Pharmacology & Pharmacy, 2014, 5, 1029-1058
Published Online October 2014 in SciRes. http://www.scirp.org/journal/pp
http://dx.doi.org/10.4236/pp.2014.511114

Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors in Type 2 Diabetes: A Literature Review of Approved Products

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Received 30 August 2014; revised 30 September 2014; accepted 16 October 2014

Abstract

Diabetes mellitus continues to be a major health issue worldwide. Despite all of the treatment options available on the market, many patients with diabetes fail to reach their treatment goals. Novel agents such as the Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors show promise in effectively lowering blood glucose. Objective: To review the scientific literature for efficacy information regarding the use of approved SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) in the treatment of Type 2 Diabetes Mellitus (T2DM). Methods: A MEDLINE (1950-August 2014) literature review was performed. All of the literature published as an original clinical trial was included in this review. Other pertinent articles published related to the original clinical trial were also included. Meta-analysis type studies were not selected for this review. Conclusions: With an increasing prevalence and incidence of type 2 diabetes mellitus worldwide, there is an apparent need for effective therapeutic strategies to combat this chronic and progressive disease. SGLT2 inhibitors offer this potential. Recently approved agents (canagliflozin, dapagliflozin and empagliflozin) have shown significant promise as mono- and add-on therapy to current glucose-lowering regimens that may not otherwise be providing sufficient glycemic control in T2DM patients.

Keywords

Canagliflozin, Dapagliflozin, SGLT2 Inhibitors, Type 2 Diabetes Mellitus, Empagliflozin

How to cite this paper: Volino, L.R., Pan, E.Y. and Mansukhani, R.P. (2014) Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors in Type 2 Diabetes: A Literature Review of Approved Products. *Pharmacology & Pharmacy*, **5**, 1029-1058.
http://dx.doi.org/10.4236/pp.2014.511114

1. Introduction

Diabetes mellitus continues to be a major health issue worldwide, affecting nearly 26 million adults in the United States. Controlling blood glucose levels is essential in managing symptoms and preventing complications associated with the disease. In 2011, close to 85% of US adults with diabetes reported taking antihyperglycemic medication [1].

Despite all the treatment options available on the market, many patients with diabetes fail to reach their treatment goals. Most of these medications depend on the presence or action of insulin to exert their therapeutic effect. This can provide little benefit to patients whose disease progression has led to deterioration in pancreatic beta cell function. Additionally, these agents are associated with concerning side effects, including the risk of inducing hypoglycemia [2]-[4].

A new class of agents has emerged with glycemic control via alternate means, specifically by inhibiting the reabsorption of glucose and increasing its excretion from the kidneys. This novel approach of the Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors shows promise in effectively lowering blood glucose in a noninsulin-dependent way. Sodium-Glucose Cotransporter 2 inhibitors exert their effect by enhancing renal glycosuria. The extent to which they induce glycosuria is dependent on the plasma glucose concentration. As a result, blood glucose levels cannot be lowered below physiological levels and hence, the risk of hypoglycemia is not concerning [5]. This mechanism of action allows use as monotherapy or in combination with current antidiabetes medications, including insulin therapy [2]-[4]. Sodium-Glucose Cotransporter 2 inhibitors have also been shown to promote weight loss at the same time, either independently or in combination with other antidiabetic agents. However they have a risk of potentially increasing the likelihood of genitourinary tract infections [6].

The United States Food and Drug Administration (FDA) recently approved three SGLT2 inhibitors, canagliflozin in 2013, dapagliflozin and empagliflozin in 2014. This article discusses the SGLT2 inhibitors as new approaches to managing type 2 diabetes mellitus (T2DM), focusing on the evidence available regarding the efficacy and safety of this emerging class of antidiabetic agents. Canagliflozin, dapagliflozin, and empagliflozin were selected for this review since they are the only agents currently approved by the FDA.

2. Data Sources

Figure 1 illustrates the literature search and selection process details used in the identification of clinical trials for this review. A literature review was performed in MEDLINE (1950-August 2014) using the keywords diabetes mellitus type 2 AND canagliflozin OR dapagliflozin OR empagliflozin. The references identified from the literature review were then evaluated. All of the literature retrieved from MEDLINE that was published as an original clinical trial was included in this review. Other pertinent articles published related to the original clinical trials were also considered. Meta-analysis type studies were not selected for this review. References included in this review were limited to studies conducted in humans and written in the English language.

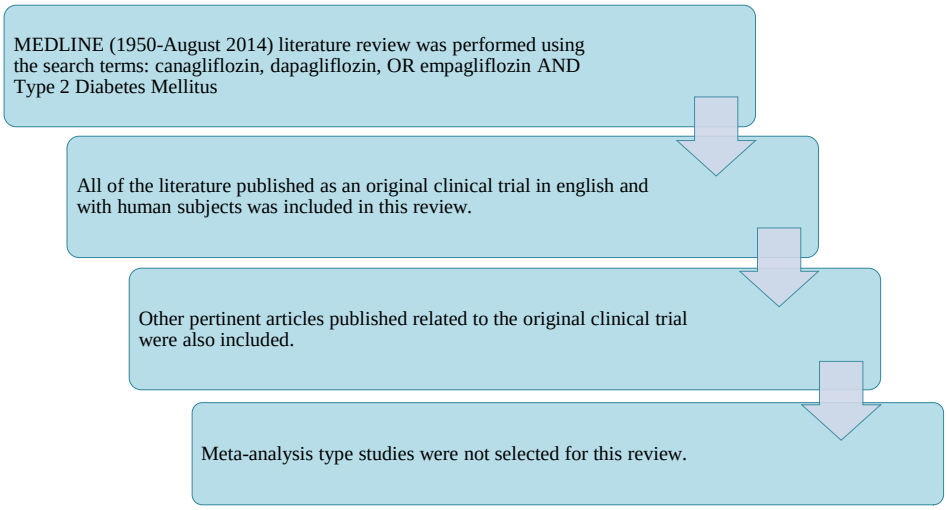

Figure 1. Literature search and clinical trial selection details.

3. SGLT2 Product Review Summaries

3.1. Canagliflozin

Canagliflozin, (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate, the first SGLT2 inhibitor approved in the United States, has an oral bioavailability of 65%, which remains the same with or without food. However, it is recommended to be taken before the first meal of the day due to its mechanism of reducing postprandial glucose excursions. Peak plasma concentrations are reached within one to two hours post-dose with a terminal half-life of 10.6 hours and 13.1 hours for the respective 100 mg and 300 mg doses. Canagliflozin exhibits extensive protein binding (99%), mainly to albumin, which does not affect plasma concentrations. It is metabolized primarily through *O*-glucuronidation and marginally through CYP3A4 (7%), and is excreted through fecal and renal routes. Though renal impairment may lead to a change in maximum plasma concentration (C_{max}) and area under the curve (AUC), these changes are not clinically relevant. However, since canagliflozin works by reducing glucose reabsorption in the kidney, pharmacodynamic response to the drug declines as the severity of renal impairment increases. Therefore, it is contraindicated in severe renal impairment, end stage renal disease, or patients on dialysis. According to Child-Pugh class grading, mild and moderate hepatic impairment do not warrant dose adjustments with canagliflozin [4].

The efficacy of canagliflozin was studied in ten trials ranging from 12 to 52 weeks and at doses of 50 mg, 100 mg, 200 mg, and 300 mg (**Table 1**) [7]-[16]. The greatest difference in hemoglobin A1C (HbA1C) (%) reduction compared to placebo was −1.16% with canagliflozin 300 mg after 26 weeks [13]. Eight out of ten studies reported that HbA1C (%) reductions were statistically significant [7] [8] [10] [11] [13]-[16]. All ten trials found that a greater percentage of patients reached the HbA1C (%) goal of <7.0% with canagliflozin treatment than with other treatments [7]-[16]. The majority of these studies also reported a statistically significant difference [7] [8] [11] [13] [14] [16].

Reductions in 2-hour postprandial glucose (2-h PPG) [10]-[14] and fasting plasma glucose (FPG) [7]-[16] were also greater in canagliflozin groups, with mean decreases in FPG ranging from −38.3 mg/dL [10] to −11.7 mg/dL [15] in two different canagliflozin 300 mg groups. Since other oral antidiabetic agents are often associated with weight gain, studies also assessed the change in body weight with canagliflozin. Most studies showed a statistically significant difference with lowering body weight in the canagliflozin groups compared to other treatment groups [7]-[14] [16]. Some evidence shows a slight, yet significant reduction in systolic blood pressure by canagliflozin compared to placebo (reduction of range of −8.1 to −3.5 mmHg) [8] [10] [13] [16] and sitagliptin (reduction range of −5.9 to −2.9 mmHg) [11] [12].

The overall incidence of adverse events was similar between canagliflozin and control group treatment, however more patients withdrew related to canagliflozin adverse events. Since the SGLT2 inhibitors work by increasing the amount of glucose in the urine, there is a risk of urinary and genital tract infections unique to this class. Adverse events such as pollakiuria, polyuria, and volume-related effects, including postural dizziness and orthostatic hypotension, were more common in canagliflozin groups [7]-[16].

As expected, based on the mechanism of action of SGLT2 inhibitors, the majority of studies reported low incidences of hypoglycemia in canagliflozin groups which were similar to sitagliptin [11] [12] [16] and placebo [7] [8] [10] [13] [16] groups. Canagliflozin was reported to have higher rates of hypoglycemia compared to placebo when combined with other hypoglycemia-associated medications such as insulin [15] or a sulfonylurea [14] [15]. Hypoglycemia occurred significantly less in canagliflozin groups (5% - 6%) compared to the glimepiride treatment group (34%) [9].

3.2. Dapagliflozin

Dapagliflozin, D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1) [2], was rejected by the FDA in January 2012 due to concerns about the cancer risk seen in studies [17]. However, after reviewing more data on its safety profile, dapagliflozin was approved by the FDA in early 2014. The pharmacokinetic and pharmacodynamic properties of dapagliflozin are similar to canagliflozin. Dapagliflozin can be administered without regard to food. The oral bioavailability of dapagliflozin 10 mg is 78%. Maximum plasma concentration is usually reached within two hours in a fasting state and administration with a high-fat meal decreases the C_{max} by up to 50% without altering the AUC, but is not clinically significant. The terminal half-life is approximately 12.9 hours following a dose of 10 mg. Dapag-

Table 1. Canagliflozin trials.

