

Canagliflozin, a new sodium–glucose cotransporter 2 inhibitor, in the treatment of diabetes

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Type 2 diabetes mellitus is a chronic disease that accounts for approximately 90–95% of all diagnosed cases of diabetes.¹ There are an estimated 25 million adults with diabetes in the United States, and their risk of death is approximately twofold higher than that of similarly aged individuals without diabetes.¹

Type 2 diabetes encompasses a spectrum of patients ranging from those who predominantly have insulin resistance and a relative insulin deficiency to those who have predominant insulin secretory defect along with insulin resistance.² The risk of developing type 2 diabetes increases with age, obesity, and a sedentary lifestyle. Uncontrolled diabetes can lead to serious complications including cardiovascular disease, nephropathy, retinopathy, and neuropathy.³ Glycemic control is fundamental in the management of diabetes and in reducing the aforementioned complications. Lifestyle modifications and pharmacologic treatments are necessary to control diabetes and maintain euglycemia.⁴

Purpose. The published evidence on the pharmacology, pharmacodynamics, pharmacokinetics, safety, and efficacy of a promising investigational agent for managing type 2 diabetes is evaluated.

Summary. Canagliflozin belongs to a class of agents—the sodium–glucose cotransporter 2 (SGLT2) inhibitors—whose novel mechanism of action offers potential advantages over other antihyperglycemic agents, including a relatively low hypoglycemia risk and weight loss-promoting effects. Canagliflozin has dose-dependent pharmacokinetics, and research in laboratory animals demonstrated high oral bioavailability (85%) and rapid effects in lowering glycosylated hemoglobin (HbA_{1c}) values. In four early-stage clinical trials involving a total of over 500 patients, the use of canagliflozin for varying periods was associated with significant mean reductions in HbA_{1c} (absolute reductions of 0.45–0.92%) and fasting plasma glucose

(decreases ranged from 16.2% to 42.4%) and weight loss ranging from 0.7 to 3.5 kg. More than a dozen Phase II or III clinical trials of canagliflozin in adults are ongoing or were recently completed, but the final results of most of those studies have not been published. Adverse effects reported in clinical trials of canagliflozin include urinary tract and genital infections, occurring in about 10% of patients. Additional and larger Phase III clinical trials to delineate the potential role of canagliflozin and other SGLT2 inhibitors in the management of diabetes (including studies involving the elderly, children, and patients with renal or hepatic dysfunction) are planned or currently underway.

Conclusion. Canagliflozin and other investigational SGLT2 inhibitors have a novel mechanism of action that may offer a future alternative treatment pathway for managing type 2 diabetes.

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However, type 2 diabetes is a progressive disease characterized by worsening glycemia; thus, patients often require higher medication dosages, additional medications, or both over time.

There are several factors that must be considered in the selection of an appropriate antihyperglycemic agent. A 2009 consensus statement from the American Diabetes Association (ADA) and the European Association

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for the Study of Diabetes (EASD) recommends using an algorithm for the selection of antihyperglycemic interventions to safely achieve and maintain glycemic targets.⁴ Key factors in medication selection addressed in the ADA–EASD guidance document include effectiveness in lowering glucose, extraglycemic effects that may reduce long-term complications, safety profiles, tolerability, ease of use, and expense.

Also in 2009, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) published an algorithm for the management of type 2 diabetes emphasizing the importance of individualized regimens for glycemic control. According to the AACE–ACE consensus document, priorities for medication selection include patient safety, minimizing the risk of hypoglycemia, minimal weight gain, efficacy in lowering glycosylated hemoglobin (HbA_{1c}) values, and effects on fasting and postprandial blood glucose levels.⁵ In addition, the AACE–ACE consensus document notes, it is important to consider the total cost of therapy to the individual and to society at large, including costs related to medications, blood glucose monitoring requirements, hypoglycemic events, drug-related adverse effects, and treatment of diabetes-associated complications.

