretion of empagliflozin following coadministration with sitagliptin (Table 1, Fig. 3).

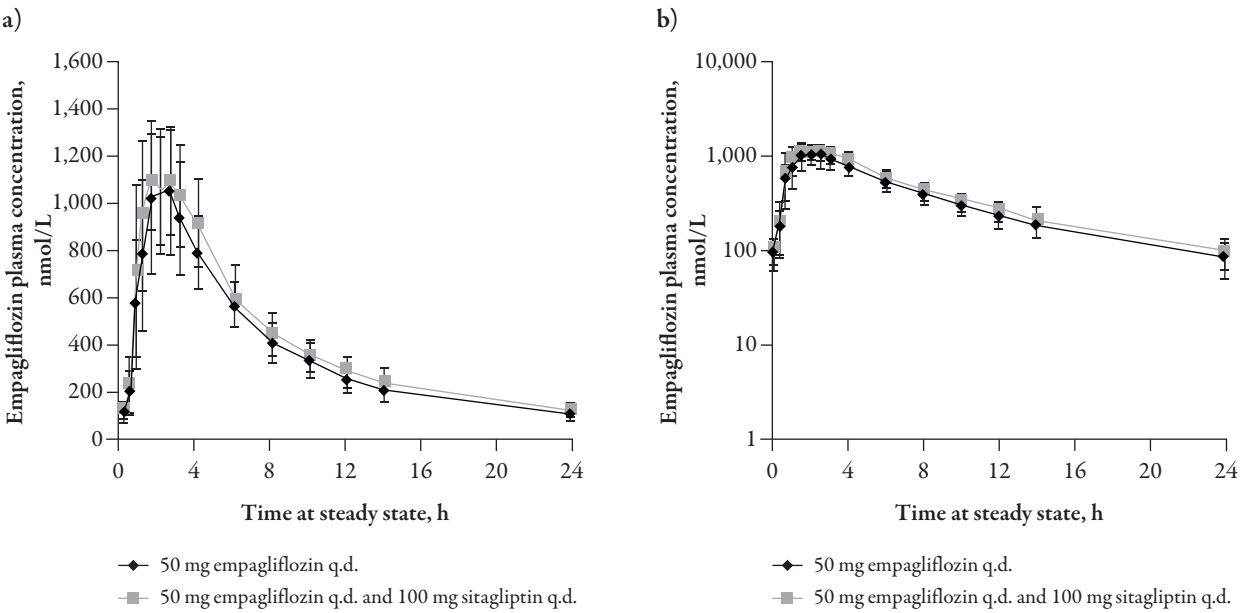

Fig. 2 Mean plasma concentration-time profiles of empagliflozin after oral administration of 50 mg empagliflozin q.d. with and without 100 mg sitagliptin q.d. at steady state (**a**, linear scale; **b**, semi-log scale; $n = 16$). *q.d.*, once daily

Table 2 Pharmacokinetics of empagliflozin and sitagliptin when given alone and in combination at steady state in healthy male subjects (data from the pharmacokinetic set; $n = 16$)

Parameter	Test	Reference	GMR	90% CI for GMR		gCV
				Lower limit (%)	Upper limit(%)	
Empagliflozin						
$AUC_{\tau,ss}$	Empagliflozin + sitagliptin	Empagliflozin	110.4	103.9	117.3	9.8
$C_{max,ss}$	Empagliflozin + sitagliptin	Empagliflozin	107.6	97.0	119.4	16.9
Sitagliptin						
$AUC_{\tau,ss}$	Empagliflozin + sitagliptin	Sitagliptin	103.1	98.9	107.3	6.5
$C_{max,ss}$	Empagliflozin + sitagliptin	Sitagliptin	108.5	100.7	116.9	12.0

$AUC_{\tau,ss}$ area under concentration-time curve of analyte in plasma at steady state over a uniform dosing interval τ, *CI* confidence interval, $C_{max,ss}$ maximum concentration of analyte in plasma at steady state, *gCV* intra-individual geometric coefficient of variation, *GMR* geometric mean ratio

