Common Drug Review
Clinical Review Report

November 2015

Drug	Dapagliflozin (Forxiga)
Indication	For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with: • Metformin, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control. • A sulfonylurea, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control. • Insulin (alone or with metformin), when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.
Listing Request	For use in patients with type 2 diabetes mellitus to improve glycemic control when: • Added on to metformin for patients with inadequate glycemic control on metformin, when a sulfonylurea is contraindicated, not tolerated or ineffective and for whom insulin is not an option. • Added on to sulfonylurea for patients with inadequate glycemic control on sulfonylurea, when metformin is contraindicated, not tolerated or ineffective and for whom insulin is not an option. • Added on to insulin (alone or with metformin) for patients with inadequate glycemic control on insulin (alone or with metformin), when a sulfonylurea is contraindicated, not tolerated or ineffective.
Dosage Form(s)	5 mg and 10 mg oral tablets
NOC Date	12-12-2014
Manufacturer	AstraZeneca Canada Inc.

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ABBREVIATIONS

A1C	glycated hemoglobin
AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
CDR	CADTH Common Drug Review
CI	confidence interval
DB	double-blind
DBP	diastolic blood pressure
DIC	deviance information criteria
DKA	diabetic ketoacidosis
DPP	dipeptidyl peptidase
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	Diabetes Treatment Satisfaction Questionnaire change version
DTSQs	Diabetes Treatment Satisfaction Questionnaire status version
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol Five-Dimension Health-Related Quality of Life Questionnaire
FDA	US Food and Drug Administration
FPG	fasting plasma glucose
GLP	glucagon-like peptide
IDC	indirect comparison
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LOCF	last observation carried forward
MCID	minimal clinically important difference
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
RCT	randomized controlled trial
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SGLT	sodium glucose cotransporter
SMBG	self-monitored blood glucose
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WDSAE	withdrawal due to serious adverse event
WMD	weighted mean difference

EXECUTIVE SUMMARY

Introduction

Diabetes is a metabolic disease characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels, on both a microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral vascular disease, cardiovascular disease) level. There are two main subtypes of diabetes: type 1, in which the primary problem is a lack of adequate insulin secretion from pancreatic beta cells, and type 2, in which cells are unresponsive to insulin. Dapagliflozin is a sodium glucose cotransporter (SGLT)–2 inhibitor which by inhibiting the glucose transporter in the kidney, results in increased excretion of glucose and ultimately an antihyperglycemic effect. Secondary effects may include weight loss secondary to reduced glucose absorption and a lowering of blood pressure.

Indication under review
For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with: • Metformin, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control. • A sulfonylurea, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control. • Insulin (alone or with metformin), when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.
Listing criteria requested by sponsor
For use in patients with type 2 diabetes mellitus to improve glycemic control when: • Added on to metformin for patients with inadequate glycemic control on metformin, when a sulfonylurea is contraindicated, not tolerated or ineffective and for whom insulin is not an option. • Added on to sulfonylurea for patients with inadequate glycemic control on sulfonylurea, when metformin is contraindicated, not tolerated or ineffective and for whom insulin is not an option. • Added on to insulin (alone or with metformin) for patients with inadequate glycemic control on insulin (alone or with metformin), when a sulfonylurea is contraindicated, not tolerated or ineffective.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of dapagliflozin for the treatment of adults with type 2 diabetes mellitus who have experienced inadequate glycemic control on therapy with metformin, or a sulfonylurea, or insulin (alone or in combination with metformin).

Results and Interpretation

Included Studies

Six multi-centre, manufacturer-sponsored double-blind (DB) randomized controlled trials (RCTs), five with DB extensions, were included in this review. Four of the studies featured patients whose type 2 diabetes was not controlled despite treatment with metformin. Patients in all these studies continued on metformin as part of their treatment regimen. In two of the studies (Study 12, N = 182, comparing dapagliflozin 10 mg and placebo, and Study 14, N = 546, comparing dapagliflozin 5 mg, 10 mg, and placebo), patients were randomly assigned to either dapagliflozin or placebo, and in Study 4, 814 patients were randomized 1:1 to either dapagliflozin or glipizide. Study 4 was a non-inferiority study, while the placebo-controlled trials were all of superiority design. Study 18 (N = 534) was designed to compare triple therapy 1:1:1 with dapagliflozin plus saxagliptin on background metformin, to

dapagliflozin or saxagliptin on background metformin. As this study was not designed to compare dapagliflozin with saxagliptin, no analysis was provided for this comparison. In Studies 12 and 14, the core component was 24 weeks with extensions to 78 weeks, and in Study 4 the core component was 52 weeks with extensions out to a total of 208 weeks. In the other two included studies, patients had previously had inadequate glycemic control on a sulfonylurea (Study 5) or insulin (Study 6). In Study 5, 597 patients continued on a background of glimepiride and were randomized 1:1:1:1 to either dapagliflozin 2.5 mg, 5 mg, 10 mg, or placebo. In Study 6, 808 patients continued on a background of insulin, and were randomized 1:1:1:1 to either dapagliflozin 2.5, 5 mg, 10 mg, or placebo. In both Study 5 and Study 6, the core phases were 24 weeks, with extensions out to 48 weeks and 104 weeks, respectively. With the exception of Study 12, the primary outcome of all studies was change from baseline in glycated hemoglobin (A1C). In Study 12, change from baseline in body weight was the primary outcome.

Key critical appraisal issues included the large proportion of patients discontinuing from Study 4. As this trial had a non-inferiority design, a higher discontinuation rate in this type of trial biases toward a finding of non-inferiority. Study 18 was not designed to compare dapagliflozin plus metformin with saxagliptin plus metformin, but was instead designed to compare triple therapy (dapagliflozin plus saxagliptin plus metformin) with dual therapy (either of these drugs plus metformin). Therefore, the relative efficacy and harms of dapagliflozin versus one of its key comparators, the dipeptidyl peptidase-4 (DPP-4) inhibitors, is unknown. The included studies were also not designed to assess key clinical outcomes such as morbidity and mortality, although this would not be unusual for a registration trial for an antidiabetes drug.

Efficacy

Quality of life data were reported in three studies, with no statistically significant changes in quality of life for dapagliflozin on the Diabetes Treatment Satisfaction Questionnaire (DTSQ) versus glipizide in Study 4, or versus placebo in Study 5, and no statistically significant difference on the EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D) versus placebo in Study 5.

In Study 4, the adjusted mean change in A1C from baseline to week 52 was similar between dapagliflozin and glipizide, and the adjusted mean difference between dapagliflozin and glipizide was 0 (95% confidence interval [CI], –0.11 to 0.11). Dapagliflozin was judged to be non-inferior to glipizide, as the upper limit of the 95% CI was less than the predefined threshold of 0.35%.

There was a statistically significant decrease in A1C with both dapagliflozin 5 mg and 10 mg doses versus placebo with backgrounds of metformin, a sulfonylurea, and insulin. In Study 14, with a metformin background, there was a statistically significant reduction in A1C versus placebo after 24 weeks in both the dapagliflozin 5 mg (adjusted mean difference –0.41; 95% CI, –0.61 to –0.21; $P < 0.0001$) and dapagliflozin 10 mg groups (–0.54; 95% CI –0.74 to –0.34; $P < 0.0001$). In Study 12, there was a statistically significant reduction versus placebo after 24 weeks in the dapagliflozin 10 mg group (adjusted mean difference –0.28; 95% CI, –0.42 to –0.15; $P < 0.0001$). There was no 5 mg group in this study.

In Study 5, with a sulfonylurea background, there was a statistically significant reduction in A1C in both the dapagliflozin 5 mg (adjusted mean difference −0.49; 95% CI, −0.67 to −0.32; $P < 0.0001$) and the dapagliflozin 10 mg groups versus placebo after 24 weeks (adjusted mean difference −0.68; 95% CI, −0.86 to −0.51, $P < 0.0001$).

In Study 6, with an insulin background, there was a statistically significant reduction in A1C after 24 weeks in both the dapagliflozin 5 mg (adjusted mean difference –0.52%; 95% CI, –0.66 to –0.38; *P* < 0.0001) and the dapagliflozin 10 mg group versus placebo (adjusted mean difference –0.60%; 95% CI, –0.74 to –0.45; *P* < 0.0001). The mean change from baseline in A1C was the primary outcome of Study 18; however, the primary analysis was between triple therapy and the two dual therapy groups, and the two dual therapy groups were not formally compared. The adjusted mean change from baseline to 24 weeks in A1C in the dapagliflozin group was –1.20% (95% CI, –1.35 to –1.04) and in the saxagliptin group was –0.88% (95% CI, –1.03 to –0.72). The proportion of patients achieving a A1C < 7% after 24 weeks, adjusted for baseline A1C, was 22.2% (95% CI, 16.1 to 28.3) in the dapagliflozin group and 18.3% (95% CI, 13.0 to 23.5) in the saxagliptin group.

In Study 4, there was no statistically significant interaction between subgroups based on baseline A1C (< 8%, ≥ 8% to < 9%, or ≥ 9% at baseline). There was a statistically significant (*P* = 0.0055) interaction between subgroups based on baseline estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease, as the improvement in A1C was numerically lower for dapagliflozin than glipizide as patients' renal function declined from normal to mild renal impairment to moderate renal impairment. In the placebo-controlled studies, in patients with a background of metformin, there was no statistically significant interaction among subgroups in Study 14 based on baseline A1C (< 8%, ≥ 8% to < 9% at baseline), and no subgroup analysis was conducted based on eGFR. In patients on a sulfonylurea background (Study 5), there was no statistically significant interaction between subgroups based on baseline A1C; however, there was a statistically significant interaction for subgroups based on eGFR (*P* = 0.0115). The largest difference between dapagliflozin groups and placebo was in patients with normal renal function whereas in patients with mild renal impairment, the differences were smaller. Although the sample size was small (N = 11 in each of the dapagliflozin groups and N = 24 with placebo), there was a notable difference in response based on dose in patients with moderate renal impairment. The difference between dapagliflozin 5 mg and placebo was smaller than the difference between dapagliflozin 10 mg and placebo. Finally, in Study 6, on a background of insulin, there was a statistically significant (*P* = 0.0023) interaction reported in the subgroup based on baseline A1C (7.5% to < 9%, or > 9%). At the lower baseline A1C, the differences between dapagliflozin 5 mg and placebo were smaller than at the higher baseline A1C. No interaction *P* value was reported for the subgroup based on baseline eGFR. There was a similar pattern to that in the other studies of an attenuation in response in patients with progressively worse renal impairment; however, without a reported *P* value, no conclusions can be drawn regarding an interaction. Note that, according to the product monograph, dapagliflozin is contraindicated for use in patients with moderate renal impairment.

In Study 4, dapagliflozin reduced fasting plasma glucose (FPG) to a numerically greater extent than glipizide after 52 weeks; however, this difference was not statistically significant (adjusted mean change versus glipizide –3.6 mg/dL; 95% CI, –8.0 to 0.9; *P* = 0.1159). This difference continued into the extension to 104 weeks, although no statistical analysis was provided. In all studies, regardless of dose studied (dapagliflozin 5 mg or dapagliflozin 10 mg), the reduction in FPG was statistically larger for dapagliflozin than for placebo, whether patients were on a background of metformin, a sulfonylurea, or insulin.

In Study 4, there was a greater reduction in body weight for dapagliflozin versus glipizide after 52 weeks (adjusted mean change versus glipizide –4.65 kg; 95% CI, –5.14 to –4.17; *P* < 0.0001), and this difference was statistically significant. A statistically greater proportion of patients treated with dapagliflozin versus glipizide achieved a reduction in weight of at least 5% from baseline to 52 weeks (adjusted mean difference of change 31%; 95% CI, 26% to 36%; *P* < 0.0001). In all studies, regardless of dose studied (dapagliflozin 5 mg or dapagliflozin 10 mg), the reduction in weight was statistically significantly larger

for dapagliflozin than for placebo, whether patients were on a background of metformin, a sulfonylurea, or insulin.

Systolic blood pressure (SBP) was reduced to a greater extent with dapagliflozin than with glipizide (adjusted mean difference –5.0 mm Hg; 95% CI, –6.7 to –3.4; $P < 0.001$), and this difference was statistically significant. Diastolic blood pressure (DBP) was also reduced to a greater extent with dapagliflozin than with glipizide (adjusted mean difference –1.2 mm Hg; 95% CI, –2.3 to –0.2; $P = 0.0179$), and this difference was statistically significant. In the placebo-controlled studies, statistical analysis for mean change in blood pressure was not reported in all studies. After 24 weeks in Study 12, for patients on a metformin background, there was no difference in change in SBP or DBP between dapagliflozin 10 mg and placebo. In Study 5 (sulfonylurea background), there was a statistically significant reduction in SBP at both dapagliflozin 5 mg and 10 mg doses, but not for DBP at either dose, versus placebo. On an insulin background, the reduction in SBP was greater only at the higher dapagliflozin 10 mg dose versus placebo, and there was no difference in DBP at either of the dapagliflozin doses.

In three network meta-analyses (NMAs) submitted by the manufacturer, dapagliflozin appeared to provide smaller reductions in A1C than other comparators available as second-line therapies in Canada.

Harms

There was a similar proportion of dapagliflozin and glipizide patients (78% in each group) who reported an adverse event (AE) in Study 4. The proportions were also similar in the extension: 88% with dapagliflozin and 87% with glipizide. The most common AE was nasopharyngitis, reported by 11% of dapagliflozin patients and 15% of glipizide patients.

Across the placebo-controlled studies, there was no clear or consistent difference in the proportion of patients with an AE between dapagliflozin and placebo groups, or between dapagliflozin 5 mg and 10 mg groups. The largest difference in proportions was in Study 14 (metformin background), in which 73% of dapagliflozin 10 mg patients and 64% of placebo patients experienced an AE. In the other study with metformin as a background, the proportion of patients in the dapagliflozin 10 mg group with an AE was 43% versus 40% with placebo.

In Study 18, 49% of dapagliflozin patients and 53% of saxagliptin patients reported an AE.

In Study 4, 9% of dapagliflozin patients and 11% of glipizide patients experienced a serious adverse event (SAE), and in the extension study, the proportions were 19% and 20%, respectively. The largest difference in proportion of specific SAEs between dapagliflozin and glipizide involved anemia, which did not occur in any dapagliflozin patients and in 1% of glipizide patients. SAEs of hypoglycemia also occurred in no dapagliflozin patients and in 1% of glipizide patients.

Among the placebo-controlled studies, the largest difference in proportion of patients with an SAE was in Study 12, in which 7% of dapagliflozin 10 mg patients and 1% of placebo patients had an SAE after 24 weeks. This gap narrowed to 18% and 15%, respectively, after 102 weeks in the extension study. In the other studies, there was no more than a 2% difference in proportion of patients with an SAE between dapagliflozin and placebo.

In Study 18, 1% of dapagliflozin patients and 3% of saxagliptin patients had an SAE.

There was no difference between dapagliflozin and glipizide groups with respect to withdrawals due to serious AEs: 2% in each group in the core study and 3% in each group in the extension study. The proportion of patients who withdrew due to an AE was 9% with dapagliflozin and 6% with glipizide in the core study, and 13% versus 11% in the extension study.

Study 12 had the largest difference between dapagliflozin 10 mg and placebo with respect to withdrawals due to AEs or serious AEs (WDAEs or WDSAEs): a total of 5% of dapagliflozin 10 mg patients and no placebo patients, and in the extension study, 15% of dapagliflozin 10 mg patients and 4% of placebo patients. In the other included studies, there was no more than a 2% difference between groups in the proportion of patients who discontinued due to an AE or SAE.

In Study 18, one dapagliflozin patient discontinued due to an AE, and none discontinued in the saxagliptin group.

In Study 4, the proportion of patients experiencing hypoglycemia was one of the study outcomes. There was a lower proportion of patients with an event of hypoglycemia after 52 weeks with dapagliflozin than with glipizide (adjusted mean difference between groups –37%; 95% CI, –42% or –32%; $P < 0.0001$), and this difference was statistically significant. There were numerically more genital infections with dapagliflozin than with glipizide (12% versus 3%) and numerically more urinary tract infections (UTIs) in female patients (14% versus 9%). There were numerically more patients in the dapagliflozin group with events of renal impairment or failure than with glipizide (6% versus 3% of patients). There were no clear differences in risk of other notable harms between dapagliflozin and glipizide.

Across the placebo-controlled studies, the proportion of patients with genital infections was consistently numerically higher with dapagliflozin than with placebo. There were no clear indications of difference in risk based on background therapy, although no statistical analyses were performed and the studies were not powered to carry out such analyses. The risk of hypoglycemia was similar between dapagliflozin groups and placebo in the studies with the metformin background, slightly numerically higher in the study with a sulfonylurea background (Study 5) and in the extension for dapagliflozin 10 mg versus placebo (11% versus 7%), and numerically higher in the study with an insulin background (Study 6) during the core study for dapagliflozin 5 mg versus placebo (45% versus 35%), but there was no difference during the extension. For other notable harms, there were no clear and/or consistent differences between dapagliflozin groups and placebo.

When compared with saxagliptin in Study 18, the only notable harm where there was a numerical difference was genital infection, with a numerically higher proportion of dapagliflozin patients than saxagliptin patients having an event (6% versus 1%).

Some differences in the occurrence of adverse effects were observed in the NMAs submitted by manufacturer. For body weight, dapagliflozin had a statistically significant greater decrease than thiazolidinediones, sulfonylureas (SUs), DPP-4 inhibitors, insulin glargine, meglitinides, and acarbose. For SBP, dapagliflozin had a statistically significant greater decrease than glimepiride and saxagliptin. For hypoglycemia, dapagliflozin had statistically significantly lower risks than SUs, insulin glargine, and nateglinide. For UTIs and genital tract infections risks, dapagliflozin was not statistically significantly different from other antidiabetes drugs approved in Canada.

Conclusions

Six manufacturer-sponsored multinational DB RCTs met the inclusion criteria for this review. All studies enrolled patients who had inadequate glycemic control on current therapies and lifestyle modifications, who were on a background of metformin (four studies), a sulfonylurea (one study), or insulin (one study). One of the studies with metformin background compared triple therapy (dapagliflozin, saxagliptin, and metformin) with dual therapy (dapagliflozin plus metformin or saxagliptin plus metformin); however, due to the study design, no formal comparisons between dapagliflozin and saxagliptin in patients on a metformin background were made. The other active-controlled study with a metformin background, Study 4, found dapagliflozin to be non-inferior to glipizide in reducing A1C after 52 weeks of therapy. The same study found that dapagliflozin elicited statistically significant weight loss and reduction in blood pressure versus glipizide. The reduction in blood pressure is modest and of questionable clinical significance. Dapagliflozin also consistently improved A1C and weight at both approved doses, regardless of whether it was added to metformin, a sulfonylurea, or insulin with or without metformin. The risk of hypoglycemia was lower with dapagliflozin than with glipizide, and this difference was statistically significant. Dapagliflozin was numerically more likely to cause urogenital infections compared with glipizide and with placebo, although the included studies were not powered to assess harms such as these. The incidence of other notable harms was low, with no clear differences in risk between groups.

In a manufacturer-submitted NMA, there were no significant differences in A1C between dapagliflozin and DPP-4 inhibitors as dual therapy with either metformin or a sulfonylurea. However, a published NMA sponsored by the manufacturer of a competitor SGLT-2 inhibitor reported that dapagliflozin added to metformin was associated with statistically lower A1C reduction (by approximately 0.2%) than either canagliflozin or empagliflozin added to metformin.

