Efficacy and Safety of Canagliflozin as Add-On Therapy to Metformin in Type 2 Diabetes

Reviewed by Dawn M. Battise, PharmD, BCACP

STUDIES

Comparison of canagliflozin versus glimepiride (study A): Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, Balis DA, Canovatchel W, Meininger G: Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 382:941–950, 2013.

Comparison of canagliflozin versus placebo and sitagliptin (study B): Lavalle-Gonzalez FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W, Meininger G: Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 56:2582–2592, 2013.

SUMMARY

Objectives. To evaluate the safety and efficacy of canagliflozin compared to glimepiride (study A) and placebo and sitagliptin (study B) in adults with type 2 diabetes with inadequate glycemic control on metformin monotherapy.

Design and methods. Study A: Adults with type 2 diabetes inadequately controlled with metformin were randomized to canagliflozin, 100 mg ($n = 478$) or 300 mg ($n = 474$), or glimepiride, uptitrated to 6 or 8 mg/day once daily ($n = 473$), all in combination with metformin. The primary efficacy endpoint was change in A1C after 52 weeks. The primary hypothesis was the noninferiority of canagliflozin, 100 or 300 mg or both, to glimepiride for A1C reduction at week 52.

Study B: Adults with type 2 diabetes inadequately controlled with metformin were randomized to canagliflozin, 100 mg ($n = 368$) or 300 mg ($n = 367$); sitagliptin, 100 mg ($n = 366$); or placebo ($n = 183$) once daily for 26 weeks, all in combination with metformin. After 26 weeks, placebo-treated patients were switched to sitagliptin 100 mg; other patients continued on the same therapy for an additional 26 weeks. The primary efficacy endpoint was change in A1C after 26 weeks. The primary hypothesis was the statistical superiority of canagliflozin 300 mg to placebo for A1C reduction at week 26. Secondary hypotheses were statistical superiority of canagliflozin 100 mg to placebo in A1C-lowering effect at week 26 and noninferiority of canagliflozin 300 mg or both canagliflozin doses to sitagliptin 100 mg in reducing A1C from baseline to week 52.

Results. Study A: After 52 weeks, the mean changes from baseline in A1C for canagliflozin 100 mg and 300 mg and glimepiride were –0.82, –0.93, and –0.81%, respectively (Table 1). An estimated treatment difference of –0.01% (95% CI –0.11 to 0.09%) indicated that canagliflozin 100 mg/day was noninferior to glimepiride. Additionally, an estimated treatment difference of –0.12% (95% CI –0.22 to –0.02%) met predefined step-down assessment of superiority indicating that canagliflozin 300 mg/day was superior to glimepiride. The incidence of serious adverse events (AEs) was similar among the groups at 5% for both doses of canagliflozin and 8% for glimepiride. The incidence of hypoglycemia was significantly higher in the glimepiride group (34%) compared to the canagliflozin 100 mg (6%) and 300 mg (5%) groups ($P < 0.0001$ for both). AEs more commonly reported with canagliflozin included genital mycotic infections and pollakiuria (abnormally frequent urination) (Table 2). The incidences of all other AEs were similar.

Study B: At week 26, canagliflozin, 100 mg and 300 mg, significantly reduced A1C from baseline compared to placebo (–0.79, –0.94, and –0.17%, respectively; $P < 0.001$ for both). The mean change in A1C from baseline for sitagliptin was –0.82% at week 26. At week 52, the mean changes from baseline in A1C for canagliflozin 100 mg and 300 mg and sitagliptin were –0.73, –0.88, and –0.73%, respectively (Table 1). An estimated treatment difference of –0.00% (95% CI –0.12 to 0.12%) indicated that canagliflozin 100 mg/day was noninferior to sitagliptin. An estimated treatment difference of –0.15% (95% CI –0.27 to –0.03%) met predefined step-down assessment of superiority