Pharmacokinetics of Sitagliptin

Following administration of multiple oral doses of 100 mg sitagliptin q.d. in treatment C, steady state was reached by day 5. Pharmacokinetic data are summarized in Table 1. Sitagliptin was rapidly absorbed with a median $t_{max,ss}$ of 3 h. Thereafter, plasma levels declined in a biphasic fashion (Fig. 4a, 4b). Sitagliptin concentration-time profiles were similar after oral administration of 100 mg sitagliptin q.d. with 50 mg empagliflozin q.d. (Fig. 4a, 4b). Based on standard bioequivalence boundaries of 80–125%, coadministration of empagliflozin with sitagliptin had no effect with respect to either AUC or C_{max} of sitagliptin (Table 2). Intra-individual gCV between treatments was low for the $AUC_{\tau,ss}$ and $C_{max,ss}$ of sitagliptin (Table 2). There were no major changes in the urinary excretion of sitagliptin following coadministration with empagliflozin (Table 1, Fig. 5).

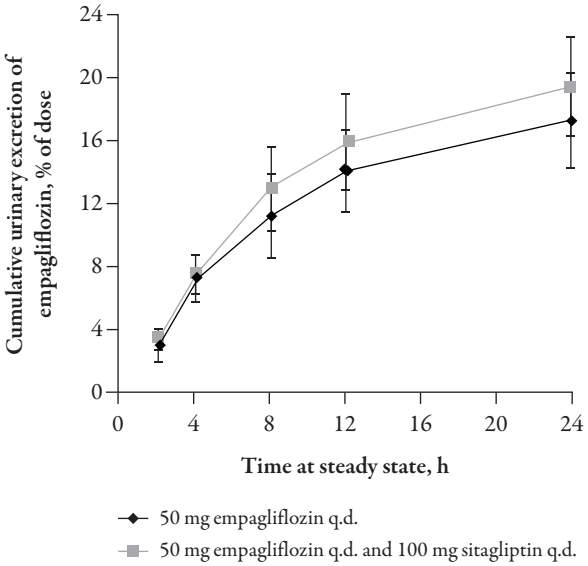

Fig. 3 Mean cumulative fractions of empagliflozin excreted in urine ($n = 16$)

Pharmacodynamics

Consistent with the mode of action of empagliflozin, and as reported in previous studies [6], increased urinary glucose

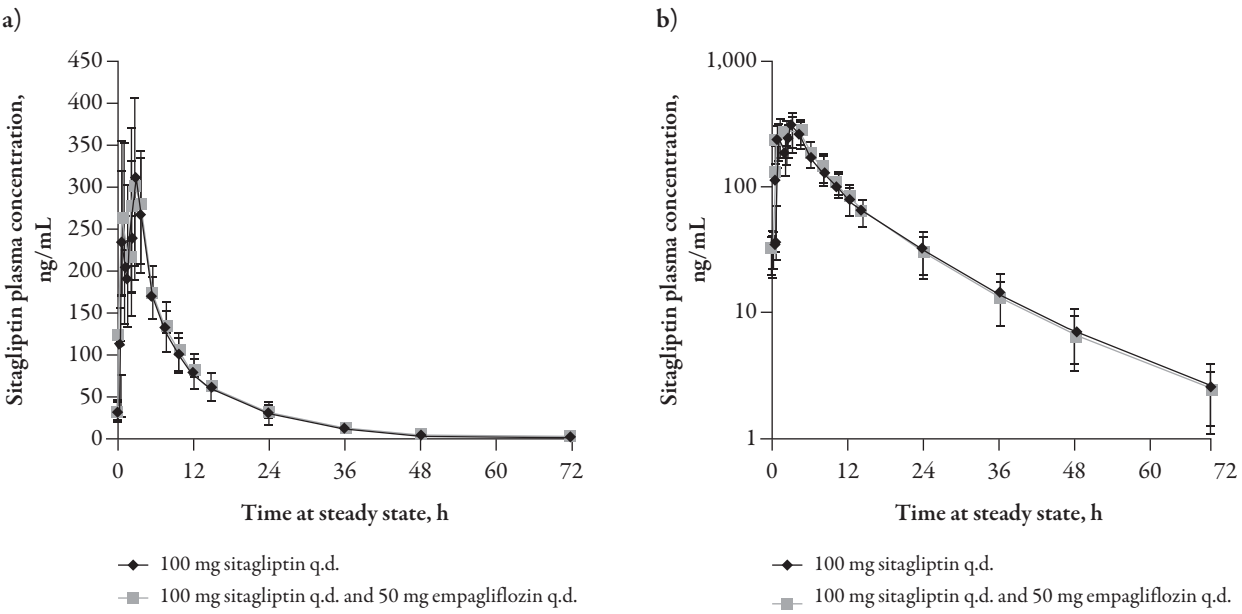

Fig. 4 Mean plasma concentration-time profiles of sitagliptin after oral administration of 100 mg sitagliptin q.d. with and without 50 mg empagliflozin q.d. at steady state (**a**, linear scale; **b**, semi-log scale; $n = 16$). *q.d.*, once daily

