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REVIEW

Fixed-Dose Combination of Canagliflozin and Metformin for the Treatment of Type 2 Diabetes: An Overview

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ABSTRACT

Metformin is recommended as a first-line therapy for patients with type 2 diabetes mellitus (T2DM). However, many patients do not achieve glycemic goals with metformin monotherapy and require subsequent combination therapy with other antihyperglycemic agents (AHAs). For newly diagnosed patients with high blood glucose, initial combination therapy may be required to achieve glycemic control. The American Association for Clinical Endocrinologists algorithm for the treatment of T2DM recommends metformin plus a sodium glucose co-transporter 2 (SGLT2) inhibitor as the first oral combination in patients who present with HbA1c ≥7.5%. Canagliflozin, an SGLT2 inhibitor, lowers the renal threshold for glucose and increases urinary glucose excretion leading to a mild osmotic diuresis and a net caloric loss. The effect of canagliflozin is insulin-independent and complementary to other AHAs, including metformin. A fixed-dose combination (FDC) of canagliflozin and metformin is also available with variable dosing, which may be attractive to some patients owing to the potential for reduced pill burden and costs. This article reviews the efficacy and safety of canagliflozin in combination with metformin based on data from the canagliflozin phase 3 clinical program. As initial combination therapy in drug-naïve patients or as dual therapy with metformin or triple therapy in combination with metformin and other AHAs, canagliflozin 100 and 300 mg improved glycemic control and provided reductions in body weight and systolic blood pressure that were sustained for up to 104 weeks. Canagliflozin was generally well tolerated across studies in combination with metformin. An increased incidence of adverse events (AEs) related to the mechanism of SGLT2 inhibition (i.e., genital mycotic infections, urinary tract infections, osmotic

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diuresis-related AEs) was observed with canagliflozin. Canagliflozin was associated with a low incidence of hypoglycemia when not used in conjunction with AHAs associated with hypoglycemia (i.e., insulin or sulfonylurea). Together, these results support the use of a canagliflozin and metformin FDC as a treatment approach for a broad range of patients with T2DM.
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Keywords: Canagliflozin; Efficacy; Endocrinology; Fixed-dose combination; Metformin; Safety; Sodium glucose co-transporter 2 inhibitors; Type 2 diabetes mellitus

INTRODUCTION

Clinical practice guidelines recommend metformin as a first-line pharmacologic therapy for the management of type 2 diabetes mellitus (T2DM) [1–3]. Metformin works by decreasing hepatic glucose production and intestinal glucose absorption and by improving insulin sensitivity, thereby enhancing peripheral glucose uptake [4, 5]. Enhanced excretion of glucagon-like peptide-1 with metformin may contribute to the intestinal glucose-lowering activity [6, 7]. Metformin may not be tolerated in all patients because of gastrointestinal side effects [8, 9].

Due to the progressive nature of T2DM, most patients eventually require combination therapy with other antihyperglycemic agents (AHAs) [2, 10, 11]. In addition, many patients can receive initial combination therapy at the time of diabetes diagnosis in order to reach glycemic goals efficiently. The guidelines related to the use of combination therapy vary among national and regional organizations. For example, the American Diabetes Association supports initiation of dual therapy in newly diagnosed patients with T2DM and HbA1c $\geq$9.0% [2]. The American Association of Clinical Endocrinologists (AACE) takes a more aggressive approach, recommending initial combination therapy for patients with HbA1c $\geq$7.5% [1]. The Texas Diabetes Council gives an option for initiation of monotherapy in patients who present with HbA1c <1% above their individualized goal; in patients with HbA1c >1.0% above their goal, initial combination therapy is recommended [12].

Sodium glucose co-transporter 2 (SGLT2) inhibitors are recommended by AACE as the first oral add-on for patients inadequately controlled on metformin [1]. Canagliflozin, an SGLT2 inhibitor, lowers plasma glucose levels in patients with T2DM by increasing urinary glucose excretion, resulting in a mild osmotic diuresis and a net caloric loss [13]. This insulin-independent mechanism of action is complementary to other types of AHAs, including metformin [2]. Across phase 3 trials, as monotherapy or in combination with metformin or other AHAs, canagliflozin 100 and 300 mg have been shown to provide not only glycemic improvement but also weight loss and blood pressure (BP) lowering in a broad range of patients with T2DM [14]. An oral fixed-dose combination (FDC) tablet of canagliflozin and metformin immediate release (IR) was approved in 2014 for the treatment of adults with T2DM [15], and findings from a study of initial combination therapy with canagliflozin plus metformin extended release (XR) have recently been published [16]. This review summarizes the clinical data in support of the canagliflozin and metformin FDC. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CANAGLIFLOZIN AND METFORMIN FDC

The canagliflozin and metformin IR FDC is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The canagliflozin and metformin IR FDC formulation is available in four dose strengths (50/500 mg, 50/1000 mg, 150/500 mg, 150/1000 mg) and should be taken twice daily with food [15]. Gradual dose escalation of metformin is recommended to limit gastrointestinal side effects associated with metformin. The twice-daily dose of canagliflozin should not exceed 150 mg (total daily dose [TDD] of 300 mg), and canagliflozin should be restricted to 50 mg twice daily (TDD of 100 mg) for patients with estimated glomerular filtration rate (eGFR) ≥45 to <60 mL/min/1.73 m^2 [15]. An oral FDC containing immediate-release canagliflozin and metformin XR in a bilayer tablet formulation was recently approved in the USA [17]; the XR FDC formulation was under development during the writing of this article and will be reviewed separately in a future publication.