TABLE 1: KEY EFFICACY OUTCOMES (ADD-ON TO METFORMIN, VERSUS SULFONYLUREA)

	Study 4		Study 4-LT1 (Week 104)	
	Dapa N = 400	**Glipizide N = 401**	**Dapa**	**Glipizide**
Mortality				
Patients, n (%)	0	3 (1)	2	5
Quality of Life (DTSQ Total)	N = 312	N = 303		
Mean (SD) baseline	30.9 (5.41)	31.5 (5.01)		
Adjusted mean (SE) change, week 52	14.3 (0.288)	13.6 (0.292)		
Adjusted mean change vs. glipizide [95% CI]	0.7 [–0.1 to 1.5], *P* = 0.0797			
Blood Glucose (FPG), mmol/L			N = 231	N = 205
Mean (SD) baseline	9.0 (2.1)	9.1 (2.3)		
Adjusted mean (SE) change, week 52[a]	–1.2 (0.1)	–1.0 (0.1)		
Adjusted mean (SE) change, week 104[a]			–1.1 (0.1)	–0.6 (0.1)
Adjusted mean change vs. glipizide [95% CI]	–0.2 [–0.4 to 0.0], *P* = 0.1159		–0.4 [–0.7 to –0.1]	
A1C, %			N = 233	N = 208
Mean (SD) baseline	7.69 (0.86)	7.74 (0.89)		
Adjusted mean (SE) change at week 52[a]	–0.52 (0.0403)	–0.52 (0.0402)		
Adjusted mean (SE) change at week 104[a]			–0.29 (0.0532)	–0.12 (0.0546)
Adjusted mean change vs. glipizide [95% CI]	0.00 [–0.11 to 0.11]		–0.18 [–0.33 to –0.03]	
P value for non-inferiority[b]	Upper confidence limit: 0.11, *P* < 0.0001			

	Study 4		Study 4-LT1 (Week 104)	
	Dapa N = 400	**Glipizide N = 401**	**Dapa**	**Glipizide**
Patients with A1C < 7.0% at week 52[c], n (%)	110 (27.5)	128 (31.9)		
Patients with A1C < 7.0% at week 104 [c], n/N (%)			70/316 (22.2)	65/323 (20.1)
Adjusted mean % (SE) [95% CI]	27.4 (2.231)	32.0 (2.326)	21.8 [17.3 to 26.3]	20.4 [16.1 to 24.7]
Adjusted mean change vs. glipizide [95% CI]	–4.6 [–10.9 to 1.7], *P* = 0.1542		1.4 [–4.7 to 7.6]	
Body Weight, kilograms			N = 234	N = 211
Mean (SD) baseline	88.4 (16.3)	87.6 (17.0)		
Adjusted mean (SE) change at week 52[a]	–3.22 (0.1756)	1.44 (0.1754)		
Adjusted mean (SE) change at week 104[a]			–3.89 (0.2428)	1.18 (0.2498)
Adjusted mean change vs. glipizide [95% CI]	–4.65 [–5.14 to –4.17], *P* < 0.0001		–5.06 [–5.72 to –4.40]	
Blood Pressure (SBP), mm Hg				
Mean (SD) baseline	132.8 (14.9)	133.8 (14.7)	N = 234	N = 211
Adjusted mean [95% CI] change at week 52[a]	–4.3 [–5.4 to –3.1]	0.8 [–0.4 to 1.9]		
Adjusted mean [95% CI] change at week 104[a]			–3.0 [–4.6 to –1.4]	0.9 [–0.8 to 2.6]
Adjusted mean change vs. glipizide [95% CI]	–5.0 [–6.7 to –3.4], *P* < 0.0001		–3.9 [–6.1 to –1.7]	
Blood Pressure (DBP), mm Hg				
Mean (SD) baseline	80.6 (8.4)	80.6 (8.5)	N = 234	N = 211
Adjusted mean [95%CI] change at week 52[a]	–1.6 [–2.3 to –0.9]	–0.4 [–1.1 to 0.3]		
Adjusted mean [95%CI] change at week 104[a]			–2.0 [–3.0 to –1.0]	–1.6 [–2.5 to –0.6]
Adjusted mean change vs. glipizide [95% CI]	–1.2 [–2.3 to –0.2], *P* = 0.0179		–0.5 [–1.8 to 0.9]	
SAEs				
Subjects with > 0 SAEs, N (%)	35 (9)	46 (11)	75 (19)	81 (20)
Notable Harms, n (%)				
Hypoglycemia	14 (4)	162 (40)	22 (5)	210 (52)
Genital infection	50 (12)	11 (3)	66 (16)	17 (4)
UTI female, n/N (%)	26/180 (14)	17/185 (9)	40/180 (22)	28/185 (15)

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; DBP = diastolic blood pressure; DTSQ = Diabetes Treatment Satisfaction Questionnaire; FPG = fasting plasma glucose; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; UTI = urinary tract infection; vs. = versus.

[a] Analysis of continuous outcomes based on separate analysis of covariance (ANCOVA) models with treatment group as effect and baseline value as a covariate for each end point.

[b] Primary end point is significantly (alpha = 0.025 one-sided) non-inferior if upper limit of 95% CI is < 0.35%.

[c] Logistic regression based on the methodology of Zhang, Tsiatis, and Davidian, and of Tsiatis, Davidian, Zhang, and Lu, with adjustment for baseline value. In case of less than 5 events per treatment group on average, the exact method is used.

Source: Clinical Study Report for Study 4.[1]

TABLE 2: KEY EFFICACY OUTCOMES (ADD-ON TO METFORMIN, VERSUS PLACEBO)

	Study 14			Study 14 (Extension to Week 102)		
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**	**Dapa 5 mg**	**Dapa 10 mg**	**Placebo**
Mortality						
Patients, n	0	0	0	0	0	1
Blood Glucose (FPG), mmol/L				N = 45	N = 53	N = 25
Mean (SD) baseline	9.4 (2.7)	8.7 (2.1)	9.2 (2.6)			
Adjusted mean (SE) change, week 24[a]	–1.2 (0.1)	–1.3 (0.2)	–0.3 (0.1)			
Adjusted mean (SE) change, week 102[a]				–1.5 (0.2)	–1.4 (0.1)	–0.6 (0.2)
Adjusted mean change vs. placebo [95% CI][b]	**5 mg:** –0.9 [–1.3 to –0.4], *P* < 0.0001 **10 mg:** –1.0 [–1.4 to –0.6], *P* < 0.0001			**5 mg:** –0.9 [–1.4 to –0.4] **10 mg:** –0.8 [–1.3 to –0.3]		
A1C, %				N = 47	N = 57	N = 28
Mean (SD) baseline	8.17 (0.96)	7.92 (0.82)	8.11 (0.96)			
Adjusted mean (SE) change at week 24	–0.70 (0.07)	–0.84 (–0.07)	–0.30 (–0.07)			
Adjusted mean (SE) change at week 102				–0.58 (0.10)	–0.78 (0.09)	0.02 (0.11)
Adjusted mean change vs. placebo [95% CI][a b]	**5 mg:** –0.41 [–0.61 to –0.21], *P* < 0.0001 **10 mg:** –0.54 [–0.74 to –0.34], *P* < 0.0001			**5 mg:** –0.60 [–0.89 to –0.31] **10 mg:** –0.80 [–1.08 to –0.52]		
Patients with A1C < 7.0% at week 24, adjusted[a] for baseline A1C, % [95% CI]	37.5 (30.0 to 45.1)	40.6 (32.9 to 48.3)	25.9 (19.1 to 32.6)			
Patients with A1C < 7.0% at week 24, adjusted[a] for baseline A1C, % [95% CI]				26.4[c] [19.4 to 33.4]	31.5[c] [23.7 to 39.3]	15.4[c] [9.5 to 21.3]
Difference [95% CI] versus placebo, %	**5 mg:** 11.7 [1.3 to 22.1], *P* = 0.0275 **10 mg:** 14.7 [4.2 to 25.3], *P* = 0.0062			**5 mg:** 11.0 [1.7 to 20.2] **10 mg:** 16.1 [6.2 to 25.9]		
Body Weight, kilograms				N = 90	N = 95	N = 73
Mean (SD) baseline	84.7 (16.3)	86.3 (17.5)	87.7 (19.2)			
Adjusted mean (SE) change at week 24[a]	–3.04 (0.24)	–2.86 (0.24)	–0.89 (0.24)			
Adjusted mean (SE) change at week 102[a]				–1.70 (0.40)	–1.74 (0.39)	1.36 (0.42)
Adjusted mean change versus placebo [95% CI]	**5 mg:** –2.16 [–2.81 to –1.50], *P* < 0.0001 **10 mg:** –1.97 [–2.63 to –1.31], *P* < 0.0001			**5 mg:** –3.06 [–4.21 to –1.92] **10 mg:** –3.10 [–4.24 to –1.96]		
Blood Pressure (SBP), mm Hg						
Mean (SD) baseline	126.9 (14.3)	126.0 (15.9)	127.7 (14.6)			
Mean (SE) change at week 24	–4.3 (1.3)	–5.1 (1.3)	–0.2 (1.2)	NR	NR	NR
Adjusted mean change versus placebo [95% CI]	NR	NR	NR	NR	NR	NR
Blood Pressure (DBP), mm Hg						
Mean (SE) baseline	80.8 (8.5)	79.0 (10.2)	80.9 (9.0)			
Mean (SE) change at week 24	–2.5 (0.8)	–1.8 (0.8)	–0.1 (0.7)	NR	NR	NR
Adjusted mean change versus placebo [95% CI]	NR	NR	NR	NR	NR	NR

	Study 14			Study 14 (Extension to Week 102)		
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**	**Dapa 5 mg**	**Dapa 10 mg**	**Placebo**
SAEs						
Subjects with > 0 SAEs, N (%)	4 (3)	4 (3)	5 (4)	9 (7)	14 (10)	14 (10)
Notable Harms						
Hypoglycemia	5 (4)	5 (4)	4 (3)	7 (5)	7 (5)	8 (6)
Genital infection	18 (13)	12 (9)	7 (5)	20 (15)	17 (13)	7 (5)
UTI female	6 (9)	9 (16)	5 (8)	7 (10)	13 (22)	5 (8)

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; DBP = diastolic blood pressure; FPG = fasting plasma glucose; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; UTI = urinary tract infection; vs. = versus.

[a] Analysis of covariance (ANCOVA) model with treatment group as an effect and baseline value as a covariate.

[b] The primary end point is tested at alpha = 0.019, applying the Dunnett adjustment. The primary analysis excluded data after rescue for all outcomes.

[c] Percentages in the extension used the original intention-to-treat set in the denominator.

Source: Clinical Study Report for Study 14.[2]

TABLE 3: KEY EFFICACY OUTCOMES (ADD-ON TO METFORMIN, VERSUS PLACEBO)

	Study 12		Study 12 (Extension to Week 102)	
	Dapa 10 mg N = 89	**Placebo N = 91**	**Dapa 10 mg N = 89**	**Placebo N = 91**
Mortality				
Patients, n	1 (1)	0	No additional deaths	
Quality of Life (EQ-5D)			N = 68	N = 70
VAS scores, mean (SD) baseline	72.8 (19.39)	73.7 (15.49)		
Adjusted mean (SE) change, week 24[a]	4.2 (1.216)	4.8 (1.200)		
Adjusted mean (SE) change, week 102[a]			6.7 (1.461)	5.4 (1.349)
Adjusted mean change vs. placebo [95% CI]	–0.6 [–3.9 to 2.8], *P* = 0.7449		1.2 [–2.6 to 5.0]	
Index scores, mean (SD) baseline	0.85 (0.163)	0.82 (0.154)		
Adjusted mean (SE) change, week 24[a]	0.03 (0.014)	0.04 (0.014)		
Adjusted mean (SE) change, week 102[a]			0.00 (0.019)	0.01 (0.018)
Adjusted mean change vs. placebo [95% CI]	–0.01 [–0.05 to 0.03], *P* = 0.4929		–0.01 [–0.06 to 0.04]	
Blood Glucose (FPG), mmol/L			N = 58	N = 49
Mean (SD) baseline	8.2 (1.4)	8.3 (1.4)		
Adjusted mean (SE) change, week 24	–0.8 (0.1)	0.1 (0.1)		
Adjusted mean (SE) change, week 102			–1.0 (0.1)	0.0 (0.1)
Adjusted mean change vs. placebo [95% CI]	–0.9 [–1.3 to –0.6], *P* < 0.0001		–0.9 [–1.3 to –0.6]	
A1C, %			N = 60	N = 49
Mean (SD) baseline	7.19 (0.444)	7.16 (0.531)		
Adjusted mean (SE) change at week 24[a]	–0.39 (0.049)	–0.10 (0.048)		
Adjusted mean (SE) change, week 102[a]			–0.30 (0.069)	0.12(0.072)
Adjusted mean change vs. placebo [95% CI]	–0.28 [–0.42 to –0.15], *P* < 0.0001		–0.42 [–0.62 to –0.22)	
Patients with A1C < 7.0% at week 24, % (SE)	63.3 (4.99)	47.1 (4.73)		
Patients with A1C < 7.0% at week 102, % (SE)			50.0[c] (5.23)	33.4[c] (4.84)
Difference [95% CI] vs. placebo, % [95% CI]	16.1% [3.3 to 29.0]		16.5% [2.8 to 30.2]	

	Study 12		Study 12 (Extension to Week 102)	
	Dapa 10 mg N = 89	**Placebo N = 91**	**Dapa 10 mg N = 89**	**Placebo N = 91**
Body Weight, kilograms			N = 69	N = 71
Mean (SD) baseline	92.06 (14.13)	90.91 (13.72)		
Adjusted mean (SE) change at week 24[b]	–2.96 (0.2766)	–0.88 (0.2746)		
Adjusted mean (SE) change at week 102[a]			–4.54 (0.45)	–2.12 (0.43)
Adjusted mean change versus placebo [95% CI]	–2.08 [–2.84 to –1.31], *P* < 0.0001		–2.42 [–3.64 to –1.21]	
Blood Pressure (SBP), mm Hg			N = 69	N = 71
Mean (SD) baseline	135.9 (13.92)	133.3 (13.66)		
Adjusted mean (SE) change at week 24[a]	–2.7 (1.088)	0.1 (1.071)		
Adjusted mean (SE) change at week 102[a]			–2.0 (1.307)	0.2 (1.233)
Adjusted mean change vs. placebo [95% CI]	–2.8 [–5.9 to 0.2], *P* = 0.0637		–2.3 [–5.7 to 1.2]	
Blood Pressure (DBP), mm Hg			N = 69	N = 71
Mean (SE) baseline	80.6 (8.09)	80.4 (8.25)		
Adjusted mean (SE) change at week 24[a]	–0.7 (0.720)	0.3 (0.709)		
Adjusted mean (SE) change at week 102[a]			–2.8 (0.720)	0.3 (0.671)
Adjusted mean change vs. placebo [95% CI]	–1.0 [–2.9 to 1.0], *P* = 0.3458		–3.0 [–4.9 to –1.1]	
SAEs				
Subjects with > 0 SAEs, N (%)	6 (7)	1 (1)	16 (18)	14 (15)
Notable Harms				
Hypoglycemia	2 (2)	3 (3)	4 (4)	5 (6)
Genital infection	3 (3)	0	3 (3)	2 (2)
UTI female	5	2	4	6

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; DBP = diastolic blood pressure; EQ-5 = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; FPG = fasting plasma glucose; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; UTI = urinary tract infection; VAS = visual analogue scale; vs. = versus.

[a] Analysis of continuous outcomes based on separate analysis of covariance (ANCOVA) models with treatment group and stratum as effect and baseline value as a covariate for each end point.

[b] Primary outcome. Logistic regression based on the methodology of Zhang, Tsiatis, and Davidian, and of Tsiatis, Davidian, Zhang, and Lu, with adjustment for baseline total body weight and stratum. In case of less than five events per treatment group on average, the exact method is used. The primary analysis for the primary outcome included data after rescue therapy, while the secondary outcomes change in A1C and FPG excluded data after rescue, and SBP/DBP and EQ-5D included data after rescue.

[c] Percentages in the extension used the original intention-to-treat set in the denominator.

Source: Clinical Study Report for Study 12.[3]

TABLE 4: KEY EFFICACY OUTCOMES (ADD-ON TO SULFONYLUREA, VERSUS PLACEBO)

	Study 5			Study 5 (Extension to Week 48)		
	Dapa 5 mg N = 142	**Dapa 10 mg N = 151**	**Placebo N = 145**	**Dapa 5 mg N = 142**	**Dapa 10 mg N = 151**	**Placebo N = 145**
Mortality						
Patients, n	0	1	0	No additional deaths		
Blood Glucose (FPG), mmol/L				N = 90	N = 107	N = 55
Mean (SE) baseline	9.7 (2.1)	9.6 (2.0)	9.6 (2.1)			

	Study 5			Study 5 (Extension to Week 48)		
	Dapa 5 mg N = 142	**Dapa 10 mg N = 151**	**Placebo N = 145**	**Dapa 5 mg N = 142**	**Dapa 10 mg N = 151**	**Placebo N = 145**
Adjusted mean (SE) change, week 24[a]	–1.2 (0.1)	–1.6 (0.1)	–0.1 (0.1)			
Adjusted mean (SE) change, week 48[a]				–0.9 (0.2)	–1.6 (0.2)	0.1 (0.2)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –1.1 [–1.5 to –0.7], *P* < 0.0001 **10 mg:** –1.5 [–1.9 to –1.1], *P* < 0.0001			**5 mg:** –1.1 [–1.6 to –0.5] **10 mg:** –1.7 [–2.2 to –1.2]		
Quality of Life (DTSQ Total)				N = 90	N = 105	N = 55
Mean (SD) baseline	27.4 (5.9)	27.6 (6.4)	28.3 (7.1)			
Adjusted mean (SE) change, week 24[a]	2.7 (0.4)	3.2 (0.4)	2.6 (0.5)			
Adjusted mean (SD) change, week 48[a]				4.6 (6.5)	4.4 (6.9)	2.2 (6.3)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** 0.1 [–1.1 to 1.3], *P* = 0.8695 **10 mg:** 0.6 [–0.6 to 1.8], *P* = 0.3575			NR		
A1C, %				N = 90	N = 107	N = 55
Mean (SD) baseline	8.12 (0.78)	8.07 (0.79)	8.15 (0.74)			
Adjusted mean (SE) change at week 24[a]	−0.63 (0.06)	−0.82 (0.06)	−0.13 (0.06)			
Adjusted mean (SE) change at week 48[a]				–0.56 (0.08)	–0.73 (0.07)	–0.04 (0.09)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** −0.49 [−0.67 to −0.32], *P* < 0.0001 **10 mg:** −0.68 [−0.86 to −0.51], *P* < 0.0001			**5 mg:** –0.53 [–0.75 to –0.30] **10 mg:** –0.70 [–0.92 to –0.47]		
Body Weight, kilograms				N = 90	N = 107	N = 55
Mean (SD) baseline	81.0 (18.6)	80.6 (17.9)	80.9 (15.8)			
Adjusted mean (SE) change at week 24[a]	–1.56 (0.23)	–2.26 (0.22)	–0.72 (0.23)			
Adjusted mean (SE) change at week 48[a]				–1.54 (0.29)	–2.41 (0.28)	–0.77 (0.33)
Adjusted mean change versus placebo [95% CI]	**5 mg:** –0.84 [–1.47 to –0.21], *P* = 0.0091 **10 mg:** –1.54 [–2.17 to –0.92], *P* < 0.0001			**5 mg:** –0.76 [–1.63 to 0.11] **10 mg:** –1.64 [–2.48 to –0.79]		
Blood Pressure (SBP), mm Hg				N = 90	N = 107	N = 55
Mean (SD) baseline	130.9 (15.1)	132.4 (13.7)	133.3 (13.9)			
Adjusted mean (SE) change at week 24[a]	–4.0 (0.96)	–5.0 (0.93)	–1.2 (0.95)			
Adjusted mean (SE) change at week 48[a]				–3.0 (1.21)	–4.2 (1.12)	1.81 (1.51)
Adjusted mean change versus placebo [95% CI]	**5 mg:** –2.8 [–5.5 to –0.2], *P* = 0.0352 **10 mg:** –3.8 [–6.4 to –1.2], *P* = 0.0047			**5 mg:** –4.81 [–8.62 to –1.01] **10 mg:** –6.02 [–9.71 to –2.32]		
Blood Pressure (DBP), mm Hg				N = 90	N = 107	N = 55
Mean (SD) baseline	77.9 (8.5)	78.7 (8.2)	79.8 (7.8)			
Adjusted mean (SE) change at week	–1.7 (0.60)	–2.8 (0.59)	–1.4 (0.60)			

	Study 5			Study 5 (Extension to Week 48)		
	Dapa 5 mg N = 142	**Dapa 10 mg N = 151**	**Placebo N = 145**	**Dapa 5 mg N = 142**	**Dapa 10 mg N = 151**	**Placebo N = 145**
24[a]						
Adjusted mean (SE) change at week 48[a]				–1.41 (0.77)	–2.15 (0.71)	0.79 (0.96)
Adjusted mean change versus placebo [95% CI]	**5 mg:** –0.3 [–1.9 to 1.4], *P* = 0.7478 **10 mg:** –1.4 [–3.0 to 0.3], *P* = 0.0993			**5 mg:** –2.20 [–4.62 to 0.22] **10 mg:** –2.94 [–5.29 to –0.59]		
SAEs						
Subjects with > 0 SAEs, N (%)	10 (7)	9 (6)	7 (5)	16 (11)	13 (9)	13 (9)
Notable Harms						
Hypoglycemia	10 (7)	12 (8)	7 (5)	15 (10)	17 (11)	10 (7)
Genital infection	9 (6)	10 (7)	1 (1)	9 (6)	13 (9)	2 (1)
UTI female	6	6	9	7	8	10

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; DBP = diastolic blood pressure; DTSQ = Diabetes Treatment Satisfaction Questionnaire; FPG = fasting plasma glucose; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; UTI = urinary tract infection; vs. = versus.