In 2012, the American College of Physicians (ACP) released a clinical practice guideline presenting evidence and providing clinical recommendations on the comparative effectiveness and safety of oral medications for type 2 diabetes.⁶ The ACP guideline focuses on the comparative effectiveness of treatment options for the intermediate- and long-term clinical outcomes of glycemic control and comparative safety based on adverse effects.

The ADA–EASD, AACE–ACE, and ACP guidance documents provide a foundation for therapy selec-

tion with a focus on key factors that will continue to need evaluation as new medications or clinical data become available regarding safety, efficacy, and long-term outcomes for patients with type 2 diabetes.^{4,5}

Due to the progressive nature of type 2 diabetes, monotherapy with oral agents is associated with a high failure rate over approximately five years.⁷ Thus, the use of combination therapy consisting of agents with complementary mechanisms of action is important in maintaining glycemic control and minimizing adverse effects.⁵ The traditional focus of therapeutic strategies has been on developing agents that improve insulin sensitivity, enhance endogenous insulin secretion, or both. However, research efforts in recent years have pursued the development of therapies with an alternative mechanism of action: the enhancement of glucose excretion through the kidneys.⁸ These efforts have led to the development of a novel class of agents, the sodium–glucose cotransporter 2 (SGLT2) inhibitors, which appear to offer that alternative mechanism of action. There are several SGLT2 inhibitors in clinical development, with trials of one agent—canagliflozin—already yielding promising data.

Development of SGLT2 inhibitors

Recent recognition of the role of the kidneys in normal glucose homeostasis has led to an increased focus on drug development and clinical research in the field of diabetes.⁹ The SGLT2 inhibitors block the reabsorption of filtered glucose in the kidneys, leading to glucosuria—a mechanism of action that holds the potential for improvement of glycemic control, as well as the potential benefit of weight loss associated with caloric loss resulting from glucosuria.^{9,10} Thus, although SGLT2 inhibitors do not target the major pathophysiological processes of type 2 diabetes (insulin resistance and impaired insulin secretion), this drug class

represents a promising new treatment pathway.¹⁰

If ultimately approved for marketing, the SGLT2 inhibitors may be an appealing option for many patients due to the agents' high target selectivity and low potential for causing hypoglycemia, ability to produce improvements in both fasting and postprandial blood glucose values, and potential weight loss-promoting (or, at a minimum, weight-neutral) effects.^{9,10} To date, all clinical investigations of SGLT2 inhibitors have focused on patients with type 2 diabetes.^{11–18} However, based on positive study results achieved using SGLT2 inhibitors in conjunction with insulin in patients with type 2 diabetes, there is also interest in the potential use of these agents in the management of type 1 diabetes.^{10,12}

The development of SGLT2 inhibitors stemmed from research on phlorizin, a naturally occurring nonselective sodium–glucose cotransporter (SGLT1 and SGLT2) inhibitor first extracted from apple tree bark 175 years ago; the flavonoid is also found in a number of other fruit trees.¹⁹ In early studies, phlorizin was shown to lower fasting and postprandial blood glucose levels without causing hypoglycemia. However, phlorizin was never marketed because it is poorly absorbed in the intestine and subject to rapid hydrolysis by lactase–phlorizin hydrolase.²⁰

Initially, numerous SGLT inhibitors were investigated in clinical trials; however, several of those studies were halted in favor of studies involving newer, more selective SGLT2 inhibitors. Several review articles discuss these early research efforts and the initial discovery of SGLT2 inhibitors in greater detail.^{8–10,20–22} In addition to canagliflozin, notable agents within this class that are currently in clinical development include dapagliflozin, empagliflozin, ipragliflozin, tofogliflozin, and TS-071.¹⁸