Author (Year)	Study Design	Subjects	Methods	Results			
					HbA1C (%) at 12 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. PBO
				PBO (N = 65)	7.75 ± 0.83	−0.22	-
				CANA 50 mg (N = 64)	8.00 ± 0.99	−0.79*	-
				CANA 100 mg (N = 64)	7.83 ± 0.96	−0.76*	-
				CANA 200 mg (N = 65)	7.61 ± 0.80	−0.70*	-
				CANA 300 mg QD (N = 64)	7.69 ± 1.02	−0.92*	-
			(Stable dose of MET ≥ 3 months)	CANA 300 mg BID (N = 64)	7.73 ± 0.89	−0.95*	-
				SITA 100 mg	7.64 ± 0.95	−0.74*	-
			Pre-treatment Screening Period: 3 - 4 weeks	*p < 0.001 vs. PBO			
					FPG (mg/dL) at 12 Weeks		
			Double-Blind Treatment Period: 12 weeks		Baseline Mean ± SD	LS Mean Change	Difference vs. PBO
			Group A: placebo daily	PBO (N = 65)	164 ± 38	3.6	-
			Group B: CANA 50 mg daily	CANA 50 mg (N = 64)	170 ± 45	−16.2*	-
Rosenstock (2012)	Randomized Double-blind Placebo-controlled Parallel-group	451 T2DM (236M; 215F)	Group C: CANA 100 mg daily	CANA 100 mg (N = 64)	168 ± 42	−25.2*	-
			Group D: CANA 200 mg daily	CANA 200 mg (N = 65)	160 ± 37	−27.0*	-
			Group E: CANA 300 mg once daily	CANA 300 mg QD (N = 64)	159 ± 44	−25.2*	-
			Group F: CANA 300 mg twice daily	CANA 300 mg BID (N = 64)	157 ± 34	−23.4*	-
				SITA 100 mg	158 ± 42	−12.6	-
			Group G: SITA 100 mg daily	*p < 0.001 vs. PBO			
					Body Weight (kg) at 12 Weeks		
			Post-treatment Period: 2 weeks		Baseline Mean ± SD	LS Mean Percent Change	Difference vs. PBO
				PBO (N = 65)	85.9 ± 19.5	−1.1	-
				CANA 50 mg (N = 64)	87.6 ± 16.3	−2.3*	-
				CANA 100 mg (N = 64)	87.7 ± 15.5	−2.6*	-
				CANA 200 mg (N = 65)	87.7 ± 17.0	−2.7*	-
				CANA 300 mg QD (N = 64)	87.3 ± 15.9	−3.4*	-
				CANA 300 mg BID (N = 64)	86.0 ± 19.7	−3.4*	-
				SITA 100 mg	87.2 ± 18.0	−0.6	-
				*p < 0.001 vs. PBO			

Continued

Bode (2013)	Randomized Double-blind Placebo-controlled	714 T2DM with (396M; 318F)	Single-blind, Placebo Run-in Period: 2 weeks Double-blind Core Treatment Period: 26 weeks Group A: placebo daily before first meal of day Group B: CANA 100 mg daily before first meal of day Group C: CANA 300 mg daily before first meal of day Double-blind Extension Period: 78 weeks		HbA1C (%) at 26 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO
				PBO (N = 237)	7.8 ± 0.8	−0.03	-
				CANA 100 mg (N = 241)	7.8 ± 0.8	−0.6	−0.57*
				CANA 300 mg (N = 236)	7.7 ± 0.8	−0.73	−0.70*
				*p < 0.001 vs. PBO			
					FPG (mg/dL) at 26 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO
				PBO (N = 237)	156.8 ± 38.9	7.4	-
				CANA 100 mg (N = 241)	160.4 ± 38.7	−18.1	−25.5*
				CANA 300 mg (N = 236)	153.2 ± 36.6	−20.3	−27.7*
				*p < 0.001 vs. PBO			
					Body Weight (kg) at 26 Weeks		
					Baseline Mean ± SD	Adjusted Mean Percent Change	Difference vs. PBO
				PBO (N = 237)	91.1 ± 17.5	0.1	-
				CANA 100 mg (N = 241)	88.4 ± 15.6	−2.4	−2.3*
				CANA 300 mg (N = 236)	88.8 ± 17.1	−3.1	−3.0*
				*p < 0.001 vs. PBO			
Cefalu (2013)	Randomized Double-blind Active-controlled Non-inferiority	1450 T2DM (756M; 694F)	Single-Blind Run-in Period: 2 weeks Study Phase: 52 weeks All groups on stable daily metformin dose for at least 10 weeks plus Group A: GLIM 1 - 6 mg or 1 - 8 mg daily (based on maximum approved dose in country of investigational site) Group B: CANA 100 mg daily Group C: CANA 300 mg daily Double-blind Extension Period: 52 weeks		HbA1C (%) at 52 Weeks		
					Baseline Mean ± SD	LS Mean Change ± SE	Difference vs. GLIM (95% CI)
				GLIM (N = 482)	7.8 ± 0.8	−0.81 ± 0.04	-
				CANA 100 mg (N = 483)	7.8 ± 0.8	−0.82 ± 0.04	−0.01 (−0.11, 0.09)
				CANA 300 mg (N = 485)	7.8 ± 0.8	−0.93 ± 0.04	−0.12 (−0.22, −0.02)
					FPG (mg/dL) at 52 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. GLIM (95% CI)
				GLIM (N = 482)	165.8 ± 37.8	−18.4	-
				CANA 100 mg (N = 483)	165.8 ± 37.8	−24.3	−5.9 (−10.8, −1.8)
				CANA 300 mg (N = 485)	164.0 ± 36.0	−27.4	−9.2 (−12.6, −5.4)

Continued

					Body Weight (kg) at 52 Weeks		
					Baseline Mean ± SD	LS Mean Percentage Change ± SE	Difference vs. GLIM (95% CI)
				GLIM (N = 482)	86.5 ± 19.8	1.0 ± 0.2	-
				CANA 100 mg (N = 483)	86.9 ± 20.1	−4.2 ± 0.2	−5.2* (−5.7, −4.7)
				CANA 300 mg (N = 485)	86.6 ± 19.5	−4.7 ± 0.2	−5.7* (−6.2, −5.1)
				*p < 0.0001 vs. GLIM			
					HbA1C (%) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO
				PBO (N = 75)	7.99 ± 0.77	0.11	-
				CANA 50 mg (N = 82)	8.13 ± 0.78	−0.61*	-
				CANA 100 mg (N = 74)	8.05 ± 0.86	−0.80*†	-
				CANA 200 mg (N = 76)	8.11 ± 0.88	−0.79*†	-
				CANA 300 mg (N = 75)	8.17 ± 0.81	−0.88*†	-
			Washout Period: 8 weeks Single-blind Run-in Period: 4 weeks	*p < 0.01 vs. PBO			
				†p < 0.05 vs. CANA 50 mg			
			Double-Blind Treatment Period: 12 weeks		FPG (mg/dL) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO
			Group A: placebo daily	PBO (N = 75)	170.7 ± 31.9	−3	-
Inagaki (2013)	Randomized Double-blind Placebo-controlled	382 T2DM (260M; 122F)	Group B: CANA 50 mg daily	CANA 50 mg (N = 82)	161.4 ± 34.6	−24.7*	-
			Group C: CANA 100 mg daily	CANA 100 mg (N = 74)	161.0 ± 32.1	−33.1*†	-
				CANA 200 mg (N = 76)	165.9 ± 31.4	−36.1*†	-
			Group D: CANA 200 mg daily	CANA 300 mg (N = 75)	169.1 ± 34.2	−38.3*†	-
			Group E: CANA 300 mg daily	*p < 0.01 vs. PBO			
				†p < 0.01 vs. CANA 50 mg			
			Follow-up Visit: 2 weeks		Body Weight (kg) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO
				PBO (N = 75)	72.56 ± 15.36	−0.78	-
				CANA 50 mg (N = 82)	65.77 ± 13.56	−1.98*	-
				CANA 100 mg (N = 74)	68.61 ± 14.86	−2.51*	-
				CANA 200 mg (N = 76)	68.97 ± 14.50	−2.39*	-
				CANA 300 mg (N = 75)	71.30 ± 12.19	−3.19*	-
				*p < 0.01 vs. PBO			

