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Pharmacokinetics and Pharmacodynamics of Twice Daily and Once Daily Regimens of Empagliflozin in Healthy Subjects

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ABSTRACT

Purpose: This study was undertaken to compare the steady-state pharmacokinetic and pharmacodynamic properties of empagliflozin 5 mg twice daily (BID) and 10 mg once daily (QD) in healthy subjects.

Methods: In an open-label, 2-way crossover study, subjects (n = 16) received empagliflozin 5 mg BID for 5 days and empagliflozin 10 mg QD for 5 days in a randomized order, with a washout period of ≥6 days between each treatment. The primary objective was the comparison of the overall exposure during a 24-hour period at steady state ($AUC_{0-24,ss}$) for empagliflozin, based on standard bioequivalence criteria, with BID and QD dose regimens.

Findings: The study population comprised 7 (43.8%) men and 9 (56.3%) women with a baseline median age of 38.0 years (range, 23–47 years) and a median body mass index of 23.3 kg/m^2 (range, 19.8–27.8 kg/m^2). Based on standard bioequivalence criteria, there was no difference in the overall exposure of empagliflozin between BID and QD dose regimens (geometric mean ratio of $AUC_{0-24,ss}$ for empagliflozin 5 mg BID compared with empagliflozin 10 mg QD = 99.36%; 90% CI, 94.29–104.71). For empagliflozin 10 mg QD, mean (%CV) AUC during the dosing interval was 1900 nmol · h/L (20.6%), mean (%CV) $C_{max,ss}$ was 330 nmol/L (25.3%), and median (range) $T_{max,ss}$ was 1.0 hour (0.7–2.0 hours). For empagliflozin 5 mg BID, mean (%CV) AUC during the dosing interval was 1010 nmol · h/L (15.1%) and 867 nmol · h/L (18.6%) after the morning and evening dose, respectively, mean (%CV) $C_{max,ss}$ was 193 nmol/L (16.5%) and 120 nmol/L (21.0%), respectively, and median $T_{max,ss}$ was 1.0 hour (range, 0.7–2.0 hours) and 2.0 hours (range, 1.0–4.0 hours), respectively. The mean (%CV) cumulative amount of glucose excreted in urine during 24 hours was 52.1 g (32.1%) with empagliflozin 5 mg BID and 43.9 g (30.3%) with empagliflozin 10 mg QD. Adverse events were reported in six subjects (37.5%) receiving empagliflozin 5 mg BID and four (25.0%) receiving empagliflozin 10 mg QD. Headache was the most frequent AE. No severe, serious, or drug-related AEs were reported.

Implications: There were no clinically relevant differences in pharmacokinetic or pharmacodynamic properties between BID and QD dose regimens of empagliflozin in healthy subjects. Both dose regimens were well tolerated. EU Clinical Trials Register (EudraCT) number: 2009-012524-90. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮)

Key words: empagliflozin, once daily, pharmacodynamics, pharmacokinetic properties, twice daily.

INTRODUCTION

Empagliflozin is a potent, selective inhibitor of sodium glucose cotransporter 2 (SGLT2).[1] By inhibiting SGLT2, empagliflozin reduces renal glucose reabsorption,[2] increasing urinary glucose excretion (UGE) and leading to a reduction in plasma glucose levels in patients with type 2 diabetes mellitus (T2DM).[3,4]

Metformin is a biguanide derivate that reduces hepatic glucose production via inhibition of gluconeogenesis.[5] It is recommended as the first-line pharmacologic treatment for patients with T2DM.[6] However, as diabetes progresses, metformin monotherapy often fails to maintain glycemic control.[6–8] Guidelines

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recommend the addition of a second anti-diabetes agent for patients not achieving glycemic targets with metformin monotherapy.[6,9] In addition, a combination of two oral anti-diabetes agents is a recommended initial treatment option for patients with high glycosylated hemoglobin (HbA1c) at diagnosis (eg, ≥9%), due to low probability of achieving target HbA1c levels with monotherapy.[6]

Compared with individual tablets, fixed-dose combinations of anti-diabetes agents reduce pill burden and have been shown to improve patient satisfaction and adherence,[10,11] and thus improve HbA1c.[10] Empagliflozin and metformin have complementary insulin-independent mechanisms of action and, in a Phase III trial, empagliflozin as add-on to metformin as individual tablets improved glucose control with a low risk of hypoglycemia and reduced body weight in patients with T2DM.[12] These indicate the potential for a fixed-dose combination of empagliflozin and metformin. As metformin immediate release is administered twice daily (BID), a fixed-dose combination of empagliflozin and metformin immediate release would require BID administration of empagliflozin. This study was undertaken to compare the pharmacokinetic and pharmacodynamic properties of multiple oral doses of empagliflozin given as a BID regimen versus a once daily (QD) regimen in healthy subjects.

METHODS

Participants

Eligible subjects were male and female, aged 18 to 50 years, with body mass index of 18.5 to 29.9 kg/m^2, and were generally in good health (as assessed by medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests).

Exclusion criteria included evidence of any clinically relevant concomitant disease, including central nervous system or psychiatric disorders; gastrointestinal surgery (except appendectomy); chronic or relevant acute infections; current smoker or alcohol or drug abuse; and participation in a trial with an investigational drug in the previous 2 months. All subjects gave signed informed consent before participating in the study.

Study Design

In an open-label, 2-way crossover study, subjects received empagliflozin 5 mg BID for 5 days and empagliflozin 10 mg QD for 5 days in a randomized order, with a washout period of ≥6 days between each treatment. Screening for eligibility took place 1 to 21 days before the first intake of study drug. Study drugs were given at the study site under the supervision of the investigator. Subjects visited the study site in the morning (and evening if they were receiving empagliflozin BID) of days 1 to 4 of each treatment period and were admitted to the study site on day 5 (pharmacokinetic and pharmacodynamic assessment day). Subjects were required to fast for ≥10 hours before study drug administration in the morning of day 1 and day 5. On day 5, study drugs were administered 2 hours before a light breakfast, and 30 minutes after dinner if receiving empagliflozin BID. Subjects were discharged on day 6 and returned to the study site for blood sampling that evening, and on the morning of days 7 and 8. All participants had an end-of-study examination 3 to 10 days after the last dose of study drug.

The study was conducted at the Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany, and was registered with the EU Clinical Trials Register (EudraCT number 2009-012524-90). The study was approved by the local Independent Ethics Committee (Baden-Württenberg, Stuttgart) and the German Competent Authority (the Federal Institute for Drugs and Medical Devices [BfArM]). It was carried out in compliance with the protocol and the principles of the Declaration of Helsinki, in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice.

End Points

The primary end points were the relative overall exposure to empagliflozin BID versus QD based on the AUC over a uniform dosing interval (τ) at steady state ($AUC_{\tau,ss}$) for empagliflozin 10 mg QD, the AUC at steady state over two dosing intervals ($AUC_{0-24,ss}$) for empagliflozin 5 mg BID on day 5, and the diurnal variability in the rate and extent of exposure to empagliflozin 5 mg BID after the morning and evening doses, based on $AUC_{\tau,ss}$ and C_{max} at steady state ($C_{max,ss}$).

Secondary pharmacokinetic end points included time to $C_{max,ss}$ ($T_{max,ss}$) and $t_{½}$ at steady state ($t_{½,ss}$). Secondary pharmacodynamic end points were cumulative UGE over 12 hours (UGE_{0-12}) and