Johnson & Johnson, in partnership with Mitsubishi Tanabe Pharma,

has pursued the clinical development of canagliflozin, previously known as JNJ-28431754 and TA-7284.¹¹ Canagliflozin is an oral SGLT2 inhibitor being investigated as a member of this new class of antihyperglycemic agents for the treatment of patients with type 2 diabetes. Data from Phase II studies of canagliflozin were presented at the ADA annual scientific sessions in 2010 and 2011.^{12-17,23-25} In recent years, a number of Phase III clinical trials involving more than 10,000 patients with type 2 diabetes were completed (Table 1); a few of those studies are ongoing. As of November 2012, the full results of the Phase III trials had not been published.^{11,26}

Mechanism of action

The kidneys play a fundamental role in glucose homeostasis through glomerular filtration and reabsorption in the proximal convoluted tubule (PCT).⁹ In a normal healthy adult, approximately 180 g of glucose is filtered daily.²⁷ The kidneys reabsorb most of the glucose, with less than 1% being excreted into the urine. The normal tubular glucose load is approximately 120 mg/min, with no glucose excreted into the urine.⁹ Glucosuria begins to occur when the tubular glucose load exceeds 220 mg/min; this corresponds to a plasma glucose concentration of approximately 200 mg/dL.²⁸ The plasma glucose concentration is an important modulator of SGLT expression and activity.²⁷ The fundamental concept underlying current research on SGLT2 inhibitors is that by blocking the effects of SGLT, increased urinary glucose excretion (UGE) and reduced plasma glucose levels can be achieved.

SGLT is responsible for the transport of glucose from the tubule into tubular epithelial cells.⁹ Two cotransporters are responsible for renal reabsorption: SGLT1 and SGLT2. SGLT1 is a high-affinity, low-capacity transporter primarily expressed along the brush border of the small

intestine. It is predominantly responsible for glucose absorption in the gastrointestinal tract. SGLT1 is also located in the S3 segment of the PCT but only accounts for approximately 10% of reabsorbed renal glucose.^{9,21} SGLT2 is a low-affinity, high-capacity transporter exclusive to the kidneys. It is located along the brush border of the S1 segment of the PCT and accounts for 90% of reabsorbed filtered glucose.

Since SGLT2 is found exclusively in the kidneys, inhibiting the reabsorption of filtered glucose leads to glucosuria without gastrointestinal adverse effects.²⁹ Another potential benefit of glucosuria associated with SGLT2 inhibition is a loss of approximately 200–300 kcal/day. This class effect may contribute to weight loss.⁹ Canagliflozin is one of many selective SGLT2 inhibitors currently under investigation.

Available evidence on canagliflozin

Pharmacokinetics. The pharmacokinetics of canagliflozin after i.v. and oral administration, at dosages of 3 and 10 mg/kg, respectively, were investigated in a study of male Sprague–Dawley rats,³⁰ which revealed a higher exposure to canagliflozin after oral administration. Oral bioavailability was 85%, and the half-life was similar with respect to i.v. and oral administration. The results indicate that the effect of inhibiting SGLT2 will continue to suppress glucose reabsorption. Single oral doses of canagliflozin (3 mg/kg) were administered to the laboratory animals with hyperglycemia induced by a high-fat diet. Six hours after administration of canagliflozin, the mean blood glucose level of the hyperglycemic rats was reduced by 48%.

Clinical studies. Several early clinical trials evaluating the efficacy and safety of canagliflozin have been completed and their results published.^{12-17,23-25}

A dose-dependent effect was observed in a randomized, double-blind, placebo-controlled, parallel-group study of canagliflozin.¹² The area under the concentration–time curve and the maximum concentration increased as the doses were increased over 28 days in 29 volunteers. The elimination half-life ranged from 12 to 15 hours and was independent of the dose administered. Steady-state drug concentrations were achieved within 7 days of dosing.