Continued

Lavalle-González (2013)	Randomized Double-blind Parallel-group Placebo- and Active-controlled	1284 T2DM (605M; 679F)	MET and SU Dose Titration/Stabilization/ Washout Period: up to 10 weeks (if applicable) Single-blind, Placebo Run-in Period: 2 weeks Double-blind, Placebo- and Active-controlled Treatment Period I: 26 weeks Group A: placebo daily Group B: SITA 100 mg daily Group C: CANA 100 mg daily Group D: CANA 300 mg daily Double-blind, Active-controlled Treatment Period II: 26 weeks (Groups B-D remained the same. Group A (placebo) switched to SITA 100 mg daily) Follow-up Period: 4 weeks	HbA1C (%) at 26 Weeks			
					Baseline Mean ± SD	LS Mean Change ± SE	Difference vs. PBO (95% CI)
				PBO (N = 183)	8.0 ± 0.9	−0.17 ± 0.06	-
				SITA 100 mg (N = 366)	7.9 ± 0.9	−0.82 ± 0.04	−0.66[†] (−0.80, −0.52)
				CANA 100 mg (N = 368)	7.9 ± 0.9	−0.79 ± 0.04	−0.62[*] (−0.76, −0.48)
				CANA 300 mg (N = 367)	7.9 ± 0.9	−0.94 ± 0.04	−0.77[*] (−0.91, −0.64)
				[*]p < 0.001 vs. PBO [†]Statistical comparison vs. PBO not performed (not pre-specified)			
				FPG (mg/dL) at 26 Weeks			
					Baseline Mean ± SD	LS Mean Change ± SE	Difference vs. PBO (95% CI)
				PBO (N = 183)	164.0 ± 37.8	1.8 ± 1.8	-
				SITA 100 mg (N = 366)	169.4 ± 41.4	−19.8 ± 1.8	−23.4[†] (−28.8, −16.2)
				CANA 100 mg (N = 368)	167.6 ± 41.4	−27.0 ± 1.8	−30.6[*] (−36.0, −23.4)
				CANA 300 mg (N = 367)	173.0 ± 45.0	−37.8 ± 1.8	−39.6[*] (−46.8, −34.2)
				[*]p < 0.001 vs. PBO [†]Statistical comparison vs. PBO not performed (not pre-specified)			
				Body Weight (kg) at 26 Weeks			
					Baseline Mean ± SD	LS Mean Percent Change ± SE	Difference vs. PBO (95% CI)
				PBO (N = 183)	86.6 ± 22.4	−1.2 ± 0.3	-
				SITA 100 mg (N = 366)	87.7 ± 21.6	−1.2 ± 0.2	0.0[†] (−0.6, 0.6)
				CANA 100 mg (N = 368)	88.8 ± 22.2	−3.7 ± 0.2	−2.5[*] (−3.1, −1.9)
				CANA 300 mg (N = 367)	85.4 ± 20.9	−4.2 ± 0.2	−2.9[*] (−3.5, −2.3)
				[*]p < 0.001 vs. PBO [†]Statistical comparison vs. PBO not performed (not pre-specified)			
				HbA1C (%) at 52 Weeks			
					Baseline Mean ± SD	LS Mean Change ± SE	Difference vs. SITA (95% CI)
				SITA 100 mg (N = 366)	7.9 ± 0.9	−0.73 ± 0.05	-
				CANA 100 mg (N = 368)	7.9 ± 0.9	−0.73 ± 0.05	0.00 (−0.12, 0.12)

Continued

				CANA 300 mg (N = 367)	7.9 ± 0.9	−0.88 ± 0.05	−0.15 (−0.27, −0.03)
					FPG (mg/dL) at 52 Weeks		
					Baseline Mean ± SD	LS Mean Change ± SE	Difference vs. SITA (95% CI)
				SITA 100 mg (N = 366)	167.6 ± 41.4	−18.0 ± 1.8	-
				CANA 100 mg (N = 368)	169.4 ± 41.4	−27.0 ± 1.8	−9.0* (−12.6, −3.6)
				CANA 300 mg (N = 367)	173.0 ± 45.0	−36.0 ± 1.8	−18.0* (−21.6, −12.6)
				*p < 0.001 vs. SITA			
					Body Weight (kg) at 52 Weeks		
					Baseline Mean ± SD	LS Mean Percent Change ± SE	Difference vs. SITA (95% CI)
				SITA 100 mg (N = 355)	87.7 ± 21.6	−1.3 ± 0.2	-
				CANA 100 mg (N = 365)	88.8 ± 22.2	−3.8 ± 0.2	−2.4* (−3.0, −1.8)
				CANA 300 mg (N = 360)	85.4 ± 20.9	−4.2 ± 0.2	−2.9* (−3.4, −2.3)
				*p < 0.001 vs. SITA			
Schernthaner (2013)	Randomized Double-blind Active-controlled	755 T2DM (422M; 333F)	MET and SU Adjustment Period (if applicable): up to 12 weeks (Including an 8-week dose-stable period) Single-blind, Placebo Run-in Period: 2 weeks Double-blind Treatment Period: 52 weeks Group A: SITA 100 mg daily Group B: CANA 300 mg daily Follow-up Period: 4 weeks		HbA1C (%) at 52 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. SITA (95% CI)
				SITA 100 mg (N = 378)	8.1 ± 0.9	−0.66	-
				CANA 300 mg (N = 377)	8.1 ± 0.9	−1.03	−0.37 (−0.50, −0.25)
					FPG (mg/dL) at 52 Weeks		
					Baseline Mean	LS Mean Change	Difference vs. SITA
				SITA 100 mg (N = 378)	165.8 ± 44.9	−5.9	-
				CANA 300 mg (N = 377)	169.4 ± 42.4	−29.9	−24.1*
				*p < 0.001 vs. SITA			
					Body Weight (kg) at 52 Weeks		
					Baseline Mean	LS Mean Percent Change	Difference vs. SITA (95% CI)
				SITA (N = 378)	89.1 ± 23.2	0.3	-
				CANA 300 mg (N = 377)	87.4 ± 23.2	−2.5	−2.8*
				*p < 0.001 vs. SITA			

Continued

Stenlöf (2013)	Randomized Double-blind Placebo-controlled	584 T2DM (258M; 326F)	AHA Washout/Diet and Exercise Period: 8 weeks Single-blind Placebo Run-in period: 2 weeks Double-blind, Placebo-controlled Treatment Period: 26 weeks Group A: placebo daily Group B: CANA 100 mg daily Group C: CANA 300 mg daily Double-blind Extension Period: 26 weeks		HbA1C (%) at 26 Weeks		
					Baseline Mean ± SD	LS Mean Percent Change	Difference vs. PBO (95% CI)
				PBO (N = 192)	8.0 ± 1.0	0.14	-
				CANA 100 mg (N = 195)	8.1 ± 1.0	−0.77	−0.91* (−1.1, −0.7)
				CANA 300 mg (N = 197)	8.0 ± 1.0	−1.03	−1.16* (−1.3, −1.0)
				*p < 0.001 vs. PBO			
					FPG (mg/dL) at 26 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 192)	167.6 ± 37.8	9	-
				CANA 100 mg (N = 195)	173.0 ± 43.2	−27	−36.0* (−41.4, −28.8)
				CANA 300 mg (N = 197)	173.0 ± 43.2	−34.2	−43.2* (−50.5, −36.0)
				*p < 0.001 vs. PBO			
					Body Weight (kg) at 26 Weeks		
					Baseline Mean ± SD	LS Mean Percent Change	Difference vs. PBO (95% CI)
				PBO (N = 192)	87.6 ± 19.5	−0.6	-
				CANA 100 mg (N = 195)	85.8 ± 21.4	−2.8	−2.2* (−2.9, −1.6)
				CANA 300 mg (N = 197)	86.9 ± 20.5	−3.9	−3.3* (−4.0, −2.6)
				*p < 0.001 vs. PBO			
Wilding (2013)	Randomized Double-blind Placebo-controlled	469 T2DM (239M; 230F)	MET and SU Maximum Effective Dose Pretreatment Period: up to 12 weeks (dose titration up to 4 weeks; stable dose for 8 weeks) Single-blind, Placebo Run-in Period: 2 weeks Double-blind Treatment Period: 26 weeks Group A: placebo daily before first meal Group B: CANA 100 mg daily before first meal Group C: CANA 300 mg daily before first meal Double-blind Extension Period: 26 weeks		HbA1C (%) at 26 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 156)	8.1 ± 0.9	−0.13	-
				CANA 100 mg (N = 157)	8.1 ± 0.9	−0.85	−0.71* (−0.90, −0.52)
				CANA 300 mg (N = 156)	8.1 ± 0.9	−1.06	−0.92* (−1.11, −0.73)
				*p < 0.001 vs. PBO			
					FPG (mg/dL) at 26 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 156)	169.4 ± 39.6	3.6	-
				CANA 100 mg (N = 157)	173.0 ± 41.4	−18	−21.6* (−30.6, −12.6)
				CANA 300 mg (N = 156)	167.6 ± 37.8	−30.6	−34.2* (−43.2, −25.2)

Continued

				*p < 0.001 vs. PBO			
					Body Weight (kg) at 26 Weeks		
					Baseline Mean ± SD	LS Mean Percent Change	Difference vs. PBO (95% CI)
				PBO (N = 156)	91.2 ± 22.6	−0.7	-
				CANA 100 mg (N = 157)	93.8 ± 22.6	−2.1	−1.4* (−2.1, −0.7)
				CANA 300 mg (N = 156)	93.5 ± 22.0	−2.6	−2.0* (−2.7, −1.3)
				*p < 0.001 vs. PBO			
					HbA1C (%) at 52 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 156)	8.1 ± 0.9	0.01	-
				CANA 100 mg (N = 157)	8.1 ± 0.9	−0.74	−0.75 (−0.95, −0.55)
				CANA 300 mg (N = 156)	8.1 ± 0.9	−0.96	−0.97 (−1.17, −0.77)
					FPG (mg/dL) at 52 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 156)	169.4 ± 39.6	10.8	-
				CANA 100 mg (N = 157)	173.0 ± 41.4	−19.8	−28.8 (−37.8, −19.8)
				CANA 300 mg (N = 156)	167.6 ± 37.8	−27	−37.8 (−46.8, −28.8)
					Body Weight (kg) at 52 Weeks		
					Baseline Mean ± SD	LS Mean Percent Change	Difference vs. PBO (95% CI)
				PBO (N = 156)	91.2 ± 22.6	−0.9	-
				CANA 100 mg (N = 157)	93.8 ± 22.6	−2.2	−1.3 (−2.1, −0.5)
				CANA 300 mg (N = 156)	93.5 ± 22.0	−3.2	−2.2 (−3.0, −1.4)
Yale (2013)	Randomized Double-blind Placebo-controlled	269 T2DM with chronic kidney disease (163M; 106F)	AHA Dose Titration Period (if required): up to 4 weeks AHA Dose Stable Period (if required): 8 weeks Single-blind, Placebo Run-in Period: 2 weeks Double-blind Core Treatment Period: 26 weeks Group A: placebo daily				
					HbA1C (%) at 26 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 90)	8.0 ± 0.9	−0.03	-
				CANA 100 mg (N = 90)	7.9 ± 0.9	−0.33	−0.30* (−0.5, −0.1)
				CANA 300 mg (N = 89)	8.0 ± 0.8	−0.44	−0.40** (−0.6, −0.2)
				*p < 0.05 vs. PBO **p < 0.001 vs. PBO			

