Canagliflozin in Conjunction With Sulfonylurea Maintains Glycemic Control and Weight Loss Over 52 Weeks: A Randomized, Controlled Trial in Patients With Type 2 Diabetes Mellitus

Jean-François Yale, MD, CSPQ, FRCPC[1]; John Xie, PhD[2]; Stephen E. Sherman, PhD[3]; and Claude Garceau, MD, FRCP[4]

[1]Department of Medicine, McGill University, Montreal, Quebec, Canada; [2]Janssen Research & Development, Raritan, New Jersey; [3]Janssen Inc., Toronto, Ontario, Canada; and [4]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec City, Quebec, Canada

ABSTRACT

Purpose: Our aim was to investigate the long-term efficacy and safety of canagliflozin, a sodium–glucose co-transporter 2 inhibitor, added to background sulfonylurea (SU) monotherapy for patients with type 2 diabetes mellitus.

Methods: The CANagliflozin cardioVascularAssessment Study (CANVAS) was a double-blind, placebo-controlled cardiovascular outcomes study that randomly assigned participants to receive placebo or canagliflozin 100 or 300 mg once daily in addition to routine therapy. CANVAS included a prespecified SU substudy of patients taking background doses of SU monotherapy; data from the primary efficacy evaluation at 18 weeks have been published previously. We performed a retrospective analysis of the SU substudy at 52 weeks to measure long-term efficacy and safety of canagliflozin used with an SU. The primary objective of the long-term extension was to assess the change from baseline to 52 weeks in glycosylated hemoglobin (HbA_{1c}).

Findings: A total of 215 patients were included in the 52-week extension study. Patients receiving both 100-mg and 300-mg doses of canagliflozin achieved a sustained reduction in HbA_{1c} relative to patients receiving placebo (–0.61% [95% CI, –0.941% to –0.282%] and –0.66% [95% CI, –0.993% to –0.332%], respectively), regardless of baseline HbA_{1c}, duration of diabetes, SU dose, estimated glomerular filtration rate, or body mass index. A sustained reduction in fasting plasma glucose was also found in both 100-mg and 300-mg groups, relative to the placebo group (–2.04 mmol/L [95% CI, –2.778 to –1.299 mmol/L] and –1.88 mmol/L [95% CI, –2.623 to –1.146 mmol/L], respectively). Weight was reduced significantly at 52 weeks in both 100-mg and 300-mg groups, relative to placebo (–1.9% [95% CI, –3.2% to –0.7%] and –2.0% [95% CI, –3.2% to –0.7%], respectively). Reduction in systolic blood pressure was also reported for both dose groups relative to the placebo group, but there was no clear difference in HDL-C, LDL-C, or triglyceride levels. Canagliflozin was generally well tolerated. While documented hypoglycemia occurred in 14% of patients on placebo, the frequency of hypoglycemia with the addition of canagliflozin was similar. There was an increased frequency of genital mycotic infections in both men (5.1%) and women (10.4%) in both canagliflozin groups combined, relative to the placebo group (0%), and their frequency increased in the higher-dose group. There was a slightly higher rate of renal impairment in those treated with canagliflozin versus placebo (2.1% vs 0%).

Implications: After 52 weeks, patients receiving canagliflozin added to background SU had sustained reductions in HbA_{1c} and fasting plasma glucose, without increasing hypoglycemia and body weight; safety findings were generally consistent with the known safety profile of the drug. ClinicalTrials.gov identifier: NCT01032629. (*Clin Ther.* ▮▮▮▮;▮:▮▮▮–▮▮▮)

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Key words: canagliflozin, cardiovascular disease, SGLT2 inhibitor, sulfonylureas, type 2 diabetes, weight loss.