The safety, tolerability, and pharmacodynamics of single-dose canagliflozin were assessed in a randomized, double-blind, placebo-controlled, escalating-dose Phase I study of 63 healthy men.²⁵ Participants ranged in age from 19 to 55 years and had a mean body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 24. Eight dosages were administered in an escalating fashion to determine if canagliflozin increased UGE in relation to increased dosages (10, 30, 100, 200, 400, 600, and 800 mg daily or 400 mg twice daily). At canagliflozin dosages exceeding 200 mg in a 24-hour period, UGE was significantly increased, with a maximum mean UGE of 70 g (range, 5 g with the 10-mg daily dosage to 70 g with daily dosages of >200 mg). The renal threshold (R_T) for glucose excretion decreased in a dose-dependent manner, with a maximal reduction to a mean \pm S.D. concentration of 61 ± 11 mg/dL. Postprandial glucose concentrations measured after breakfast were lowered at canagliflozin dosages of >200 mg daily.

A double-blind multiple-dose study was conducted in patients who had stopped taking other antihyperglycemic medications for two weeks and were randomly assigned to receive canagliflozin (30, 100, 200, or 400 mg daily or 300 mg twice daily) or a placebo for two weeks.¹⁴ The study was completed by 97 participants with a mean age of 53 years, a mean weight of 91.8 kg, and

Table 1.
Summary of Ongoing and Recently Completed Phase III Clinical Trials of Canagliflozin^{26,a}

Trial	Design	Patients	Evaluated Canagliflozin-Containing Regimens
<i>Ongoing</i>			
CANTATA-SU	Randomized, double-blind, parallel-group	Type 2 diabetes; glycemic control not optimized with metformin monotherapy	Canagliflozin 100 or 300 mg daily
CANVAS	Randomized, double-blind, parallel-group, placebo-controlled	Type 2 diabetes	Canagliflozin 100 or 300 mg daily plus metformin alone or in combination with a sulfonyleurea
NCT01106651	Randomized, double-blind, placebo-controlled, parallel-group	Type 2 diabetes inadequately controlled with glucose-lowering therapy	Low- or high-dose canagliflozin daily
NCT01381900	Randomized, double-blind, placebo-controlled, parallel-group	Type 2 diabetes; inadequate glycemic control with metformin alone or in combination with a sulfonyleurea	Canagliflozin 100 or 300 mg daily
NCT1387737	Randomized, two-group, parallel-group, open-label, multicenter	Type 2 diabetes not optimally controlled with diet and exercise or with oral antihyperglycemic agents	Low- or high-dose canagliflozin daily
<i>Recently Completed^b</i>			
CANTATA-D	Randomized, double-blind, placebo- and active-controlled, parallel-group	Type 2 diabetes inadequately controlled with metformin alone	Canagliflozin 100 or 300 mg daily
CANTATA-D2	Randomized, double-blind, active-controlled	Type 2 diabetes inadequately controlled with metformin and sulfonyleureas	Canagliflozin 300 mg daily
CANTATA-M	Randomized, double-blind, placebo-controlled, parallel-group	Type 2 diabetes inadequately controlled with diet and exercise	Canagliflozin 100 or 300 mg daily
CANTATA-MP	Randomized, double-blind, placebo-controlled, three-group, parallel-group	Type 2 diabetes; inadequate glycemic control with metformin and pioglitazone	Canagliflozin 100 or 300 mg daily, with stable doses of metformin and pioglitazone
CANTATA-MSU	Randomized, double-blind, placebo-controlled, parallel-group	Type 2 diabetes; inadequate glycemic control with metformin and sulfonyleurea	Canagliflozin 100 or 300 mg daily
NCT01064414	Randomized, double-blind, placebo-controlled, three-group, parallel-group	Type 2 diabetes with moderate renal impairment	Canagliflozin 100 or 300 mg daily