[a] Primary end point is tested at alpha = 0.019 applying the Dunnett adjustment, and secondary end points are tested following a sequential testing procedure at alpha = 0.05. Logistic regression analysis of responses are based on the methodology of Zhang, Tsiatis, and Davidian, and of Tsiatis, Davidian, Zhang, and Lu, with adjustment for baseline value. In case of less than 5 events per treatment group on average, the exact method is used. Analysis of continuous outcomes based on separate analysis of covariance (ANCOVA) models with treatment group as an effect and baseline value as a covariate for each end point. All primary analyses of efficacy outcomes were carried out excluding data after rescue.

Source: Clinical Study Report for Study 5.[4]

TABLE 5: KEY EFFICACY OUTCOMES (ADD-ON TO INSULIN, VERSUS PLACEBO)

	Study 6			Study 6 (Extension to Week 104)		
	Dapa 5 mg N = 211	**Dapa 10 mg N = 194**	**Placebo N = 193**	**Dapa 5/10 mg**	**Dapa 10 mg**	**Placebo**
Mortality						
Patients, n (%)	1 (< 1)	0	0	2 (1)	1 (1)	0
Blood Glucose (FPG), mmol/L				N = 87	N = 96	N = 48
Mean (SE) baseline	10.3 (3.3)	9.6 (3.0)	9.4 (3.2)			
Adjusted mean (SE) change, week 24[a]	–1.0 (0.2)	–1.2 (0.2)	0.2 (0.2)			
Adjusted mean (SE) change, week 104[a]				–1.7 (0.2)	–1.0 (0.2)	–0.6 (0.3)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –1.2 [–1.7 to –0.7], *P* < 0.0001 **10 mg:** –1.1 [–1.8 to –0.4], *P* < 0.0001			**5 mg:** –1.1 [–1.8 to –0.4] **10 mg:** –0.4 [–1.1 to 0.3]		
A1C, %				N = 89	N = 100	N = 50
Mean (SD) baseline	8.61 (0.89)	8.58 (0.82)	8.46 (0.76)			
Adjusted mean (SE) change at week 24[a]	–0.82 (0.05)	–0.90 (0.05)	–0.30 (0.05)			
Adjusted mean (SE) change at week 104[a]				–0.71 (0.08)	–0.71 (0.08)	–0.06 (0.10)
Adjusted mean change vs. placebo [95% CI] [a]	**5 mg:** –0.52 [–0.66 to –0.38], *P* < 0.0001 **10 mg:** –0.60 [–0.74 to –0.45], *P* < 0.0001			**5 mg:** –0.65 [–0.90 to –0.41] **10 mg:** –0.65 [–0.90 to –0.41]		

	Study 6			Study 6 (Extension to Week 104)		
	Dapa 5 mg N = 211	**Dapa 10 mg N = 194**	**Placebo N = 193**	**Dapa 5/10 mg**	**Dapa 10 mg**	**Placebo**
% patients achieving A1C < 7% adjusted for baseline A1C [95% CI]	19.8 (14.8 to 24.9)	21.5 (16.0 to 27.1)	8.7 (4.7 to 12.8)			
% patients achieving A1C < 7% adjusted for baseline A1C [95% CI]				11.3[b] (7.3 to 15.4)	6.9[b] (3.4 to 10.4)	4.6[b] (1.6 to 7.5)
Difference [95% CI] vs. placebo, %	**5 mg:** 11.1% [4.6 to 17.6], *P* = 0.0009 **10 mg:** 12.8% [5.9 to 19.8], *P* = 0.0003			**5 mg:** 6.8% [1.7 to 11.8] **10 mg:** 2.3% [–2.3 to 6.9]		
Body Weight, kilograms				N = 128	N = 141	N = 107
Mean (SD) baseline	93.2 (17.4)	94.6 (16.8)	94.2 (19.5)			
Adjusted mean (SE) change at week 24[a]	–0.98 (0.17)	–1.67 (0.18)	0.02 (0.18)			
Adjusted mean (SE) change at week 104[a]				–0.95 (0.37)	–1.40 (0.36)	1.79 (0.39)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –1.00 [–1.50 to –0.50], *P* < 0.0001 **10 mg:** –1.68 [–2.19 to –1.18], *P* < 0.0001			**5 mg:** –2.74 [–3.80 to –1.69] **10 mg:** –3.19 [–4.24 to –2.14]		
Blood Pressure (SBP), mm Hg				N = 128	N = 140	N = 103
Mean (SD) baseline	137.8 (16.2)	140.6 (16.7)	136.1 (17.2)			
Adjusted mean (SE) change at week 24[a]	–6.0 (0.87)	–6.9 (0.91)	–3.9 (0.93)			
Adjusted mean (SE) change at week 104[a]				–4.5 (1.10)	–6.4 (1.08)	–2.44 (1.21)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –2.1 [–4.6 to 0.4], *P* = 0.0962 **10 mg:** –3.0 [–5.5 to –0.4], *P* = 0.0228			**5 mg:** –2.07 [–5.29 to 1.14] **10 mg:** –3.98 [–7.18 to –0.78]		
Blood Pressure (DBP), mm Hg				N = 128	N = 140	N = 103
Mean (SD) baseline	81.1 (8.9)	79.9 (9.3)	80.0 (9.6)			
Adjusted mean (SE) change at week 24[a]	–2.8 (0.50)	–3.0 (0.52)	–1.9 (0.53)			
Adjusted mean (SE) change at week 104[a]				–2.6 (0.64)	–3.9 (0.63)	–1.90 (0.70)
Adjusted mean change vs. placebo [95% CI][f]	**5 mg:** –0.9 [–2.3 to 0.6], *P* = 0.2356 **10 mg:** –1.1 [–2.5 to 0.4], *P* = 0.1489			**5 mg:** –0.74 [–2.61 to 1.13] **10 mg:** –2.04 [–3.88 to –0.19]		
SAEs						
Subjects with > 0 SAEs, N (%)	10 (5)	14 (7)	14 (7)	32 (15)	36 (18)	39 (20)
Notable Harms						
Hypoglycemia	96 (45)	83 (42)	69 (35)	130 (61)	119 (61)	122 (62)
Genital infection	16 (8)	18 (9)	4 (2)	27 (13)	28 (14)	6 (3)
UTI female	15/112(13)	14/108(13)	6/99 (6)	21/112(19)	21/108(19)	7/99 (7)

A1C = glycated hemoglobin; CI = confidence interval; DBP = diastolic blood pressure; FPG = fasting plasma glucose; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; UTI = urinary tract infection; vs. = versus.

[a] Primary end point is tested at alpha = 0.019 applying the Dunnett adjustment, and secondary end points are tested following a sequential testing procedure at alpha = 0.05. Logistic regression analysis of responses are based on the methodology of Zhang, Tsiatis, and Davidian, and of Tsiatis, Davidian, Zhang, and Lu, with adjustment for baseline value and stratum. In case of less than 5 events per treatment group on average, the exact method is used. Analysis of continuous outcomes based on separate analysis of covariance (ANCOVA) models with treatment group and stratum as effect and baseline value as a covariate for each end point. The primary analyses for all efficacy outcomes excluded data after insulin up-titration.

[b] Percentages in the extension used the original intention-to-treat set in the denominator.

Source: Clinical Study Report (CSR) for Study 6.[5]

TABLE 6: KEY EFFICACY OUTCOMES (ADD-ON TO METFORMIN, TRIPLE THERAPY VERSUS DUAL THERAPY)

	Study 18		
	Dapa/Saxa N = 179	**Dapa N = 179**	**Saxa N = 176**
Mortality			
Patients, n	0	0	0
Blood Glucose (FPG), mmol/L			
Mean (SD) baseline	10.0 (2.5)	10.3 (2.6)	10.7 (2.5)
Adjusted mean [95% CI] change, week 24	–2.1 [–2.4 to –1.8]	–1.8 [–2.1 to –1.5]	–0.8 [–1.1 to –0.5]
Adjusted mean change, Dapa vs. Saxa [95% CI]	Not evaluated		
A1C, %			
Mean (SD) baseline	8.93 (1.19)	8.87 (1.17)	9.03 (1.05)
Adjusted mean [95% CI] change at week 24	–1.47 [–1.62 to –1.31]	–1.20 [–1.35 to –1.04]	–0.88 [–1.03 to –0.72]
Adjusted mean change, Dapa vs. Saxa [95% CI]	Not evaluated		
Patients with A1C < 7.0% at week 24, adjusted for baseline A1C, % [95% CI]	41.4 [34.5 to 48.2]	22.2 [16.1 to 28.3]	18.3 [13.0 to 23.5]
Difference [95% CI], Dapa vs. Saxa, %	Not evaluated		
Body Weight, kilograms			
Mean (SD) baseline	87.1 (18.0)	86.3 (18.6)	88.0 (18.7)
Adjusted mean [95% CI] change at week 24	–2.1 [–2.5 to –1.6]	–2.4 [–2.9 to –1.9]	0 [–0.5 to 0.5]
Adjusted mean change, Dapa vs. Saxa [95% CI]	Not evaluated		
SAEs			
Subjects with > 0 SAEs, N (%)	2 (1)	2 (1)	6 (3)
Notable Harms			
Hypoglycemia	2 (1)	2 (1)	2 (1)
Genital infection	0	10 (6)	1 (1)
UTI	1 (1)	7 (5)	9 (5)

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; FPG = fasting plasma glucose; SAE = serious adverse event; Saxa = saxagliptin; SD = standard deviation; UTI = urinary tract infection; vs. = versus.
Source: Clinical Study Report for Study 18.[6]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Diabetes is a metabolic disease characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels, on both a microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral artery disease, cardiovascular disease) level. There are two main subtypes of diabetes: type 1, in which the primary problem is a lack of adequate insulin secretion from pancreatic beta cells, and type 2, in which cells are unresponsive to insulin. Type 2 diabetes is more common than type 1 diabetes, accounting for approximately 90% of all cases.[7] The etiology of type 1 diabetes is unknown, although onset is typically early in life. In contrast, onset of type 2 diabetes is typically later in life, although this is changing with the current epidemic of childhood obesity in Western societies. Poor diet and minimal exercise, and associated weight gain, are considered to be risk factors for type 2 diabetes.[8] There is overlap between the two types; most notably, patients with type 2 diabetes, who in the initial stages of their disease can secrete insulin, or may be hyperinsulinemic, progress to a stage where insulin secretion is reduced, similar to type 1 diabetes.

Diabetes is a chronic, metabolic disease with significant health impacts on individuals and societies. The incidence of diabetes is increasing at a dramatic rate around the world. The International Diabetes Federation estimated that 371 million people had diabetes in 2012, and this figure is expected to increase to 552 million by 2030.[9] The prevalence of diabetes in Canada was 6.8% (2.4 million Canadians) in 2009 and is expected to rise to 3.7 million people by 2019.[10] People with diabetes are more likely to be hospitalized and to experience complications requiring specialist care. By 2020, the diabetes-associated costs to the Canadian health care system will be an estimated $16.9 billion per year.[11]

1.2 Standards of Therapy

There are many classes of antidiabetes drugs used in treating type 2 diabetes, including insulin. Those most commonly used in Canada are metformin, sulfonylureas, and incretins, with metformin widely considered the first-line drug of choice. Other drug classes include thiazolidinediones, which have had considerable safety issues, prescribing restrictions, and market withdrawals since their arrival on the market in the 1990s; meglitinides, which act in a manner similar to the sulfonylureas; and alpha-glucosidase inhibitors, which have a simple mechanism (block glucose absorption) and are typically used in combination with other agents. Insulin and insulin analogues can be used in rapid-acting, intermediate, or longer-acting forms, and are all administered by injection.

1.3 Drug

Dapagliflozin is a sodium glucose cotransporter (SGLT)-2 inhibitor; by inhibiting the glucose transporter in the kidney, it increases the excretion of glucose, resulting in an antihyperglycemic effect. A secondary effect of increased glucose in the urine is an osmotic diuresis, which may also lower blood pressure, with systolic blood pressure (SBP) lowered to a greater extent than diastolic blood pressure (DBP). The increased excretion of glucose also leads to a loss of calories, and a reduction in body weight. Dapagliflozin is administered orally, once daily, at an initial dose of 5 mg, with an increase to 10 mg once daily recommended if glycemic control not achieved. Other SGLT-2 inhibitors approved in Canada are empagliflozin and canagliflozin.

Dapagliflozin is indicated for use in patients with type 2 diabetes mellitus to improve glycemic control in combination with:

- Metformin, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control
- A sulfonylurea, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control
- Insulin (alone or with metformin), when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

Indication under review
For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with: • Metformin, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control • A sulfonylurea, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control • Insulin (alone or with metformin), when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.
Listing criteria requested by sponsor
For use in patients with type 2 diabetes mellitus to improve glycemic control when: • Added on to metformin for patients with inadequate glycemic control on metformin, when a sulfonylurea is contraindicated, not tolerated or ineffective and for whom insulin is not an option • Added on to sulfonylurea for patients with inadequate glycemic control on sulfonylurea, when metformin is contraindicated, not tolerated or ineffective and for whom insulin is not an option • Added on to insulin (alone or with metformin) for patients with inadequate glycemic control on insulin (alone or with metformin), when a sulfonylurea is contraindicated, not tolerated or ineffective.

TABLE 7: KEY CHARACTERISTICS OF METFORMIN, SULFONYLUREAS, DPP-4 INHIBITORS, GLP-1 ANALOGUES, THIAZOLIDINEDIONES, AND INSULIN

	SGLT-2 Inhibitors	Biguanides (Metformin)	Sulfonylureas
Mechanism of Action	Inhibits the SGLT-2 transporter in the kidney, leading to increased glucose excretion	Reduces gluconeogenesis Increases conversion of glucose to glycogen Increases degradation of glucose	Promotes insulin secretion by binding to the sulfonylurea receptor (SUR-1)
Indication[a]	Canagliflozin In type 2 diabetes: • As monotherapy in patients for whom metformin is inappropriate • In combination with metformin or a sulfonylurea when diet and exercise plus monotherapy with one of these agents does not provide adequate glycemic control • In combination with metformin and either a sulfonylurea or	Type 2 diabetes that cannot be controlled by proper dietary management, exercise, and weight reduction, or when insulin therapy is not appropriate Treatment of obese patients with diabetes	Type 2 diabetes in adults, alone or in combination with other antihyperglycemic agents as an adjunct to exercise and diet

	SGLT-2 Inhibitors	Biguanides (Metformin)	Sulfonylureas
	pioglitazone when diet, exercise, and dual therapy (with metformin plus either a sulfonylurea or pioglitazone) does not provide adequate glycemic control • In combination with insulin (with or without metformin) when diet and exercise, and therapy with insulin (with or without metformin) do not provide adequate glycemic control		
Route of Administration	Oral	Oral	Oral
Recommended Dose	100 mg to 300 mg once daily	850 mg to 1,000 mg twice daily	Varies by drug
Serious Side Effects / Safety Issues	Contraindications: Renally impaired patients with eGFR less than 45 mL/min/1.73 m^2, end stage renal disease or patients on dialysis Warnings and precautions: • reduced intravascular volume • hypoglycemia when combined with antihyperglycemics • increase in LDL-C • hyperkalemia • impaired renal function	Contraindications: • acute or chronic metabolic acidosis including diabetic ketoacidosis • severe renal impairment • Warnings: • lactic acidosis (rare)	Contraindications: • ketoacidosis • severe liver or renal impairment • Precautions: • hypoglycemia

DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; LDL-C = low-density lipoprotein cholesterol; SGLT = sodium glucose cotransporter.
[a] Health Canada indication.
Source: Product monographs from the electronic edition of the *Compendium of Pharmaceuticals and Specialties* (e-CPS).[12]

TABLE 8: KEY CHARACTERISTICS OF DPP-4 INHIBITORS, GLP-1 ANALOGUES, THIAZOLIDINEDIONES, AND INSULIN

	GLP-1 Analogues	Thiazolidinediones (Pioglitazone)	DPP-4 Inhibitors	Insulin/Insulin Analogues
Mechanism of Action	Stimulates GLP-1, which: • leads to insulin secretion • inhibits glucagon release • delays gastric emptying • reduces food intake	PPAR-gamma agonists: • increase uptake of FFA • increase uptake of glucose • reduce glucose synthesis	Increase GLP-1 by inhibiting the DPP-4 enzyme, which inactivates GLP-1 and: • leads to insulin secretion • inhibits glucagon release • delays gastric emptying • reduces food intake	Substitute for endogenously secreted insulin
Indication[a]	Liraglutide: Type 2 diabetes in combination with metformin or metformin and a	Type 2 diabetes that cannot be adequately controlled by diet and exercise alone. May be used as monotherapy	Saxagliptin: Type 2 diabetes in combination with metformin or a sulfonylurea, or insulin	Patients with diabetes who require insulin for control of hyperglycemia

	GLP-1 Analogues	Thiazolidinediones (Pioglitazone)	DPP-4 Inhibitors	Insulin/Insulin Analogues
	sulfonylurea, when these drugs, with diet and exercise, do not provide adequate glycemic control Type 2 diabetes in combination with metformin and a basal insulin, when liraglutide and metformin, with diet and exercise, do not provide adequate glycemic control	or in combination with a sulfonylurea or metformin when monotherapy fails to adequately control blood glucose	(with or without metformin) or metformin and a sulfonylurea, when these drugs used alone, with diet and exercise, do not provide adequate glycemic control Sitagliptin: Type 2 diabetes as monotherapy, or in combination with metformin or a sulfonylurea and metformin, or insulin (with or without metformin) or pioglitazone, or metformin and pioglitazone, when these drugs, with diet and exercise, do not provide adequate glycemic control Linagliptin: Type 2 diabetes as monotherapy or in combination with metformin or a sulfonylurea, or metformin and a sulfonylurea, when these drugs, with diet and exercise, do not provide adequate glycemic control	
Route of Administration	Subcutaneous	Oral	Oral	Subcutaneous
Recommended Dose	1.2 to 1.8 mg once daily	15 to 30 mg once daily	Varies by drug	Titrated
Serious Side Effects / Safety Issues	Warnings/precautions: • thyroid cancer • prolonged PR interval • hypoglycemia (when combined with sulfonylurea) • pancreatitis	Serious warnings: • bone fractures in women • fluid retention • Warnings and precautions: • bladder cancer • heart failure • hepatitis/hepatic failure	Contraindications: • diabetic ketoacidosis • Warnings/precautions: • heart failure • pancreatitis • immune suppression	Serious warnings and precautions: • hypoglycemia • immune responses

DPP-4 = dipeptidyl peptidase-4; FFA = free fatty acids; GLP-1 = glucagon-like peptide 1; PPAR = peroxisome proliferator-activated receptor.

[a] Health Canada indication.

Source: Product monographs from the electronic edition of the *Compendium of Pharmaceuticals and Specialties* (e-CPS).[12]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of dapagliflozin for the treatment of adults with type 2 diabetes mellitus who have experienced inadequate glycemic control on therapy with metformin, or a sulfonylurea, or insulin (alone or in combination with metformin).

2.2 Methods

Studies were selected for inclusion in the systematic review based on the relevant studies provided by the manufacturer and the selection criteria presented in Table 9.

TABLE 9: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with type 2 diabetes mellitus who have experienced inadequate glycemic control on therapy with metformin, or a sulfonylurea, or insulin (alone or in combination with metformin)
Intervention	Dapagliflozin at a dose of 5 mg once daily in combination with metformin, or a sulfonylurea, or insulin (alone or in combination with metformin) In patients tolerating the drug and needing additional glycemic control, the dose of dapagliflozin can be increased to 10 mg once daily
Comparators	SGLT-2 inhibitors Incretins (DPP-4 inhibitors, GLP-1 analogues) Thiazolidinediones Insulin secretagogues (sulfonylureas, meglitinides) Metformin Insulin or insulin analogues Alpha-glucosidase inhibitors or Placebo In combination with metformin, or a sulfonylurea or insulin (alone or in combination with metformin)
Outcomes	**Key efficacy outcomes** • mortality • diabetes-related morbidity (macrovascular, microvascular) • glycemic control (A1C, FPG) • quality of life (measured by any validated scale) • body weight • blood pressure **Other outcomes** • health care resource utilization **Harms outcomes** • total adverse events • serious adverse events • withdrawals due to adverse events • notable harms: hypoglycemia; urogenital adverse events; renal adverse events; elevated lipids; heart failure; ketoacidosis; bladder cancer
Study Design	Published and unpublished phase 3 DB RCTs ≥ 12 weeks' duration

A1C = glycated hemoglobin; DB = double-blind; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT = sodium glucose cotransporter; FPG = fasting plasma glucose; RCT = randomized controlled trial.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–2015 May 28) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were dapagliflozin and diabetes.