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Table 1. Efficacy Results

	A1C (%)		FPG (mg/dl)		PPG (mg/dl)		Body Weight (kg)		Systolic BP (mmHg)		Diastolic BP (mmHg)		LDL Cholesterol (mg/dl)		HDL Cholesterol (mg/dl)		Non-HDL Cholesterol (mg/dl)		TG (mg/dl)	
	BL	Δ	BL	Δ	BL	Δ	BL	Δ	BL	Δ	BL	Δ	BL	Δ	BL	Δ	BL	Δ	BL	Δ
Study A : 0–52 weeks																				
52 weeks: Canagliflozin 100 mg/day	7.8	–0.82	166	–24	NR	NR	86.8	–3.7	130.0	–3.3	78.7	–1.8	101	4.6	46.4	3.1	135	1.2	186	–19.5
OR Canagliflozin 300 mg/day	7.8	–0.93	164	–27	NR	NR	86.6	–4.0	130.0	–4.6	79.2	–2.5	108	9.7	46.4	3.9	143	8.5	186	–8.9
OR Glimepiride 1–8 mg/day (mean 5.6 mg/day)	7.8	–0.81	166	–18	NR	NR	86.6	0.7	129.5	0.2	79.0	–0.1	104	1.9	46.4	-0.4	135	2.3	168	–0.9
Study B: 0–26 weeks																				
Canagliflozin 100 mg/day	7.9	–0.79	169	–27	257	–49	88.87	–3.3	128	–3.8	77.7	–2.2	108	3.1	46.4	4.3	147	0.8	195	–8.9
OR Canagliflozin 300 mg/day	8.0	–0.94	173	–38	261	–58	85.4	–3.6	129	–5.1	77.9	–2.1	108	7.0	46.4	5.0	143	3.1	186	–23.9
OR Placebo	8.0	–0.17	164	2	248	–11	86.6	–1.1	128	1.5	77.8	0.3	104	–4.3	42.5	1.5	143	3.9	186	–2.7
OR Sitagliptin 100 mg/day	7.9	–0.82	169	–20	256	–49	87.7	–1.1	128	–1.8	77.5	–1.1	108	0.8	46.4	1.9	143	0.8	177	–7.1
Study B: 0–52 weeks*																				
Canagliflozin 100 mg/day		–0.73		–27		NR		–3.3		–3.5		–1.8		4.3		4.6		1.5		–10.6
OR Canagliflozin 300 mg/day		–0.88		–36		NR		–3.7		–4.7		–1.8		4.3		5.4		1.9		–16.8
OR Sitagliptin 100 mg/day		–0.73		–18		NR		–1.2		–0.7		–0.3		3.1		2.3		1.2		–13.3

**Data are reported as change from baseline (week 0) to 52 weeks.*
Δ, change; BL, baseline; BP, blood pressure; FPG, fasting plasma glucose; PPG, postprandial glucose; TG, triglycerides; NR, not reported.

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Table 2. Overall Safety and Selected AEs (%) Over 52 Weeks

	Canagliflozin		Glimepiride	Placebo/ Sitagliptin*	Sitagliptin
	100 mg	300 mg			
Study A					
Any AE	64	69	69	–	–
AE possibly, probably, very likely related	24	30	23	–	–
Genital mycotic infection	9	11	1	–	–
Urinary tract infection	6	6	5	–	–
Pollakiuria	3	3	< 1	–	–
Polyuria	< 1	< 1	< 1	–	–
Postural dizziness	< 1	< 1	< 1	–	–
Postural hypotension	< 1	< 1	0	–	–
Study B					
Any AE	72.3	62.7	–	66.7	64.5
AE possibly, probably, very likely related	26.4	19.9	–	12.6	19.7
Hypoglycemia, overall	6.8	6.8	–	2.7	4.1
Genital mycotic infection	8.4	6.5	–	1.1	1.9
Urinary tract infection	7.9	4.9	–	6.6	6.3
Pollakiuria	5.7	3.0	–	0.5	0.5
Polyuria	0.5	0.5	–	0	0
Postural dizziness	0.5	0.5	–	0.5	0.3
Postural hypotension	0	0.3	–	0	0

**Patients received placebo during weeks 0–26 and then were switched to sitagliptin during weeks 27–52.*

indicating that canagliflozin 300 mg/day was superior to sitagliptin.

The incidence of overall AEs was higher with canagliflozin 100 mg, whereas serious AEs were more frequent with sitagliptin (Table 2). Over 52 weeks, the incidences of hypoglycemia were 6.8, 6.8, 4.1, and 2.7% for canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin, and placebo/sitagliptin, respectively. AEs more commonly reported with canagliflozin included genital mycotic infection, pollakiuria, and polyuria. The incidences of all other AEs were similar.

