Lack of a Pharmacokinetic Interaction Between Saxagliptin and Dapagliflozin in Healthy Subjects: A Randomized Crossover Study

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ABSTRACT

Purpose: This single-dose, open-label, randomized, 3-period, 3-treatment crossover drug–drug interaction study was conducted to evaluate differences in the pharmacokinetic properties of saxagliptin and dapagliflozin when coadministered.

Methods: Healthy subjects (N = 42) were randomized to receive saxagliptin 5 mg alone, dapagliflozin 10 mg alone, or saxagliptin 5 mg plus dapagliflozin 10 mg coadministered; there was a washout period of ≥6 days between treatments. Serial blood samples for determining saxagliptin, 5-hydroxy saxagliptin (5-OH saxagliptin; major active metabolite) and dapagliflozin plasma concentrations and pharmacokinetic parameters were collected before and up to 60 hours after the dose. No interaction was to be concluded if the 90% CIs for the geometric mean ratios of the combination compared with each drug given alone for C_{max} and AUC_{inf} were within 0.80 to 1.25.

Findings: The results indicated that dapagliflozin had no effect on the pharmacokinetic properties of saxagliptin, 5-OH saxagliptin, or saxagliptin total active moiety and vice versa. The 90% CIs for C_{max} and AUC_{inf} for all comparisons were contained entirely within the 0.80 to 1.25 equivalence intervals. Other pharmacokinetic parameters (apparent oral clearance or half-life) of saxagliptin or dapagliflozin were similar when each medicine was administered alone or when coadministered. No safety profile or tolerability findings of concern were observed during the study. All adverse events were mild, and no serious adverse events were reported.

Implications: These data indicate that coadministration of saxagliptin and dapagliflozin exhibits no pharmacokinetic interaction and is well tolerated. ClinicalTrials.gov identifier: NCT01662999.

(*Clin Ther*. 2016;38:1890–1899)

Key words: dapagliflozin, dipeptidyl peptidase-4 (DPP-4) inhibitor, drug interaction, saxagliptin, sodium-glucose cotransporter 2 (SGLT-2) inhibitor.

INTRODUCTION

The prevalence of diabetes in the United States is 9.3%, with 21.0 million people diagnosed and 8.1 million undiagnosed.[1] Guidelines recommend diet, physical activity, and general diabetes education as the foundation of type 2 diabetes (T2D) treatment.[2] Guidelines also recommend individualized targets for glycated hemoglobin (HbA_{1C}) and glucose-lowering medications.[2] If a patient's HbA_{1C} target is not reached after approximately 3 months of monotherapy treatment, dual combination therapy is suggested.[2–4]

Saxagliptin[*] is a dipeptidyl peptidase-4 (DPP-4) inhibitor that decreases fasting and postprandial glucose concentrations in the bloodstream by slowing the inactivation of incretin hormones.[5] Saxagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D at recommended doses of 2.5 mg or 5 mg.[5] Dapagliflozin,[†] a selective renal sodium-glucose cotransporter type-2 inhibitor, increases the excretion of urinary glucose by reducing

[*]Trademark: Onglyza® (AstraZeneca, Wilmington, Delaware).
[†]Trademark: Forxiga® (European Union) or Farxiga® (United States); AstraZeneca.

Accepted for publication July 8, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.07.005
0149-2918/$ - see front matter

the reabsorption of filtered glucose and lowering the renal glucose threshold.[6,7] Dapagliflozin also is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D at recommended doses of 5 mg or 10 mg.[6]

Fixed-dose combinations of ≥2 glucose-lowering medications are commonly used in clinical practice.[8] Fixed-dose combinations can potentially improve medication compliance,[9] thereby leading to improved disease management.[8] In addition, a fixed-dose combination product may be more cost-effective than administering the tablets separately.[8] However, the pharmacokinetic properties and tolerability of the drug–drug interactions need to be assessed before determining whether medications can be combined into a fixed-dose combination product.

This study was conducted to support the potential development of a fixed-dose combination product containing saxagliptin and dapagliflozin. The highest Food and Drug Administration (FDA)–approved doses of saxagliptin (5 mg) and dapagliflozin (10 mg) were selected for evaluation because they were the highest doses that could be potentially developed as a fixed-dose combination product. Specifically, this study assessed the pharmacokinetic interactions and the safety profile and tolerability of coadminstration of saxagliptin and dapagliflozin.

METHODS

Study Design and Subjects

This was a single-dose, open-label, randomized, 3-period, 3-treatment crossover drug interaction study of saxagliptin 5 mg and dapagliflozin 10 mg administered individually and concomitantly to healthy subjects. This study was conducted at a single site (ICON Clinical Pharmacology, Omaha, Nebraska). The study protocol was approved by the institutional review board (IntegReview, Austin, Texas) in conformance with 21 Code of Federal Regulations (CFR) §50 and 21 CFR §56. The study was conducted in accordance with Good Clinical Practice as defined by the International Conference on Harmonization. All subjects provided written informed consent before initiation of any study-related procedures.

Subjects were healthy adults aged 18 to 45 years with a body mass index of 18 to 30 kg/m^2. Women of childbearing potential had to use a highly effective birth control method for ≥1 month before study drug administration and for ≥8 weeks after dosing was completed. Subjects were excluded if they had any significant acute or chronic medical illnesses or a history of gastrointestinal disease.

Treatments and Assessments

Healthy subjects were randomly assigned equally to 1 of 6 treatment sequences and received the following 3 treatments: saxagliptin 5 mg alone (treatment A), dapagliflozin 10 mg alone (treatment B), and saxagliptin 5 mg plus dapagliflozin 10 mg coadministered (treatment C); there was a washout period of ≥6 days between treatments (Figure 1). Serial blood samples for determining plasma concentrations of saxagliptin; its active metabolite 5-hydroxy saxagliptin (5-OH saxagliptin), which has approximately one half of the DPP-4 inhibition potency of parent saxagliptin; and dapagliflozin were collected before and up to 60 hours after the dose.

Safety profile evaluations included physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory evaluations. Subjects also were monitored for adverse events (AEs), including hypoglycemia, throughout the study.

Statistical Analyses: General and Pharmacokinetic Properties

Continuous variables were summarized using mean, SD, median, minimum, and maximum. Categorical variables were summarized using the frequency count and the percentage of subjects in each category. Data from each treatment (saxagliptin alone, dapagliflozin alone, and saxagliptin plus dapagliflozin) were summarized separately.

Pharmacokinetic parameters were derived from plasma concentration versus actual blood sample collection time data by using noncompartmental techniques (WinNonlin® Professional Network Edition, version 5.2; Pharsight Corp, Sunnyvale, California) and actual times. To assess the effect of the coadministration of saxagliptin and dapagliflozin on the pharmacokinetic properties of saxagliptin, 5-OH saxagliptin, saxagliptin total active moiety (the molar sum of saxagliptin plus 5-OH saxagliptin corrected for their difference in DPP-4 inhibition), and dapagliflozin, a linear mixed-model was fit on $\log_e$-transformed C_{max}, AUC_{0-t}, and AUC_{inf} of each analyte separately. The model included treatment and