Comparator Regimen	Endpoints	Duration
Glimepiride initiated at 1 mg and escalated to maximum of 6 or 8 mg once daily	<i>Primary:</i> Change from baseline HbA _{1c} through 52 wk <i>Secondary:</i> Percentage change in body weight from baseline through 52 wk	104 wk
Placebo	<i>Primary:</i> Major CV events (e.g., CV death, MI, stroke) <i>Secondary:</i> Fasting insulin secretion, albuminuria progression; effectiveness in lowering blood glucose in subgroups of pts also receiving other antidiabetic agents	4 yr
Placebo	<i>Primary:</i> Change in HbA _{1c} at 26 wk <i>Secondary:</i> Change in BMD at 26, 52, and 104 wk; bone strength in pt subgroup at 52 wk; changes in bone turnover markers at 12 and 26 wk; change in body composition at 26 wk	104 wk
Placebo	<i>Primary:</i> Change from baseline HbA _{1c} at 18 wk <i>Secondary:</i> Changes from baseline in FPG and body weight and rate of attainment of goal HbA _{1c} values (<7% and <6.5%) at 18 wk; treatment-related adverse events over 20 wk	20 wk, with 2-wk single-blind placebo run-in period
NA	<i>Primary:</i> Safety and tolerability, as assessed by adverse events, hypoglycemic events, laboratory tests, ECG, and vital signs <i>Secondary:</i> Changes in HbA _{1c} , FPG, body weight, and BP	52 wk
Placebo for 26 wk, followed by sitagliptin 100 mg for 26 wk	<i>Primary:</i> Change in HbA _{1c} at 26 wk <i>Secondary:</i> Change in HbA _{1c} at 52 wk; rates of attainment of goal HbA _{1c} values (<7% and <6.5%) at 26 and 52 wk; PPG at 26 wk; FPG, body weight, DBP, SBP, and FPL at 26 and 52 wk	52 wk
Sitagliptin 100 mg daily	<i>Primary:</i> Change in HbA _{1c} at 52 wk <i>Secondary:</i> Changes in body weight, FPG, SBP, TG, and HDL cholesterol at 52 wk	52 wk
Placebo for 26 wk, followed by sitagliptin 100 mg for 26 wk	<i>Primary:</i> Change in HbA _{1c} at 26 wk <i>Secondary:</i> Changes in FPG, body weight, and PPG at 26 wk; changes in DBP, SBP, and FPL, and rates of attainment of goal HbA _{1c} value (<7%) at 26 wk in high-risk cohort	52 wk
Placebo for 26 wk, with stable doses of metformin and pioglitazone; after 26 wk, crossover to sitagliptin 100 mg for 26 wk, with stable doses of metformin and pioglitazone	<i>Primary:</i> Change from baseline HbA _{1c} at 26 wk <i>Secondary:</i> Change from baseline HbA _{1c} at 52 wk; rate of attainment of goal HbA _{1c} values (<7% and <6.5%) at 26 and 52 wk; changes from baseline DBP, SBP, body weight, FPG, FPL, and β -cell function at 26 and 52 wk; proportion of pts needing rescue therapy and time to rescue therapy at 26 and 52 wk	52 wk
Placebo	<i>Primary:</i> Change in HbA _{1c} at 26 wk <i>Secondary:</i> Change in HbA _{1c} at 52 wk; changes in FPG, DBP, SBP, and body weight; rates of attainment of goal HbA _{1c} values (<7% and <6.5%); proportion of pts needing rescue therapy and time to rescue therapy at 26 and 52 wk	52 wk
Placebo	<i>Primary:</i> Change in HbA _{1c} at 26 wk; safety and tolerability <i>Secondary:</i> Change in FPG at 26 wk; changes in FPL, body weight, DBP, SBP, and renal function at 26 and 52 wk; glycemic control at 52 wk	26 wk with 26-wk extension

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Table 1 (continued)

Trial	Design	Patients	Evaluated Canagliflozin-Containing Regimens
NCT01413204	Randomized, double-blind, placebo-controlled, parallel-group, multicenter (Japan)	Type 2 diabetes not optimally controlled with diet and exercise	Low- or high-dose canagliflozin daily
NCT01665638	Randomized, double-blind, placebo-controlled, two-way crossover	Healthy (nondiabetic)	Single oral dose of canagliflozin 300 mg

^aHbA_{1c} = glycosylated hemoglobin, BMD = bone mineral density, BP = blood pressure, CV = cardiovascular, DBP = diastolic blood pressure, FPL = fasting plasma lipids, FPG = fasting plasma glucose, HDL = high-density lipoprotein, MI = myocardial infarction, NA = not applicable, PPG = postprandial glucose, SBP = systolic blood pressure, TG = triglycerides.