No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on May 28, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on October 21, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), and Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

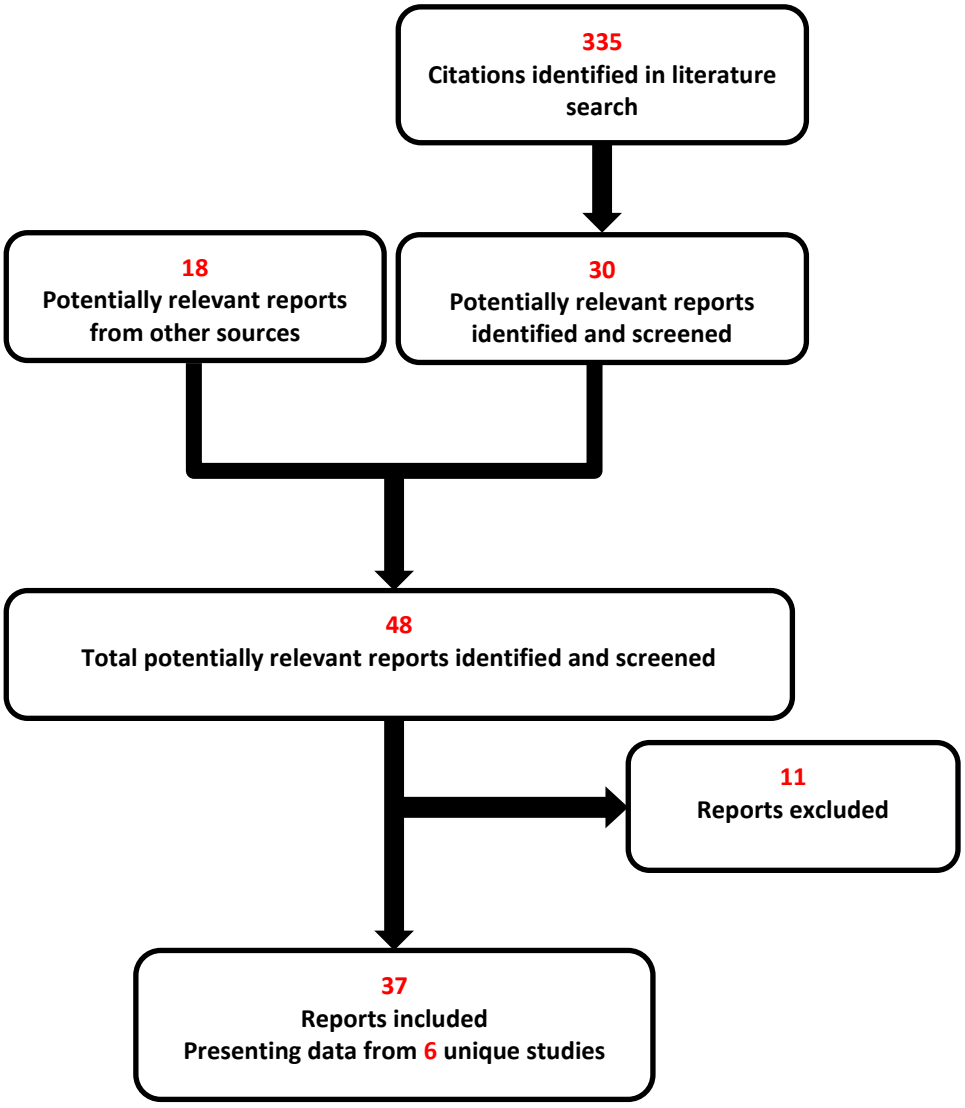
Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 10 to Table 15. Excluded studies (with reasons) are presented in Appendix 3.

3. RESULTS

3.1 Findings from the Literature

A total of six studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 10 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 10: DETAILS OF INCLUDED STUDIES (ADD-ON TO METFORMIN, VERSUS SULFONYLUREA)

		Study 4
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	95 centres: 10 countries
	Randomized (N)	816
	Inclusion Criteria	Adults with type 2 diabetes Treated with oral antidiabetes therapy that included metformin for at least 8 weeks before enrolment In addition to metformin, subjects were only allowed to be on **one** further oral antidiabetes drug and only up to the half maximum dose available. **Inclusion criteria at randomization:** A1C > 6.5% and ≤ 10.0%[a] FPG ≤ 15 mmol/L
	Exclusion Criteria	Type 1 diabetes, history of DKA or hyperosmolar non-ketonic coma, or corticosteroid-induced type 2 diabetes Symptoms of poorly controlled diabetes including, but not limited to, marked polyuria and polydipsia with > 10% weight loss during the 3 months before enrolment History of unstable or rapidly progressing renal disease CHF defined as NYHA class III or IV, unstable CHF and/or LVEF of ≤ 40% Significant cardiovascular history within the past 6 months, such as MI, unstable angina pectoris, TIA, unstable or previously undiagnosed arrhythmia, cardiac surgery or revascularization (coronary angioplasty or bypass grafts), or CVA Renal failure or renal dysfunction (creatinine clearance < 60 mL/min)
DRUGS	**Intervention**	Dapagliflozin 2.5 mg, 5 mg, 10 mg once daily Plus Open-label metformin (dose titration first 18 weeks of study)
	Comparator(s)	Glipizide 5 mg, 10 mg, 20 mg once daily Plus Open-label metformin (dose titration first 18 weeks of study)
DURATION	**Phase**	
	Lead-in	10 weeks (2 weeks lead-in, 8 weeks dose stabilization)
	DB	52 weeks
	Follow-up	Extension to total of 208 weeks
OUTCOMES	**Primary End Point**	A1C at week 52
	Other End Points	Key secondary: Total body weight at week 52 Patients with an episode of hypoglycemia at week 52 Patients with reduction in body weight of at least 5% at week 52
NOTES	**Publications**	Nauck et al. 2011[13], Nauck et al. 2014[14], Nauck et al. 2013[15], Del Prato et al. 2015[16]

A1C = glycated hemoglobin; CHF = congestive heart failure; CVA = cerebrovascular accident; DB = double-blind; DKA = diabetic ketoacidosis; FDA = US Food and Drug Administration; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; RCT = randomized controlled trial; TIA = transient ischemic attack.

[a] Subjects with A1C > 6.5% to < 7% were no longer eligible when the cohort of randomized subjects having A1C < 7% was approximately 25%, and the lower bound of A1C for enrolment was set at A1C ≥ 7% for the remainder of the study.

Source: Clinical Study Report (CSR) for Study 4.[1] Note: Five additional reports were included (CSR,[1] FDA clinical and statistical reviews,[17,18] Health Canada Reviewers Report,[19] manufacturer's submission[7]).

TABLE 11: DETAILS OF INCLUDED STUDIES (ADD-ON TO METFORMIN, VERSUS PLACEBO)

		Study 14
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	80 sites: US, Canada, North and South America
	Randomized (N)	546
	Inclusion Criteria	Men and women, aged ≥ 18 to ≤ 77 years at time of enrolment visit C peptide ≥ 0.34 nmol/L at enrolment visit BMI ≤ 45.0 kg/m^2 at the enrolment visit Subjects with type 2 diabetes with inadequate glycemic control, defined as central laboratory A1C ≥ 7.0 and ≤ 10.0% obtained at the enrolment visit Stable metformin therapy for ≥ 8 weeks before enrolment at ≥ 1,500 mg per day
	Exclusion Criteria	UACR > 203.4 mg/mmol/Cr AST > 3.0 × upper limit of normal ALT > 3 × upper limit of normal Serum total bilirubin > 34.2 µmol/L SCr ≥ 133 µmol/L for males; ≥ 124 µmol/L for females Symptoms of poorly controlled diabetes including but not limited to marked polyuria and polydipsia with > 10% weight loss during the three months before enrolment History of DKA or hyperosmolar nonketotic coma Severe uncontrolled hypertension: SBP ≥ 180 mm Hg and/or DBP ≥ 110 mm Hg CVD within past 6 months (MI, CABG, unstable CHF, CHF NYHA class III/IV, TIA or significant CVD, unstable arrhythmia) Unstable or rapid progressing renal disease
DRUGS	**Intervention**	Dapagliflozin tablets 2.5 mg, P.O., once daily, or Dapagliflozin 5 mg, P.O., once daily, or Dapagliflozin 10 mg, P.O., once daily, (Plus open-label metformin)
	Comparator(s)	Matching placebo (Plus open-label metformin)
DURATION	**Phase**	
	Lead-in	2 weeks
	DB	24 weeks
	Follow-up	Extension to 78 weeks
OUTCOMES	**Primary End Point**	Change from baseline in A1C at week 24
	Other End Points	Key secondary: Change from baseline in FPG at week 24 Change from baseline in total body weight at week 24 Proportion of subjects achieving A1C < 7.0% at week 24 Change from baseline in A1C in subjects with baseline A1C ≥ 9% at week 24 Change in FPG from baseline at week 1 Proportion of subjects achieving A1C ≤ 6.5% at week 24 Exploratory: Change from baseline in seated SBP and DBP in subjects with baseline seated SBP > 140 mm Hg at week 24

		Study 14
NOTES	**Publications**	Bailey et al. 2013[20,21], Bailey et al. 2010[22]

A1C = glycated hemoglobin; ACS = acute coronary syndrome; ALT = alanine transaminase; AST = aspartate transaminase; BP = blood pressure; BMI = body mass index; CABG = coronary artery bypass graft; CHF = congestive heart failure; CVD = cardiovascular disease; DB = double-blind; DBP = diastolic blood pressure; DKA = diabetic ketoacidosis; FDA = US Food and Drug Administration; FPG = fasting plasma glucose; MDG = mean daily glucose; MI = myocardial infarction; NYHA = New York Heart Association; P.O. = orally; RCT = randomized controlled trial; SBP = systolic blood pressure; SCr = serum creatinine; TIA = transient ischemic attack; UACR = urine albumin:creatinine ratio.
Source: Clinical Study Report (CSR) for Study 14.[2] Note: 5 additional reports were included (CSR,[2] FDA clinical and statistical reviews,[17,18] Health Canada Reviewers Report,[19] manufacturer's submission[7]).

TABLE 12: DETAILS OF INCLUDED STUDIES (ADD-ON TO METFORMIN, VERSUS PLACEBO)

		Study 12
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	40 sites: Europe
	Randomized (N)	182
	Inclusion Criteria	**At enrolment:** Female patients aged ≥ 55 and ≤ 75 years who were post-menopausal (or had had a hysterectomy) for a period of ≥ 5 years or males aged ≥ 30 and ≤ 75 years, with type 2 diabetes A1C ≥ 6.5% and ≤ 8.5%, BMI ≥ 25 kg/m^2, body weight ≤ 120 kg Ongoing treatment with metformin, stable dose of ≥ 1,500 mg/d for ≥ 12 weeks before **Before lead-in:** A1C ≥ 6.5% and ≤ 8.5% FPG ≤ 13.2 mmol/L **At randomization:** A1C ≥ 6.5% and ≤ 8.5% FPG ≤ 13.2 mmol/L
	Exclusion Criteria	Type 1 diabetes, diabetes insipidus, corticosteroid-induced type 2 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketonic coma, or known condition of congenital renal glucosuria Symptoms of poorly controlled diabetes, including but not limited to marked polyuria and polydipsia with > 5% weight loss during the 3 months before enrolment Body weight change > 5% within 3 months prior to enrolment Severe uncontrolled hypertension: SBP ≥ 180 mm Hg and/or DBP ≥ 110 mm Hg Renal failure or renal dysfunction (creatinine clearance using Cockcroft and Gault formula < 60 mL/min) or serum creatinine ≥ 133 µmol/L for male subjects and ≥ 124 µmol/L for female subjects Significant cardiovascular history within the past 6 months before the enrolment visit (MI, unstable angina, TIA, unstable or previously undiagnosed arrhythmia, unstable CHF, cardiac surgery or revascularization) History of unstable or rapidly progressing renal disease
DRUGS	**Intervention**	Dapagliflozin 10 mg, P.O., once daily (Plus open-label metformin)
	Comparator(s)	Placebo (Plus open-label metformin)

		Study 12
DURATION	**Phase**	
	Lead-in	2 weeks
	DB	24 weeks
	Follow-up	Extension to 78 weeks
OUTCOMES	**Primary End**	Total body weight after 24 weeks
	Other End Points	Key secondary: Body weight decrease ≥ 5% Other secondary: Additional weight and glycemic variables • Lean tissue mass as measured by DXA • Blood pressure • Adipose tissue markers • Patient-reported outcomes
NOTES	**Publications**	Bolinder et al. 2012[23], Bolinder et al. 2014[24], Grandy et al. 2014[25,26]

A1C = hemoglobin; ACS = acute coronary syndrome; BMI = body mass index; CHF = congestive heart failure; DB = double-blind; DBP = diastolic blood pressure; DXA = dual-energy X-ray absorptiometry; FDA = US Food and Drug Administration; FPG = fasting plasma glucose; MI = myocardial infarction; P.O. = orally; RCT = randomized controlled trial; SBP = systolic blood pressure; TIA = transient ischemic attack.
Source: Clinical Study Report (CSR) for Study 12.[3] Note: 5 additional reports were included (CSR,[3] FDA clinical and statistical reviews,[17,18] Health Canada Reviewers Report,[19] manufacturer's submission[7]).

TABLE 13: DETAILS OF INCLUDED STUDIES (ADD-ON TO SULFONYLUREA, VERSUS PLACEBO)

		Study 5
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	84 centres: 7 countries: Europe, Asia/Pacific
	Randomized (N)	N = 597
	Inclusion Criteria	Adults with type 2 diabetes, on stable sulfonylurea monotherapy, ≥ 50% the maximal recommended dose for ≥ 8 weeks before **Inclusion criteria before lead-in period:** Inadequate glycemic control, defined as A1C ≥ 7% and ≤ 10% FPG ≤ 15 mmol/L C peptide (≥ 0.33 nmol/L) **Inclusion criteria at randomization:** A1C ≥ 7% and ≤ 10% FPG ≤ 15 mmol/L C peptide (0.33 nmol/L)
	Exclusion Criteria	Type 1 diabetes, diabetes insipidus, corticosteroid-induced type 2 diabetes, and history of DKA or hyperosmolar non-ketonic coma Symptoms of poorly controlled diabetes such as marked polyuria and polydipsia with > 10% weight loss during the three months prior to enrolment Use of glimepiride dose > 4 mg/d at enrolment and 8 weeks before enrolment AST > 3 × upper level of normal ALT > 3 × upper level of normal Serum total bilirubin > 34 µmol/L Calculated creatinine clearance < 50 mL/min (by Cockcroft-Gault) or a measured serum creatinine of > 177 µmol/L

		Study 5
		UACR > 203.4 mg/mmol
DRUGS	**Intervention**	Dapagliflozin tablets 2.5 mg, P.O., once daily, or Dapagliflozin 5 mg, P.O., once daily, or Dapagliflozin 10 mg, P.O., once daily (Plus glimepiride tablets P.O., 4 mg/d)
	Comparator(s)	Placebo (matching) (Plus glimepiride tablets P.O., 4 mg/d)
DURATION	**Phase**	
	Lead-in	10 weeks (1 week enrolment, 8 weeks lead-in, 1 week qualification)
	DB	24 weeks (plus 24 weeks DB extension)
	Follow-up	3 week
OUTCOMES	**Primary End Point**	Change in A1C from baseline to 24 weeks
	Other End Points	Key secondary: Change in body weight from baseline to week 24 Change in 2-hour post-challenge PG rise in response to an OGTT, baseline to week 24 Subjects achieving a therapeutic glycemic response: A1C < 7% at week 24 Change in body weight in subjects with baseline BMI ≥ 27 kg/m^2 from baseline to week 24 Change in FPG from baseline to week 24 Other secondary: DTSQc and DTSQ scores at week 24
NOTES	**Publications**	Strojek et al. 2011[27], Strojek et al. 2014[28], Matthaei et al. 2015[29]

A1C = glycated hemoglobin; ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; DB = double-blind; DKA = diabetic ketoacidosis; DTSQ = Diabetes Treatment Satisfaction Questionnaire; DTSQc = Diabetes Treatment Satisfaction Questionnaire change version; FDA = US Food and Drug Administration; FPG = fasting plasma glucose; PG = plasma glucose; P.O. = orally; OGTT = oral glucose tolerance test; RCT = randomized controlled trial; UACR = urine albumin:creatinine ratio.

Note: Open-label glimepiride could be down-titrated to 2 mg during the treatment period to mitigate recurrent hypoglycemic events at the discretion of the investigator. If further hypoglycemic events occurred, the open-label glimepiride could be down-titrated to 0 mg at the discretion of the investigator. No up-titration was allowed during the treatment period.

Note: Patients entering the study on a stable dose of 4 mg per day glimepiride monotherapy could skip the open-label sulfonylurea lead-in period and qualification period; instead, they could enter the study at the randomization visit.

Source: Clinical Study Report (CSR) for Study 5.[4] Note: 5 additional reports were included (CSR,[4], FDA clinical and statistical reviews,[17,18] Health Canada Reviewers Report,[19] manufacturer's submission[7]).

TABLE 14: DETAILS OF INCLUDED STUDIES (ADD-ON TO INSULIN, VERSUS PLACEBO)

		Study 6
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	126 sites: Canada, US, Europe
	Randomized (N)	808
	Inclusion Criteria	Men and women diagnosed with type 2 diabetes Age ≥ 18 and ≤ 80 years at time of consent Inadequate glycemic control, defined as A1C ≥ 7.5% and ≤ 10.5%, and who, according to investigators' judgment, were on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks before enrolment. Patients could also be treated with maximally two oral antidiabetes drugs under the approved prescribing information. Oral antidiabetes treatment should be at a stable dose for at least 8 weeks. Patients on metformin therapy should be on at least 1,500 mg/d of metformin or at the maximum tolerable dose for a period of at least 8 weeks before enrolment. Patients on other oral antidiabetes drugs should be on at least half maximum daily recommended dose of the drugs for a period of at least 8 weeks before enrolment. Daily insulin requirements over the past 7 days with insulin dose documentation that did not vary more than 10% on more than one occasion of the calculated mean daily insulin dose at Visit 2 (for example, for patient whose calculated mean daily insulin dose at visit 2 was 50 IU, daily doses in the preceding 7 days with insulin dose documentation could not be < 45 and > 55 IU on more than one occasion). Body mass index ≤ 45 kg/m^2
	Exclusion Criteria	Clinical diagnosis of type 1 diabetes, MODY or secondary diabetes mellitus (e.g., chronic pancreatitis, partial pancreatectomy) Symptoms of poorly controlled diabetes that, in the judgment of the investigator, would preclude participation in this trial including, but not limited to, marked polyuria and polydipsia with greater than 10% weight loss during the 3 months before enrolment Treatment with more than 2 additional oral antidiabetes drugs Calculated creatinine clearance < 50 mL/min/1.73m^2 (calculated by Cockcroft-Gault formula) or a measured serum creatinine value of > 177 µmol/L. Patients on concomitant metformin therapy were to be excluded if serum creatinine ≥ 133 µmol/L for male patients and ≥ 124 µmol/L for female patients. CHF defined as NYHA class III or IV, and/or LVEF of ≤ 40%
DRUGS	**Intervention**	Dapagliflozin tablets, 2.5 mg, P.O., once daily, or Dapagliflozin tablets 5 mg, P.O., once daily, or Dapagliflozin tablets 10 mg, P.O., once daily Plus insulin (plus a maximum of 2 oral antidiabetes drugs at a stable dose on entry)
	Comparator(s)	Placebo Plus insulin (plus a maximum of 2 oral antidiabetes drugs at a stable dose on entry)
DURATION	**Phase**	
	Lead-in	2 weeks (enrolment)
	DB	24 weeks
	Follow-up	Extensions to a total of 80 weeks
OUTCOMES	**Primary End Point**	Change in A1C from baseline to week 24
	Other End Points	Change in body weight from baseline to week 24 Absolute change in calculated mean daily insulin dose from baseline to week 24 Proportion of subjects with calculated mean daily insulin dose reduction from baseline to week 24 Change in FPG from baseline to week 24

		Study 6
NOTES	**Publications**	Wilding et al. 2012[30], Wilding et al. 2014[31]

A1C = glycated hemoglobin; CHF = congestive heart failure; DB = double-blind; FDA = US Food and Drug Administration; FPG = fasting plasma glucose; LVEF = left ventricular ejection fraction; MODY = maturity onset diabetes of the young; NYHA = New York Heart Association; RCT = randomized controlled trial.
Source: Clinical Study Report (CSR) for Study 6.[5] Note: 5 additional reports were included (CSR,[5] FDA clinical and statistical reviews,[17,18] Health Canada Reviewers Report,[19] manufacturer's submission[7]).