PHARMACOLOGY AND BIOEQUIVALENCE

Findings from phase 1 pharmacokinetic, bioequivalence, and food-effect studies of canagliflozin have confirmed that there are no clinically relevant differences between single-pill FDCs of canagliflozin and metformin IR compared with concomitant administration of the individual components [18, 19]. Phase 1 pharmacodynamic study results have also shown that there are no clinically meaningful differences between the once-daily canagliflozin dosing used in the phase 3 program, which is approved as a single-component formulation [20], and the same TDD administered twice daily, which is used in the FDC with metformin IR [15, 21]. No safety differences have been observed between the FDC of canagliflozin and metformin IR and coadministration of the individual components [18, 19], or between once-daily vs twice-daily dosing of canagliflozin [21]. Efficacy results from a dose-ranging phase 2 study of canagliflozin as add-on to metformin confirmed the dose selections of canagliflozin 100 and 300 mg used in the phase 3 program [22]. A subsequent phase 2 study established that twice-daily treatment with canagliflozin (50 or 150 mg) in patients with T2DM inadequately controlled with metformin monotherapy was comparable to results observed in phase 3 studies of once-daily canagliflozin (100 or 300 mg) added on to metformin monotherapy [23].

PHASE 3 STUDIES OF CANAGLIFLOZIN IN COMBINATION WITH METFORMIN

Canagliflozin has been evaluated in an extensive clinical development program, but no phase 3 clinical trials have been conducted on the canagliflozin/metformin FDC. The efficacy and safety of the canagliflozin/metformin FDC is supported by data from six phase 3 studies or substudies of once-daily canagliflozin 100 or 300 mg in patients with T2DM as add-on to metformin with or without other AHAs, and a phase 3 initial combination therapy study of canagliflozin plus metformin XR, which also evaluated canagliflozin versus metformin monotherapy (Table 1) [16, 24–30].

Table 1 Study design and patient populations of phase 3 studies of canagliflozin in combination with metformin ± other AHAs in patients with T2DM [16, 24–30]

Study	Study design	Key inclusion criteria	Background therapy	Patients
Initial combination with CANA + MET [16]	Initial combination therapy with CANA + MET vs each component for 26 weeks	18–75 years old; HbA1c 7.5–12.0%; eGFR ≥60 mL/min/1.73 m^2	Drug-naïve patients (not on AHA therapy or off for ≥12 weeks before screening)	$N = 1186$; CANA 100 mg/MET, $n = 237$; CANA 300 mg/MET, $n = 237$; CANA 100 mg, $n = 237$; CANA 300 mg, $n = 238$; MET, $n = 237$
Add-on to MET vs PBO/SITA [24]	PBO-controlled, 26-week core period; active-controlled (vs SITA), 26-week extension period	18–80 years old; HbA1c 7.0–10.5%; eGFR ≥55 mL/min/1.73 m^{2*}	Stable MET dose (≥2000 mg/day [or ≥1500 mg/day if unable to tolerate a higher dose]) for ≥8 weeks	$N = 1284$; PBO/SITA, $n = 183$; SITA 100 mg, $n = 366$; CANA 100 mg, $n = 368$; CANA 300 mg, $n = 367$
Add-on to MET vs GLIM [25, 30]	Active-controlled (vs GLIM) 52-week core period and 52-week extension	18–80 years old; HbA1c 7.0–9.5%; eGFR ≥55 mL/min/1.73 m^{2*}	Stable MET dose (≥2000 mg/day [or ≥1500 mg/day if unable to tolerate higher dose]) for ≥10 weeks	$N = 1450$; GLIM, $n = 482$; CANA 100 mg, $n = 483$; CANA 300 mg, $n = 485$
Add-on to MET + SU vs SITA [28]	Active-controlled (vs SITA), 52-week treatment period	≥18 years old; HbA1c 7.0–10.5%; eGFR ≥55 mL/min/1.73 m^{2*}	Stable MET dose (≥2000 mg/day [or ≥1500 mg/day if unable to tolerate a higher dose]) and SU (at least half of maximally labeled dose) for ≥8 weeks	$N = 755$; CANA 300 mg, $n = 377$; SITA 100 mg, $n = 378$
Add-on to MET + SU vs PBO [27]	PBO-controlled, 26-week core period and 26-week extension period	18–80 years old; HbA1c 7.0–10.5%; eGFR ≥55 mL/min/1.73 m^{2*}	Stable MET dose (≥2000 mg/day [or ≥1500 mg/day if unable to tolerate a higher dose]) and SU (at least half of maximally labeled dose) for ≥8 weeks	$N = 469$, PBO, $n = 156$; CANA 100 mg, $n = 157$; CANA 300 mg, $n = 156$

Table 1 continued

Study	Study design	Key inclusion criteria	Background therapy	Patients
Add-on to MET + PIO vs PBO/SITA [26]	PBO-controlled, 26-week core period; active-controlled (vs SITA), 26-week extension period	18–80 years old; HbA1c 7.0–10.5%; eGFR ≥55 mL/min/1.73 m^{2*}	Stable MET dose (≥2000 mg/day [or ≥1500 mg/day if unable to tolerate a higher dose]) and PIO 30 or 45 mg/day for ≥8 weeks	$N = 342$; PBO/SITA, $n = 115$; CANA 100 mg, $n = 113$; CANA 300 mg, $n = 114$
Add-on to MET + insulin vs PBO [29]	Prespecified 18-week substudy of a subset of patients from the ongoing PBO-controlled CANVAS trial	≥30 years old with documented, symptomatic, atherosclerotic cardiovascular disease, or ≥50 years old with ≥2 cardiovascular risk factors at screening; HbA1c 7.0–10.5%; eGFR ≥30 mL/min/1.73 m^2	Stable MET dose(≥2000 mg/day) and insulin (≥30 IU/day; basal and/or bolus)	$N = 432$; PBO, $n = 145$; CANA 100 mg, $n = 139$; CANA 300 mg, $n = 148$

AHA antihyperglycemic agent, *T2DM* type 2 diabetes mellitus, *CANA* canagliflozin, *MET* metformin, *eGFR* estimated glomerular filtration rate, *PBO* placebo, *SITA* sitagliptin, *GLIM* glimepiride, *SU* sulfonylurea, *PIO* pioglitazone, *CANVAS* CANagliflozin cardioVascular Assessment Study

* The required eGFR was ≥60 mL/min/1.73 m^2 if based on restriction of metformin use in the local label

Key efficacy analyses in these studies included changes from baseline in HbA1c, body weight, and systolic BP (Tables 2, 3, 4); safety and tolerability were assessed on the basis of adverse event (AE) reports.

