Pharmacokinetics, Pharmacodynamics, and Safety of Single-Dose Canagliflozin in Healthy Chinese Subjects

Xia Chen, MD[1]; Pei Hu, MD[1]; Nicole Vaccaro, BS[2]; David Polidori, PhD[2]; Christopher R. Curtin, BS[3]; Hans Stieltjes, MSc[4]; Sue Sha, MD, PhD[3]; Sveta Weiner, MS[3]; and Damayanthi Devineni, PhD[3]

[1]Phase I Unit of Clinical Pharmacology Research Center, Peking Union Medical College Hospital, Beijing, China; [2]Janssen Research & Development, LLC, San Diego, California; [3]Janssen Research & Development, LLC, Raritan, New Jersey; and [4]Janssen Research & Development, Division of Janssen Pharmaceutica NV, Beerse, Belgium

ABSTRACT

Purpose: Canagliflozin, an orally active sodium–glucose cotransporter 2 inhibitor, is approved in many countries as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended dose of canagliflozin is 100 or 300 mg once daily. This Phase I study was conducted to evaluate the pharmacokinetics, pharmacodynamics, and safety profile of canagliflozin in healthy Chinese subjects.

Methods: In this double-blind, single-dose, 3-way crossover study, 15 healthy subjects were randomized (1:1:1) to receive single oral doses of canagliflozin 100 mg, canagliflozin 300 mg, or placebo. Pharmacokinetic, pharmacodynamic, and safety assessments were made at prespecified time points.

Findings: All participants are healthy Chinese adults. Mean AUC and C_{max} of canagliflozin increased in a dose-dependent manner after single-dose administration ($AUC_{0-\infty}$, 10,521 ng · h/mL for 100 mg, 33,583 ng · h/mL for 300 mg; C_{max}, 1178 ng/mL for 100 mg, 4113 ng/mL for 300 mg). The mean apparent $t_{½}$ and the median T_{max} of canagliflozin were independent of dose ($t_{½}$, 16.0 hours for 100 mg, 16.2 hours for 300 mg; T_{max}, ~1 hour). Mean CL/F and renal clearance of canagliflozin were comparable between the 2 doses. Mean plasma metabolite to parent molar ratios for C_{max} and $AUC_{0-\infty}$ were similar with both doses. Canagliflozin decreased the 24-hour mean renal threshold for glucose, calculated by using measured creatinine clearance to estimate the glomerular filtration rate (67.9 and 60.7 mg/dL for canagliflozin 100 and 300 mg, respectively) and 24-hour increased urinary glucose excretion (33.8 and 42.9 g for canagliflozin 100 and 300 mg, respectively) in a dose-dependent manner; the 24-hour plasma glucose profile remained largely unchanged. No deaths, hypoglycemic events, or discontinuations due to adverse events were observed.

Implications: Pharmacokinetics (AUC and C_{max}) of canagliflozin increased in a dose-dependent manner after single oral doses of canagliflozin (100 and 300 mg) in these healthy Chinese subjects. T_{max} and $t_{½}$ of canagliflozin were independent of the dose. Canagliflozin decreased the 24-hour mean renal threshold for glucose and increased urinary glucose excretion in a dose-dependent manner; these results are consistent with those observed in other patient populations. Canagliflozin was generally safe and well tolerated in these healthy Chinese subjects. ClinicalTrials.gov identifier: NCT01707316. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮)

Key words: canagliflozin, pharmacodynamics, pharmacokinetics, safety, sodium-glucose cotransporter 2 inhibitor.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a growing concern, accounting for >90% of the diagnosed cases of diabetes worldwide.[1] In China, the diabetes epidemic is accelerating at an alarming rate, with ~92.4 million adults estimated to be diabetic.[2] Although many

Accepted for publication April 30, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.04.015
0149-2918/$ - see front matter

medications are available for the management of this disease, the use of antihyperglycemic agents is often limited by weight gain, episodes of hypoglycemia, edema, potential cardiovascular disorders, and/or adverse gastrointestinal effects.[3,4]