Continued

					FPG (mg/dL) at 26 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. PBO (95% CI)
			Group B: CANA 100 mg daily	PBO (N = 90)	160.4 ± 43.2	0.5	-
				CANA 100 mg (N = 90)	169.4 ± 46.3	−14.9	−15.4[†] (−28.5, −2.3)
			Group C: CANA 300 mg daily	CANA 300 mg (N = 89)	158.6 ± 58.0	−11.7	−12.2[*] (−25.4, 1.0)
				[*]p = NS for CANA vs. PBO			
			Double-blind Extension Period: 26 weeks	[†]Statistical comparison vs. PBO not performed owing to multiplicity control			
					Body Weight (kg) at 26 Weeks		
					Baseline Mean ± SD	LS Mean Percent Change	Difference vs. PBO (95% CI)
				PBO (N = 90)	92.8 ± 17.4	0.3	-
				CANA 100 mg (N = 90)	90.5 ± 18.4	−1.2	−1.6[†] (−2.3, −0.8)
				CANA 300 mg (N = 89)	90.2 ± 18.1	−1.5	−1.8[†] (−2.6, −1.0)
				[†]Statistical comparison for CANA vs. PBO not performed (not prespecified)			
Forst (2014)	Randomized Double-blind Placebo- and Active-controlled	342 T2DM (216M; 126F)	Single-blind, Placebo Run-in Period: 2 weeks		HbA1C (%) at 26 Weeks		
					Baseline Mean ± SD	LS Mean Change	Difference vs. PBO
			Double-blind, Placebo-Controlled Core Treatment Period: 26 weeks	PBO/SITA (N = 115)	8.0 ± 1.0	−0.26	-
				CANA 100 mg (N = 113)	8.0 ± 0.9	−0.89	−0.62[*]
			Group A: placebo daily	CANA 300 mg (N = 114)	7.9 ± 0.9	−1.03	−0.76[*]
				[*]p < 0.001 vs. PBO			
			Group B: CANA 100 mg daily		FPG (mg/dL) at 26 Weeks		
					Baseline Mean	LS Mean Change	Difference vs. PBO
			Group C: CANA 300 mg daily	PBO/SITA (N = 115)	164.0 ± 39.6	2.5	-
				CANA 100 mg (N = 113)	169.4 ± 39.6	−26.8	−29.4[*]
			Double-blind Active-control Extension Period: 26 weeks	CANA 300 mg (N = 114)	164.0 ± 41.4	−33.2	−35.7[*]
			Group A: SITA 100 mg daily	[*]p < 0.001 vs. PBO			
					Body Weight (kg) at 26 Weeks		
			Group B: CANA 100 mg daily		Baseline Mean ± SD	LS Mean Percent Change	Difference vs. PBO
			Group C: CANA 300 mg daily	PBO/SITA (N = 115)	93.8 ± 22.4	−0.1	-
				CANA 100 mg (N = 113)	94.2 ± 22.2	−2.8	−2.7[*]

Continued

CANA 300 mg (N = 114)	94.4 ± 25.9	−3.8	−3.7*

*p < 0.001 vs. PBO

	HbA1C (%) at 52 Weeks		
	Baseline Mean ± SD	LS Mean Change (95% CI)	LS Mean Change (95% CI)
PBO/SITA (N = 115)	8.0 ± 1.0	-	-
CANA 100 mg (N = 113)	8.0 ± 0.9	−0.92 (−1.06, −0.79)	-
CANA 300 mg (N = 114)	7.9 ± 0.9	−1.03 (−1.17, −0.89)	-
	FPG (mg/dL) at 52 Weeks		
	Baseline Mean	LS Mean Change (95% CI)	Difference vs. PBO
PBO/SITA (N = 115)	164.0 ± 39.6	-	-
CANA 100 mg (N = 113)	169.4 ± 39.6	−26.7 (−32.4, −21.1)	-
CANA 300 mg (N = 114)	164.0 ± 41.4	−31.5 (−37.2, −25.8)	-
	Body Weight (kg) at 52 Weeks		
	Baseline Mean	LS Mean Percent Change (95% CI)	Difference vs. PBO
PBO/SITA (N = 115)	93.8 ± 22.4	-	-
CANA 100 mg (N = 113)	94.2 ± 22.2	−2.7 (−3.6, −1.9)	-
CANA 300 mg (N = 114)	94.4 ± 25.9	−3.7 (−4.6, −2.9)	-

95% CI = 95% confidence interval; AHA = antihyperglycemic agent; AM = morning; CANA = canagliflozin; F = Female; FPG = Fasting Plasma Glucose; GLIM = glimepiride; HbA1C = hemoglobin A1C; LS = least squares; M = Male; MET = metformin; NS = not significant; PBO = placebo; SD = standard deviation; SE = standard error; SITA = sitagliptin; SU = sulfonylurea; T2DM = Type 2 Diabetes Mellitus Patients

liflozin is 91% protein bound, which is unchanged in patients with renal or hepatic impairment. It is metabolized primarily by UGT1A9 with minor CYP-activity and is eliminated mainly through the kidneys. At steady state, T2DM patients with mild, moderate, or severe renal impairment (determined by estimated glomerular filtration rate (eGFR)) experience 45% to 3-fold higher systemic exposure of the drug without a corresponding higher 24-hour urinary glucose excretion. The steady state 24-hour urinary glucose excretion is 42% - 90% lower in these patients [2].

Dapagliflozin is not recommended in patients with moderate renal impairment as improvement in glycemic control was not seen in this population. Additionally, dapagliflozin is not expected to be effective in patients with severe renal impairment or end stage renal disease (ESRD). Dapagliflozin is contraindicated in these populations along with patients on dialysis. According to Child-Pugh class grading, mild, moderate, and severe hepatic impairment do not warrant dose adjustments with dapagliflozin, but the risk-benefit for use in patients with severe impairment should be individually assessed as the safety and efficacy have not been specifically studied in this population [2].

Overall, 11 studies assessing the use of dapagliflozin in T2DM were identified (**Table 2**) [18]-[28]. The majority of trials evaluated the effectiveness of dapagliflozin as add-on therapy to standard treatments [18] [20] [22] [24]-[28]. The time period for the 11 studies ranged from 12 to 102 weeks, and investigators used dapagliflozin

doses of 1 - 20 mg [18]-[28]. Dapagliflozin consistently showed statistically significant decreases in mean HbA1C (%) compared to control groups [18]-[23] [25] [26] [28]. The largest difference in HbA1C (%) reduction between dapagliflozin and placebo groups was −0.84% after 24 weeks of treatment with dapagliflozin 5 mg [19]. No difference in the adjusted mean change in HbA1C (%) from baseline between the dapagliflozin and glipizide groups was observed in a 52-week study, which concluded that dapagliflozin was statistically noninferior to glipizide [24]. A few trials found a statistically significant difference in patients achieving an HbA1C of <7% at the end of the study period in the dapagliflozin treatment groups compared to placebo [18]-[20] [22] [26].

The majority of studies found a statistically significant decrease with mean FPG in dapagliflozin treatment groups compared to control groups [18]-[23] [25] [26] [28]. Three of the four studies that assessed 2-h PPG after an oral glucose tolerance test (OGTT) found statistically significant decreases in dapagliflozin groups compared to control groups [19] [25] [26]. Although [27] did not report statistical significance, 2-h PPG was found to be lower in the dapagliflozin groups. All studies found a greater decrease in body weight after treatment with dapagliflozin compared to the control [18]-[28].

The most common adverse events were diarrhea, headache, nasopharyngitis, upper respiratory tract infection, urinary tract infection, influenza, back pain, hypertension, cough, and arthralgia [18]-[28]. Nine trials documented >55% of subjects experiencing at least one adverse event but <10% of subjects discontinued a study due to an adverse event [18]-[22] [24] [25] [27] [28]. Fewer adverse events overall were reported by [23] (38.9% - 53.8%) and [26] (47.3% - 51.9%). Of the reported events, approximately 25% or fewer were determined to be drug-related in five trials [18]-[20] [22] [26]. The overall incidence of urinary and genital tract infections was low (<15%), but more common in dapagliflozin groups compared to control groups [18]-[25] [27] [28]. In five of the studies, the events were reported as mild or moderate and responded adequately to treatment [18]-[21] [26]. Among four other trials, there was a total of 12 patients who withdrew from the study because of a UTI or genital infection [24]-[26] [28].

Hypoglycemic events did not occur frequently (<10%) or severely and were similar to placebo or treatment groups in most studies [18]-[23] [25]. The incidence of hypoglycemia was higher in treatment groups using dapagliflozin with hypoglycemia-associated medications such as insulin (25% - 29.2% versus 13% in placebo) [28], insulin with insulin-sensitizers (53.6% - 60.4% versus 51.8% in placebo) [27] and sulfonylureas (6.9% - 7.9% versus 4.8% in placebo) [26]. A serious adverse event related to hypoglycemia was also reported for dapagliflozin 5 mg [28]. A significantly higher proportion of patients experienced hypoglycemia on glipizide (40.8%) compared to dapagliflozin (3.5%) with six episodes of hypoglycemia leading to discontinuation in the glipizide group [24].

Blood pressure was also monitored in trials. Some studies reported that systolic blood pressure was slightly reduced in both dapagliflozin and control groups [18] [21] [22] [26] [28], while others reported that it was lowered only in dapagliflozin treatment groups compared to control groups [19] [20] [23]-[25] [27]. Overall, most studies found that dapagliflozin treatment was associated with only a few incidences of hypotension (<5%) [18]-[22] [24] [28]. An incidence of syncope was reported in a patient receiving dapagliflozin 10 mg [26], while an episode of severe hypotension was noted in a patient on dapagliflozin 5 mg [19].