Efficacy

Initial Combination Therapy with Canagliflozin and Metformin

A 26-week initial combination therapy study assessed the efficacy and safety of canagliflozin and metformin XR versus canagliflozin or metformin monotherapy in drug-naïve patients [16]. Greater reductions in HbA1c were seen with canagliflozin 100 mg/metformin and canagliflozin 300 mg/metformin compared with metformin alone at 26 weeks (−1.77%, −1.78%, and −1.30%, respectively; $P = 0.001$ for both comparisons; Table 2). Canagliflozin 100 and 300 mg monotherapy were noninferior in HbA1c lowering compared with metformin (−1.37%, −1.42%, and −1.30%, respectively). A greater proportion of patients achieved HbA1c <7.0% with both canagliflozin 100 mg/metformin and canagliflozin 300 mg/metformin than metformin alone at week 26 (49.6, 56.8, and 43.0%, respectively; $P = 0.027$ for canagliflozin 100 mg/metformin vs metformin and $P = 0.016$ for canagliflozin 300 mg/metformin vs metformin). Canagliflozin 100 mg/metformin

Table 2 Changes from baseline in HbA1c in phase 3 studies of canagliflozin in combination with metformin ± other AHAs [16, 24–30]

Study	Duration, week	HbA1c, %	Treatment groups				
			MET	**CANA 100 mg**	**CANA 300 mg**	**CANA 100 mg/MET**	**CANA 300 mg/MET**
Initial combination with CANA + MET [16]	26	Baseline[a]	8.8	8.8	8.8	8.8	8.9
		Change[b]	−1.30	−1.37[c]	−1.42[c]	−1.77[d,e]	−1.78[d,f]
			PBO	**CANA 100 mg**	**CANA 300 mg**		
Add-on to MET vs PBO/SITA [24]	26	Baseline[a]	8.0	7.9	8.0	–	–
		Change[b]	−0.17	−0.79[g]	−0.94[g]	–	–
			SITA 100 mg	**CANA 100 mg**	**CANA 300 mg**		
	52	Baseline[a]	7.9	7.9	8.0	–	–
		Change[b]	−0.73	−0.73	−0.88	–	–
			GLIM	**CANA 100 mg**	**CANA 300 mg**		
Add-on to MET vs GLIM [25, 30]	52	Baseline[a]	7.8	7.8	7.8	–	–
		Change[b]	−0.81	−0.82	−0.93	–	–
	104	Baseline[a]	7.8	7.8	7.8	–	–
		Change[b]	−0.55	−0.65	−0.74	–	–
			SITA 100 mg		**CANA 300 mg**		
Add-on to MET + SU vs SITA [28]	52	Baseline[a]	8.1	–	8.1	–	–
		Change[b]	−0.66	–	−1.03	–	–

Table 2 continued

			PBO	CANA 100 mg	CANA 300 mg		
Add-on to MET + SU vs PBO [27]	26	Baseline[a]	8.1	8.1	8.1	–	–
		Change[b]	−0.13	−0.85[g]	−1.06[g]	–	–
	52	Baseline[a]	8.1	8.1	8.1	–	–
		Change[b]	0.01	−0.74	−0.96	–	–
Add-on to MET + PIO vs PBO/SITA [26]	26	Baseline[a]	8.0	8.0	7.8	–	–
		Change[b]	−0.26	−0.89[g]	−1.03[g]	–	–
	52	Baseline[a]	–	8.0	7.8	–	–
		Change[b]	–	−0.92	−1.03	–	–
Add-on to MET + insulin vs PBO [29]	18	Baseline[a]	8.2	8.2	8.2	–	–
		Change[b]	−0.03	−0.64[g]	−0.79[g]	–	–

AHA antihyperglycemic agent, *CANA* canagliflozin, *MET* metformin, *PBO* placebo, *SITA* sitagliptin, *GLIM* glimepiride, *SU* sulfonylurea, *PIO* pioglitazone, *LS* least squares

[a] Data are means

[b] Data are LS mean changes from baseline

[c] Noninferiority $P = 0.001$ versus MET

[d] $P = 0.001$ versus MET

[e] $P = 0.001$ versus CANA 100 mg

[f] $P = 0.001$ versus CANA 300 mg

[g] $P < 0.001$ versus PBO

Table 3 Percent changes from baseline in body weight in phase 3 studies of canagliflozin in combination with metformin ± other AHAs [16, 24–30]

Study	Duration, week	Body weight, kg	Treatment group				
			MET	**CANA 100 mg**	**CANA 300 mg**	**CANA 100 mg/MET**	**CANA 300 mg/MET**
Initial combination with CANA + MET [16]	26	Baseline[a]	92.1	90.3	93.0	88.3	91.5
		Change[b]	−2.1	−3.0[c]	−3.9[d]	−3.5[e]	−4.2[e]
			PBO	**CANA 100 mg**	**CANA 300 mg**		
Add-on to MET vs PBO/SITA [24]	26	Baseline[a]	86.7	88.7	85.4	–	–
		Change[b]	−1.2	−3.7[f]	−4.2[f]	–	–
			SITA 100 mg	**CANA 100 mg**	**CANA 300 mg**		
	52	Baseline[a]	87.6	88.7	85.4	–	–
		Change[b]	−1.3	−3.8[g]	−4.2[g]	–	–
			GLIM	**CANA 100 mg**	**CANA 300 mg**		
Add-on to MET vs GLIM [25, 30]	52	Baseline[a]	86.6	86.8	86.6	–	–
		Change[b]	1.0	−4.2[h]	−4.7[h]	–	–
	104	Baseline[a]	86.6	86.8	86.6	–	–
		Change[b]	0.9	−4.1	−4.2	–	–
			SITA 100 mg		**CANA 300 mg**		
Add-on to MET + SU vs SITA [28]	52	Baseline[a]	89.6	–	87.6	–	–
		Change[b]	0.3	–	−2.5[g]	–	–