Canagliflozin,* a sodium–glucose cotransporter 2 inhibitor, is approved in many countries as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.[5–7] It acts on the proximal renal tubules, thereby reducing glucose reabsorption and increasing urinary glucose excretion (UGE). This novel insulin-independent approach lowers plasma glucose (PG) and increases caloric loss (4 kcal/g of glucose).[8,9] The recommended starting dose of canagliflozin is 100 mg/d, to be administered before the first meal of the day; in patients with an estimated glomerular filtration rate (eGFR) of $\geq$60 mL/min/1.73 m^2 who require additional glycemic control, the dosage may be increased to 300 mg/d.[9–12]

Canagliflozin is mostly metabolized through the *O*-glucuronidation metabolic elimination pathway, and the 2 major metabolites are the inactive M5 and M7 *O*-glucuronide conjugates of the unchanged drug.[13,14] The pharmacokinetic (PK) characteristics of canagliflozin have been evaluated after single and multiple oral dose administration in healthy subjects and in patients with T2DM in Western populations.[13–15] After oral administration in healthy subjects and in patients with T2DM, canagliflozin was rapidly absorbed, with the median T_{max} occurring 1 to 2 hours postdose.[16] In healthy subjects, the mean AUC of canagliflozin increased in a dose-dependent manner across a wide range of doses (25–1600 mg), whereas C_{max} increased in a dose-proportional manner from 50 to 300 mg[16,17] and even up to 1200 mg (unpublished data). In patients with T2DM, the C_{max} and AUC of canagliflozin also increased in a linear manner over the dose range of 50 to 300 mg.[13] Mean terminal $t_{½}$ ranged from 10.6 to 13.1 hours with the 100- and 300-mg doses.

No dose-related clinical adverse drug reactions were reported for single doses up to 1600 mg of canagliflozin in healthy subjects (unpublished data). The highest multiple-dose canagliflozin regimen evaluated in clinical studies was 300 mg BID, which was used both in a 4-week dose-ranging study in patients with T2DM[18] and in a 12-week, Phase II dose-ranging study in patients with T2DM.[7] It was found to be safe and generally well tolerated in both studies.

Ethnicity is one factor that may account for the observed differences in both PK and pharmacodynamics (PD) of drugs, resulting in variability in response to drug therapy.[19] The dose- and weight-normalized PK parameters of canagliflozin demonstrated no apparent differences in canagliflozin exposure among healthy Western, Indian, and Japanese subjects, as well as between Western and Japanese patients with T2DM.[20] Moreover, after canagliflozin treatment at comparable doses, the PD parameters (UGE, both 24-hour and fasting PG, and renal threshold for glucose excretion [RT_G]) exhibited a similar pattern of dose-dependent changes in Western,[13–15] Korean,[21] and Japanese patients with T2DM.[22,23]

To further explore potential interethnic differences in the PK and PD characteristics of canagliflozin, a Phase I study was conducted in healthy Chinese subjects. The doses selected for the present study (100 and 300 mg) were previously evaluated in healthy Western subjects and were found to be generally well tolerated.[14,15] In addition, these doses were shown to be efficacious in global Phase III trials in patients with T2DM.[9,24–26]

SUBJECTS AND METHODS

Study Population

Fifteen healthy Chinese men and women, aged between 18 and 55 years, with a body mass index between 18 and 28 kg/m^2 and weight $\geq$50 kg, were enrolled. Participants were excluded from the study if there was evidence of the following: any clinically significant medical illness, history of smoking or drug or alcohol abuse, or known allergy to canagliflozin. Pregnant or breastfeeding women were also excluded. Subjects were prohibited from taking any over-the-counter or prescribed medications except acetaminophen for at least 14 days before study initiation and throughout the study. Women on hormone replacement therapy or contraceptives continued the same medication throughout the study.

The study protocol was approved by the local independent ethics committee and was conducted in accordance with the ethical principles originating in the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice Guideline, and applicable regulatory requirements and in

*Trademark: Invokana® (Janssen Pharmaceuticals, Inc, Titusville, New Jersey).