3.3. Empagliflozin

Approved by the FDA in August 2014, empagliflozin, D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S), is the newest SGLT2 inhibitor to enter the market. Similar to the other available agents, empagliflozin is approved for use in T2DM patients, as an adjunct to diet and exercise [3]. Plasma concentrations peak at approximately 1.5 hours post-oral administration [3] [29] with a reduction in AUC (16%) and C_{max} (37%) when taken after a high-fat and high-calorie meal. Although reductions in systemic exposure were noted, the impact on clinical outcomes was not deemed significant. As a result, empagliflozin may be taken with or without food. Empagliflozin has a plasma protein binding of roughly 86%. Metabolism occurs primarily via glucuronidation with minimal metabolite exposure. The terminal half-life of empagliflozin is 12.4 hours. Empagliflozin is primarily eliminatedrenally. Increases in AUC have occurred in patients with renal impairment, kidney failure or ESRD. Empagliflozin is contraindicated in severe renal impairment, ESRD, or dialysis [3].

The impact on plasma concentration varies based on the degree of renal and hepatic impairment. Patients with moderate renal impairment, kidney failure, or ESRD have peak plasma concentrations comparable to patients

Table 2. Dapagliflozin trials.

Author (Year)	Study Design	Subjects	Methods	Results			
					HbA1C (%) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO (N = 23)	8.4 ± 0.9	0.03 (−0.2, 0.4)	-
				DAPA 10 mg (N = 24)	8.4 ± 0.7	−0.61 (−0.9, −0.4)	−0.7 (−1.1, −0.3)
			Stabilization of Insulin Sensitizer Therapy and Insulin: ≥6 weeks with insulin treatment for ≥12 weeks	DAPA 20 mg (N = 24)	8.5 ± 0.9	−0.69 (−0.9, −0.4)	−0.78 (−1.2, −0.4)
					FPG (mg/dL) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
Wilding (2009)	Randomized Double-blind Placebo-controlled	71 T2DM (42M; 29F)	Double-blind Treatment Period: 12 weeks Group A: placebo daily + insulin Group B: DAPA 10 mg daily + insulin Group C: DAPA 20 mg daily + insulin	PBO (N = 23)	165.9 ± 51.5	17.8 (1.4, 34.2)	-
				DAPA 10 mg (N = 24)	156.0 ± 39.0	2.4 (−13.6, 18.3)	−15.4 (−38.4, 7.5)
				DAPA 20 mg (N = 24)	161.6 ± 55.0	−9.6 (−25.6, 6.3)	−27.4 (−50.3, −4.6)
					Body Weight (kg) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO (N = 23)	101.8 ± 16.5	−1.9 (−2.9, −0.9)	-
				DAPA 10 mg (N = 24)	103.4 ± 10.2	−4.5 (−5.5, −3.5)	−2.6 (−4.0, −1.2)
				DAPA 20 mg (N = 24)	101.2 ± 15.3	−4.3 (−5.3, −3.3)	−2.4 (−3.8, −1.0)
					HbA1C (%) at 24 Weeks		
			Single-blind, Placebo Lead-in Period : 2 weeks		Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
Bailey (2010)	Randomized Double-blind Parallel Group Placebo-Controlled	546 T2DM (292M; 254F)	Double-blind Treatment Period: 24 weeks (All groups on stable MET dose) Group A: placebo + MET daily in AM Group B: DAPA 2.5 mg + MET daily in AM Group C: DAPA 5 mg + MET daily in AM	PBO (N = 137)	8.11 ± 0.96	−0.3 (−0.44, −0.16)	-
				DAPA 2.5 mg (N = 137)	7.99 ± 0.90	−0.67*† (−0.81, −0.53)	-
				DAPA 5 mg (N = 137)	8.17 ± 0.96	−0.70**† (−0.85, −0.56)	-
				DAPA 10 mg (N = 135)	7.92 ± 0.82	−0.84**† (−0.98, −0.70)	-
				*p = 0.0002 **p < 0.0001			

Continued

				†Significant vs. PBO at α = 0.019 applying Dunnett's adjustment			
					FPG (mg/dL) at 24 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO (N = 137)	165.6 ± 46.3	−5.9 (−11.2, −0.7)	-
				DAPA 2.5 mg (N = 137)	161.4 ± 43.1	−17.8*† (−23.1, −12.4)	-
				DAPA 5 mg (N = 137)	169.2 ± 49.0	−21.4**† (−26.8, −16.2)	-
				DAPA 10 mg (N = 135)	156.0 ± 38.7	−23.4**† (−28.8, −18.0)	-
			Group D: DAPA 10 mg + MET daily in AM	*p = 0.0019			
				**p < 0.0001			
			Double-blind Extension Period: to 102 weeks (refer to Bailey 2013)	†Significant after sequential testing procedure at α=0.05			
					Body Weight (kg) at 24 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO
				PBO (N = 137)	87.7 ± 19.2	−0.9 (−1.4, −0.4)	-
				DAPA 2.5 mg (N = 137)	84.9 ± 17.8	−2.2† (−2.7, −1.8)	-
				DAPA 5 mg (N = 137)	84.7 ± 16.3	−3.0† (−3.5, −2.6)	-
				DAPA 10 mg (N = 135)	86.3 ± 17.5	−2.9† (−3.3, −2.4)	-
				*p < 0.0001			
				†Significant after sequential testing procedure at α=0.05			
Ferrannini (2010)	Randomized Double-blind Parallel-group Placebo-controlled	Total: 558 T2DM (276M; 282F) Main AM Cohort: 274 T2DM (132M; 142F)	Diet/exercise Placebo Lead-in Period: 2 weeks (1 week for patients with enrollment HbA1C 10.1% - 12%)		HbA1C (%) at 24 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO
				PBO (N = 75)	7.84 ± 0.87	−0.23 (−0.43, −0.02)	-
			Double-blind Placebo Controlled Treatment Period: 24 weeks	DAPA 2.5 mg (N = 65)	7.92 ± 0.90	−0.58 (−0.80, −0.36)	-
				DAPA 5 mg (N = 64)	7.86 ± 0.94	−0.77* (−0.99, −0.55)	-
			Patients with HbA1C 7.0% - 10% entered main AM cohort groups:	DAPA 10 mg (N = 70)	8.01 ± 0.96	−0.89** (−1.10, −0.67)	-
				*p = 0.0005 vs. PBO			
			Group A: placebo daily in AM	**p < 0.0001 vs. PBO			
					FPG (mg/dL) at 24 Weeks		

Continued

					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO
				PBO (N = 75)	159.9 ± 42.1	−4.1 (−11.8, 3.5)	-
				DAPA 2.5 mg (N = 65)	164.1 ± 48.0	−15.2 (−23.5, −7.0)	-
			Group B: DAPA 2.5 mg daily in AM	DAPA 5 mg (N = 64)	162.2 ± 45.0	−24.1* (−32.5, −15.6)	-
			Group C: DAPA 5 mg daily in AM	DAPA 10 mg (N = 70)	166.6 ± 41.5	−28.8** (−36.8, −20.9)	-
				*p < 0.001			
			Group D: DAPA 10 mg daily in AM	**p < 0.0001 (α = 0.019 [two-sided] applyinh Dunnett adjustment)			
			(Exploratory cohort assessments not included)		Body Weight (kg) at 24 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO
				PBO (N = 75)	88.8 ± 19.0	−2.2 (−3.3, −1.3)	-
				DAPA 2.5 mg (N = 65)	90.8 ± 22.8	−3.3 (−4.2, −2.3)	-
				DAPA 5 mg (N = 64)	87.6 ± 17.1	−2.8 (−3.8, −1.9)	-
				DAPA 10 mg (N = 70)	94.2 ± 18.7	−3.2 (−4.0, −2.3)	-
					HbA1C (%) at 52 Weeks		
			MET Stabilization Period: 8 weeks		Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. GLIP (95% CI)
			Single-blind, Placebo Lead-in Period: 2 weeks	GLIP (N = 401)	7.7 ± 0.9	−0.52 (−0.60, 0.44)	-
			Double-blind Treatment Period: 52 weeks (18-week titration period with 3 week intervals and 34-week maintenance period)	DAPA (N = 400)	7.7 ± 0.9	−0.52 (−0.60, 0.44)	0 (−0.11, 0.11)
					FPG (mg/dL) at 52 Weeks		
					Baseline Mean	Adjusted Mean Change (95% CI)	Difference vs. GLIP (95% CI)
Nauck (2011)	Randomized Double-blind Parallel-group Active-controlled Noninferiority	801 T2DM (441M; 360F)	Group A: DAPA 2.5 mg, titrated to 5 or 10 mg if FPG ≥ 6.1 mmol/L + metformin	GLIP (N = 401)	164.0 ± 41.4	−18.7 (−22.0, −17.7)	-
				DAPA (N = 400)	162.2 ± 37.8	−22.3 (−25.6, −19.3)	−3.6 (−7.9, 0.9)
					Body Weight (kg) at 52 Weeks		
					Baseline Mean	Adjusted Mean Change (95% CI)	Difference vs. GLIP (95% CI)
			Group B GLIP 5 mg, titrated to 10 or 20 mg if FPG ≥ 6.1 mmol/L + metformin	GLIP (N = 401)	87.6	1.44 (1.09, 1.78)	-
			Extension Period: 156 weeks	DAPA (N = 400)	88.4	−3.22 (−3.56, −2.87)	−4.65* (−5.14, −4.17)
				*p < 0.0001 vs. GLIP			