Table 3 continued

			PBO	CANA 100 mg	CANA 300 mg		
Add-on to MET + SU vs PBO [27]	26	Baseline[a]	90.8	93.5	93.5	–	–
		Change[b]	−0.7	−2.1[f]	−2.6[f]	–	–
	52	Baseline[a]	90.8	93.5	93.5	–	–
		Change[b]	−0.9	−2.2	−3.2	–	–
Add-on to MET + PIO vs PBO/SITA [26]	26	Baseline[a]	94.0	94.2	94.4	–	–
		Change[b]	−0.1	−2.8[f]	−3.8[f]	–	–
	52	Baseline[a]	–	94.2	94.4	–	–
		Change[b]	–	−2.7	−3.7	–	–
Add-on to MET + insulin vs PBO [29]	18	Baseline[a]	102.3	99.7	101.1	–	–
		Change[b]	0.0	−1.7[f]	−2.7[f]	–	–

AHA antihyperglycemic agent, *CANA* canagliflozin, *MET* metformin, *PBO* placebo, *SITA* sitagliptin, *GLIM* glimepiride, *SU* sulfonylurea, *PIO* pioglitazone, *LS* least squares

[a] Data are means

[b] Data are LS mean percent changes from baseline

[c] $P = 0.016$ versus MET

[d] $P = 0.002$ versus MET

[e] $P = 0.001$ versus MET

[f] $P < 0.001$ versus PBO

[g] $P < 0.001$ versus SITA 100 mg

[h] $P < 0.0001$ versus GLIM

Table 4 Changes from baseline in systolic BP in phase 3 studies of canagliflozin in combination with metformin ± other AHAs [16, 24–30]

Study	Duration, week	Systolic BP, mmHg	Treatment group				
			MET	**CANA 100 mg**	**CANA 300 mg**	**CANA 100 mg/MET**	**CANA 300 mg/MET**
Initial combination with CANA + MET [16]	26	Baseline[a]	129.4	128.9	130.1	127.6	128.1
		Change[b]	−0.3	−2.2	−2.4	−2.2[c]	−1.7[c]
			PBO	**CANA 100 mg**	**CANA 300 mg**		
Add-on to MET vs PBO/SITA [24]	26	Baseline[a]	128.0	128.0	128.7	–	–
		Change[b]	1.5	−3.8[d]	−5.1[d]	–	–
			SITA 100 mg	**CANA 100 mg**	**CANA 300 mg**		
	52	Baseline[a]	128.0	128.0	128.7	–	–
		Change[b]	−0.7	−3.5[e]	−4.7[e]	–	–
			GLIM	**CANA 100 mg**	**CANA 300 mg**		
Add-on to MET vs GLIM [25, 30]	52	Baseline[a]	129.5	130.0	130.0	–	–
		Change[b]	0.2	−3.3	−4.6	–	–
	104	Baseline[a]	129.5	130.0	130.0	–	–
		Change[b]	1.7	−2.0	−3.1	–	–
			SITA 100 mg		**CANA 300 mg**		
Add-on to MET + SU vs SITA [28]	52	Baseline[a]	130.1	–	131.2	–	–
		Change[b]	0.9	–	−5.1[e]	–	–

Table 4 continued

			PBO	CANA 100 mg	CANA 300 mg		
Add-on to MET + SU vs PBO [27]	26	Baseline[a]	130.1	130.4	130.8	–	–
		Change[b]	−2.7	−4.9	−4.3	–	–
	52	Baseline[a]	130.1	130.4	130.8	–	–
		Change[b]	0.1	−3.7	−2.9	–	–
Add-on to MET + PIO vs PBO/SITA [26]	26	Baseline[a]	128.2	126.4	126.7	–	–
		Change[b]	−1.2	−5.3[f]	−4.7[g]	–	–
	52	Baseline[a]	–	126.4	126.7	–	–
		Change[b]	–	−3.4	−3.7	–	–
Add-on to MET + insulin vs PBO [29]	18	Baseline[a]	138.3	136.2	141.7	–	–
		Change[b]	−1.7	−5.2	−7.7[d]	–	–

BP blood pressure, *AHA* antihyperglycemic agent, *CANA* canagliflozin, *MET* metformin, *PBO* placebo, *SITA* sitagliptin, *GLIM* glimepiride, *SU* sulfonylurea, *PIO* pioglitazone, *LS* least squares, *NS* not significant

[a] Data are means

[b] Data are LS mean changes from baseline

[c] P = NS versus MET

[d] $P < 0.001$ versus PBO

[e] $P < 0.001$ versus SITA 100 mg

[f] $P < 0.01$ versus PBO

[g] $P < 0.025$ versus PBO

and canagliflozin 300 mg/metformin provided greater body weight reductions compared with metformin alone (−3.5%, −4.2%, and −2.1%; $P = 0.001$ for both comparisons; Table 3). Reductions in systolic BP were numerically greater with canagliflozin 100 mg/metformin and canagliflozin 300 mg/metformin compared with metformin alone (−2.2, −1.7, and −0.3 mmHg, respectively; Table 4).