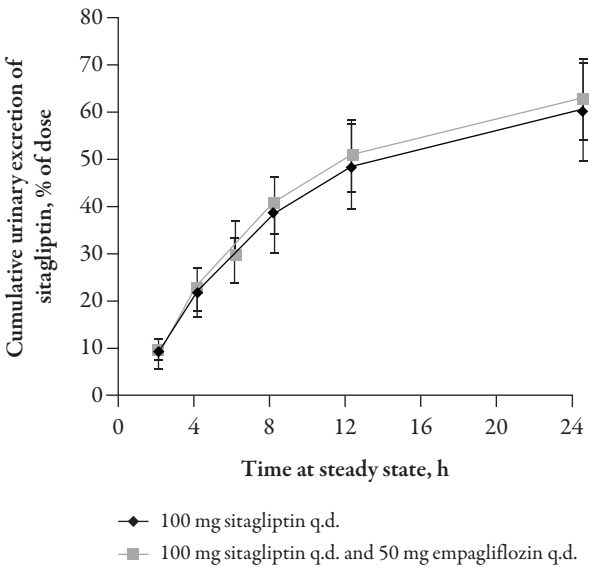

Fig. 5 Mean cumulative fractions of sitagliptin excreted in urine ($n = 16$)

excretion was observed after administration of empagliflozin alone and in combination with sitagliptin.

Safety and Tolerability

Each of the 16 subjects received a total of 500 mg empagliflozin and 1,000 mg sitagliptin during the trial. A total of five subjects (31.3%) reported at least one AE. Three (18.8%) subjects experienced an AE while taking empagliflozin alone and three (18.8%) while taking sitagliptin alone. No AEs were reported during the coadministration period. There were no drug-related AEs as judged by the investigator. The most frequently reported AEs were diarrhea (three subjects on empagliflozin alone) and headache (two subjects on sitagliptin alone). Glossodynia was reported in one subject on empagliflozin alone, and nausea, vomiting, and rash were each reported in one subject on sitagliptin alone. All but one of the reported AEs was of mild or moderate intensity; one subject on sitagliptin alone experienced a headache of severe intensity. No serious AEs occurred. All subjects recovered without the need for special treatment and no AE led to discontinuation. No cases of hypoglycemia (defined as blood glucose <70 mg/dL or 3.9 mmol/L) were reported. Overall, laboratory tests revealed no trends of clinical relevance and there were no clinically relevant findings with respect to vital signs (blood pressure, pulse rate), glucose bedside tests, ECG recordings, or relevant signs of infection. The global tolerability assessment was "good" for all subjects in every treatment period.

DISCUSSION

Empagliflozin acts via an insulin-independent mode of action and may represent a promising novel treatment option for patients with type 2 diabetes. Combination treatment with a DPP-4 inhibitor, such as sitagliptin [15], vildagliptin [16], saxagliptin [17], or linagliptin [18] may be desirable due to their complementary modes of action.

The present study suggests that sitagliptin coadministration had no clinically relevant effect on the AUC or C_{max} of empagliflozin. Similarly, empagliflozin coadministration had no clinically relevant effect on the AUC or C_{max} of sitagliptin. Renal clearance of empagliflozin and sitagliptin was similar whether the drugs were administered alone or together. Similarly, no clinically relevant interaction was observed between empagliflozin and linagliptin in a recent drug–drug interaction study [19]. Thus, the observations in these two studies suggest that coadministration of empagliflozin and a DPP-4 inhibitor does not affect the relative bioavailability of these drugs to an extent that is clinically relevant.