Continued

Strojek (2011)	Randomized Double-blind Parallel-group Placebo-Controlled	592 T2DM (285M; 307F)	Open-label, Lead in Period: 8 weeks of GLIM daily Qualification Period: 1 week Double-blind Placebo-controlled Treatment Period: 24 weeks Group A: placebo before first meal of day + GLIM Group B: DAPA 2.5 mg daily before first meal of day + GLIM Group C: DAPA 5 mg daily before first meal of day + GLIM Group D: DAPA 10 mg daily before first meal of day + GLIM Extension Period: 24 weeks	HbA1C (%) at 24 Weeks			
					Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 145)	8.15 ± 0.74	−0.13	-
				DAPA 2.5 mg (N = 154)	8.11 ± 0.75	−0.58	−0.44* (−0.61, −0.27)
				DAPA 5 mg (N = 142)	8.12 ± 0.78	−0.63	−0.49* (−0.67, −0.32)
				DAPA 10 mg (N = 151)	8.07 ± 0.79	−0.82	−0.68* (−0.86, −0.51)
				*p < 0.0001 vs. PBO at α = 0.019 applying Dunnett's adjustment			
				FPG (mg/dL) at 24 Weeks			
					Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 145)	172.6 ± 37.3	−2	-
				DAPA 2.5 mg (N = 154)	172.3 ± 38.4	−16.8	−15 (−21.8, −7.9)
				DAPA 5 mg (N = 142)	174.4 ± 38.2	−21.3	−19.3* (−26.3, −12.3)
				DAPA 10 mg (N = 151)	172.1 ± 36.8	−28.5	−26.5* (−33.5, −19.5)
				*p < 0.0001 vs. PBO			
				Body Weight (kg) at 24 Weeks			
					Baseline Mean	Adjusted Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 145)	80.94	−0.72	-
				DAPA 2.5 mg (N = 154)	81.89	−1.18	−0.46* (−1.08, 0.15)
				DAPA 5 mg (N = 142)	81	−1.56	−0.84** (−1.47, −0.21)
				DAPA 10 mg (N = 151)	80.56	−2.26	−1.54*** (−2.17, −0.92)
				*p = 0.1410 vs. PBO **p = 0.0091 vs. PBO (significant after sequential testing procedure at α = 0.05) ***p < 0.0001 vs. PBO (significant after sequential testing procedure at α = 0.05)			
Bailey (2012)	Randomized Double-blind Parallel- group Placebo-controlled	282 T2DM (141M; 141F)	Qualification Period: 2 weeks Single-blind, Placebo Lead-in Period: 2 weeks	HbA1C (%) at 24 Weeks			
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO (N = 68)	7.8 ± 1.12	0.02 (−0.22, 0.25)	-
				DAPA 1 mg (N = 72)	7.8 ± 0.98	−0.68	−0.69*

Continued

						(−0.91, −0.45)	(−1.02, −0.37)
				DAPA 2.5 mg (N = 74)	8.1 ± 1.07	−0.72 (−0.95, −0.49)	−0.74* (−1.07, −0.41)
				DAPA 5 mg (N = 68)	7.9 ± 1.03	−0.82 (−1.06, −0.58)	−0.84* (−1.17, −0.50)
				*p < 0.0001 vs. PBO			
					FPG (mg/dL) at 24 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
			Double-blind Treatment Period: 24 weeks	PBO (N = 68)	161.6 ± 57.5	4.1 (−4.1, 12.4)	-
			Group A: placebo daily with morning meal	DAPA 1 mg (N = 72)	155.5 ± 48.3	−11 (−19.1, −3.1)	−15.1* (−26.7, −3.6)
			Group B: DAPA 1 mg daily with morning meal	DAPA 2.5 mg (N = 74)	159.8 ± 51.5	−21.6 (−29.5, −13.7)	−25.8** (−37.1, −14.2)
			Group C: DAPA 2.5 mg daily with morning meal	DAPA 5 mg (N = 68)	157.1 ± 41.6	−28.5 (−36.8, −20.2)	−32.6** (−44.3, −20.7)
				*p = 0.0103 vs. PBO			
			Group D: DAPA 5 mg daily with morning meal	**p < 0.0001 vs. PBO			
					Body Weight (kg) at 24 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
			Safety-assessment Follow-up Period: 4 weeks	PBO (N = 68)	90.0 ± 17.98	−0.96 (−1.74, −0.19)	-
				DAPA 1 mg (N = 72)	88.2 ± 18.49	−2.69 (−3.44, −1.94)	−1.73* (−2.81, −0.65)
				DAPA 2.5 mg (N = 74)	84.3 ± 18.18	−2.64 (−3.38, −1.90)	−1.68** (−2.76, −0.60)
				DAPA 5 mg (N = 68)	85.4 ± 19.43	−2.69 (−3.47, −1.91)	−1.73*** (−2.83, −0.63)
				*p = 0.0018 vs. PBO			
				**p = 0.0024 vs. PBO			
				***p = 0.0022 vs. PBO			
			Single-blind Placebo Lead-in Period: 1 week				
					HbA1C (%) at 24 Weeks - Study I		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. Monotherapy (95% CI)
Henry (2012)	Two Randomized Double-blind Active-controlled	1236 T2DM (573M; 663F)	Double-blind Treatment Period: 24 weeks	MET + PBO (N = 201)	9.2 ± 1.3	−1.35 (−1.53, −1.18)	-
			Study I: Group A: MET XR + placebo combination with evening meal	DAPA 5 mg + MET (N = 194)	9.2 ± 1.3	−2.05 (−2.23, −1.88)	−0.86* (−1.11, −0.62) −0.70** (−0.94, −0.45)

Continued

	DAPA 5 mg + PBO (N = 203)	9.1 ± 1.4	−1.19 (−1.36, −1.02)	-
		HbA1C (%) at 24 Weeks - Study II		
		Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. Monotherapy (95% CI)
	MET + PBO (N = 208)	9.1 ± 1.3	−1.44 (−1.59, −1.29)	-
	DAPA 10 mg + MET (N = 211)	9.1 ± 1.3	−1.98 (−2.13, −1.83)	−0.53* (−0.74, −0.32) −0.54** (−0.75, −0.33)
	DAPA 10 mg + PBO (N = 219)	9.1 ± 1.3	−1.45 (−1.59, −1.31)	-
Group B: DAPA 5 mg + MET XR combination with evening meal	*p < 0.0001 vs. DAPA + PBO **p < 0.0001 vs. MET + PBO			
		FPG (mg/dL) at 24 Weeks - Study I		
Group C: DAPA 5 mg + placebo combination with evening meal		Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. Monotherapy (95% CI)
	MET + PBO (N = 201)	197.1 ± 60.4	−33.5 (−38.9, −28.3)	-
Study II: Group A: MET XR + placebo combination with evening meal	DAPA 5 mg + MET (N = 194)	193.9 ± 56.2	−61.1 (−66.5, −55.7)	−19.1* (−26.7, −11.4) −27.6** (−35.1, −19.8)
Group B: DAPA 10 mg + MET XR combination with evening meal	DAPA 5 mg + PBO (N = 203)	190.8 ± 56.6	−42 (−47.4, −36.8)	-
		FPG (mg/dL) at 24 Weeks - Study II		
Group C: DAPA 10 mg + placebo combination with evening meal		Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. Monotherapy (95% CI)
	MET + PBO (N = 208)	190.5 ± 54.1	−34.8 (−39.8, −29.7)	-
	DAPA 10 mg + MET (N = 211)	189.5 ± 58.0	−60.4 (−65.2, −55.3)	−13.9* (−20.9, −7.0) −25.6** (−32.6, −18.6)
	DAPA 10 mg + PBO (N = 219)	198.0 ± 61.8	−46.5 (−51.4, −41.4)	-
	*p < 0.0001 vs. DAPA + PBO (after sequential testing procedure at α = 0.05)			
	**p < 0.0001 vs. MET + PBO (after sequential testing procedure at α = 0.05)			
		Body Weight (kg) at 24 Weeks - Study I		
		Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. Monotherapy (95% CI)

Continued

				MET + PBO (N = 201)	85.6 ± 20.0	−1.29 (−1.76 to −0.82)	-
				DAPA 5 mg + MET (N = 194)	84.1 ± 19.5	−2.66 (−3.14, −2.19)	−0.05* (−0.72, 0.61)
							−1.37** (−2.04, −0.71)
				DAPA 5 mg + PBO (N = 203)	86.2 ± 21.1	−2.61 (−3.07, −2.15)	-
					Body Weight (kg) at 24 Weeks - Study II		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. Monotherapy (95% CI)
				MET + PBO (N = 208)	87.2 ± 19.4	−1.36 (−1.83, −0.89)	-
				DAPA 10 mg + MET (N = 211)	88.4 ± 19.7	−3.33 (−3.80, −2.86)	−1.97*** (−2.64, −1.30)
				DAPA 10 mg + PBO (N = 219)	88.5 ± 19.3	−2.73 (−3.19, −2.27)	−1.37**** (−2.03, −0.71)
				*p = 0.8769 vs. DAPA + PBO **p < 0.0001 vs. MET + PBO ***p < 0.0001 vs. MET + PBO (after sequential testing procedure at α = 0.05) ****p < 0.0001 vs. DAPA vs. MET (after sequential testing procedure at α = 0.05)		
Rosenstock (2012)	Randomized Double-blind Parallel-group Placebo-Controlled	420 T2DM (208M; 212F)	PIO dose-optimization period for treatment-naïve patients or those receiving MET, SU, or low dose TZD: 10 weeks Single-blind, Lead-in Period: 2 weeks Double-blind Treatment Period: 24 weeks Group A: placebo + PIO 30 mg or 45 mg Group B: DAPA 5 mg + PIO 30 mg or 45 mg Group C: DAPA 10 mg + PIO 30 mg or 45 mg Extension Period: 24 weeks		HbA1C (%) at 24 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change ± SE	Difference vs. PBO
				PBO (N = 139)	8.34 ± 1.00	−0.42 ± 0.08	-
				DAPA 5 mg (N = 141)	8.40 ± 1.03	−0.82 ± 0.08*	-
				DAPA 10 mg (N = 140)	8.37 ± 0.96	−0.97 ± 0.08**	-
				*p = 0.0007 vs. PBO **p < 0.0001 vs. PBO			
					FPG (mg/dL) at 24 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change ± SE	Difference vs. PBO
				PBO (N = 139)	160.7 ± 47.0	−5.5 ± 2.9	-
				DAPA 5 mg (N = 141)	168.6 ± 52.1	−24.9 ± 2.9*	-
				DAPA 10 mg (N = 140)	164.9 ± 46.3	−29.6 ± 2.9*	-
				*p < 0.0001 vs. PBO			
					Body Weight (kg) at 24 Weeks		