Canagliflozin as Dual Therapy with Metformin

A 52-week study assessed the efficacy and safety of canagliflozin 100 and 300 mg versus placebo at week 26 and versus sitagliptin 100 mg as add-on to metformin [24]. Reductions in HbA1c at week 26 were greater with canagliflozin 100 and 300 mg compared with placebo (−0.79%, −0.94%, and −0.17%, respectively; $P < 0.001$ for both comparisons; Table 2). At week 52, canagliflozin 100 mg was noninferior and canagliflozin 300 mg was statistically superior to sitagliptin 100 mg in HbA1c lowering (−0.73%, −0.88%, and −0.73%, respectively; Table 2). A greater proportion of patients achieved HbA1c <7.0% with canagliflozin 100 and 300 mg compared to placebo at week 26 (46%, 58%, and 30%, respectively) and compared with sitagliptin 100 mg at week 52 (55%, 41%, and 51%, respectively). Canagliflozin 100 and 300 mg significantly reduced body weight compared with placebo (−3.7%, −4.2%, and −1.2%, respectively; $P < 0.001$ for both comparisons; Table 3) at week 26. Greater reductions in body weight were seen with canagliflozin 100 and 300 mg versus sitagliptin 100 mg at week 52 (−3.8%, −4.2%, and −1.3%, respectively; $P < 0.001$ for both comparisons; Table 3). At week 26, systolic BP reductions were seen with canagliflozin 100 and 300 mg (−3.8 and −5.1 mmHg, respectively) compared with an increase of 1.5 mmHg with placebo ($P < 0.001$ for both comparisons; Table 4). At week 52, reductions in systolic BP were larger with canagliflozin 100 and 300 mg compared with sitagliptin 100 mg (−3.5, −4.7, and −0.7 mmHg, respectively; $P < 0.001$ for both comparisons; Table 4).

A 104-week study assessed the efficacy and safety of canagliflozin 100 and 300 mg versus glimepiride as add-on to metformin at weeks 52 and 104 [25, 30]. At week 52, canagliflozin 100 mg demonstrated noninferiority and canagliflozin 300 mg demonstrated superiority in HbA1c lowering compared with glimepiride (−0.82%, −0.93%, and −0.81%, respectively; Table 2) [25]. Reductions in HbA1c were sustained at week 104 (−0.65%, −0.74%, and −0.55%, respectively; Table 2) [30]. At week 52, 54, 60, and 56% of patients achieved HbA1c <7.0% with canagliflozin 100 and 300 mg and glimepiride, respectively [25]. At week 104, 43, 50, and 44% of patients achieved HbA1c <7.0%, respectively [30]. Body weight at week 52 was significantly reduced with canagliflozin 100 and 300 mg (−4.2% and −4.7%, respectively), compared with a 1.0% increase with glimepiride ($P < 0.0001$ for both comparisons; Table 3) [25]. Reductions in body weight with canagliflozin 100 and 300 mg versus glimepiride were maintained at week 104 (−4.1%, −4.2%, and 0.9%, respectively; Table 3) [30]. Reductions in systolic BP were seen with canagliflozin 100 and 300 mg (−3.3 and −4.6 mmHg) compared to an increase of 0.2 mmHg with glimepiride at 52 weeks (Table 4) [25]. At week 104, changes in systolic BP were −2.0, −3.1, and 1.7 mmHg, respectively (Table 4) [30].

Canagliflozin in Combination with Metformin Plus Other AHAs

A 52-week study evaluated the efficacy and safety of canagliflozin 300 mg versus sitagliptin

100 mg as add-on to metformin plus sulfonylurea [28]. Canagliflozin 300 mg demonstrated superiority in HbA1c lowering versus sitagliptin 100 mg at week 52 (−1.03% and −0.66%, respectively; Table 2). The greater HbA1c lowering with canagliflozin 300 mg was accompanied by a greater proportion of patients achieving HbA1c <7.0% with canagliflozin 300 mg versus sitagliptin 100 mg (48% vs 35%). Canagliflozin 300 mg significantly reduced body weight compared to sitagliptin 100 mg (−2.5% vs 0.3%; $P < 0.001$; Table 3). Canagliflozin 300 mg also significantly reduced systolic BP (−5.1 mmHg) versus an increase of 0.9 mmHg with sitagliptin 100 mg ($P < 0.001$; Table 4).

A placebo-controlled study evaluated the efficacy and safety of canagliflozin 100 and 300 mg as add-on to metformin plus sulfonylurea at weeks 26 and 52 [27]. Canagliflozin 100 and 300 mg provided greater reductions in HbA1c compared with placebo at week 26 (−0.85%, −1.06%, and −0.13%, respectively; $P < 0.001$ for both comparisons); these reductions were maintained at week 52 (−0.74%, −0.96%, and 0.01%, respectively; Table 2). A greater proportion of patients receiving canagliflozin 100 and 300 mg achieved HbA1c <7.0% at week 26 than those receiving placebo (43, 57, and 18%, respectively; $P < 0.001$ for both comparisons). At week 52, 39, 53, and 19% of patients achieved HbA1c <7.0% with canagliflozin 100 and 300 mg and placebo, respectively. Significant body weight reductions were seen with canagliflozin 100 and 300 mg compared with placebo at week 26 (−2.1%, −2.6%, and −0.7%, respectively; $P < 0.001$ for both comparisons) and were sustained at week 52 (−2.2%, −3.2%, and −0.9%, respectively; Table 3). Canagliflozin 100 and 300 mg provided numerically greater reductions in systolic BP compared with placebo at week 26 (−4.9, −4.3, and −2.7 mmHg, respectively); changes in systolic BP were −3.7, −2.9, and 0.1 mmHg, respectively, at week 52 (Table 4).

In a study as add-on to metformin plus pioglitazone, the efficacy and safety of canagliflozin 100 and 300 mg were assessed versus placebo at week 26 [26]. The study included a 26-week extension during which patients receiving placebo were switched to sitagliptin 100 mg; this arm was not included in efficacy evaluations at week 52. At week 26, greater reductions in HbA1c were seen with canagliflozin 100 and 300 mg versus placebo (−0.89%, −1.03%, and −0.26%, respectively; $P < 0.001$ for both comparisons; Table 2). A greater proportion of patients achieved HbA1c <7.0% with canagliflozin 100 and 300 mg versus placebo (47, 64, and 33%, respectively). Reductions in body weight were greater with canagliflozin 100 and 300 mg compared with placebo at week 26 (−2.8%, −3.8%, and −0.1%, respectively; $P < 0.001$ for both comparisons; Table 3). Similarly, canagliflozin 100 and 300 mg provided larger reductions in systolic BP compared with placebo (−5.3, −4.7, and −1.2 mmHg, respectively; Table 4). Reductions in HbA1c, body weight, and systolic BP with canagliflozin 100 and 300 mg were maintained at week 52 (Tables 2, 3, 4).