Both empagliflozin and sitagliptin were well tolerated. Five subjects reported at least one AE during the trial; no serious AEs or hypoglycemia were reported. No AEs were reported during

coadministration of empagliflozin and sitagliptin. In the drug–drug interaction study of empagliflozin and linagliptin, the combination was also well tolerated, with no hypoglycemia reported [19].

This study was restricted to evaluate any potential drug–drug interaction in a well-controlled phase 1 trial. Any effects on efficacy and safety when empagliflozin and a DPP-4 inhibitor are coadministered are being investigated in a phase 3 trial.

In summary, coadministration of empagliflozin with the DPP-4 inhibitor sitagliptin had no clinically relevant effect on the pharmacokinetics of either drug in healthy volunteers. These data support the coadministration of empagliflozin and sitagliptin without dose adjustments.

ACKNOWLEDGMENTS

Assays for plasma and urine concentrations of empagliflozin and sitagliptin were performed by Bioanalytical Systems, Inc., West Lafayette, Indiana, USA. The authors acknowledge Lois Rowland for coordinating bioanalytical work. The authors would also like to acknowledge Anna Larbalestier for her assistance in the supervision of the statistical analysis and writing the clinical trial report. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Keni Lee and Elizabeth Ng of Fleishman-Hillard Group Ltd. during the preparation of this manuscript. Dr. Brand is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Conflict of Interest. Sponsorship for this study was funded by Boehringer Ingelheim. All authors are employees of Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version.

REFERENCES

1. Gerich JE, Meyer C, Woerle HJ, Stumvoll M. Renal gluconeogenesis: its importance in human glucose homeostasis. Diabetes Care. 2001;24:382–91.

2. Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. Trends Pharmacol Sci. 2011;32:63–71.

3. Kipnes M. Sodium-glucose cotransporter 2 inhibitors in the treatment of Type 2 diabetes: a review of Phase II and III trials. Clin Investig. 2011;1:145–56.

4. Grempler R, Thomas L, Eckhardt M, et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes Metab. 2012;14:83–90.

5. Port A, Macha S, Seman L, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of BI 10773, a sodium glucose cotransporter-2 (SGLT-2), in healthy volunteers. Diabetes. 2010;59(Suppl. 1):A155.

6. Seman L, Macha S, Jones P, et al. Safety and tolerability of BI 10773, a sodium glucose cotransporter-2 (SGLT-2) inhibitor, following 8-days treatment in patients with type 2 diabetes. Diabetes. 2010;59(Suppl. 1):A156.

7. Kim D, Wang L, Beconi M, et al. (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a] pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine: a potent, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J Med Chem. 2005;48:141–51.

8. Januvia (sitagliptin) [package insert]. 2010; Merck & Co, Inc. Whitehouse Station, NJ, USA.

9. Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. Pharmacol Rev. 2008;60:470–512.

10. Bergman AJ, Stevens C, Zhou Y, et al. Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers. Clin Ther. 2006;28:55–72.

11. Herman GA, Stevens C, Van DK, et al. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. Clin Pharmacol Ther. 2005;78:675–88.

12. Cheung BM, Ong KL, Cherny SS, Sham PC, Tso AW, Lam KS. Diabetes prevalence and therapeutic target achievement in the United States, 1999 to 2006. Am J Med. 2009;122:443–53.

13. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract. 2009;15:540–59.

14. MedDRA Introductory Guide. 12th ed. Chantilly, VA: MedDRA Maintenance and Support Services Organization; 2009.

15. Gallwitz B. Sitagliptin: Profile of a novel DPP-4 inhibitor for the treatment of type 2 diabetes. Drugs Today (Barc). 2007;43:13–25.

16. Keating GM. Vildagliptin: a review of its use in type 2 diabetes mellitus. Drugs. 2010;70:2089–112.

17. Kania DS, Gonzalvo JD, Weber ZA. Saxagliptin: a clinical review in the treatment of type 2 diabetes mellitus. Clin Ther. 2011;33:1005–22.

18. Scott LJ. Linagliptin: in type 2 diabetes mellitus. Drugs. 2011;71:611–24.

19. Friedrich C, Metzmann K, Rose P, Mattheus M, Pinnetti S, Woerle H-J. Pharmacokinetics and pharmacodynamics of BI 10773, a sodium glucose cotransporter-2 (SGLT-2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, following co-administration in healthy volunteers. Diabetes. 2011;60(Suppl. 1):A616–7.