Continued

					Baseline Mean ± SD	Adjusted Mean Change ± SE	Difference vs. PBO
				PBO (N = 139)	86.4 ± 21.3	1.64 ± 0.28	-
				DAPA 5 mg (N = 141)	87.8 ± 20.7	0.09 ± 0.28*	-
				DAPA 10 mg (N = 140)	84.8 ± 22.2	−0.14 ± 0.28*	-
				*p < 0.0001 vs. PBO			
					HbA1C (%) at 48 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO
				PBO (N = 139)	8.34 ± 1.00	−0.54 (−0.70, −0.38)	-
				DAPA 5 mg (N = 141)	8.40 ± 1.03	−0.95 (−1.10, −0.80)	-
				DAPA 10 mg (N = 140)	8.37 ± 0.96	−1.21 (−1.36, −1.06)	-
					FPG (mg/dL) at 48 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO
				PBO (N = 139)	160.7 ± 47.0	−13.1 (−20.2, −6.0)	-
				DAPA 5 mg (N = 141)	168.6 ± 52.1	−22.8 (−29.1 to −16.4)	-
				DAPA 10 mg (N = 140)	164.9 ± 46.3	−33.1 (−39.0, −27.2)	-
					Body Weight (kg) at 48 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO
				PBO (N = 139)	86.4 ± 21.3	2.99 (2.19, 3.79)	-
				DAPA 5 mg (N = 141)	87.8 ± 20.7	1.35 (0.61, 2.09)	-
				DAPA 10 mg (N = 140)	84.8 ± 22.2	0.69 (−0.03, 1.41)	-
Wilding (2012)	Randomized Double-blind Parallel-group Placebo-controlled	800 T2DM (382M; 418F)	Pre-enrollment OAD/ Insulin Stabilization Period: at least 8 weeks Enrollment Period: 2 weeks		HbA1C (%) at 24 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 193)	8.47 ± 0.77	−0.39	-
				DAPA 2.5 mg (N = 202)	8.46 ± 0.78	−0.79	−0.40* (−0.54, −0.25)

Continued

	DAPA 5 mg (N = 211)	8.62 ± 0.89	−0.89	−0.49* (−0.65, −0.34)
	DAPA 10 mg (N = 194)	8.57 ± 0.82	−0.96	−0.57* (−0.72, −0.42)
	*p < 0.001 vs. PBO			
		FPG (mg/dL) at 24 Weeks		
		Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO
Double-blind Placebo-controlled Treatment Period: 24 weeks (with open-label insulin/existing OAD therapies) Group A: placebo + insulin Group B: DAPA 2.5 mg daily + insulin Group C: DAPA 5 mg daily + insulin Group D: DAPA 10 mg daily + insulin Double-blind Extension Period I: 24 weeks Double-blind Extension Period II: 56 weeks	PBO (N = 193)	170.6 ± 57.2	-	-
	DAPA 2.5 mg (N = 202)	180.1 ± 59.9	−11.71* (−21.4, −2.0)	-
	DAPA 5 mg (N = 211)	185.4 ± 58.7	−20.18* (−29.9, −10.6)	-
	DAPA 10 mg (N = 194)	173.1 ± 54.9	−19.82* (−29.6, −10.1)	-
	*p < 0.001 vs. baseline			
		Body Weight (kg) at 24 Weeks		
		Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO (95% CI)
	PBO (N = 193)	94.5 ± 19.8	0.43	-
	DAPA 2.5 mg (N = 202)	93.0 ± 16.7	−0.92	−1.35* (−1.90, −0.80)
	DAPA 5 mg (N = 211)	93.3 ± 17.4	−1	−1.42* (−1.97, −0.88)
	DAPA 10 mg (N = 194)	94.5 ± 16.8	−1.61	−2.04* (−2.59, −1.48)
	*p < 0.001 vs. PBO			
		HbA1C (%) at 48 Weeks		
		Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO (95% CI)
	PBO (N = 193)	8.47 ± 0.77	−0.47	-
	DAPA 2.5 mg (N = 202)	8.46 ± 0.78	−0.79	−0.32* (−0.48, −0.16)
	DAPA 5 mg (N = 211)	8.62 ± 0.89	−0.96	−0.49* (−0.65, −0.33)
	DAPA 10 mg (N = 194)	8.57 ± 0.82	−1.01	−0.54* (−0.70, −0.38)
	*p < 0.001 vs. PBO			
		FPG (mg/dL) at 48 Weeks		

Continued

					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO
				PBO (N = 193)	170.6 ± 57.2	-	-
				DAPA 2.5 mg (N = 202)	180.1 ± 59.9	−12.43* (−23.1, −2.0)	-
				DAPA 5 mg (N = 211)	185.4 ± 58.7	−16.2* (−26.7, −6.0)	-
				DAPA 10 mg (N = 194)	173.1 ± 54.9	−16.94* (−27.6, −6.5)	-
				*p < 0.001 vs. baseline			
					Body Weight (kg) at 48 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change	Difference vs. PBO (95% CI)
				PBO (N = 193)	94.5 ± 19.8	0.82	-
				DAPA 2.5 mg (N = 202)	93.0 ± 16.7	−0.96	−1.78* (−2.53, −1.03)
				DAPA 5 mg (N = 211)	93.3 ± 17.4	−1	−1.82* (−2.56, −1.07)
				DAPA 10 mg (N = 194)	94.5 ± 16.8	−1.61	−2.43* (−3.18, −1.68)
				*p < 0.001 vs. PBO			
Bailey (2013)	Randomized Double-blind Parallel Group Placebo-Controlled	546 T2DM (292M; 254F)	Double-blind Extension Treatment Period: 78 weeks (All groups on stable MET dose) Group A: placebo + MET daily in AM Group B: DAPA 2.5 mg + MET daily in AM Group C: DAPA 5 mg + MET daily in AM Group D: DAPA 10 mg + MET daily in AM		HbA1C (%) at 102 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO (N = 137)	8.12 ± 0.96	0.02 (−0.20, 0.23)	-
				DAPA 2.5 mg (N = 137)	7.99 ± 0.90	−0.48 (−0.68, −0.29)	−0.50* (−0.79, −0.21)
				DAPA 5 mg (N = 137)	8.17 ± 0.96	−0.58 (−0.77, −0.39)	−0.60** (−0.89, −0.31)
				DAPA 10 mg (N = 135)	7.92 ± 0.82	−0.78 (−0.97, −0.60)	−0.80** (−1.08, −0.52)
				*p = 0.0008 **p < 0.0001 vs. PBO			
					FPG (mg/dL) at 102 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO (N = 137)	165.6± 46.5	−10.5 (−17.5, −3.4)	-
				DAPA 2.5 mg	161.4 ± 43.1	−19.3	−8.8*

Continued

				(N = 137)		(−25.6, −13.0)	(−17.8, 0.2)
				DAPA 5 mg (N = 137)	169.2 ± 49.0	−26.5 (−32.1, −20.9)	−16.0** (−24.7, −7.4)
				DAPA 10 mg (N = 135)	156.0 ± 38.7	−24.5 (−29.7, −19.3)	−14.1*** (−22.5, −5.6)
				*p = 0.0518 vs. PBO			
				**p = 0.0003 vs. PBO			
				***p = 0.0012 vs. PBO			
					Body Weight (kg) at 102 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO (N = 137)	87.74 ± 19.24	1.36 (0.53, 2.20)	-
				DAPA 2.5 mg (N = 137)	84.90 ± 17.77	−1.1 (−1.91, −0.29)	−2.46* (−3.63, −1.30)
				DAPA 5 mg (N = 137)	84.73 ± 16.26	−1.7 (−2.48, −0.91)	−3.06* (−4.21, −1.92)
				DAPA 10 mg (N = 135)	86.28 ± 17.53	−1.74 (−2.51, −0.96)	−3.10* (−4.24, −1.96)
				*p < 0.0001 vs. PBO			
Kaku (2013)	Randomized Double-blind Parallel-group Placebo-controlled	279 T2DM (215M; 64F)	Washout Period: 6 weeks if on prior OAD Single-blind Placebo Lead-in Period: 4 weeks Double-blind Treatment Period: 12 weeks Group A: placebo daily Group B: DAPA 1 mg daily Group C: DAPA 2.5 mg daily Group D: DAPA 5 mg daily Group E: DAPA 10 mg daily Follow-up Period: 4 weeks				
					HbA1C (%) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change ± SE	Difference vs. PBO (95% CI)
				PBO (N = 54)	8.12 ± 0.71	0.37 ± 0.07	-
				DAPA 1 mg (N = 59)	8.10 ± 0.79	−0.12 ± 0.07	−0.49* (−0.68, −0.29)
				DAPA 2.5 mg (N = 56)	7.92 ± 0.74	−0.11 ± 0.07	−0.48* (−0.67, −0.28)
				DAPA 5 mg (N = 58)	8.05 ± 0.66	−0.37 ± 0.07	−0.74* (−0.93, −0.54)
				DAPA 10 mg (N = 52)	8.18 ± 0.69	−0.44 ± 0.07	−0.80* (−1.00, −0.61)
				*p < 0.0001 vs. PBO (tested at α = 0.015 applying Dunnett adjustment			
					FPG (mg/dL) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change ± SE	Difference vs. PBO
				PBO (N = 54)	158.94 ± 31.08	11.17 ± 3.43	-
				DAPA 1 mg (N = 59)	163.53 ± 33.06	−15.61 ± 3.43*	-
				DAPA 2.5 mg (N = 56)	159.17 ± 31.98	−19.83 ± 3.37*	-

Continued

DAPA 5 mg (N = 58)	164.49 ± 23.56	−23.51 ± 3.43*	-
DAPA 10 mg (N = 52)	163.36 ± 29.74	−31.94 ± 3.57*	-
*p < 0.0001 vs. PBO			
	Body Weight (kg) at 12 Weeks		
	Baseline Mean ± SD	Adjusted Mean Change ± SE	Difference vs. PBO
PBO (n = 54)	68.88 ± 14.94	−0.05 ± 0.19	-
DAPA 1 mg (n = 59)	68.40 ± 11.04	−1.25 ± 0.18*	-
DAPA 2.5 mg (n = 56)	66.61 ± 14.29	−1.24 ± 0.18*	-
DAPA 5 mg (n = 58)	68.92 ± 12.43	−2.06 ± 0.18*	-
DAPA 10 mg (n = 52)	70.35 ± 17.48	−1.91 ± 0.19*	-
	*p < 0.0001 vs. PBO		

95% CI = 95% confidence interval; AHA = antihyperglycemic agent; AM = morning; DAPA = dapagliflozin; F = Female; FPG = Fasting Plasma Glucose; GLIM = glimepiride; GLIP = glipizide; HbA1C = hemoglobin A1C; M = Male; MET = metformin; PBO = placebo; SD = standard deviation; SE = standard error; SITA = sitagliptin; SU = sulfonylurea; T2DM = Type 2 Diabetes Mellitus Patients; TZD = thiazolidinedione.

with normal renal function. On the other hand, patients with mild and severe renal impairment have approximately 20% higher peak plasma concentrations. Renal function should be evaluated prior to and throughout empagliflozin treatment. Use of empagliflozin should be avoided in patients with eGFR's of <45 mL/min/1.73m^2. Mild to severe hepatic impairment may also result in AUC and C_{max} elevations, but dose adjustments are not warranted [3].