TABLE 15: DETAILS OF INCLUDED STUDIES (ADD-ON TO METFORMIN, TRIPLE THERAPY VERSUS DUAL THERAPY)

		Study 18
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	145 sites: North America, Puerto Rico, Europe, South Korea, South Africa
	Study period	June 5, 2012, to January 17, 2014
	Randomized (N)	534
	Inclusion Criteria	Patients ≥ 18 years with type 2 diabetes and inadequate glycemic control, defined as A1C ≥ 8.0% and ≤ 12.0% (64 mmol/mol to 108 mmol/mol) at screening, were eligible. Patients had to be on stable metformin therapy (≥ 1,500 mg/d) for ≥ 8 weeks before screening and have C peptide concentrations ≥ 0.34 nmol/L and BMI ≤ 45.0 kg/m^2 at screening.
	Exclusion Criteria	Uncontrolled hypertension (systolic blood pressure ≥ 160 mm Hg and diastolic blood pressure ≥ 100 mm Hg) at randomization FPG > 15 mmol/L during the 4-week lead-in period Cardiovascular disease within 3 months of screening Congestive heart failure (NYHA class IV) eGFR 60 mL/min/1.73 m^2 or serum creatinine ≥ 133 µmol/L in men or ≥ 124 µmol/L in women Significant hepatic disease Patients who received any antidiabetes medication, other than metformin, for more than 14 days during the 12 weeks before screening
DRUGS	**Intervention**	Dapagliflozin 10 mg/d plus saxagliptin 5 mg/d Plus metformin
	Comparator(s)	Dapagliflozin 10 mg/d plus placebo plus metformin Or Saxagliptin 5 mg/d plus placebo plus metformin
DURATION	**Phase**	
	Lead-in	4 weeks (open-label metformin XR)
	Double-blind	24 weeks
	Follow-up	
OUTCOMES	**Primary End Point**	Mean change in A1C from baseline to 24 weeks
	Other End Points	Mean change in 2-hour PPG Mean change in FPG Proportion of patients achieving glycemic control (A1C < 7%) Mean change in body weight

		Study 18
NOTES	**Publications**	Rosenstock et al. 2015[32]

A1C = glycated hemoglobin; BMI = body mass index; eGFR = estimated glomerular filtration rate; FDA = US Food and Drug Administration; FPG = fasting plasma glucose; NYHA = New York Heart Association; PPG = postprandial plasma glucose; RCT = randomized controlled trial; XR = extended release.
Source: Clinical Study Report (CSR) for Study 18.[6] Note: Five additional reports were included (CSR,[6] FDA clinical and statistical reviews,[17,18] Health Canada Reviewers Report,[19] manufacturer's submission[7]).

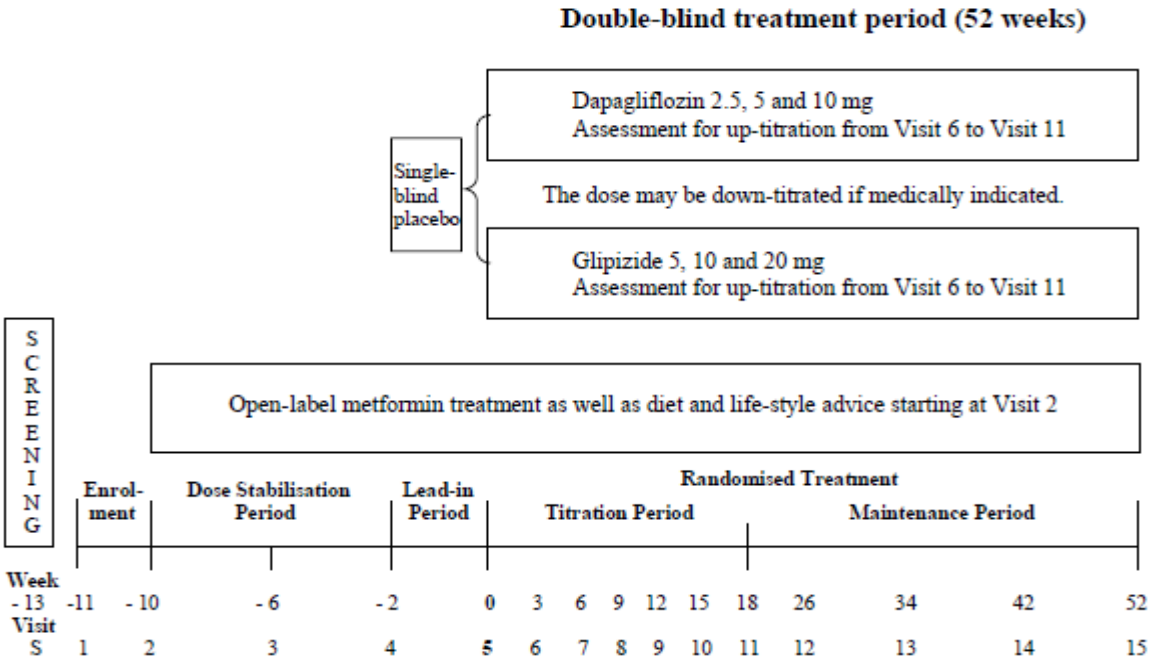
3.2 Included Studies

3.2.1 Description of Studies

Six multi-centre, manufacturer-sponsored double-blind (DB) randomized controlled trials (RCTs), five with DB extensions, were included in this review. Three of the studies featured patients whose type 2 diabetes was not controlled despite treatment with metformin. Patients in all these studies continued on metformin as part of their treatment regimen. In two of the studies (Study 12 [N = 182] and Study 14 [N = 546]), patients were randomized to either dapagliflozin or placebo, and in Study 4 (N = 814), patients were randomized 1:1 to either dapagliflozin or glipizide. In Studies 12 and 14, the core component was 24 weeks with extensions to 78 weeks, and in Study 4, the core component was 52 weeks with extensions out to a total of 104 weeks (LT1) and then 208 weeks (LT2). In the other two included studies, patients had previously had inadequate glycemic control on a sulfonylurea (Study 5) or insulin (Study 6). In Study 5, 597 patients continued on a background of glimepiride and were randomized 1:1:1:1 to either dapagliflozin 2.5 mg, 5 mg, 10 mg, or placebo. In Study 6, 808 patients continued on a background of insulin and were randomized 1:1:1:1 to either dapagliflozin 2.5, 5 mg, 10 mg, or placebo. In both Study 5 and Study 6, the core phases were 24 weeks, with extensions out to 48 weeks and 104 weeks, respectively. Study 18 was a 24-week study designed to compare triple therapy (dapagliflozin and saxagliptin, plus background metformin) with dual therapy (dapagliflozin plus metformin or saxagliptin plus metformin). Patients were randomized 1:1:1 to each of these interventions; however, because the study was designed to compare triple with dual therapy, no analysis was provided that compared dapagliflozin with saxagliptin.

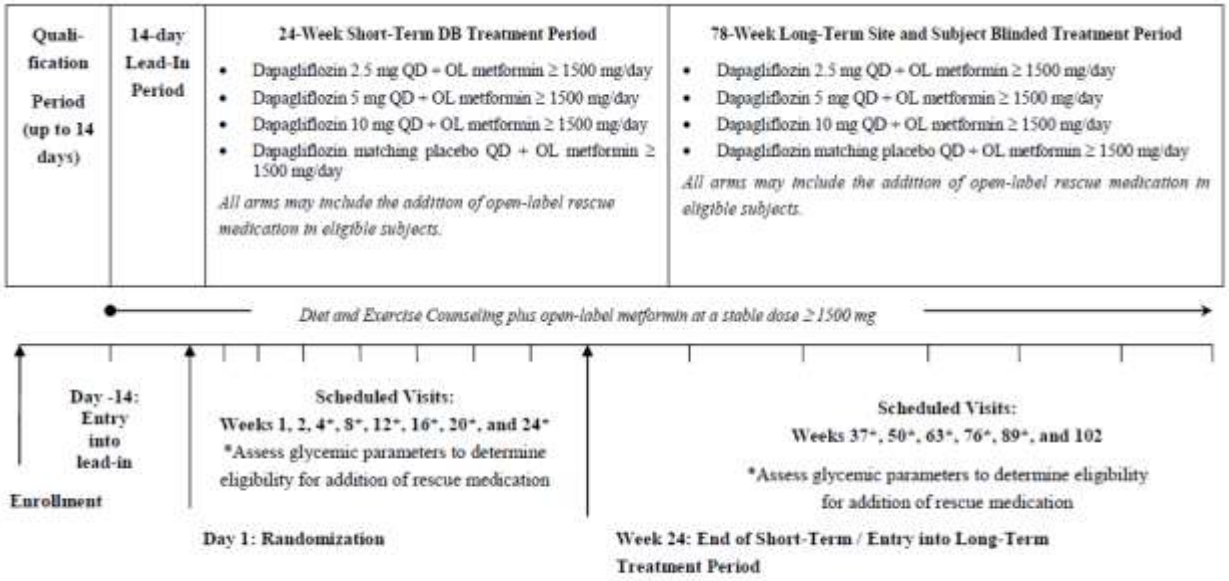
Randomization was stratified based on study site in Study 4 and Study 18, and by gender in Study 12. Stratification was not described in Study 4. In Study 5, randomization was not stratified, and in Study 6, randomization was stratified by use of concomitant oral antidiabetes drugs.
With the exception of Study 12, the primary outcome of all studies was change from baseline in A1C. In Study 12, change from baseline in body weight was the primary outcome. Common secondary outcomes included change from baseline in body weight, fasting plasma glucose (FPG), and blood pressure.

FIGURE 2: DESIGN OF STUDY 4



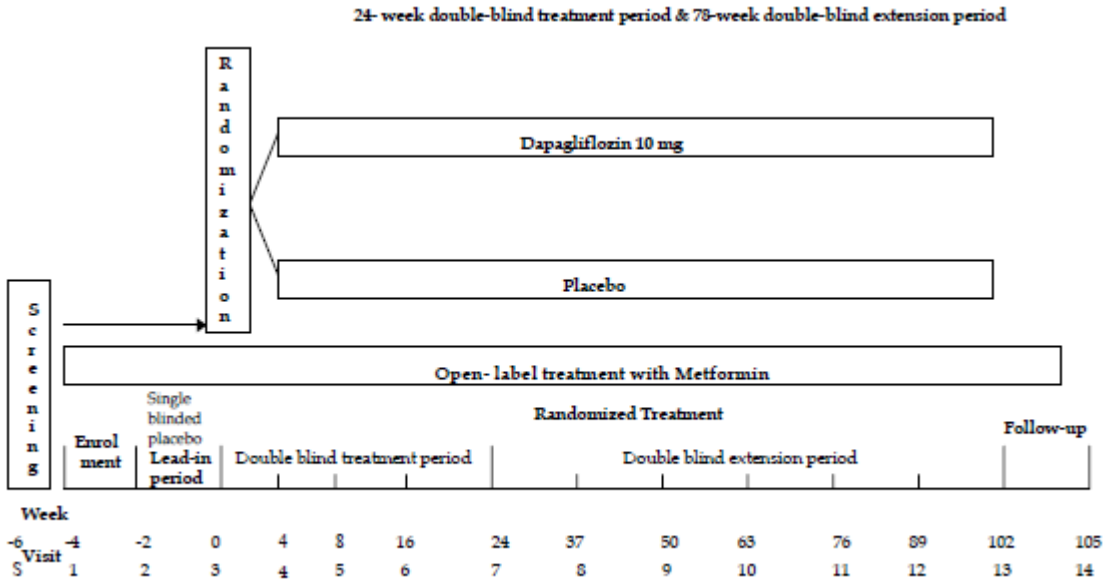
Source: Clinical Study Report for Study 4.[1]

FIGURE 3: DESIGN OF STUDY 14



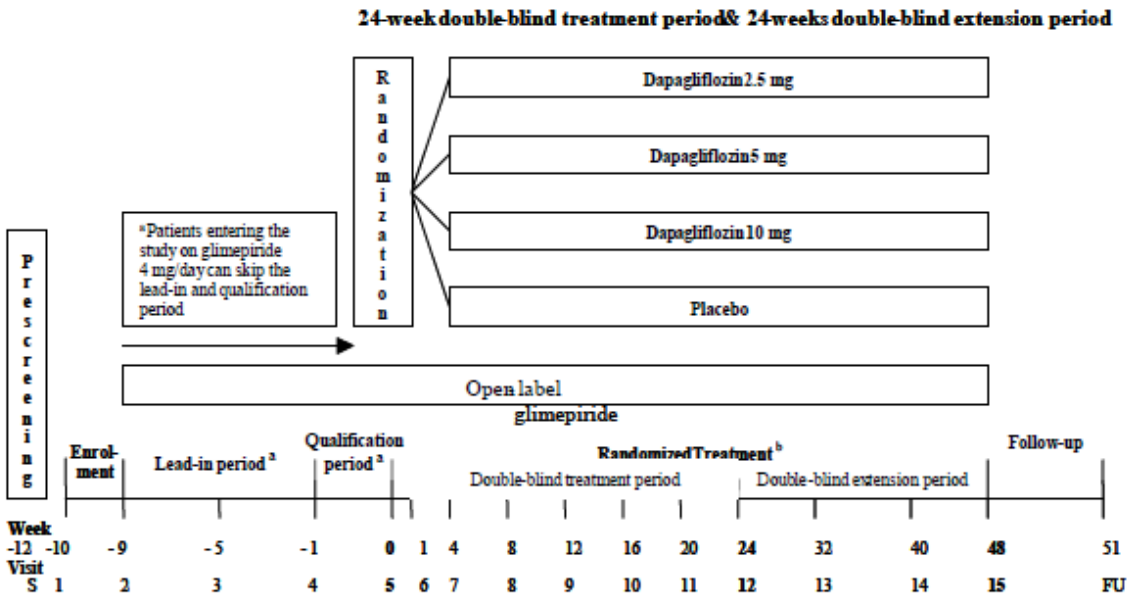
OL = open-label; QD = once daily.
Source: Clinical Study Report for Study 14.[2]

FIGURE 4: DESIGN OF STUDY 12



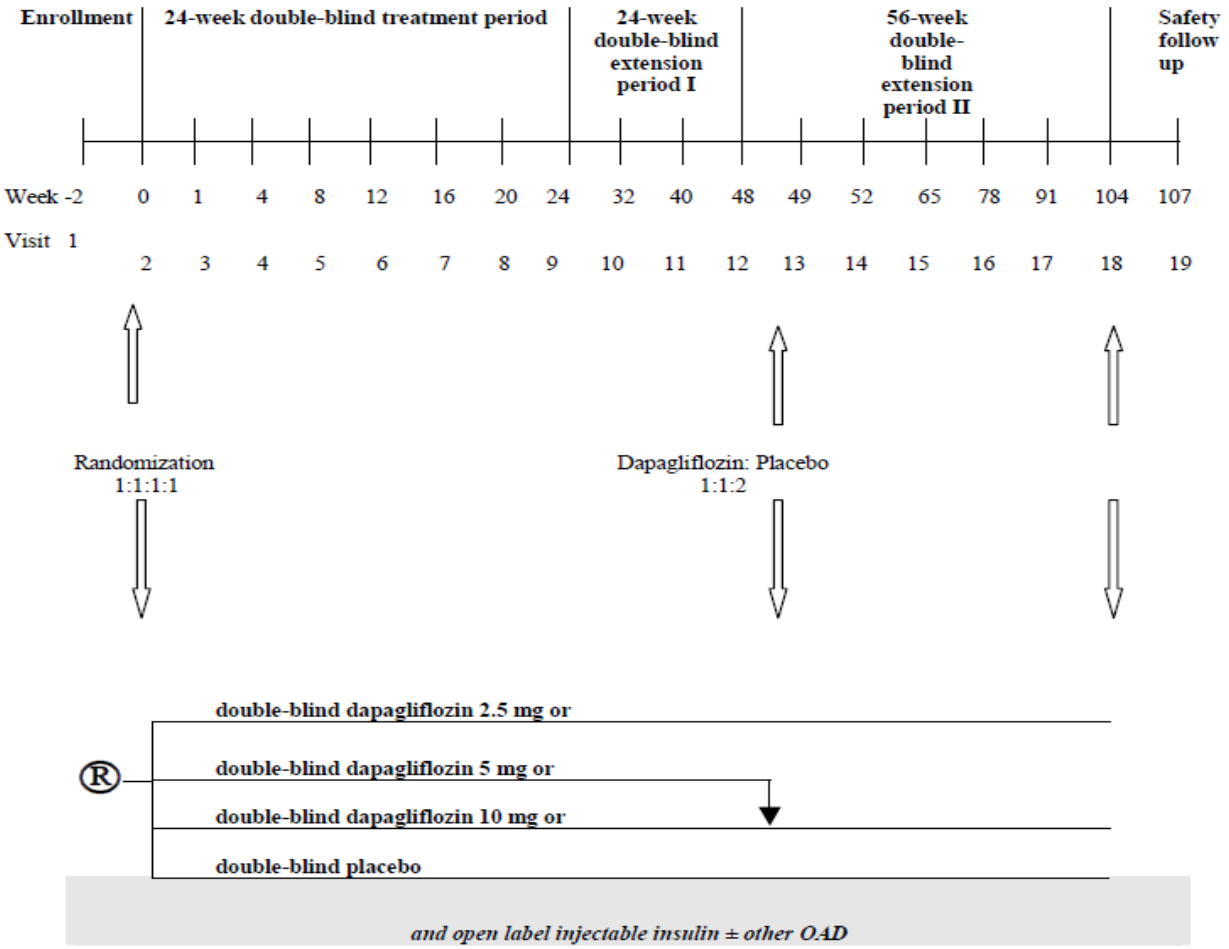
Source: Clinical Study Report for Study 12.[3]

FIGURE 5: DESIGN OF STUDY 5



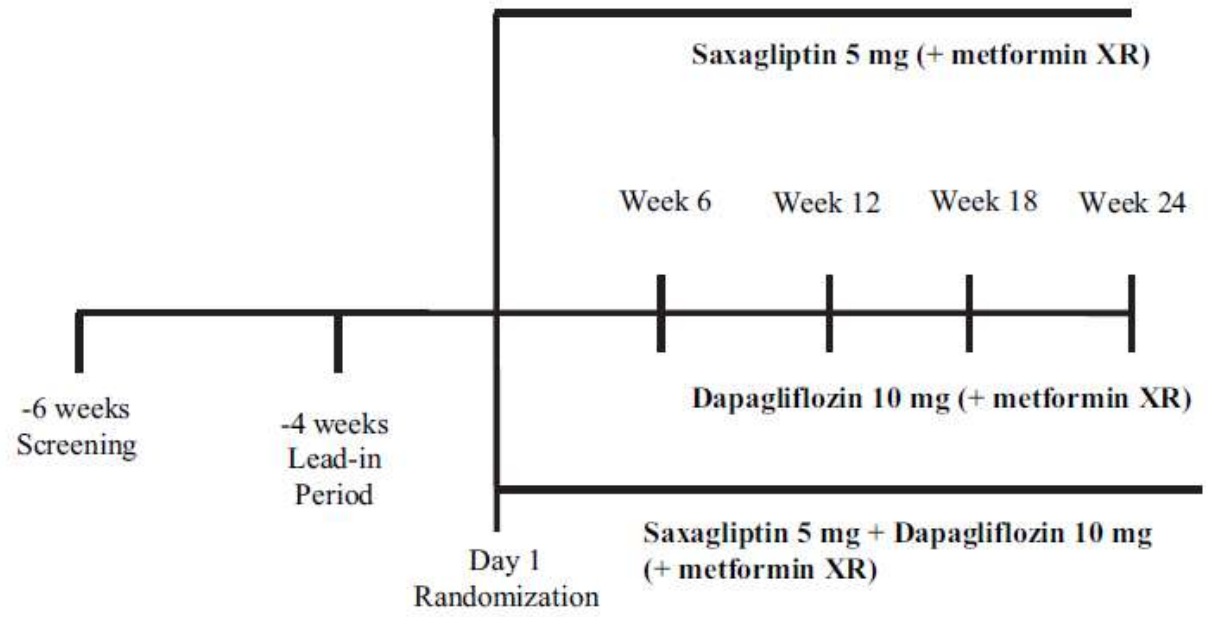
Source: Clinical Study Report for Study 5.[4]

FIGURE 6: DESIGN OF STUDY 6



OAD = oral antidiabetic drug
Source: Clinical Study Report for Study 6.[5]

FIGURE 7: DESIGN OF STUDY 18



XR = extended release.
Source: Clinical Study Report for Study 18.[6]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients in all studies had type 2 diabetes inadequately controlled on the background regimen for that study. Patients were typically stable on this regimen for a period of at least eight weeks before enrolment and were enrolled after having met metabolic criteria such as glycated hemoglobin (A1C), FPG, and (occasionally) C peptide during screening. Patients with poorly controlled diabetes were excluded, as were patients with significant cardiovascular disease (i.e., recent cardiovascular events such as myocardial infarction or transient ischemic attack, or unstable arrhythmia). Patients with unstable or rapidly progressing renal disease were also excluded, as were patients who had a creatinine clearance that fell below a certain threshold (< 50 or < 60 mL/min/1.73 m^2).

b) Baseline Characteristics

Across studies, patients were aged between 53 and 61 years, on average, with the youngest population in Study 14 (mean 53 years) (Table 17). Across studies, there was a relatively equal proportion of males and females. In many studies, the large majority of patients were white (80% to 100% of patients), while in Study 5 approximately one-third were Asian (Table 18). In most studies, a large proportion of patients had a history of cardiovascular disease (74% to 90%), and the majority of these patients had hypertension. Mean body mass index (BMI), when reported, was approximately 30 kg/m^2, with the highest in Study 6 (mean BMI 33 kg/m^2). Study 6 used insulin background therapy and had the longest duration of disease (14 years versus five to seven years in the other studies) (Table 19). This longer duration of diabetes in Study 6 was also reflected in a higher proportion of patients having experienced one or more clear sequelae of the disease, such as neuropathy (41% of patients), retinopathy (27%), or nephropathy (13%).