Conclusion. As add-on therapy to metformin, canagliflozin 100 mg is noninferior and canagliflozin 300 mg is superior to glimepiride and sitagliptin over 52 weeks. The incidence of hypoglycemia with canagliflozin was significantly lower than with glimepiride and similar to sitagliptin. AEs more commonly reported with canagliflozin were associated with its mechanism of action (i.e., increased urinary glucose excretion and osmotic diuresis) and included genital mycotic infection, pollakiuria, and polyuria.

COMMENTARY

The progressive nature of β-cell decline observed in patients with type 2 diabetes often necessitates treatment intensification beyond lifestyle management and metformin.[1,2]

However, there are barriers to current treatment options, including limited glycemic durability,[3] AEs such as hypoglycemia and weight gain,[4,5] and injectable route of administration.

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In healthy individuals, nearly all of the filtered glucose is reabsorbed by the kidneys, and < 1% is excreted in the urine. The majority of renal glucose reabsorption is mediated by sodium glucose cotransporter-2 (SGLT-2), a high-capacity, low-affinity transporter expressed in the early portion of the proximal renal tubule. Increased renal capacity for glucose reabsorption has been observed in patients with type 2 diabetes, and this maintains and exacerbates the hyperglycemia.[6,7]

SGLT-2 inhibitors are a new class of oral antihyperglycemic agents that lower plasma glucose via a novel, insulin-independent mechanism of action targeting the kidney. Two SGLT-2 inhibitors, canagliflozin and dapagliflozin, are currently approved in the United States for the treatment of patients with type 2 diabetes. SGLT-2 inhibitors reduce glucose reabsorption in the kidney, resulting in the excretion of excess glucose in the urine, thereby lowering plasma glucose in individuals with hyperglycemia. The increased urinary glucose excretion is associated with a net loss of calories that contributes to body weight reduction and a mild osmotic diuresis that may be associated with a lowering of blood pressure.[6,7]

The two studies reviewed demonstrate that, when added to metformin monotherapy, canagliflozin 100 mg is noninferior and canagliflozin 300 mg is superior to glimepiride and sitagliptin in terms of A1C lowering. Additionally, the results show a decreased incidence of hypoglycemia compared to glimepiride and benefits in weight loss. Genital mycotic infections are more common with canagliflozin than with glimepiride or sitagliptin in both men and women. The incidence of urinary tract infection is similar between canagliflozin and sitagliptin and is slightly increased with canagliflozin (6% for both doses) compared to glimepiride (5%). Additionally, canagliflozin increases the incidence of pollakiuria and polyuria, AEs associated with increased urination, although the incidences of volume-related AEs are similar between groups. These results are generally similar to another 52-week study showing superior A1C reduction and similar safety with the addition of canagliflozin 300 mg compared to sitagliptin 100 mg to metformin plus sulfonylurea.[8]

Additional Study Results

Study A: In addition to the A1C results, other benefits were observed with canagliflozin. Reductions in fasting plasma glucose (FPG) were greater with canagliflozin in either dose compared to glimepiride. A statistically significant ($P < 0.0001$) reduction in body weight was observed at both doses of canagliflozin compared to a slight weight increase with glimepiride. Weight loss plateaued after 26 weeks, and, in a body composition substudy, it was shown that two-thirds of body weight loss resulted from reduction in body fat mass and one-third resulted from the loss of lean body mass. This ratio is consistent with changes in body composition observed with other glucose-lowering drugs associated with weight reduction.[9,10] Canagliflozin 100 mg and 300 mg resulted in modest reductions in systolic blood pressure compared to no change with glimepiride. Canagliflozin resulted in increases in HDL and LDL cholesterol.

The overall frequency of AEs and rates of discontinuation were similar among all groups. Serious AEs were slightly more frequent with glimepiride. In addition to a significantly lower incidence of documented hypoglycemia with canagliflozin in both doses, there was a lower incidence of severe hypoglycemia for both doses of canagliflozin (< 1%) compared to glimepiride (3%). The frequency of selected AEs is summarized in Table 2.

