Single-Dose Pharmacokinetics and Pharmacodynamics of Canagliflozin, a Selective Inhibitor of Sodium Glucose Cotransporter 2, in Healthy Indian Participants

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ABSTRACT

Purpose: Canagliflozin, an orally active selective inhibitor of sodium glucose cotransporter 2, has been approved in several countries for the treatment of type 2 diabetes mellitus. This study assessed the pharmacokinetic (PK) and pharmacodynamic (PD) properties and tolerability of single-dose canagliflozin 200 or 300 mg in healthy Indian participants.

Methods: In this Phase 1, single-center, open-label, 2-period crossover study, healthy adult participants were randomly assigned to receive a single dose of canagliflozin 200 mg in period 1, followed by canagliflozin 300 mg in period 2, or vice versa. The 2 periods were separated by a washout interval of 14 days. The PK and PD properties and tolerability of canagliflozin were assessed at prespecified time points.

Findings: Of 15 randomized participants, 14 completed the study. After the administration of single doses of 200 and 300 mg, the mean (SD) C_{max} values were 1792 (430) ng/mL and 2789 (941) ng/mL, respectively; $AUC_{0-\infty}$, values were 18,706 (3818) ng · h/mL and 28,207 (5901) ng · h/mL, respectively. The T_{max} and $t_{½}$ of canagliflozin were independent of dose (T_{max}, 1.5 hours at both doses; $t_{½}$, 13.0 and 12.6 hours with 200 and 300 mg). Over the first 4 hours, mean (SD) renal threshold for glucose (RT_G) values were 60.8 (8.90) and 61.2 (7.04) mg/dL with the 200- and 300-mg doses, respectively. No effect on plasma glucose concentrations over 0 to 4 hours relative to baseline was observed with either dose. The only treatment-emergent adverse event (TEAE) reported in >1 participant was dizziness (2 participants with the 200-mg dose). None of the participants in the 300-mg group reported any TEAEs. No deaths, discontinuations due to TEAEs, or hypoglycemic episodes were reported.

Implications: The mean plasma exposure (C_{max} and AUC) to canagliflozin increased in a dose-dependent manner after the administration of single-dose oral canagliflozin 200 and 300 mg in these healthy Indian participants. The T_{max} and $t_{½}$ of canagliflozin appeared to be independent of dose. Overall, PK characteristics were consistent with previous findings in other ethnic populations. The reductions in RT_G with canagliflozin were similar to those reported in Western participants, whereas the amount of urinary glucose excretion was somewhat less than those previously observed in studies in Western participants. Canagliflozin was generally well tolerated in these healthy Indian participants. ClinicalTrials.gov identifier: NCT01748526. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: canagliflozin, India, pharmacodynamics, pharmacokinetics, safety.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major global health problem, accounting for nearly 90% of the diagnosed cases of diabetes. The prevalence of T2DM is on the rise globally at an alarming rate, with a projected increase to 552 million by 2030.[1] Low- and middle-income countries face the greatest threat of diabetes, with almost 80% of all diabetes-related deaths occurring in these countries.[2] In India, the prevalence of diabetes, largely T2DM, has been growing at an exponential rate, with almost 65 million

Accepted for publication November 12, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.11.008
0149-2918/$ - see front matter

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people estimated to be diabetic; the rate is estimated to rise to 109 million by 2035.[3] Many antihyperglycemic therapies are available for the management of T2DM, although the use of these agents is to some extent limited by adverse events (AEs), including hypoglycemia, fluid retention, weight gain, edema, and potential cardiovascular and/or gastrointestinal disorders.[4–7]

Canagliflozin is an orally active sodium glucose cotransporter (SGLT)2 inhibitor approved in numerous countries across the globe for use, as an adjunct to diet and exercise, in improving glycemia control in adults with T2DM.[8–10] Canagliflozin reduces renal glucose reabsorption by inhibiting SGLT2–mediated glucose reabsorption in the proximal renal tubules, thereby increasing urinary glucose excretion (UGE) and decreasing plasma glucose (PG) levels.[11] In patients with T2DM, canagliflozin treatment has been reported to improve glycemic control and to reduce weight.[8,12]

The recommended starting dosage of canagliflozin is 100 mg/d, to be administered before the first meal of the day. The dose may be increased to 300 mg/d in patients who have an estimated glomerular filtration rate (eGFR) of $\geq$60 mL/min/1.73 m^2, who require additional glycemic control, and/or who have a low risk for AEs associated with reduced intravascular volume, for which there is a risk with canagliflozin treatment.[13]

The absolute oral bioavailability of canagliflozin is 65%, and canagliflozin is strongly bound to plasma proteins (~99%), mainly albumin.[14,15] Canagliflozin is metabolized mostly 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. Approximately 33% of the drug is excreted in urine as metabolites (M5, 13.3%; M7, 17.2%) or as unchanged canagliflozin ($\leq$1%).[16]

Studies in healthy participants[17,18] and in patients with T2DM[19] have reported dose-dependent increases canagliflozin C_{max} and AUC across a dose range of 50 to 300 mg. Dose-dependent decreases in the renal threshold for glucose (RT_G) and increases in UGE were observed in healthy participants[18,20] and in patients with T2DM,[19,21] with maximal effects observed with doses of >200 mg. In healthy participants, PG was generally unaltered by treatment, with the exception of reduced postprandial excursions noted with doses of >200 mg,[20,22] attributed to delayed intestinal glucose absorption during periods of drug absorption.[22] In patients with T2DM, dose-dependent reductions in fasting and 24-hour mean PG (MPG) were observed with canagliflozin treatment.[19,21]

Genetic polymorphism of drug-metabolizing enzymes is a main factor that determines the difference in individual responses to drugs.[23,24] In participants carrying the *UGT1A9*3* or *UGT2B4*2* allele, only modest increases in canagliflozin exposure were observed (mean AUC values were 26% and 18% higher, respectively, in these participants than in individuals not carrying these alleles). These modest increases in canagliflozin exposure are not expected to be clinically relevant.[13] Previously published literature suggests that there are no apparent differences in the dose- and weight-normalized PK parameters of canagliflozin exposure among Western, Chinese, and Japanese healthy participants,[18,25,26] as well as between Western and Japanese patients with T2DM.[19,27] Moreover, similar changes in PD parameters (RT_G and fasting and 24-hour mean PG) were seen in Western, Korean, and Japanese healthy participants and patients with T2DM at comparable doses of canagliflozin.[18–21,26,27]

The present study was carried out to evaluate the PK and PD properties and tolerability of single-dose oral canagliflozin 200 and 300 mg/day in healthy Indian participants. In previous studies, a reduction in postprandial glucose excursions was seen in participants when canagliflozin 300-mg doses were administered before the meal.[20,22] These data suggest that at doses of $\geq$300 mg, a blunting of intestinal glucose absorption occurred. This reduction in postprandial glucose excursions could be due to inhibition of intestinal SGLT1 by high local intraluminal concentrations of canagliflozin. This study was done in parallel with a Phase IIb study wherein canagliflozin doses of 50, 100, 200, 300 mg once daily and 300 mg twice daily were administered.[28] Therefore, it was anticipated that the therapeutic doses of canagliflozin might be in the range of 100 mg once daily, to a maximum of 300 mg twice daily, and thus, in the present study, doses of 200 and 300 mg once daily were studied.

PATIENTS AND METHODS

Study Population

Healthy Indian participants of either sex, aged between 18 and 55 years (inclusive), having a body

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