^bNo study results posted on National Institutes of Health website ClinicalTrials.gov as of November 2012.

a mean HbA_{1c} of 8%. The results of the study indicated a dose-dependent increase in UGE and a decrease in R_r. Significant dose-dependent reductions in 24-hour postprandial glucose concentrations, fasting plasma glucose (FPG) concentrations, and weight were observed in patients receiving canagliflozin compared with those given a placebo. Weight loss in patients receiving canagliflozin averaged 1.0–1.5 kg greater than weight loss with the placebo.

Combination therapy was evaluated in patients with type 2 diabetes inadequately controlled on metformin in a double-blind, placebo-controlled, dose-ranging study that assessed the safety, tolerability, and efficacy of canagliflozin.¹³ Patients were randomly assigned to receive a placebo, canagliflozin (50, 100, 200, or 300 mg daily or 300 mg twice daily), or sitagliptin 100 mg daily. All patients continued to use metformin. The baseline characteristics of the 451 patients included a mean age of 53 years, a mean HbA_{1c} value of 7.7%, a mean FPG concentration of 162 mg/dL, and a mean weight of 87 kg. After 12 weeks of therapy, both the canagliflozin and sitagliptin groups had significant changes from baseline in FPG concentrations (mean decreases of 30.6 and 18 mg/dL,

respectively; $p \leq 0.001$) and HbA_{1c} (decreases of 0.73% and 0.56%, respectively; $p \leq 0.001$) relative to placebo users. Significant dose-related changes in weight loss were demonstrated with canagliflozin relative to placebo (weight loss range, 1.3–2.3%; $p \leq 0.01$ for the 50- and 100-mg daily dosages, $p \leq 0.001$ for dosages of 200 and 300 mg daily and 300 mg twice daily); significant changes in weight were not observed with sitagliptin. In previous trials assessing metformin's effect on body weight, decreases in weight from baseline ranged from 2.9 to 9 kg.³¹ Many of the trials evaluating the effects of metformin on weight were small and had weak study designs; thus, the true effect of metformin on weight loss remains unknown.

A randomized double-blind, placebo-controlled, parallel-group 28-day study assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of canagliflozin in patients with type 2 diabetes mellitus.¹² Twenty-nine participants who were not optimally controlled on stable insulin doses were randomly assigned to receive canagliflozin 100 mg daily, canagliflozin 300 mg twice daily, or a placebo. Baseline patient characteristics included a median age of 50 years and a mean BMI of

32.3; mean HbA_{1c} values were 8.38%, 8.42%, and 8.27% in the groups receiving canagliflozin 100 mg daily, canagliflozin 300 mg twice daily, and placebo, respectively; at 28 days, the corresponding mean changes from baseline HbA_{1c} were –0.73%, –0.92%, and –0.19%, respectively. Among patients receiving canagliflozin 100 mg daily and 300 mg twice daily, the mean 24-hour UGE increased by 71.9 and 129.2 g, respectively; the mean weight loss in those groups was 0.7 and 1.2 kg, respectively (no change in weight from baseline was observed with placebo use).

Monotherapy with canagliflozin was studied in a multicenter randomized, double-blind, placebo-controlled, dose-ranging study in Japanese patients with type 2 diabetes. Patients were randomly assigned to receive canagliflozin (50, 100, 200, or 300 mg) or a placebo daily for 12 weeks. After 12 weeks, HbA_{1c} values and mean FPG and postprandial plasma glucose concentrations were significantly reduced in the canagliflozin treatment groups compared with the placebo group. Body weight was reduced by up to 3.19 kg in the canagliflozin groups, compared with a mean weight loss of 0.78 kg with placebo use. Systolic and diastolic blood pressures were also signifi-