Baseline characteristics were generally similar between groups within studies. If there were variations, they tended to be for demographic characteristics such as gender or race, while key baseline characteristics for disease, such as A1C and BMI, were similar between groups.

TABLE 16: SUMMARY OF BASELINE CHARACTERISTICS (VERSUS SULFONYLUREA, ADD-ON TO METFORMIN)

	Study 4	
	Dapagliflozin N = 400	**Glipizide N = 401**
Mean (SD) age, years	58.1 (9.4)	58.6 (9.8)
Male, n (%)	221 (55)	220 (55)
Race, n (%)		
White	327 (82)	323 (81)
Black/African-American	26 (7)	24 (6)
Asian	27 (7)	34 (9)
Other	20 (5)	20 (5)
BMI, kg/m^2		
Mean (SD)	31.7 (5.1)	31.2 (5.1)
Prior history of CVD, n (%)		
Yes	294 (74)	295 (74)
Hypertension only	222 (56)	217 (54)
At least one other than hypertension	72 (18)	78 (20)
No	106 (27)	106 (26)
Mean (SD) duration of type 2 diabetes, years	6.1 (4.6)	6.6 (5.9)
Mean (SD) A1C, %	7.7 (0.9)	7.7 (0.9)
Patients, < 8.0, n (%)	262 (66)	246 (61)
≥ 8 and < 9, n (%)	103 (26)	104 (26)
≥ 9.0, n (%)	35 (9)	51 (13)
Mean (SD) FPG, mmol/L	9.0 (2.1)	9.1 (2.3)
Mean (SD) baseline eGFR	NR	NR
History of diabetic complications, n (%)		
Diabetic neuropathy	23 (6)	23 (6)
Diabetic retinopathy	22 (6)	24 (6)
Diabetic nephropathy	15 (4)	10 (3)
Microalbuminuria	42 (11)	39 (10)

A1C = glycated hemoglobin; BMI = body mass index; CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; NR = not reported; SD = standard deviation.
Source: Clinical Study Report for Study 4.[1]

TABLE 17: SUMMARY OF BASELINE CHARACTERISTICS (VERSUS PLACEBO, ADD-ON TO METFORMIN)

	Study 14			Study 12	
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**	**Dapa 10 mg N = 89**	**Placebo N = 91**
Mean (SD) age, years	54.3 (9.4)	52.7 (9.9)	53.7 (10.3)	60.6 (8.2)	60.8 (6.8)
Male, n (%)	69 (50)	77 (57)	76 (56)	49 (55)	51 (56)
Race, n (%)					
White	118 (86)	121 (90)	124 (91)	89 (100)	91 (100)

	Study 14			Study 12	
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**	**Dapa 10 mg N = 89**	**Placebo N = 91**
Black/African-American	6 (4)	4 (3)	2 (2)	0	0
Asian	4 (3)	1 (1)	3 (2)	0	0
Other	6 (4)	5 (4)	7 (5)	0	0
BMI					
Mean (SD)	NR	NR	NR	32.1 (3.9)	31.7 (3.9)
Mean (SD) weight, kg	84.7 (16.3)	86.1 (17.6)	87.9 (19.2)	92.1 (14.1)	90.9 (13.7)
Prior history of CVD, n (%)					
Yes	NR	NR	NR	80 (90)	78 (86)
Hypertension only	74 (54)	70 (52)	75 (55)	59 (66)	52 (57)
Mean (SD) Duration of type 2 diabetes, years	6.4 (5.8)	6.1 (5.4)	5.8 (5.1)	6.0 (4.5)	5.5 (5.3)
Mean (SD) A1C, %	8.2 (0.96)	8.0 (0.84)	8.1 (0.96)	7.2 (0.44)	7.2 (0.53)
Mean (SD) FPG, mmol/L	9.4 (2.7)	8.7 (2.1)	9.2 (2.6)	8.2 (1.4)	8.3 (1.4)
Mean (SD) baseline eGFR	NR	NR	NR	NR	NR
History of diabetic complications, n (%)					
Diabetic neuropathy	16 (12)	25 (19)	16 (12)	7 (8)	4 (4)
Diabetic retinopathy	6 (4)	4 (3)	2 (2)	1 (1)	4 (4)
Diabetic nephropathy	6 (4)	6 (4)	3 (2)	0	1 (1)
Microalbuminuria	11 (8)	11 (8)	8 (6)	4 (5)	3 (3)

A1C = glycated hemoglobin; BMI = body mass index; CVD = cardiovascular disease; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; NR = not reported; SD = standard deviation.
Source: Clinical Study Report for Study 14[2] and Study 12.[3]

TABLE 18: SUMMARY OF BASELINE CHARACTERISTICS (VERSUS PLACEBO, ADD-ON TO SULFONYLUREA)

	Study 5		
	Dapa 5 mg N = 142	**Dapa 10 mg N = 151**	**Placebo N = 145**
Mean (SD) age, years	60.2 (9.7)	58.9 (8.3)	60.3 (10.2)
Male, n (%)	71 (50)	66 (44)	71 (49)
Race, n (%)			
White	96 (68)	106 (70)	101 (70)
Asian	46 (32)	45 (30)	44 (30)
BMI			
Mean (SD)	29.8 (5.2)	29.8 (5.6)	29.7 (4.6)
Mean (SD) weight, kg	81.0 (18.6)	80.6 (17.9)	80.9 (15.8)
Prior history of CVD, n (%)	109 (77)	117 (78)	124 (86)
Hypertension only	54 (38)	71 (47)	69 (48)
Mean (SD) duration of type 2 diabetes, years	7.4 (5.7)	7.2 (5.5)	7.4 (5.7)
Mean (SD) A1C, %	8.1 (0.8)	8.1 (0.8)	8.2 (0.7)
Mean (SD) FPG, mmol/L	9.7 (2.1)	9.6 (2.0)	9.6 (2.1)
Mean (SD) baseline eGFR	NR	NR	NR
History of diabetic complications, n (%)			
Diabetic neuropathy	33 (23)	30 (20)	30 (21)
Diabetic retinopathy	17 (12)	16 (11)	14 (10)

	Study 5		
	Dapa 5 mg N = 142	**Dapa 10 mg N = 151**	**Placebo N = 145**
Diabetic nephropathy	6 (4)	5 (3)	7 (5)
Microalbuminuria	4 (3)	8 (5)	13 (9)

A1C = glycated hemoglobin; BMI = body mass index; CVD = cardiovascular disease; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; SD = standard deviation.
Source: Clinical Study Report for Study 5.[4]

TABLE 19: SUMMARY OF BASELINE CHARACTERISTICS (VERSUS PLACEBO, ADD-ON TO INSULIN)

	STUDY 6		
	Dapa 5 mg N = 211	**Dapa 10 mg N = 194**	**Placebo N = 193**
Mean (SD) age, years	59.3 (7.9)	59.3 (8.8)	58.8 (8.6)
Male, n (%)	100 (47)	87 (45)	95 (49)
Race, n (%)			
White	200 (95)	184 (95)	186 (96)
Black	5 (2)	5 (3)	6 (3)
Asian	3 (1)	3 (2)	0
Other	3 (1)	2 (1)	1 (1)
BMI			
Mean (SD)	33.0 (5.3)	33.4 (5.1)	33.1 (5.9)
Mean (SD) weight, kg	93.3 (17.4)	94.5 (16.8)	94.5 (19.8)
Prior history of CVD, n (%)	177 (84)	175 (90)	170 (88)
Hypertension only	110 (52)	92 (47)	109 (57)
Mean (SD) duration of type 2 diabetes, years	13.1 (7.8)	14.2 (7.3)	13.5 (7.3)
Mean (SD) A1C, %	8.6 (0.9)	8.6 (0.8)	8.5 (0.8)
Mean (SD) FPG, mmol/L	10.3 (3.3)	9.6 (3.0)	9.4 (3.2)
Mean (SD) baseline eGFR	NR	NR	NR
History of diabetic disease, n (%)			
Diabetic neuropathy	86 (41)	78 (40)	79 (41)
Diabetic retinopathy	57 (27)	59 (30)	48 (25)
Diabetic nephropathy	34 (16)	23 (12)	24 (12)
Microalbuminuria	43 (20)	33 (15)	30 (16)
Previous use of, n (%):			
Metformin only	78 (37)	83 (43)	78 (40)
Metformin and sulfonylurea	12 (6)	8 (4)	13 (7)
Metformin and thiazolidinedione	2 (1)	0	1 (1)
Metformin and other oral antidiabetes drugs	2 (1)	1 (1)	1 (1)
Other drugs or drug combinations	13 (6)	6 (1)	4 (2)

A1C = glycated hemoglobin; BMI = body mass index; CVD = cardiovascular disease; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; SD = standard deviation.
Source: Clinical Study Report for Study 6.[5]

TABLE 20: SUMMARY OF BASELINE CHARACTERISTICS (TRIPLE THERAPY VERSUS DUAL THERAPY, ADD-ON TO METFORMIN)

	Study 18		
	Dapa/Saxa N = 179	**Dapa N = 179**	**Saxa N = 176**
Mean (SD) age, years	53 (10)	54 (10)	55 (10)
Male, n (%)	85 (47)	89 (50)	94 (53)
Race, n (%)			
White	120 (67)	131 (73)	121 (69)
Black	22 (12)	16 (9)	22 (13)
Asian	12 (7)	10 (6)	11 (6)
Other	25 (14)	22 (12)	22 (13)
BMI			
Mean (SD)	31.8 (4.8)	31.5 (5.3)	31.8 (5.1)
Mean (SD) weight, kg	87 (18)	86 (19)	88 (19)
Prior history of CVD	NR	NR	NR
Hypertension only	95 (53)	102 (57)	111 (63)
Mean (SD) duration of type 2 diabetes, years	7.1 (5.0)	7.4 (5.4)	8.2 (5.5)
Mean (SD) A1C, %	8.92 (1.18)	8.87 (1.16)	9.03 (1.05)
Mean (SD) FPG, mmol/L	10.0 (2.5)	10.3 (2.6)	10.7 (2.5)
History of diabetic disease, n (%)			
Diabetic neuropathy	19 (11)	23 (13)	25 (14)
Diabetic retinopathy	3 (2)	4 (2)	3 (2)
Diabetic nephropathy	2 (1)	1 (1)	5 (3)
Microalbuminuria	8 (5)	7 (4)	11 (6)

A1C = hemoglobin; BMI = body mass index; CVD = cardiovascular disease; Dapa = dapagliflozin; FPG = fasting plasma glucose; NR = not reported; Saxa = saxagliptin; SD = standard deviation.
Source: Clinical Study Report for Study 18.[6]

3.2.3 Interventions

a) Study 4

Study 4 compared dapagliflozin, titrated across a range of doses from 2.5 mg to 10 mg, with glipizide, titrated from 5 mg to 20 mg, each on a background of metformin. The dose titration schedule is described below.

Patients in both treatment groups received open-label metformin at a dose of 1,500 mg, 2,000 mg, or 2,500 mg per day during the 52-week treatment period. The patient's metformin dose during the 52-week short-term treatment period was based on his or her metformin dose and other oral antidiabetes therapy during the eight weeks before enrolment. Patients who had not received metformin monotherapy at a stable dose of 1,500 mg, 2,000 mg, or 2,500 mg per day during the eight weeks before the enrolment visit had to pass through an eight-week dose-stabilization period.

The 52-week short-term period consisted of a titration period (week 0 to week 18) and a maintenance treatment period (week 19 to week 52). During the titration period, patients were up-titrated to the optimal effect (FPG < 6.1 mmol/L,) or the highest tolerable dose. All patients started with the investigational product at dose level 1 (dapagliflozin 2.5 mg or glipizide 5 mg). They could be up-titrated in three-week intervals to dose level 2 (dapagliflozin 5 mg or glipizide 10 mg) and level 3 (dapagliflozin

10 mg or glipizide 20 mg). During the maintenance treatment period, patients continued on the dose level they had reached at the end of the titration period. At any time during the study, the investigational product could be down-titrated to mitigate recurrent hypoglycemic events. Patients who experienced recurrent hypoglycemic events at dose level 1 could be down-titrated to 0 at the investigator's discretion. Patients could be up-titrated again to the maximum tolerable dose until the end of the titration period; thereafter, no up-titration was allowed until the end of the maintenance treatment period. Use of a rescue therapy protocol was only mentioned for the extension. Dipeptidyl peptidase (DPP)-4 inhibitors were used first line as rescue, and insulin could be used second line if glycemic control was inadequate after three months of DPP-4 inhibitors, or if DPP-4 inhibitors were not available in that jurisdiction.

b) Study 14

Study 14 compared three different doses of dapagliflozin (2.5 mg, 5 mg, or 10 mg) with placebo, all on a metformin background. Changes to blinded study medication were not permitted at any time during the study. In addition, the dose of open-label metformin was to remain unchanged for the duration of the study. Patients whose current dose of metformin did not correspond to a multiple of the dose contained in manufacturer-provided tablets had their dose modified to the next nearest corresponding manufacturer-provided tablet dose.

Patients with lack of glycemic control during the short-term treatment period were eligible to receive open-label rescue medication with pioglitazone 15 mg or acarbose in addition to their current DB treatment, based on the central laboratory FPG and confirmatory FPG results.

c) Study 12

Study 12 compared dapagliflozin 10 mg once daily with placebo, all on a background of metformin.

Metformin tablets 500 mg were administered orally at a dosage of ≥ 1,500 mg per day according to the investigator's instruction for the two-week lead-in period, the 24-week short-term treatment period, and the 78-week extension period. Patients' metformin dose during the 24-week short-term treatment period was based on their metformin dose during the last 12 weeks before enrolment and was kept stable. Rescue medication was sitagliptin 100 mg, and was dispensed if necessary.

d) Study 5

Study 5 compared three different dosages of dapagliflozin (2.5 mg, 5 mg, or 10 mg) with placebo, all on a background of the sulfonylurea glimepiride, at a dose of 4 mg per day. Before randomization, patients had been on a stable sulfonylurea monotherapy dose that was at least half the maximal recommended dose for a minimum of eight weeks' duration. Patients could either switch to glimepiride monotherapy during the lead-in period or, if they had been on a stable dose of 4 mg per day glimepiride monotherapy before enrolment, they could skip the lead-in period. Possibility of down-titration of open-label glimepiride, down to 2 mg during the treatment period, could be considered as an option to discontinuation in case of one or more minor hypoglycemic events, to mitigate recurrent hypoglycemic events. If further hypoglycemic events occurred, the open-label glimepiride could be down-titrated to 0 mg at the discretion of the investigator.

Subjects received open-label rescue therapy (metformin, pioglitazone, or rosiglitazone) in addition to their current randomized treatment and open-label glimepiride therapy if repeated FPG measurements from the central laboratory showed lack of efficacy based on progressively stricter glycemic criteria. For

example, rescue was initiated in weeks 4 through 7 if FPG was more than 15 mmol/L, in weeks 8 through 11 if FPG was more than 13.2 mmol/L, and in weeks 12 through 24 if FPG was more than 11.1 mmol/L.

Patients with a central laboratory FPG value meeting the criterion of the lack of glycemic control at a study visit were scheduled for an additional visit (within three to five days) to obtain the second central laboratory FPG value and review their glucometer readings. If the repeated central laboratory FPG value still met the criterion, the patient remained in the study but had to receive rescue therapy. The rescue therapy consisted of open-label metformin, pioglitazone, or rosiglitazone, prescribed at the investigator's discretion but according to local standards of care and approved prescribing guidance.

e) Study 6

Study 6 compared three different dosages of dapagliflozin (2.5 mg, 5 mg, or 10 mg) with placebo, all on a background of insulin, with or without a maximum of two additional oral antidiabetes drugs. Insulin was titrated as described below.

Eligible patients were randomized at visit 2 if the calculated mean daily insulin dose over the previous seven documented days was at least 30 IU and if insulin doses on single days did not vary by more than 10% of the calculated mean daily insulin dose on more than one occasion. Patients were instructed to keep the dose of their insulin (and oral antidiabetes drug, if applicable) unchanged. The appropriateness of the current insulin dose was reviewed by the investigator at each study visit, and changes in dose were considered if clinically indicated. Up-titration was defined as an increase in mean daily insulin dose that met both of the following criteria:

1. The increase in insulin dose is more than 5 IU (i.e., 6 IU or greater)
   and
2. The increase in insulin dose is greater than 10% of the baseline insulin dose (baseline insulin dose is calculated daily mean insulin dose documented at visit 2, week 0).

Insulin dose changes during hospitalization or temporary increases (e.g., due to an infection) were not considered as up-titration, as long as such an increase was for a period of not more than 10 days and the insulin dose was expected to return to the baseline level.

Up-titration of insulin was considered by the investigator under the following circumstances:

- **From visit 3 to visit 6:**
  - If the FPG measurement taken at the site at visits 3 (week 1), 4 (week 4), 5 (week 8), or 6 (week 12) exceeded 13.3 mmol/L, and this FPG result was confirmed by both the central laboratory and a repeat FPG measurement at the site at a return visit within 72 hours, or
  - If at least three fasting self-monitored blood glucose (SMBG) diary measurements from the previous seven days exceeded 13.3 mmol/L. Diary fasting SMBG values that met these criteria were recorded in the electronic case report form (eCRF).

- **From visit 6 to visit 9:**
  - If the FPG measurement taken at the site at visits 7 (week 16), 8 (week 20), **or** 9 (week 24) exceeded 12.2 mmol/L, and this FPG result was confirmed by both the central laboratory and a repeat FPG measurement at the site at a return visit within 72 hours, or
  - If at least three fasting SMBG diary measurements from the previous seven days exceeded 220 mg/dL (12.2 mmol/L). Diary fasting SMBG values that met these criteria were recorded in the eCRF.

The last A1C and FPG values measured by the central laboratory before the up-titration of insulin dose were carried forward for the efficacy analyses at week 24 (visit 9). **Reduction** of daily insulin dose was ordered by the investigator under the following circumstances:

- **Within the first seven days of active randomized treatment:**
  - If the patient reported two or more readings of plasma glucose value ≤ 4.4 mmol/L.

- **After the first seven days of active randomized treatment:**
  - If the patient reported two of more readings of plasma glucose value ≤ 3.8 mmol/L. Patients were encouraged to contact the investigator in such a case to allow the reduction of insulin dose.

f) Study 18

Dose titration of blinded study medication was not permitted at any time during the study. In addition, the dose of open-label metformin remained unchanged for the entire duration of the DB treatment period. Patients with lack of glycemic control from weeks 6 to 24 during the DB treatment period were eligible to receive open-label rescue medication, in addition to their current DB treatment. Lack of glycemic control was defined as an FPG more than 13.3 mmol/L in weeks 6 to 11, or an FPG of more than 11.1 mmol/L in weeks 12 to 24. During the DB treatment period, all rescue decisions were based on the central laboratory FPG result and a repeat, confirmatory FPG measurement.

If patients met the protocol-specified glycemic criteria based on FPG, they completed a rescue visit. It was mandatory for patients who met rescue criteria in the DB treatment period to first complete the rescue visit procedures before receiving open-label rescue medication in order to ensure important trial end point measurements were collected. Following completion of the rescue visit, patients were given open-label antidiabetes rescue medication (insulin or other antidiabetes agents except glucagon-like peptide-1 [GLP-1] analogues, other DPP-4/SGLT-2 inhibitors, or metformin) to be initiated at the lowest starting dose and titrated in accordance with the approved product label in the applicable country at the discretion of the Investigator, in addition to their DB study medication. Patients given rescue medication then continued in the DB treatment period according to their original visit schedule.

3.2.4 Outcomes

Change from baseline in A1C was the primary outcome in all but one study (study 12). Blood samples for clinical laboratory tests were obtained by standardized techniques and assessed by the central laboratory. In all studies but Study 4 and Study 18, A1C was assessed at baseline and every four weeks. In Study 4, laboratory assessments were performed every three weeks during the 18-week dose-titration period and every eight weeks until week 42, and then at 52 weeks. In Study 18, A1C was assessed at baseline and every six weeks.