In a prespecified analysis of a subset of patients with either a history or high risk of cardiovascular disease enrolled in the CANagliflozin cardioVascular Assessment Study (CANVAS) who were on background metformin plus insulin, the efficacy and safety of canagliflozin 100 and 300 mg were assessed versus placebo at week 18 [29]. Canagliflozin 100 and 300 mg reduced HbA1c compared with placebo (−0.64%, −0.79%, and 0.03%, respectively; $P < 0.001$ for both comparisons; Table 2). A greater proportion of patients

achieved HbA1c <7.0% with canagliflozin 100 and 300 mg versus placebo (19%, 29%, and 9%, respectively; $P = 0.008$ for canagliflozin 100 mg vs placebo; $P < 0.001$ for canagliflozin 300 mg vs placebo). Significant reductions in body weight were seen with canagliflozin 100 and 300 mg compared with placebo (−1.7%, −2.7%, and 0.0%, respectively; $P < 0.001$ for both comparisons; Table 3). Canagliflozin 100 and 300 mg provided larger reductions in systolic BP compared with placebo (−5.2, −7.7, and −1.7 mmHg, respectively; $P < 0.001$ for canagliflozin 300 mg vs placebo; Table 4).

Safety and Tolerability

Canagliflozin in combination with metformin has been associated with a favorable safety and tolerability profile across phase 3 studies (Table 5) [16, 24–30]. Rates of AEs leading to discontinuation and serious AEs were generally low with canagliflozin versus comparators [16, 24–30]. Not surprisingly, the incidence of AEs related to SGLT2 inhibition (e.g., genital mycotic infections, urinary tract infections, osmotic diuresis-related AEs) was generally higher with canagliflozin versus comparators [16, 24–30]. Risk factors for genital mycotic infection include a prior history of recurrent genital mycotic infections and uncircumcision. Older patients, those with reduced renal function, those with reduced BP, and those taking diuretics may be vulnerable to the volume depletion effects of canagliflozin. These patients, in particular, should be advised to drink plenty of non-sugar-containing fluids, and consideration should be given to reducing or holding their diuretics until after they are reassessed. Gastrointestinal intolerability is a common side effect of metformin [9]; however, the combination of canagliflozin and metformin has not been associated with an increased incidence of gastrointestinal-related AEs (i.e., diarrhea, nausea, and vomiting) [31]. Reports of hypoglycemia have been generally low with canagliflozin among patients not on background therapy associated with hypoglycemia (i.e., sulfonylurea or insulin) and in patients treated with initial canagliflozin/metformin combination therapy [16, 24–30].

No serious AEs of diabetic ketoacidosis have been seen with canagliflozin as add-on to metformin alone or in combination with pioglitazone, or in the subset of patients from the CANVAS trial on background metformin plus insulin [32]. There was one serious ketoacidosis AE with canagliflozin 100 mg in the placebo-controlled add-on to metformin plus sulfonylurea study [27], and the patient subsequently received a diagnosis of type 1 diabetes mellitus [32]. In the initial combination study [16], there was one serious AE of ketoacidosis in a patient in the canagliflozin 300 mg group with confounding factors that included acute infection, chronic pancreatitis, and heart failure class II [32]. It is important to note that patients with HbA1c >10.5% were excluded from these studies.

The incidence of fractures was low and similar with canagliflozin versus comparators across the phase 3 program in non-CANVAS studies, including those as add-on to metformin with or without other AHAs [33].

Across studies, canagliflozin was generally associated with reductions in triglycerides and increases in both high-density lipoprotein cholesterol and low-density lipoprotein cholesterol [16, 24–30]. Changes in laboratory parameters (i.e., alanine aminotransferase, aspartate aminotransferase, bilirubin, blood urea nitrogen, creatinine, urate, and hemoglobin) with canagliflozin were not clinically meaningful. Treatment with

Table 5 Safety summary from phase 3 studies of canagliflozin in combination with metformin [16, 24–30]

Parameter	Combination of CANA + MET
Overall safety and tolerability	Generally well tolerated; low incidence of AEs leading to study discontinuation and serious AEs
Genital mycotic infections	Higher incidence versus PBO, SITA, and GLIM; low incidence with CANA/MET in initial combination therapy
	Generally mild or moderate in intensity; few led to study discontinuation
	Generally higher incidence in women than in men; more likely to occur in patients with a history of genital mycotic infections and in uncircumcised males
UTIs	Low incidence across studies; higher incidence versus GLIM and PBO; similar incidence compared with SITA
	Generally mild to moderate in intensity and few led to discontinuation; low incidence of serious or upper UTIs
Osmotic diuresis–related AEs (e.g., pollakiuria, polyuria, thirst)	Generally low incidence
	Higher incidence versus PBO, SITA, and GLIM; few led to study discontinuation
Volume depletion–related AEs (e.g., orthostatic hypotension, dizziness postural)	Generally low incidence; dose-dependent increase in incidence seen across studies
	Incidence was higher in patients taking loop diuretics, in patients with moderate renal impairment (i.e., eGFR $\geq$30 to <60 mL/min/1.73 m^2), and in patients aged $\geq$75 years
Gastrointestinal-related AEs (i.e., diarrhea, nausea, vomiting)	No increase in incidence with CANA as add-on to MET $\pm$ other AHAs versus PBO, SITA, or GLIM; incidence was low with CANA/MET as initial combination therapy
Hypoglycemia	Low incidence when not used in combination with background AHAs associated with hypoglycemia (e.g., SU or insulin)
	Significantly lower incidence versus GLIM
	Slightly higher incidence with CANA as add-on to MET versus SITA; similar incidence with CANA as add-on to MET + SU versus SITA with greater HbA1c lowering with CANA; incidence with CANA/MET was similar to MET in initial combination therapy
	Low incidence across studies of severe hypoglycemia episodes
Diabetic ketoacidosis AEs	Low incidence across studies
	No serious AEs of diabetic ketoacidosis with CANA as add-on to MET, MET + PIO, or in the MET + insulin subset of CANVAS
	1 serious event each with CANA 100 mg as add-on to MET + SU and with CANA 300 mg as initial combination therapy
Fractures	Incidence low and similar across studies in non-CANVAS studies