In the canagliflozin group, small to moderate decreases in alanine aminotransferase, gamma-glutamyltransferase, and serum urate were noted in addition to increases in bilirubin, blood urea nitrogen, and hemoglobin. Canagliflozin 100 mg, canagliflozin 300 mg, and glimepiride were associated with small decreases in estimated glomerular filtration rate (GFR) at 52 weeks of –1.7, –3.0, and –5.1 ml/min/1.73 m^2, respectively. These laboratory values were not prespecified for statistical comparison.

Study B: In addition to the A1C results, additional benefits were observed. At 52 weeks, there was a significantly greater reduction in FPG, body weight, and systolic blood pressure with either dose of canagliflozin compared to sitagliptin ($P < 0.001$ for all analyses). Weight loss plateaued at week 34 for both canagliflozin and sitagliptin. At 26 weeks, there was a significantly greater reduction in postprandial glucose (PPG) with either dose of canagliflozin compared to placebo ($P < 0.001$ for both). At 26 and 52 weeks, there was no statistically significant difference between canagliflozin and placebo in triglyceride levels; however, at 26 weeks, there was a significant increase in HDL cholesterol with either dose of canagliflozin ($P < 0.001$ for both). Other lipid endpoints were not prespecified for statistical comparison, but canagliflozin did have numerically higher increases in LDL cholesterol.

At 52 weeks, the overall frequency of AEs and discontinuation resulting from AEs were slightly higher with canagliflozin 100 mg. One episode each of severe

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hypoglycemia was reported with canagliflozin 100 mg and sitagliptin. The frequency of selected AEs is summarized in Table 2.

In the canagliflozin group, decreases in alanine aminotransferase and serum urate were noted in addition to increases in bilirubin, blood urea nitrogen, and hemoglobin. In the sitagliptin group, increases in alanine aminotransferase, aspartate aminotransferase, and serum urate were noted in addition to decreases in bilirubin and hemoglobin. At 52 weeks, canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin, and placebo/sitagliptin demonstrated decreases in the estimated GFR of –1.4, –1.5, –2.4, and –1.4 ml/min/1.73 m^2, respectively.

Study Limitations

The patient population did present some limitations. Only people with an A1C of 7.0–9.5% (study A) and 7.0–10.5% (study B) at baseline were included, so data cannot be generalized to those with more severe hyperglycemia. Also, most participants in both studies were Caucasian, which limits conclusions in other populations that are known to be at risk for diabetes. Additionally, patients with a GFR < 55 ml/min/1.73 m^2 were excluded, so safety among people with impaired renal function was not evaluated. Other investigation in patients with stage 3 chronic kidney disease (GFR ≥ 30 and < 50 ml/min/1.73 m^2) has shown similar incidences of overall AEs with either dose of canagliflozin and placebo, although slightly higher incidences of urinary tract infections and AEs related to osmotic diuresis and reduced intravascular volume were observed with canagliflozin 300 mg.[11]

Although benefits related to cardiovascular risk factors were observed over 52 weeks in these studies, there are insufficient data at this time to determine any prolonged cardiovascular risk reduction. The limited study timeframes preclude any conclusions about the durability of glycemic response and long-term safety.

Practice Implications

The unique mechanism of action of canagliflozin offers a complementary treatment option that provides important benefits of improved glycemic control, weight loss, and reduction in systolic blood pressure, with an incidence of hypoglycemia similar to that of sitagliptin and lower than that of glimepiride. The reviewed studies demonstrate an advantage in A1C and FPG lowering, and study B also implies a possible beneficial impact on PPG. This could make canagliflozin particularly useful in patients who maintain an elevated A1C despite having normal FPG levels.

Post-marketing clinical trials have been required by the U.S. Food and Drug Administration to further assess cardiovascular, bone, and renal safety with canagliflozin.[12] Cardiovascular assessment is ongoing in CANVAS (the Canagliflozin Cardiovascular Assessment Study).[12,13]

In summary, canagliflozin can offer important benefits over current oral glucose-lowering agents. In practice, educating patients about the risk of genital mycotic infections and the potential for AEs related to increased urination (pollakiuria and polyuria) will be important. Post-marketing data will be important in evaluating long-term safety.

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Dawn M. Battise, PharmD, BCACP, is an assistant professor of pharmacy at the Wingate University School of Pharmacy in Wingate, N.C.

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