Comparator Regimen	Endpoints	Duration
Placebo	<i>Primary:</i> Change in HbA _{1c} <i>Secondary:</i> Changes in FPG, body weight, and BP at 24 wk; changes in PPG and insulin and urinary glucose excretion after oral glucose tolerance test; safety and tolerability, as assessed by adverse event rates, hypoglycemic events, laboratory and ECG testing, and vital signs	24 wk
NA	<i>Primary:</i> Change from baseline in C-peptide kinetic parameters on day 1 of two treatment periods <i>Secondary:</i> Adverse treatment-related events	Up to 22 days after day 1 of treatment period 1

cantly reduced in the canagliflozin groups.¹⁷

The effects of canagliflozin in obese patients were studied in a double-blind, ascending multiple-dose study.²⁴ Forty men and 40 women were randomly assigned to receive canagliflozin (30, 100, 300, or 600 mg daily or 300 mg twice daily) or a placebo after 15 days of adhering to a diet designed to maintain a fixed body weight. After 14 days, the mean 24-hour UGE was significantly increased in all dosage groups ($p < 0.0001$) except for the group receiving canagliflozin 30 mg daily ($p = 0.06$). There were no meaningful changes from baseline values in FPG, mean 24-hour plasma glucose, or insulin levels. Weight loss among canagliflozin users over the 14-day period averaged 2.9 kg in those receiving 30 mg daily ($p = 0.002$), 2.7 kg in those receiving 100 mg daily ($p = 0.008$), 2.1 kg in those receiving 300 mg daily ($p = 0.13$), 3.4 kg in those receiving 600 mg daily ($p < 0.0001$), and 3.5 kg in those receiving 300 mg twice daily ($p < 0.0001$). The R_T for glucose excretion decreased in a dose-dependent manner to a mean \pm S.D. concentration of 64 ± 16 mg/dL.

As previously mentioned, a number of clinical trials evaluating the role of canagliflozin in the treatment

of type 2 diabetes were recently completed (most results not published as of November 2012), and others are ongoing (Table 1).^{11,26}

The Canagliflozin Treatment and Trial Analysis (CANTATA) series of trials evaluated the efficacy and safety of canagliflozin (100 or 300 mg daily) in managing type 2 diabetes poorly controlled with standard-of-care treatments, with the change in HbA_{1c} values specified as the primary end point of all studies (the CANTATA-SU trial, evaluating the effects of adding a sulfonylurea to combination therapy with canagliflozin and metformin, has not been completed).

The ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) is assessing the agent's impact on the risks of major cardiovascular events, including death, myocardial infarction, and stroke, over periods of four years or longer.²⁶

Additional ongoing clinical trials are evaluating several pharmacokinetic and pharmacodynamic properties of canagliflozin. These studies include evaluations of the agent's drug interaction potential and its safety and efficacy in patients with hepatic or renal dysfunction.

Safety evaluations. At this time, there are minimal safety data available regarding canagliflozin. The

results of ongoing large Phase III clinical trials should provide additional safety data. In one study, patients were randomly assigned to receive either single-dose placebo, moxifloxacin 400 mg, canagliflozin 300 mg, or canagliflozin 1200 mg and were assessed for electrocardiogram (ECG) changes, specifically the Q-T-Q-Tc interval.²³ Continuous postdose heart monitoring for up to 24 hours showed similar ECG changes in the canagliflozin and placebo groups. Urine volume, electrolyte excretion, and renal function have also been assessed in patients receiving canagliflozin; to date, there is no evidence that canagliflozin alters any of these data points.^{24,25}