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) has been developed to assess patients' satisfaction with treatment and perception of change in hyper- and hypoglycemia. The DTSQ has two versions: the DTSQ status version (DTSQs) and the DTSQ change version (DTSQc). Both versions have eight items and differ from each other only in item 7. However, the DTSQc instructions and response options differ from those of the DTSQs, as the change version assesses relative change in satisfaction rather than absolute satisfaction. The DTSQs was used at baseline (visit 5) and at visit 12, and the DTSQc at visit 15 (end of maintenance randomized treatment period).

The scoring of the DTSQs is presented below and includes measures of satisfaction:

- Treatment Satisfaction: The following items will produce a Treatment Satisfaction score — Items 1, 4, 5, 6, 7, and 8 (range 0 to 36). The higher the score, the greater the satisfaction with treatment.
- Individual satisfaction with treatment items (1, 4, 5, 6, 7, and 8): All items are rated from 6 (very satisfied, convenient, flexible, etc.) to 0 (very dissatisfied, inconvenient, inflexible, etc.). The higher the score, the greater the satisfaction with each aspect of treatment.
- "Perceived frequency of hyperglycemia" (item 2) and "Perceived frequency of hypoglycemia" (item 3): Both items are rated from 6 (most of the time) to 0 (none of the time). Lower scores indicate levels closer to the ideal, and higher scores indicate problems.

The scoring of the DTSQc is presented below and includes measures of relative change in satisfaction:

- Treatment Satisfaction (change): items 1, 4, 5, 6, 7, and 8 are summed to produce a treatment satisfaction (change) score (range +18 to –18). The higher (lower) the score, the greater the improvement (deterioration) in satisfaction with treatment. A score of 0 represents no change.
- Individual satisfaction with treatment change items (1, 4, 5, 6, 7, and 8), range +3 to –3. The higher (lower) the score, the greater the improvement (deterioration) in satisfaction of each aspect of treatment.
- "Perceived frequency of hyperglycemia" (item 2) and "Perceived frequency of hypoglycemia" (item 3) range from +3 ("much more of the time now") to –3 ("much less of the time now"). Negative scores indicate fewer problems with blood glucose levels. Positive scores indicate more problems than before.

No minimal clinically important difference (MCID) was identified for the DTSQs or DTSQc.

Health-related quality of life was assessed using the EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D) in Study 12. The descriptive system of the EQ-5D consists of five questions assessing the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses to the five questions define a health state for which a utility index can be derived by converting healthy states by applying preference weights elicited from general population samples. The scores can range from below 0 (worse than death) to 100, and higher scores represent better perceived health. The second component of the EQ-5D is a visual analogue scale (VAS), asking patients to rate their health from 0 to 100 (0 represents worst imaginable health state and 100 represents best imaginable health). If a patient could not give or decide upon a response, no response was recorded. The investigator or designated site personnel checked that all items had been completed by the patient, but responses were not scrutinized. An MCID specific to diabetes for the EQ-5D has not been identified.

Three blood pressure measurements were taken, using a standardized cuff adapted to the size of the patient's arm. All three readings were recorded. For analysis, the average of the three blood pressure readings was used. Blood pressure readings were taken with the patient seated comfortably with the arms raised to the level of the heart and in a supported position. All readings were recorded as accurately as possible, and the same blood pressure machine was used for all assessments for a given patient.

The patient's weight was recorded in kilograms, to one decimal place, on a fasting stomach with light clothing and no shoes. All readings were to be recorded as accurately as possible and the same scale used for all assessments for a given patient.

Across studies, where described, FPG was typically self-monitored at least every second day during the lead-in period, the placebo lead-in, and the titration period, and at least once a week during the remaining treatment and extension periods. If self-monitored FPG was above 15 mmol/L, the patients were to repeat the self-monitoring of FPG within one or two days, depending on the study. If this second FPG was above 15 mmol/L, the patient contacted the study centre and, if appropriate, scheduled a FPG measurement at the centre (analyzed by the central laboratory).

Major hypoglycemic events were typically defined as symptomatic events requiring external assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value less than 3.0 mmol/L, and prompt recovery after glucose or glucagon administration. A minor hypoglycemic event was defined as either a symptomatic event with a capillary or plasma glucose value less than 3.5 mmol/L, and no need for external assistance, or an asymptomatic blood glucose measurement less than 3.5 mmol/L.

3.2.5 Statistical Analysis

a) Study 4

To demonstrate non-inferiority of dapagliflozin in comparison with glipizide as add-on therapy to metformin for changes from baseline to week 52 in A1C within a non-inferiority margin of 0.35%, assuming a standard deviation (SD) of 1.25%, and at a one-sided significance level of 0.025, 280 evaluable patients were needed in each treatment group to provide approximately 90% power (given a true difference of 0 between the two treatment groups). Assuming a 5% exclusion rate from the full analysis set, 295 patients per treatment group were needed for the full analysis set. Additionally, to have 90% power for the per-protocol population, assuming a 25% exclusion rate from the per-protocol population, 373 patients per treatment group (746 patients total) were planned for randomization. In six-month dapagliflozin studies, an SD of 1.1% was selected based on the phase 2 dapagliflozin study as well as historical data from other diabetes programs. A slightly larger SD, 1.25%, was chosen for this study because of the titration regimen for dapagliflozin and the longer duration of the trial.

The primary analysis was based on the full analysis set, after a protocol amendment. It is not clear why this amendment was made, as originally the primary analysis was to be performed on the per-protocol set. The analysis was repeated with the per-protocol set to examine the robustness of the results. An assessment of the primary variable in patients completing 52 weeks of treatment was also performed. Secondary and tertiary efficacy analyses used the full analysis set as the primary analysis set, and selected secondary end points were also analyzed with the per-protocol analysis set. Missing values at week 52 were replaced by last observation carried forward (LOCF).

The absolute change from baseline to week 52 in A1C was analyzed using an analysis of covariance (ANCOVA) model with a factor for treatment group (fixed effect) and covariate for baseline A1C. The model was used to derive a least squares estimate of the treatment difference in mean change, with corresponding two-sided 95% confidence interval (CI). If the upper limit of the 95% CI was < 0.35%, then dapagliflozin as add-on therapy to metformin was considered to be non-inferior to glipizide as add-on therapy to metformin. Further, two-sided 95% CIs were calculated for the mean change within each treatment group. According to the manufacturer, this non-inferiority margin was derived from the literature; non-inferiority margins of 0.2% to 0.4% for change from baseline A1C are commonly used in studies comparing oral antidiabetes agents. Although this value of 0.35% falls within this range, there is no further indication of how this number was determined. The secondary outcomes were superiority analyses.

To preserve the type 1 error rate ≤ 0.050 (two-sided) across the primary end point and three key secondary end points, a hierarchical closed testing procedure was used to interpret the statistical significance of these treatment comparisons. The non-inferiority of the primary end point was tested first, followed by the key secondary end points in the order specified. The primary comparison was tested at a one-sided 0.025 significance level. The key secondary analyses were conducted at a two-sided 0.050 significance level. However, a comparison was confirmed as statistically significant only if it achieved its specified significance level and all preceding comparisons had achieved their specified significance levels.

Continuous secondary efficacy variables were analyzed by means of an ANCOVA for change from baseline using treatment group as a fixed effect and baseline value as a covariate. By analogy to the primary efficacy variable, the model was used to derive point estimates and two-sided 95% CIs for the mean change within each treatment group as well as for the difference in mean change between the two treatment groups. Nominal *P* values for the difference between the treatment groups were provided. When examining results within a subgroup (e.g., changes in body weight among subjects with baseline BMI ≥ 30 kg/m^2), the same methods were used. However, only point estimates and 95% CIs were reported. Treatment-by-subgroup interaction *P* values were reported.

b) Study 14

With 129 patients per treatment group with post-baseline measurements, there was 90% power to detect a difference in means of 0.5% between each dapagliflozin plus metformin treatment group and the placebo plus metformin group, assuming an SD of 1.1%. Assuming that 5% of patients did not have a post-baseline assessment, a total of 544 patients (136 patients per treatment group) needed to be randomized.

The primary efficacy analysis compared the change in A1C from baseline at week 24 (or the last post-baseline observation before rescue and before week 24 if no week 24 assessment was available or rescue medication was taken before the week 24 assessment) for each of the three dapagliflozin plus metformin treatment groups and the placebo plus metformin group. This analysis was based on an ANCOVA model with the treatment group as an effect and the baseline value as a covariate. Each comparison between a dapagliflozin plus metformin group and the placebo plus metformin group was carried out at the two-sided 0.019 significance level using Dunnett adjustment so that the familywise type 1 error rate was controlled at the 0.05 significance level. Missing data were imputed using the LOCF method. Efficacy analyses were based on the randomized data set, described below.

The familywise type 1 error rate related to the primary and (key) secondary efficacy end points was controlled at the two-sided 0.05 level within each treatment group by using a hierarchical closed testing procedure. In other words, the hierarchical closed testing procedure handled each investigative treatment separately. The significance or non-significance of the treatment comparisons for the primary efficacy end point determined whether the statistical tests were performed to compare treatments for the secondary efficacy end points. Only for those primary investigative treatment groups significantly superior to control for the primary efficacy end point were comparisons for the first secondary end point performed. The steps were to be repeated for all (key) secondary end points until the testing stopped. The testing stopped for a treatment group if the previous comparison was not significant.

Subgroup analyses for the primary outcome were carried out based on race, gender, ethnicity, baseline A1C (< 8%, ≥ 8 and < 9%, ≥ 9%), age (< 65 years, ≥ 65 years), geographic region, and gender/age (female ≤ 50 years, female > 50 years). The subgroup-by-treatment interaction was assessed for the primary

efficacy end point (LOCF) using an ANCOVA model with subgroup and subgroup-by-treatment group interaction as two additional effects.

The ANCOVA of the primary efficacy end point was repeated in sensitivity analyses to assess the robustness of the primary efficacy analysis including patients in:

- The randomized subjects data set who had a baseline assessment and a week 24 A1C assessment (i.e., completers analysis without LOCF methodology) (excluding any post-rescue assessments)
- The randomized subjects data set who had a baseline assessment and any post-baseline short-term DB treatment-period A1C assessment (excluding any post-rescue assessment) utilizing a longitudinal repeated measures methodology
- The randomized subjects data set who had a baseline assessment and any post-baseline short-term DB treatment period A1C assessment (regardless of rescue) utilizing a longitudinal repeated measures methodology that included an additional indicator variable to represent whether rescue had occurred at each visit
- The evaluable subjects data set who had a baseline assessment and any post-baseline short-term DB treatment period A1C assessment.

c) Study 12

The sample size for this study was selected to demonstrate a difference in the mean change in body weight from baseline to week 24 between dapagliflozin plus metformin versus metformin monotherapy (i.e., placebo plus metformin) as the primary efficacy outcome. An earlier study (MB102008), which was analyzed before developing the protocol for the present study, provided 12-week data for changes in body weight. The average, placebo-corrected change in weight for the 10 mg dapagliflozin group was 1.3 kg at 12 weeks, and the SD across the dapagliflozin doses was 2.6 kg. It was anticipated that data over 24 weeks would demonstrate a greater weight reduction, 2 kg, as well as greater variability. Assuming an approximately 50% increase in variability, an SD of 4.0 kg was selected for this calculation. To detect a difference of 2 kg between the treatment groups, 86 evaluable patients per treatment group were required for 90% power at a two-sided significance level of 0.050. Assuming that 5% of the randomized patients would be excluded from the primary analysis because of missing data (e.g., lost to follow-up), at least 182 patients total needed to be randomized.

The following testing procedure was used to control the type 1 error rate ≤ to 0.050 (two-sided) across the primary and key secondary efficacy variables. First, the primary efficacy variable was tested at a significance level of 0.050. Only if the primary variable proved significant, the results of the key secondary variables were interpreted as significant using Hochberg's method, which is a variation of the Bonferroni correction procedure. The primary efficacy variable and continuous secondary efficacy variables were analyzed using an ANCOVA with treatment group and gender as fixed effects and baseline value as a covariate. The model was used to derive a least squares estimate of the treatment difference in mean change with corresponding *P* value and two-sided 95% CI. Further, two-sided 95% CIs for the mean change within each treatment group were calculated. Comparisons between treatment groups in proportions were performed using the methodology of Zhang, Tsiatis, and Davidian, and of Tsiatis, Davidian, Zhang, and Lu, with adjustment for baseline value. Efficacy was evaluated using the full analysis set. The safety analysis set was used in all summaries of safety data.

The LOCF approach was used for all variables regardless of rescue medication, except for glycemic variables. For glycemic variables (e.g., A1C, FPG), if a patient initiated rescue medication, the last value taken on or before the first rescue dose was used for analysis.

To preserve the type 1 error rate ≤ 0.050 (two-sided) across the primary and three key secondary variables, the following testing procedure was used. The primary end point was tested at a two-sided significance level of 0.050. If the *P* value was significant, then the results of the key secondary end points were interpreted using Hochberg's method. Nominal *P* values for the differences between the dapagliflozin group and the placebo group were determined. If the largest of the three *P* values was 0.050 or less (two-sided), then all key secondary end points were declared statistically significant. If the largest of the *P* values was > 0.050 (two-sided), then it was not significant. However, the second largest of the three *P* values was assessed for significance at a 0.025 level (two-sided). If this *P* value was significant, then both it and the smallest *P* value were declared statistically significant. However, if this *P* value was not significant, then the smallest *P* value was assessed for significance at a 0.0167 level (two-sided).

Subgroup analyses for change in total body weight from baseline to week 24 were conducted for gender, age (< 65, ≥ 65 years), baseline BMI (< 27,, ≥ 27 and < 30, ≥ 30 kg/m^2), country, baseline A1C and baseline estimated glomerular filtration rate (eGFR).

d) Study 5

Each pairwise treatment group comparison was tested at a significance level of approximately 0.019, according to the Dunnett method, in order to maintain an overall type 1 error rate ≤ 0.050 for the primary objective. To detect a difference of 0.5% between each dapagliflozin group versus placebo for changes in A1C from baseline to week 24, assuming an SD of 1.1%, and at a two-sided significance level of 0.019, 129 evaluable patients were needed in each treatment group to provide 90% power. Assuming that 5% of the patients would not be evaluable in the full analysis set, 136 patients per treatment group (544 patients total) were planned for randomization.

The change from baseline to week 24 in A1C was analyzed on the full analysis set using an ANCOVA with a factor for treatment group (fixed effect) and a covariate for baseline A1C. The model was used to derive least squares estimates of the treatment differences (each dapagliflozin dose group versus placebo) in mean change with corresponding *P* value and two-sided 95% CI. Further, two-sided 95% CIs for the mean change within each treatment group were calculated.

Continuous secondary efficacy variables and exploratory variables were analyzed by means of an ANCOVA for change from baseline using treatment group as a fixed effect and baseline value as a covariate. By analogy to the primary efficacy variable, the model was used to derive point estimates and two-sided 95% CIs for the mean change within each treatment group as well as for the difference in mean change between each dapagliflozin group versus placebo. Nominal *P* values for the difference from placebo were provided. For efficacy outcomes, missing values were replaced by the LOCF approach.

To preserve the type 1 error rate ≤ 0.050 (two-sided) across the primary objective and five key secondary end points, a hierarchical step-wise procedure was used to interpret the statistical significance of the treatment comparisons. Pairwise comparisons for the primary end point were evaluated using the Dunnett method, with a two-sided significance level of 0.019. For each dapagliflozin treatment group, if the primary comparison was statistically significant, the inference drawn from the key secondary end points proceeded in a step-wise fashion. The key secondary end points were evaluated at a two-sided significance level of 0.050 in the order specified in the objectives. If or when a nominal *P* value > 0.050 was reached, it was declared not statistically significant, and no further inference was made on the remaining end points in the sequence.

The ANCOVA of the primary efficacy end point was repeated in sensitivity analyses, including completers' analysis (patients in the full analysis set who had a baseline assessment and a week 24 A1C assessment), and utilizing a longitudinal repeated measures methodology on the full analysis set, repeated for excluding and including any post-rescue assessments.

Subgroup analyses for change in A1C from baseline to week 24 (LOCF) were conducted for gender, age (< 65, ≥ 65, ≥ 75 years), female age (≤ 50 and > 50 years), race, ethnicity, geographic region (Asia/Pacific, Europe), baseline A1C (< 8%, ≥ 8 and < 9%, ≥ 9%), baseline BMI (< 25 kg/m^2, ≥ 25 kg/m^2) and eGFR (≥ 30 to < 60, ≥ 60 to < 90, ≥ 90 mL/min/1.73 m^2). Treatment-by-subgroup interaction *P* values were presented.

e) Study 6

Each pairwise treatment group comparison was tested at a significance level of approximately 0.019, according to the Dunnett method, in order to maintain an overall type 1 error rate < 0.050 for the primary objective. To detect a difference of 0.5% between each dapagliflozin group versus placebo for changes from baseline to week 24 in A1C, assuming an SD of 1.2%, and at a two-sided significance level of 0.019, 153 evaluable patients were needed in each treatment group to provide 90% power. Assuming that 5% of the patients were not evaluable in the full analysis set, 161 patients per treatment group (644 patients total) were planned for randomization (808 were randomized). Originally, it was anticipated that approximately 1,600 patients would be enrolled; however, the number was decreased due to a lower screening failure rate than anticipated. No reason for the lower screening failure rate was described.

The change in A1C from baseline to week 24 was analyzed on the full analysis set using an ANCOVA with factors for treatment group and use of oral diabetes drug(s) as fixed effects and a covariate for baseline A1C. The model was used to derive least squares estimates of the treatment differences (each dapagliflozin dose group versus placebo) in mean change with corresponding *P* value and two-sided 95% CI. Further, two-sided 95% CIs for the mean change within each treatment group were calculated. The primary and secondary efficacy analyses are based on the full analysis set. Missing values were replaced by the LOCF approach.

To preserve the type 1 error rate ≤ 0.050 (two-sided) across the primary objective and within each dose group for the four key secondary end points, a hierarchical step-wise procedure was used to interpret the statistical significance of these treatment comparisons. Testing was performed for all efficacy comparisons. However, the pairwise comparisons for the primary end point were assessed at a significance level of 0.019 according to the Dunnett method. If the primary result was significant for a dapagliflozin treatment group, then the key secondary end points were assessed sequentially at a significance level of 0.05. If a result was not significant for a treatment group, then subsequent *P* values were not assessed for statistical significance.

Subgroup analyses for change in A1C from baseline to week 24 were done for baseline use of oral antidiabetes drugs, gender, age (< 65, ≥ 65, ≥ 75 years), female age (≤ 50 and > 50 years), race, ethnicity (Hispanic/Latino versus not Hispanic/Latino), geographic region (North America, Europe), baseline A1C (< 8%, ≥ 8 and < 9%, ≥ 9%), and baseline BMI (< 25 kg/m^2, ≥ 25 kg/ m^2). Treatment-by-subgroup interaction *P* values were reported.

f) Study 18

Power calculations were based on an ANCOVA with LOCF, with the expectation that this would provide a good estimate of the power for the primary analysis using a longitudinal repeated measures model. With 163 subjects per treatment group, there was 90% power to detect a difference in mean A1C of 0.4% between the saxagliptin plus dapagliflozin plus metformin treatment group and the saxagliptin plus metformin and dapagliflozin plus metformin groups, assuming a SD of 1.0%. Assuming that 5% of patients would not have a post-baseline assessment, a total of approximately 516 patients (172 patients per treatment group) needed to be randomized. Assuming that 50% of screened patients would fail to meet screening criteria, a total of 1,032 patients needed to be screened.

The primary efficacy analysis was performed using a longitudinal repeated measures analysis with terms for baseline value, treatment group, time, the interaction of treatment group and time, and the interaction of baseline value and time, including only observations before rescue. Point estimates and 95% CIs were calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

A hierarchical closed testing procedure was performed to control the familywise type 1 error rate at the two-sided 0.05 level for all treatment groups across the primary and secondary efficacy end points. Within each treatment group, the statistical testing proceeded to each secondary end point only if all previous end points were significant. If the procedure had reached a result that was not significant, the testing would have been stopped. At each step in the sequential testing, point estimates, 95% CIs for treatment effects and mean treatment differences were calculated. As previously noted, *P* values for treatment comparison were presented when all preceding comparisons were significant.

Sensitivity analyses for A1C included additional repeated measures analyses and ANCOVA analyses. The repeated measures analyses included two separate analyses, including values after rescue and including or excluding a time-dependent covariate for rescue. Two separate ANCOVA analyses of the change from baseline at week 24 were performed, with terms for treatment group and baseline value in the model. One analysis was based on measurements at week 24 or the last post-baseline measurement before week 24 and before rescue (if applicable), if no week 24 assessment was available (i.e., LOCF). The second sensitivity analysis using ANCOVA was based on all subjects completing the DB period without requiring glycemic rescue therapy.

Subgroup analyses for change in A1C from baseline to week 24 were conducted for gender, age (< 65, ≥ 65, ≥ 75 years), female age (≤ 50 and > 50 years), race, geographic region (North America, Europe), and baseline A1C (< 8%, ≥ 8 and < 9%, ≥ 9%). Treatment-by-subgroup interaction *P* values were reported.

