A Randomized, Open-Label, Crossover Study to Evaluate the Pharmacokinetics of Empagliflozin and Linagliptin After Coadministration in Healthy Male Volunteers

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ABSTRACT

Background: Empagliflozin is an oral, potent, and selective inhibitor of sodium glucose cotransporter 2, inhibition of which reduces renal glucose reabsorption and results in increased urinary glucose excretion. Linagliptin is an oral inhibitor of dipeptidyl peptidase-4 approved for the treatment of type 2 diabetes in the United States, Europe, Japan, and Canada. Due to their complementary modes of action, there is a good rationale to combine empagliflozin with linagliptin to improve glycemic control in patients with type 2 diabetes.

Objective: This study was conducted to investigate the pharmacokinetics of empagliflozin and linagliptin after coadministration in healthy volunteers.

Methods: This was an open-label, randomized, multiple-dose, crossover study with 3 treatments in 2 treatment sequences. Sixteen healthy male subjects received treatment A (empagliflozin 50 mg once daily [QD] for 5 days), treatment B (empagliflozin 50 mg QD and linagliptin 5 mg QD for 7 days), and treatment C (linagliptin 5 mg QD for 7 days) in sequence AB then C, or sequence C then AB.

Results: Sixteen healthy male subjects aged between 18 and 50 years with a body mass index of 18.5 to 29.9 kg/m^2 were included in the study. Linagliptin total exposure (AUC over a uniform dosing interval τ at steady state geometric mean ratio [GMR], 1.03 [90% CI, 0.96–1.11]) and peak exposure (C_{max} at steady state GMR, 1.01 [90% CI, 0.87–1.19) exposure was unaffected by coadministration of empagliflozin. Empagliflozin total exposure (AUC over a uniform dosing interval τ at steady state GMR, 1.02 [90% CI, 0.97–1.07]) was unaffected by coadministration of linagliptin. There was a reduction in empagliflozin peak exposure (C_{max} at steady state GMR, 0.88 [90% CI, 0.79–0.99]) when linagliptin was coadministered that was not considered clinically meaningful. No adverse events were reported during the coadministration period. No hypoglycemia was reported. Empagliflozin and linagliptin were well tolerated.

Conclusion: These data support the coadministration of empagliflozin and linagliptin without dose adjustments. European Union Drug Regulating Authorities Clinical Trials Registration: EudraCT 2008-006089-27. (*Clin Ther.* 2013;35:A33–A42) © 2013 Published by Elsevier HS Journals, Inc.

Key words: diabetes, DPP-4 inhibitor, drug–drug interaction, empagliflozin, linagliptin, SGLT2 inhibitor.

INTRODUCTION

Treatment of type 2 diabetes includes lifestyle changes (eg, diet, exercise) and may include oral antidiabetic drugs or subcutaneous injection (eg, insulin, glucagon-like peptide-1 analogs).[1] Due to the progressive deterioration in β-cell function seen in type 2 diabetes, the use of combination therapy is often necessary to help patients reach or maintain therapeutic goals.[2,3] However, the use of antidiabetic agents is associated with adverse effects, including hypoglycemia, weight gain, edema, and gastrointestinal problems.[4] There is a need for drugs with novel mechanisms of action that can be used alone or in combination with other antidiabetic agents to improve glycemic control in patients with type 2 diabetes without adverse effects that limit their clinical use.

In healthy individuals, plasma glucose filtered through the kidney glomeruli is almost completely reabsor-

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bed from the urine back into the blood. The sodium glucose cotransporter 2 (SGLT2), located in the proximal tubule of the nephron, is estimated to facilitate ~90% of this reabsorption.[5] Inhibition of this transporter blocks glucose reabsorption, leading to excretion of glucose into the urine and a decrease in plasma glucose levels, making SGLT2 inhibition a promising, insulin-independent approach to treating diabetes.[6,7]

Empagliflozin is an orally available, potent, and selective inhibitor of SGLT2.[8] In healthy volunteers and in patients with type 2 diabetes, empagliflozin has been shown to be rapidly absorbed, reaching C_{max} within 1 to 3 hours.[9,10] Its $t_{1/2}$ ranged from 10 to 19 hours in patients with type 2 diabetes, with steady state reached by day 5.[10] In Phase I and II studies in patients with type 2 diabetes, once daily (QD) administration of empagliflozin has been shown to be well tolerated and to result in dose-dependent reductions in glycosylated hemoglobin and fasting plasma glucose compared with placebo.[10–13]

Linagliptin is an oral inhibitor of dipeptidyl peptidase-4 (DPP-4)[14] that is approved in the United States, Europe, Japan, and Canada for the treatment of type 2 diabetes; it does not require dose adjustment in any patient group, including those with declining renal function.[15,16] Studies in patients with type 2 diabetes have shown that the therapeutic dose of linagliptin 5 mg QD was well tolerated and significantly reduced glycosylated hemoglobin levels to a clinically meaningful degree versus placebo both as monotherapy[17] and as add-on treatment to background therapies.[18–20]

Due to their complementary modes of action, there is potential to combine empagliflozin with linagliptin as an add-on to metformin to improve glycemic control in patients with type 2 diabetes. No clinically relevant drug–drug interactions were observed when empagliflozin or linagliptin was coadministered with metformin in healthy volunteers.[21,22]

This open-label study explored the pharmacokinetics of empagliflozin and linagliptin when coadministered as multiple oral doses in healthy volunteers.

METHODS

Subjects

Sixteen healthy male subjects aged between 18 and 50 years with a body mass index of 18.5 to 29.9 kg/m^2 were included in the study. The main exclusion criteria were concomitant disease that may influence the pharmacokinetics or pharmacodynamics of the investigational drugs, allergy/hypersensitivity, excessive smoking (>10 cigarettes, >3 cigars, or >3 pipes per day), alcohol abuse, drug abuse, blood donation in the previous 4 weeks, and participation in another trial with an investigational drug in the previous 2 months.

The trial was performed at the Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany, and was conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki (1996 version), and in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice. The trial was approved by an independent ethics committee affiliated with the State Medical Council Baden-Württemberg. All subjects provided signed and dated informed consent before admission to the study.

Study Design

This study was an open-label, randomized, multiple-dose, crossover design with 3 treatments (A, B, and C) in 2 treatment sequences (AB then C, or C then AB) (**Figure 1**). Subjects were screened for eligibility up to 21 days before the first study day and then allocated to 1 of the treatment sequences. In treatment AB, empagliflozin 50 mg QD was administered for 5 days (treatment A), immediately followed by coadministration of empagliflozin 50 mg QD and linagliptin 5 mg QD over 7 days (treatment B). In treatment C, linagliptin 5 mg QD alone was administered for 7 days. Treatments AB were separated from treatment C by a washout period of at least 35 days. Study medications were administered with ~240 mL of water after the subject had fasted overnight (at least 10 hours). Intake of water was not allowed for 1 hour before and 1 hour after drug administration. On days when pharmacokinetic assessments took place, standardized meals were served and fluid intake was limited to 3.5 L per day. An end-of-study examination was performed within 5 days after last drug administration.

Pharmacokinetic Methods

The primary end points used to evaluate the pharmacokinetics of empagliflozin and linagliptin after coadministration versus dosing alone were AUC over a uniform dosing interval τ at steady state ($AUC_{\tau,ss}$) and C_{max} of empagliflozin at steady state ($C_{max,ss}$) of empagliflozin and linagliptin. The sec-