As with any antihyperglycemic agent, the potential for hypoglycemia associated with canagliflozin use is of major concern. The overall frequency of hypoglycemia in clinical trials of canagliflozin has been low, and the majority of cases were defined as nonsevere.^{12,13,25} The highest risk for hypoglycemia appears to be with concurrent use of insulin therapy. In a recent study, patients with uncontrolled type 2 diabetes who were receiving a stable dosage of insulin were started on either canagliflozin 100 mg daily or 300 mg twice daily.¹² While specific hypoglycemia criteria

were not defined, the authors reported that no severe hypoglycemic events were noted. However, 41% ($n = 12$) of all patients did experience an episode of nonsevere hypoglycemia ($n = 9$ in the canagliflozin group; $n = 3$ in the placebo group). This rate is higher than the rates of hypoglycemic events reported in other studies, in which under 10% of patients experienced hypoglycemia.^{13,24,25}

Perhaps the most unique safety concerns about canagliflozin and other agents in this medication class include the risk for urinary tract infections (UTIs) or genital infections. When compared to placebo and sitagliptin, the frequency of UTIs was slightly increased in the 451 patients studied (5% canagliflozin, 3.8% pooled placebo and sitagliptin group).¹⁵ Similarly, the rate of vulvovaginal candidiasis was increased in patients receiving canagliflozin in this trial (10.4% canagliflozin, 2.9% placebo, 3.7% sitagliptin). The aforementioned trial is the largest trial published to date. Additional studies completed have shown a less drastic increase in urinary tract or genital infections when compared with placebo.^{14,24} In a smaller study of 80 obese patients, only 1 woman experienced an asymptomatic UTI.²⁴ In another study of 97 patients, a similar event rate was noted, with 1 woman experiencing vaginal candidiasis.¹⁴ The overall low frequencies within these studies may be attributed to the smaller study population, thus explaining the discrepancy in infection rates.

Clinical trials completed to date have excluded patients with clinically significant diabetic complications such as retinopathy, nephropathy or macroalbuminuria, neuropathy, gastroparesis, and diabetic ketoacidosis.^{12-17,23,24,26} In addition, patients enrolled in completed clinical trials were on stable antihyperglycemic regimens and not experiencing severe hypoglycemic episodes. These studies also did not involve patients

with cardiovascular, hematologic, respiratory, hepatic, or gastrointestinal disease; endocrine or metabolic disorders; neurologic or psychiatric disease; malignant neoplasms; or any other significant illness, as determined by the investigators. Overall, there have been no clinically meaningful changes in laboratory safety tests, vital signs, or ECG findings associated with canagliflozin use.

The eligibility criteria for the completed clinical trials stipulated that patients be 18–65 years of age, but a general expansion of eligibility criteria to include men and women up to 80 years of age is planned. Currently, there are no published data on the efficacy or safety of the use of canagliflozin in pediatric or geriatric patients.²⁶

Dosage and administration. Canagliflozin dosages of up to 800 mg daily and 400 mg twice daily have demonstrated efficacy in increasing UGE and decreasing R_T values.²⁵ Other completed studies have focused on dosages of 300 or 400 mg daily or 300 mg twice daily.^{12-14,24} Clinical data from completed trials support once-daily dosing of canagliflozin (100 or 300 mg).¹² Further clinical trials are needed to assess multiple dosing regimens for canagliflozin, either as monotherapy or in combination with other antihyperglycemic agents. The effects of renal or hepatic dysfunction on dosing have yet to be determined, with clinical trials currently underway.²⁶

Future outlook

Currently, additional SGLT2 inhibitors are being studied in clinical trials, but dapagliflozin is the only agent for which a greater amount of supportive data has been published.^{18,26} A recent review article summarizing dapagliflozin trial results indicated overall favorable effects on FPG, HbA_{1c} , and body weight³²; however, some data indicating increased rates of breast and bladder cancer in association with

dapagliflozin use raised significant Food and Drug Administration (FDA) safety concerns.^{33,34}

In May 2012, Janssen Research & Development (a unit of Johnson & Johnson) submitted a new drug application for canagliflozin to FDA; the application is under review.³⁵

Conclusion

Canagliflozin and other investigational SGLT2 inhibitors have a novel mechanism of action that may offer a future alternative treatment pathway for managing type 2 diabetes.

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