Table 5 continued

Parameter	Combination of CANA + MET
Fasting plasma lipids	Triglycerides were generally reduced across studies
	High-density lipoprotein cholesterol and low-density lipoprotein cholesterol were generally increased across studies
Clinical laboratory parameters	Transient reduction in eGFR early in treatment that attenuated over time
	No clinically meaningful changes in alanine aminotransferase, aspartate aminotransferase, bilirubin, blood urea nitrogen, creatinine, urate, and hemoglobin
	Small changes in serum electrolytes (i.e., potassium, magnesium, phosphate)

CANA canagliflozin, *MET* metformin, *AE* adverse event, *PBO* placebo, *SITA* sitagliptin, *GLIM* glimepiride, *UTI* urinary tract infection, *eGFR* estimated glomerular filtration rate, *SU* sulfonylurea, *PIO* pioglitazone, *CANVAS* CANagliflozin cardioVascular Assessment Study

canagliflozin in combination with metformin was associated with a transient reduction in eGFR that attenuated over time [16, 24–30].

CANAGLIFLOZIN/METFORMIN FDC PLACE IN THERAPY

Guidelines for treating patients with T2DM emphasize a personalized approach for improving glycemic control to minimize diabetes-related complications and drug-related side effects [1, 2]. Metformin is typically used as a first-line pharmacotherapy for patients with T2DM [1, 2]. However, for patients unable to attain glycemic control with metformin alone, the selection of additional AHAs is warranted. In newly diagnosed patients with high initial HbA1c levels, an initial combination approach consisting of therapies with complementary mechanisms of action is recommended [1, 2]. The use of an FDC can simplify combination treatment compared to two-pill administration and can potentially provide increased therapy adherence and reduced medication errors [34–40]. In addition, FDC therapies with variable dosing may provide for faster and greater efficacy with lower risk of AEs compared with monotherapy. FDC medications that do not directly increase the risk of hypoglycemia and do not cause weight gain, and preferably cause weight loss, may lead to increased compliance, reduced hospitalization, and better cardiorenal outcomes by reducing metabolic risk factors [34].

The AACE T2DM disease management algorithm recommends SGLT2 inhibitors as the first orally administered add-on therapy to metformin [1]; thus, an FDC of the SGLT2 inhibitor canagliflozin with metformin may be valuable for many patients. Results from phase 3 studies in patients with T2DM show that the combination of canagliflozin plus metformin, including canagliflozin and metformin as initial combination therapy, provides substantial improvements in glycemic control, along with other benefits including weight loss and reductions in systolic BP [16, 24–30]. As canagliflozin 300 mg provided superior glycemic control to sitagliptin or glimepiride as add-on to metformin

[24, 25, 30], the canagliflozin/metformin combination may be a better therapeutic option than combination therapy with these other agents. Overall, canagliflozin in combination with metformin with or without other AHAs was generally well tolerated. These data support the use of the canagliflozin and metformin FDC in patients with T2DM.

Canagliflozin also demonstrated efficacy and safety in patients with T2DM and cardiovascular disease or chronic kidney disease, many of whom were on background metformin [29, 41, 42]. It has been hypothesized that canagliflozin may provide cardiovascular and renoprotective benefits, which will be assessed in ongoing outcomes studies, including CANVAS (ClinicalTrials.gov Identifier: NCT01032629), CANVAS-R (renal endpoints; NCT01989754), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE; NCT02065791).

CONCLUSION

Attaining early and sustained glycemic control can reduce the risk of diabetes-related complications. For many patients with T2DM, the use of combination therapies with metformin may be valuable to help them attain their individualized glycemic goals. Across phase 3 studies, including as initial combination therapy in drug-naïve patients, canagliflozin in combination with metformin provided favorable glycemic efficacy and additional benefits of weight loss, BP reduction, and a low risk of hypoglycemia. Together, the beneficial efficacy and favorable safety profiles for canagliflozin in combination with metformin support the use of the canagliflozin and metformin FDC as a therapeutic approach in a broad range of patients with T2DM.