Two pivotal trials evaluating the efficacy of empagliflozin in T2DM patients over 12 weeks were identified and summarized in **Table 3**. One study [30] assessed empagliflozin as monotherapy and another [31] as add-on therapy to metformin. Doses ranged from 1 mg to 50 mg. Significant reductions in HbA1C, FPG, and weight were observed in the 5 mg, 10 mg, 25 mg, and 50 mg empagliflozin groups when compared to placebo [30] [31]. Both studies reported greater proportions of empagliflozin groups reaching HbA1Cs ≤ 7% compared to placebo (30% - 45% of empagliflozin 5 mg and 25 mg versus 22% of placebo [30] and 35.7% - 38.0% of empagliflozin 10 mg, 25 mg, and 50 mg versus 15.5% of placebo [31]). Similar reductions were observed with sitagliptin 100 mg (33.8%) compared to placebo (15.5%) [31].

Overall, adverse events were similar among empagliflozin, placebo, and open-label agent groups. Pollakiuria, thirst, nasopharyngitis, urinary tract infections, and genital infections were the most common adverse events reported by empagliflozin subjects. Although the incidence of UTIs was comparable among study groups within each trial, an increased number of genital infections occurred in the empagliflozin groups. Hypoglycemic episodes among treatment and placebo groups were not significantly different. Additionally, both studies reported a trend toward a potential dose-related increase in hematocrit in the empagliflozin groups (0.6% - 2.5%) [30] [31]. Blood pressure (systolic and diastolic) changes trended toward dose-dependent decreases in the empagliflozin (5 mg, 10 mg, and 25 mg) versus placebo groups but were not statistically significant. The greatest change occurred in the empagliflozin 25 mg group [31].

3.4. Other SGLT2s

Although canagliflozin, dapagliflozin, and empagliflozin are the only SGLT2 inhibitors on the US market, several other candidates are currently in development. These include ipragliflozin, tofogliflozin, and ertugliflozin.

Table 3. Empagliflozin trials.

Author (Year)	Study Design	Subjects	Methods	Results			
					HbA1C (%) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO (N = 82)	7.8 ± 0.8	0.1 (−0.09, 0.27)	-
				EMPA 5 mg (N = 81)	7.9 ± 0.8	0.4* (−0.61, −0.25)	-
				EMPA 10 mg −81	8.0 ± 0.8	−0.5* (−0.66, −0.30)	-
			Screening Period: up to 1 week (2 visits)	EMPA 25 mg (N = 82)	7.8 ± 0.8	−0.6* (−0.81, −0.45)	-
			Oral AHA Washout Period (if applicable): 4 weeks	MET (N = 80)	8.1 ± 0.9	−0.7* (−0.92, −0.57)	-
			Open-label Placebo Run-in Period: 2 weeks	*p < 0.0001 vs. PBO			
					FPG (mg/dL) at 12 Weeks		
			Double-blind Treatment Period: 12 weeks		Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
Ferrannini (2013)	Randomized Double-blind Placebo-controlled	406 T2DM (211M; 195F)	Group A: placebo once daily	PBO (N = 82)	171.2 ± 39.6	0.7 (−6.3, 7.7)	-
			Group B: EMPA 5 mg once daily	EMPA 5 mg (N = 81)	178.4 ± 45.0	−23.2* (−30.5, −16.2)	-
			Group C: EMPA10 mg once daily	EMPA 10 mg −81	178.4 ± 46.8	−29.0* (−36.0, −21.8)	-
			Group D: EMPA 25 mg once daily	EMPA 25 mg (N = 82)	171.2 ± 25.2	−31.0* (−38.2, −24.1)	-
			Group E: Open-label MET (up to 1000 mg twice daily or maximum tolerated dose)	MET (N = 80)	176.6 ± 43.2	−29.9* (−38.0, −21.8)	-
					Body Weight (kg) at 12 Weeks		
			Follow-up Visit: 4 - 7 days after last treatment		Baseline Mean	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO (N = 82)	82.2	−0.75 (−1.26, −0.23)	-
				EMPA 5 mg (N = 81)	82.8	−1.81 (−2.32, −1.29)	-
				EMPA 10 mg −81	76.8	−2.33 (−2.84, −1.82)	-
				EMPA 25 mg (N = 82)	81.2	−2.03 (−2.54, −1.52)	-
				MET (N = 80)	81.1	−1.32 (−1.84, −0.81)	-

Continued

					HbA1C (%) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO (N = 71)	8.0 ± 0.7	0.15 (−0.00, 0.30)	-
				EMPA 1 mg (N = 71)	7.8 ± 0.7	−0.09 (−0.24, 0.07)	-
				EMPA 5 mg −71	8.0 ± 0.7	−0.23* (−0.39, −0.08)	-
				EMPA 10 mg (N = 71)	7.9 ± 0.7	−0.56** (−0.71, −0.41)	-
			Screening Period: over 1 week	EMPA 25 mg (N = 70)	8.1 ± 0.8	−0.55** (−0.70, −0.40)	-
			Oral (non-metformin) AHA Washout Period (if applicable): 4 weeks	EMPA 50 mg (N = 70)	7.9 ± 0.7	−0.49** (−0.64, −0.33)	-
			Placebo Run-in Period: 2 weeks	SITA (N = 71)	8.1 ± 0.9	−0.45** (−0.65, −0.25)	-
			Double-blind Treatment Period: 12 weeks	*p ≤ 0.001 vs. PBO			
				**p ≤ 0.0001 vs. PBO			
					FPG (mg/dL) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
Rosenstock (2013)	Randomized Double-blind Placebo-controlled	495 T2DM (250M; 245F)	Group A: placebo once daily + MET	PBO (N = 71)	174 ± 40	5 (−2, 12)	-
			Group B: EMPA 5 mg once daily + MET	EMPA 1 mg (N = 71)	173 ± 40	−2 (−9, 5)	-
			Group C: EMPA10 mg once daily + MET	EMPA 5 mg −71	180 ± 43	−16* (−23, −9)	-
			Group D: EMPA 25 mg once daily + MET	EMPA 10 mg (N = 71)	173 ± 36	−22* (−29, −16)	-
			Group E: Open-label SITA100mg once daily + MET	EMPA 25 mg (N = 70)	180 ± 48	−27* (−34, −20)	-
			Follow-up Visit: 1 week after last treatment	EMPA 50 mg (N = 70)	175 ± 35	−28* (−35, −21)	-
				SITA (N = 71)	178 ± 44	−13** (−22, −3)	-
				*p ≤ 0.0001 vs. PBO			
				**p ≤ 0.01 vs. PBO			
					Body Weight (kg) at 12 Weeks		
					Baseline Mean ± SD	Adjusted Mean Change (95% CI)	Difference vs. PBO (95% CI)
				PBO	87.7 ± 15.7	−1.2	-

Continued

	(N = 71)		(−1.8, −0.5)	
	EMPA 1 mg (N = 71)	90.6 ± 18.9	−1.6 (−2.2, −0.9)	-
	EMPA 5 mg −71	87.0 ± 14.8	−2.3* (−2.9, −1.7)	-
	EMPA 10 mg (N = 71)	87.9 ± 14.4	−2.7** (−3.4, −2.1)	-
	EMPA 25 mg (N = 70)	90.5 ± 16.9	−2.6** (−3.2, −2.0)	-
	EMPA 50 mg (N = 70)	91.6 ± 15.8	−2.9*** (−3.5, −2.2)	-
	SITA (N = 71)	88.0 ± 15.0	−0.8 (−1.5, −0.2)	-
	*p ≤ 0.01 vs. PBO			
	**p ≤ 0.001 vs. PBO			
	***p ≤ 0.0001 vs. PBO			

95% CI = 95% confidence interval; AHA = antihyperglycemic agent; EMPA = empagliflozin; F = Female; FPG = Fasting Plasma Glucose; HbA1C = hemoglobin A1C; M = Male; MET = metformin; PBO = placebo; SD = standard deviation; SITA = sitagliptin; T2DM = Type 2 Diabetes Mellitus Patients.

4. Conclusion

Considering the increasing prevalence and incidence of type 2 diabetes mellitus worldwide, there is an obvious need for effective therapeutic strategies to combat this chronic and progressive disease. The need for agents with novel mechanisms of action is becoming more and more crucial owing to the need for individualized glycemic targets and glucose-lowering therapies, concerning side effects of many current therapies, and the progressive *β*-cell function decline associated with T2DM. SGLT2 inhibitors offer this potential and recently approved canagliflozin, dapagliflozin, and empagliflozin have shown significant promise as mono- and add-on therapy to current glucose-lowering regimens that may not otherwise be providing sufficient glycemic control in T2DM patients. Short-term benefits have certainly been made clear through the variety of clinical trials performed on these drugs, however there is still a need to establish long-term safety and efficacy. The significance of the unique side effects of increased genital mycotic infections and associated adverse events must also be considered. Several other agents in this class are in phase III trials and show similar promise in their efficacy as add-on treatments.

Acknowledgements

We acknowledge Jennifer Heo, Sarah Jaffery, and Malay Naik for editorial review.

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