INTRODUCTION

Worldwide, there are more than 284 million cases of diabetes, 90% of which are classified as type 2 (T2DM).[1] T2DM is associated with obesity, physical inactivity, increased blood pressure, abnormal blood lipid levels, and increased risk of thrombosis.[2] As such, patients with T2DM experience high mortality and morbidity, with twice the risk of developing cardiovascular disease.[3] Moreover, the prevalence of T2DM and the complexity of its management are growing exponentially, placing an enormous burden on health care resources worldwide.[4]

For patients with T2DM, an important goal of treatment is to maintain glycemic control; however, most are unable to do so through lifestyle changes alone, and will eventually require multiple therapies.[5] Although metformin is widely recommended as first-line therapy, sulfonylureas (SUs) may be selected when metformin is contraindicated or because of physician or patient preference.[5] While SUs are effective for controlling hyperglycemia, glycemic control is often transient, and their use is associated with hypoglycemia and weight gain.[5] Patients therefore often require additional therapies and would benefit from agents that can sustain glycemic control without increasing hypoglycemia and weight gain.[6,7]

Sodium–glucose co-transporter 2 inhibitors are a class of antidiabetic agents that act by preventing glucose reabsorption in the proximal tubule, leading to an increase in urinary glucose excretion, which reduces plasma glucose concentration.[8,9] Of agents in this class, canagliflozin, dapagliflozin, and empagliflozin have been approved in Canada,[10–12] the United States,[13] and Europe,[14] as, among other indications, add-on therapy when adequate glucose control cannot be achieved with SUs alone.

Canagliflozin has been shown to improve glycemic control and reduce body weight and systolic blood pressure in patients with T2DM when used as monotherapy or added to metformin, metformin plus SU, metformin plus pioglitazone, or metformin plus sitagliptin.[8,15–18] The use of canagliflozin given as add-on therapy for patients on background SUs has been examined as part of a substudy of the recently completed CANVAS study. CANVAS was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial, with a total of 4330 patients randomly assigned to receive placebo, canagliflozin 100 mg, or canagliflozin 300 mg.[19] Results from the prespecified SU substudy at 18 weeks found significant improvements in glycosylated hemoglobin (HbA_{1c}) versus placebo (–0.74% [95% CI, –1.15% to –0.33%]; $P < 0.001$ and –0.83% [95% CI, –1.24% to –0.42%]; $P < 0.001$) and fasting plasma glucose (FPG) (–2.1 mmol/L [95% CI, –3.0 to –1.2 mmol/L] and –2.7 mmol/L [95% CI, –3.6 to –1.7 mmol/L) with canagliflozin 100 and 300 mg, respectively. In addition, body weight was reduced with canagliflozin 300 mg (–1.8% [95% CI, –3.2% to –0.4%]; $P = 0.014$), but unchanged with canagliflozin 100 mg (–0.4% [95% CI, –1.8% to 1.0%]; $P = 0.557$). Safety findings included an increase in hypoglycemic episodes (at the 300-mg dose), as well as male and female genital mycotic infections, pollakiuria, and thirst. Here, we present results from the 52-week follow-up of patients from the SU substudy to examine the ability of canagliflozin to maintain glycemic control and to provide further safety and tolerability data.

METHODS

Design

The CANVAS study and SU substudy are randomized, double-blinded trials and have been described previously by Neal et al[19] and Fulcher et al[20], respectively. At 52 weeks follow-up, we performed a retrospective analysis of the SU substudy to examine the longer-term efficacy and safety of canagliflozin. The subset of patients included in the extension of the SU substudy were participants who were taking approved therapeutic doses of SU monotherapy at baseline. This is in contrast to the previous 18-week study, which included only those patients with ≥½ maximal doses of SU. Specifically, the present study included patients receiving glipizide ≥2.5 mg, glipizide extended release ≥5 mg, glyburide or glibenclamide ≥1.25 mg, glimepiride ≥1 mg, gliclazide ≥40 mg, or gliclazide modified release ≥30 mg (Figure 1).

Background Drug Treatments

Participants were required to have stable background SU monotherapy for 8 weeks before screening