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REFERENCES

1. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2016 executive summary. Endocr Pract. 2016;22:84–113.
2. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38:140–9.
3. American Diabetes Association. Standards of medical care in diabetes—2016. Diabetes Care. 2016;39:S1–108.
4. Ferrannini E. The target of metformin in type 2 diabetes. N Engl J Med. 2014;371:1547–8.
5. Buse JB, Defronzo RA, Rosenstock J, et al. The primary glucose-lowering effect of metformin resides in the gut, not the circulation: results from short-term pharmacokinetic and 12-week dose-ranging studies. Diabetes Care. 2016;39:198–205.
6. Mannucci E, Ognibene A, Cremasco F, et al. Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. Diabetes Care. 2001;24:489–94.
7. Napolitano A, Miller S, Nicholls AW, et al. Novel gut-based pharmacology of metformin in patients with type 2 diabetes mellitus. PLoS One. 2014;9:e100778.
8. GLUCOPHAGE/GLUCOPHAGE® XR (metformin hydrochloride) extended-release tablets [package insert]. Princeton: Bristol-Myers Squibb Company; 2015.
9. Jabbour S, Ziring B. Advantages of extended-release metformin in patients with type 2 diabetes mellitus. Postgrad Med. 2011;123:15–23.
10. Cook MN, Girman CJ, Stein PP, Alexander CM. Initial monotherapy with either metformin or sulphonylureas often fails to achieve or maintain current glycaemic goals in patients with type 2 diabetes in UK primary care. Diabet Med. 2007;24:350–8.
11. Cook MN, Girman CJ, Stein PP, Alexander CM, Holman RR. Glycemic control continues to deteriorate after sulfonylureas are added to metformin among patients with type 2 diabetes. Diabetes Care. 2005;28:995–1000.
12. Texas Diabetes Council. Glycemic control algorithm for type 2 diabetes mellitus in adults. 2015. http://www.tdctoolkit.org/algorithms-guidelines/. Accessed 11 Aug 2016.
13. Chao EC, Henry RR. SGLT2 inhibition—a novel strategy for diabetes treatment. Nat Rev Drug Discov. 2010;9:551–9.
14. Rosenthal N, Meininger G, Ways K, et al. Canagliflozin: a sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes mellitus. Ann N Y Acad Sci. 2015;1358:28–43.
15. INVOKAMET® (canagliflozin and metformin hydrochloride) tablets for oral use [package insert]. Titusville: Janssen Pharmaceuticals, Inc; 2016.
16. Rosenstock J, Chuck L, González-Ortiz M, Merton K, Craig J, Capuano G. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy in drug-naïve type 2 diabetes. Diabetes Care. 2016;39:353–62.
17. INVOKAMET® XR (canagliflozin and metformin hydrochloride extended-release) tablets, for oral use. Titusville: Janssen Pharmaceuticals; 2016.
18. Devineni D, Curtin CR, Ariyawansa J, et al. Bioequivalence of canagliflozin/metformin immediate release fixed-dose combination tablets compared with concomitant administration of single components of canagliflozin and metformin in healthy fed participants. J Bioequiv Avail. 2014;6:164–73.
19. Murphy J, Wang SS, Stieltjes H, Wajs E, Devineni D. Effect of food on the pharmacokinetics of canagliflozin/metformin (150/1,000 mg) immediate-release fixed-dose combination tablet in healthy participants. Int J Clin Pharmacol Ther. 2015;53:256–64.
20. INVOKANA® (canagliflozin) tablets, for oral use [package insert]. Titusville: Janssen Pharmaceuticals; 2016.
21. Devineni D, Polidori D, Curtin CR, et al. Pharmacokinetics and pharmacodynamics of once- and twice-daily multiple-doses of canagliflozin, a selective inhibitor of sodium glucose co-transporter 2, in healthy participants. Int J Clin Pharmacol Ther. 2015;53:438–46.
22. Rosenstock J, Aggarwal N, Polidori D, et al. Dose-ranging effects of canagliflozin, a

sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care. 2012;35:1232–8.

23. Qiu R, Capuano G, Meininger G. Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with type 2 diabetes mellitus. J Clin Transl Endocrinol. 2014;1:54–60.

24. Lavalle-González FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia. 2013;56:2582–92.

25. Cefalu WT, Leiter LA, Yoon KH, et al. 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. 2013;382:941–50.

26. Forst T, Guthrie R, Goldenberg R, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. Diabetes Obes Metab. 2014;16:467–77.

27. Wilding JP, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. Int J Clin Pract. 2013;67:1267–82.

28. Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week, randomized trial. Diabetes Care. 2013;36:2508–15.

29. Rosenstock J, Matthews DR, Desai M, Capuano G, Meininger G, Canovatchel W. Impact of canagliflozin added-on to insulin and metformin in type 2 diabetes: a substudy of the CANVAS trial. Poster presented at the 75th Scientific Sessions of the American Diabetes Association (ADA); June 5–9, 2015; Boston, Massachusetts.

30. Leiter LA, Yoon KH, Arias P, et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care. 2015;38:355–64.

31. Usiskin K, Kline I, Fung A, Mayer C, Meininger G. Safety and tolerability of canagliflozin in patients with type 2 diabetes: pooled analysis of phase 3 study results. Postgrad Med. 2014;126:16–34.

32. Erondu N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. Diabetes Care. 2015;38:1680–6.

33. Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2016;101:157–66.

34. Bell DS. Combine and conquer: advantages and disadvantages of fixed-dose combination therapy. Diabetes Obes Metab. 2013;15:291–300.

35. Hutchins V, Zhang B, Fleurence RL, Krishnarajah G, Graham J. A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. Curr Med Res Opin. 2011;27:1157–68.

36. Williams SA, Buysman EK, Hulbert EM, Bergeson JG, Zhang B, Graham J. Hemoglobin A1c outcomes and health care resource use in type 2 diabetes mellitus patients treated with combination oral antidiabetic drugs through step therapy and loose-dose and fixed-dose combinations. Manag Care. 2012;21:40–8.

37. Cheong C, Barner JC, Lawson KA, Johnsrud MT. Patient adherence and reimbursement amount for antidiabetic fixed-dose combination products compared with dual therapy among Texas Medicaid recipients. Clin Ther. 2008;30:1893–907.

38. Ray J, Huet D, Valentine W, Palmer A, Cugnardey N, Renaudin C. Long-term costs and clinical outcomes associated with metformin-glibenclamide combination tablets (Glucovance®) in patients with type 2 diabetes sub-optimally controlled by metformin: a modelling study in the French setting. Br J Diabetes Vasc Dis. 2008;8:39–44.

39. Colombo G, Rossi E, De Rosa M, Benedetto D, Gaddi A. Antidiabetic therapy in real practice: indicators for adherence and treatment cost. Patient Prefer Adher. 2012;6:653–61.

40. Genovese S, Tedeschi D. Effects of vildagliptin/metformin therapy on patient-reported outcomes: work productivity, patient satisfaction, and resource utilization. Adv Ther. 2013;30:152–64.

41. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013;15:463–73.

42. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. Diabetes Obes Metab. 2014;16:1016–27.