Analysis Populations

All efficacy analyses were based on the full analysis set or the randomized subjects data set.

g) Studies 4, 5, 6, and 12

The full analysis set included all randomized patients (as randomized) who received at least one dose of study medication during the 24-week DB treatment period and who had a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable during the DB treatment period. Missing values were replaced by the LOCF approach.

The per-protocol analysis set is a subset of the full analysis set consisting of patients who did not violate the terms of the protocol that could affect the primary efficacy end point significantly.

Safety analysis was based on the safety analysis set, which consisted of all patients who received at least one dose of DB study medication during the short-term DB treatment period.

h) Studies 14 and 18

The randomized subjects data set consisted of all randomized patients who took at least one dose of DB study medication during the short-term DB period. When using the randomized subjects data set, patients were presented in the treatment group to which they were randomized at the start of the short-term DB treatment period, even if the treatment they received was different.

The evaluable subjects data set was a subset of the randomized subjects data set. It excluded primary efficacy variable data that may have been affected by protocol deviations, as determined by the medical monitor.

The treated subjects data set consisted of all patients who received at least one dose of DB study medication during the short-term DB treatment period. Unlike the randomized subjects set, the treated subjects data set included any patient who accidentally received DB study medication, but was not randomized into the study.

3.3 Patient Disposition

The highest discontinuation rate among core studies was in Study 4: 21% with dapagliflozin and 23% with glipizide. Study 4 also had the longest duration (52 weeks) (Table 21). For the other core studies, all 24 weeks in length, the proportion of patients discontinuing was approximately 10% or less, with the exception being Study 6, in which 15% of placebo patients discontinued treatment (Table 25). Study 6 was also the study that enrolled patients with the longest duration of disease, with higher BMI and A1C. Discontinuations continued into the extensions and, depending on the length of the extension, could exceed 20% of the original randomized population. Across core studies, AEs and withdrawn consent were common reasons for discontinuation.

Discontinuations were generally similar between groups within studies. One exception was Study 6, in which the proportion of patients discontinuing was 9% for dapagliflozin 10 mg and 15% for placebo (Table 25Table 25).

TABLE 21: PATIENT DISPOSITION (ADD-ON TO METFORMIN, VERSUS SULFONYLUREA)

	Study 4		Study 4-LT1		Study 4-LT2	
	Dapagliflozin N = 406	**Glipizide N = 408**	**Dapagliflozin N = 315**	**Glipizide N = 309**	**Dapagliflozin N = 204**	**Glipizide N = 188**
Enrolled, N	1,217					
Entered lead-in	922					
Randomized and treated	406	408				
Discontinued, N (%)	84 (21)	94 (23)	87 (21)	6)	43 (10)	47 (12)
adverse event	33 (8)	19 (5)	6 (2)	8 (2)	14 (3)	14 (3)
incorrect enrolment	1 (< 1)	1 (< 1)	–	–	–	–
no longer meets study criteria	6 (2)	27 (7)	59 (15)	79 (19)	9 (2)	12 (3)
withdrawn consent	23 (6)	32 (8)	15 (4)	11 (3)	14 (3)	3)
lost to follow-up	3 (1)	3 (1)	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)

	Study 4		Study 4-LT1		Study 4-LT2	
	Dapagliflozin N = 406	**Glipizide N = 408**	**Dapagliflozin N = 315**	**Glipizide N = 309**	**Dapagliflozin N = 204**	**Glipizide N = 188**
poor/ non-compliance	5 (1)	1 (< 1)	0	1 (< 1)	1 (< 1)	1 (< 1)
safety	1 (< 1)	0	–	–	–	–
death	1 (< 1)	3 (1)	0	1 (< 1)	2 (1)	1 (< 1)
other	11 (3)	8 (2)	6 (2)	4 (1)	2 (1)	7 (2)
Full analysis set, N	400 (99)	401 (98)				
Per-protocol, N	360 (89)	353 (87)				
Safety, N	406 (100)	408 (100)				
Entered extension, n (%)	315 (78)	309 (76)	204 (50)	188 (46)		
Extension completers, n (%)			228 (56)	204 (50)	161 (40)	141 (35)

Source: Clinical Study Report for Study 4.[1]

TABLE 22: PATIENT DISPOSITION (ADD-ON TO METFORMIN, VERSUS PLACEBO)

	Study 12		Study 12 Extension	
	Dapagliflozin 10 mg N = 91	**Placebo N = 91**	**Dapagliflozin 10 mg**	**Placebo**
Enrolled, N	314			
Entered lead-in, N	210			
Randomized, N (%)	91 (100)	91 (100)		
Discontinued, N (%)	8 (9)	5 (6)	22 (24)	22)
adverse event	2 (2)	0	(4)	0
no longer meets study criteria	1 (1)	1 (1)	11 (12)	14)
withdrawn consent	4 (4)	1 (1)	6 (7)	(3)
poor/non-compliance	0	2 (2)	0	(3)
death	1 (1.1)	0	1 (1)	0
administrative reason by sponsor	0	1(1.1)	0	1 (1)
Full analysis set, N	89 (98)	91 (100)		
Per-protocol, N	83 (91)	85 (93)		
Safety, N	91 (100)	91 (100)		
Extension completers, N			79 (86)	78 (86)

Source: Clinical Study Report for Study 12.[3]

TABLE 23: PATIENT DISPOSITION (ADD-ON TO METFORMIN, VERSUS PLACEBO)

	Study 14			Study 14 Extension		
	Dapagliflozin 5 mg N = 137	**Dapagliflozin 10 mg N = 135**	**Placebo N = 137**	**Dapagliflozin 5 mg N = 122**	**Dapagliflozin 10 mg N = 119**	**Placebo N = 115**
Enrolled, N	915					
Entered lead-in	562					
Randomized	137	135	137	122	119	115

	Study 14			Study 14 Extension		
	Dapagliflozin 5 mg N = 137	**Dapagliflozin 10 mg N = 135**	**Placebo N = 137**	**Dapagliflozin 5 mg N = 122**	**Dapagliflozin 10 mg N = 119**	**Placebo N = 115**
Discontinued, N (%)	15 (11)	14 (10)	18 (13)	33 (27)	24 (20)	42 (37)
adverse event	2 (2)	3 (2)	4 (3)	3 (3)	2 (2)	5 (4)
administrative reason by sponsor	0	1 (1)	1 (1)	-	-	-
no longer meets study criteria	0	2 (2)	0	1 (1)	0	1 (1)
withdrawn consent	5 (4)	2 (2)	6 (4)	8 (7)	4 (3)	4 (4)
lost to follow-up	4 (3)	5 (4)	5 (4)	3 (3)	7 (6)	4 (4)
poor/non-compliance	2 (2)	0	0	1 (1)	2 (2)	0
lack of efficacy	–	–	–	17 (14)	9 (8)	27 (24)
death	–	–	–	0	0	0
other	1 (1)	1 (1)	0	0	0	1 (1)
Evaluable, n (%)	135 (99)	135 (100)	133 (97)			
Treated, n (%)	137 (100)	135 (100)	137 (100)			
Extension completers, n (%)				89 (73)	95 (80)	73 (64)

Source: Clinical Study Report for Study 14.[2]

TABLE 24: PATIENT DISPOSITION (ADD-ON TO SULFONYLUREA, VERSUS PLACEBO)

	Study 5			Study 5 (Extension)		
	Dapagliflozin 5 mg N = 145	**Dapagliflozin 10 mg N = 151**	**Placebo N = 146**	**Dapagliflozin 5 mg N = 132**	**Dapagliflozin 10 mg N = 141**	**Placebo N = 133**
Enrolled, N	859					
Entered lead-in						
Randomized	145	151	146			
Discontinued, N (%)	13 (9)	10 (7)	13 (9)	4 (3)	8 (5)	6 (4)
adverse event	3 (2)	3 (2)	3 (2)	0	0	2 (1)
no longer meets study criteria	2 (1)	0	2 (1)	1 (1)	1 (1)	1 (1)
withdrawn consent	3 (2)	2 (1)	8 (6)	2 (1)	4 (3)	0
lost to follow-up	1 (1)	1 (1)	0	0	1 (1)	1 (1)
poor/non-compliance	3 (2)	0	0	–	–	–
death	0	1 (1)	0	0	0	0
other	1 (1)	3 (2)	0	1 (1)	2 (1)	1 (1)
incorrect enrolment	–	–	–	0	0	1 (1)
Full analysis set, n (%)	142 (98)	151 (100)	145 (99)			
Per-protocol, n (%)	139 (96)	149 (99)	144 (99)			
Safety, n (%)	145 (100)	151 (100)	146 (100)			
Entered extension n (%)	132 (91)	141 (93)	133 (91)			
Completed extension, n (%)				128 (88)	133 (88)	127 (87)

Source: Clinical Study Report for Study 5.[4]

TABLE 25: PATIENT DISPOSITION (ADD-ON TO INSULIN, VERSUS PLACEBO)

	Study 6			Study 6 (Extension to Week 104)		
	Dapagliflozin 5 mg N = 212	**Dapagliflozin 10 mg N = 196**	**Placebo N = 197**	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**	**Placebo**
Enrolled, N	1240					
Randomized, N	212	196	197			
Discontinued, n (%)	26 (12)	18 (9)	29 (15)	21 (10)	6 (3)	14 (7)
adverse event	9 (4)	6 (3)	6 (3)	5 (2)	1 (1)	4 (2)
no longer meets study criteria	0	0	1 (1)	0	1 (1)	0
withdrawn consent	8 (4)	6 (3)	14 (7)	12 (6)	3 (2)	4 (2)
lost to follow-up	1 (1)	2 (1)	1 (1)	-	-	-
poor/non-compliance	4 (2)	3 (2)	3 (2)	0	0	2 (1)
death	1 (1)	0)	0	0	1 (1)	0
other	0	0	1 (1)	4 (2)	0	4 (2)
Full analysis set, n (%)	211 (100)	194 (99)	193 (98)	211 (100)	194 (99)	193 (98)
Per-protocol, n (%)	201 (95)	187 (95)	179 (91)			
Safety, n (%)	212 (100)	196 (100)	197 (100)	212 (100)	196 (100)	197 (100)
Entered extension, n (%)	150 (71)	148 (76)	122 (62)			
Extension completers, n (%)				129 (61)	142 (72)	108 (55)

Source: Clinical Study Report for Study 6.[5]

TABLE 26: PATIENT DISPOSITION (ADD-ON TO METFORMIN, TRIPLE VERSUS DUAL THERAPY)

	Study 18		
	Dapagliflozin/ Saxagliptin N = 179	**Dapagliflozin N = 179**	**Saxagliptin N = 176**
Enrolled, N	1,282		
Entered lead-in	639		
Randomized, N	179	179	176
Discontinued, N (%)	8 (5)	18 (10)	15 (9)
adverse event	0	0	0
subject request to discontinue study treatment	0	0	1(1)
administrative reason by sponsor	0	0	0
no longer meets study criteria	0	0	0
withdrawn consent	2 (1)	8 (5)	8 (5)
lost to follow-up	5 (3)	8 (5)	6 (3)
poor/non-compliance	0	0	0
lack of efficacy	0	0	0
death	0	0	0
other	1 (1)	1 (1)	0
pregnancy	0	1 (1)	0
Evaluable, N	NR	NR	NR
Treated, N	NR	NR	NR

Source: Clinical Study Report for Study 18.[6]

3.4 Exposure to Study Treatments

Exposure during the core study phase was longest in Study 4, which had the longest core phase of 52 weeks. Patients in the dapagliflozin group had slightly longer exposure (320 days) compared with the glipizide group (314 days) in this study. Across the placebo-controlled studies, which were all 24 weeks in duration, exposure was typically around 150 to 160 days, with no clear difference between groups within studies. Including extensions, the longest mean exposure to dapagliflozin was again in Study 4, at 880 days, versus 831 days with glipizide. This extension followed patients to 208 weeks.

3.5 Critical Appraisal

3.5.1 Internal Validity

Across studies, randomization was carried out using an automated response system, and adequate measures appear to have been taken to maintain allocation concealment, although no procedures to confirm this were described. Both the core studies and the extensions were DB, and blinding was achieved through the use of a placebo matched in appearance to the study drug. There are adverse effects associated with SGLT-2 inhibitors that could potentially lead to unblinding, most notably urogenital infections, as these are events that are relatively common and readily detectable by the patient.

Efficacy analyses were generally based on the full analysis set, which consisted of patients who had been randomized, received at least one dose, and had a baseline and at least one post-baseline assessment. Therefore, this was not a true intention-to-treat analysis, in which all patients are included in the analysis regardless of whether they received a dose and had assessments performed. The difference in sample size between the full analysis set and a true intention-to-treat was small in each study and unlikely to have affected results. Study 4 originally based the primary analysis on the per-protocol set, and this was appropriate for a non-inferiority design; however, it appears that after a protocol amendment, this was changed to the full analysis set. No reason for this change was provided. A sensitivity analysis was carried out in the per-protocol set, and the results did not change.

A hierarchical testing procedure was used to account for multiple comparisons among the key secondary end points. This is a common and appropriate strategy to account for multiplicity, and the manufacturer appears to have adhered to its stated hierarchical testing procedure.

There was a relatively large proportion of patients who discontinued from Study 4, the 52-week study: > 20% of the population in each group. Once the proportion of patients discontinuing exceeds a certain threshold, one can no longer be assured that the populations being compared are equivalent to each other, as it is possible that there may have been a disproportionate loss of patients in a certain subgroup. Concern over the potential for bias is increased when there is a differential proportion of discontinuations between groups; however, that does not appear to be the case in this study. The fact that Study 4 was a non-inferiority design also increases risk of bias, as there is no way to find differences in patients who are not followed; therefore, this biases toward a finding of non-inferiority. With respect to the extensions, there was a relatively large proportion of patients in all studies who failed to complete the study.

Study 4 was a non-inferiority study, and this is a common and appropriate design when there is an active comparator group. The manufacturer described the margin for non-inferiority and its application, as well as how it was derived. However, although the range of values from which the margin was chosen appears to be supported by the literature, it is not clear how the manufacturer chose the value for the margin of 0.35%, within the range of 0.20% to 0.40%. The non-inferiority margin was for the primary

outcome of change from baseline in A1C. It is not clear whether an MCID for A1C has been fully characterized in type 2 diabetes; therefore, it remains to be seen what would constitute an appropriate margin for non-inferiority for this outcome. The chosen non-inferiority margin of 0.35% is more than half of the improvement in A1C from baseline seen for both groups (0.52%).

Study 18 met the inclusion criteria for this systematic review, because it contained a group that had dapagliflozin plus metformin and a group that had a gliptin with metformin, a comparator of interest. However, the study was not planned to compare the two regimens; rather, it was planned to compare triple therapy (dapagliflozin, saxagliptin, and metformin) with those dual therapy groups. Thus, the study does not yield any results upon which conclusions can be drawn, and it is entirely hypothesis-generating.

The included trials were not designed to detect differences among secondary outcomes, and this included key outcomes such as body weight, which was a primary outcome in only one small study (Study 12). Additionally, studies were not powered to assess differences in harms, and this was particularly the case in Study 4, which was the only study with an active comparator.

Numerous subgroup analyses were performed in each of the included studies. However, where statistical comparisons were made between groups, there do not appear to have been any adjustments for multiple comparisons; therefore, these findings must be considered hypothesis-generating.

Missing data were generally imputed by use of LOCF in the primary analyses of all studies. This is an appropriate but conservative method for imputation that may affect findings. Sensitivity analyses were generally carried out in order to support these primary analyses, and this thus mitigates any concern with using this method.

3.5.2 External Validity

The ability to adjust dosing for background therapy was limited in many of the included studies. For example, in Studies 12 and 14, metformin background therapy could not be adjusted. In Study 4, it was not clear whether metformin dose could be adjusted. Although protocols for use of rescue therapy were often described, protocols for dose adjustments during hypoglycemic events were often not described, aside from Study 5, which used a sulfonylurea as background. The restrictions of dose adjustments to background therapy may be a generalizability issue, although it is understood that allowing dose adjustments to background therapy may confound the analysis.

The threshold for what was defined as a “minor” hypoglycemic event (< 3.5 mmol/L) is lower than the < 3.9 mmol/L often used in trials in diabetes.

In some studies, particularly Study 12, baseline A1C was relatively low, and therefore the degree to which populations in these studies were reflective of patients who would be considered for treatment with dapagliflozin in clinical practice is unclear.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 9). See Appendix 4 for detailed efficacy data.

3.6.1 Mortality

There were few deaths across the studies, with no clear pattern of deaths that could be attributed to either dapagliflozin or its comparators.

3.6.2 Morbidity

The included studies were not designed to specifically assess morbidity.

3.6.3 Quality of Life

In Study 4, for patients on a metformin background, there was no statistically significant difference in quality of life between dapagliflozin and glipizide after 52 weeks when assessed using the DTSQc (adjusted mean change versus glipizide of 0.7; 95% CI, –0.1 to 1.5; *P* = 0.0797) (Table 27). No MCID was found for the DTSQ.

Study 5 (sulfonylurea background) reported quality of life using the DTSQ, and there was no statistically significant difference in total scores after 24 weeks between dapagliflozin 5 mg (adjusted mean change versus placebo of 0.1; 95% CI, –1.1 to 1.3; *P* = 0.8695) and dapagliflozin 10 mg (adjusted mean change versus placebo of 0.6; 95% CI, –0.6 to 1.8; *P* = 0.3575) (Table 30).

Study 12 (metformin background) reported quality of life using the EQ-5D, and there was no statistically significant difference between dapagliflozin and placebo for overall VAS scores after 24 weeks (adjusted mean change versus placebo of –0.6; 95% CI, –3.9 to 2.8; *P* = 0.7449) or index scores after 24 weeks (adjusted mean change versus placebo of –0.01; 95% CI, –0.05 to 0.03; *P* = 0.4929) (Table 29). No MCID was found for the EQ-5D in diabetes.

No other studies reported quality of life data.

3.6.4 Glycated Hemoglobin

In Study 4, for patients on a metformin background, the adjusted mean change from baseline to week 52 was similar between dapagliflozin (–0.52%; standard error [SE] 0.04) and glipizide (–0.52%; SE 0.04), and the adjusted mean difference between dapagliflozin and glipizide was 0.00% (95% CI, –0.11% to 0.11%) (Table 27). Dapagliflozin was judged to be non-inferior to glipizide, as the upper limit of the 95% CI was less than the predefined threshold of 0.35%. There was no difference between dapagliflozin and glipizide in the proportion of patients achieving A1C of < 7% after 52 weeks (difference in proportions versus placebo, adjusted for baseline A1C, –4.6%; 95% CI, –10.9 to 1.7; *P* = 0.1542). The differences in adjusted mean changes in A1C from baseline between the dapagliflozin and the glipizide groups were consistent in LOCF and observed values at all time points for measurements. The per-protocol analysis (excluding any assessments of subjects who did not complete at least the week 18 visit and any assessments affected by a relevant protocol deviation) showed only marginal differences in mean reduction in A1C (–0.55% in the dapagliflozin and –0.56% in the glipizide group) compared with the primary analysis. At week 52 (LOCF), the difference in adjusted mean change from baseline in A1C between treatment groups was 0.00% (95% CI, –0.12% to 0.12%).

There was no statistical analysis provided for extension data; however, there appeared to be a numerically larger decrease in A1C from the original baseline to 104 weeks in dapagliflozin compared with glipizide, with an adjusted mean difference between groups of –0.18% (95% CI, –0.33% to –0.03%). The proportion of patients achieving glycemic control was 22% with dapagliflozin and 20% with glipizide.

In study 14, which included a metformin background, there was a statistically significant reduction in A1C versus placebo after 24 weeks in both the dapagliflozin 5 mg (adjusted mean difference of –0.41%; 95% CI, –0.61 to –0.21, *P* < 0.0001) and dapagliflozin 10 mg groups (–0.54%; 95% CI, –0.74 to –0.34; *P* < 0.0001) (Table 28). Sensitivity analyses were performed for the primary end point, and the results of longitudinal repeated measures analyses of A1C at week 24, excluding data after rescue, were consistent with the results of the primary efficacy analysis. In Study 12, there was a statistically significant reduction versus placebo after 24 weeks in the dapagliflozin 10 mg group (adjusted mean difference –0.28%; 95% CI, –0.42 to –0.15; *P* < 0.0001) (Table 29). There was no 5 mg group in this study. There was also a larger proportion of patients on dapagliflozin 5 mg versus placebo achieving an A1C less than 7% after 24 weeks in Study 14 (difference in proportions versus placebo, adjusted for baseline A1C, 11.7%; 95% CI, 1.3 to 22.1; *P* = 0.0275) and patients on dapagliflozin 10 mg versus placebo (difference in proportions versus placebo, adjusted for baseline A1C, 14.7%; 95% CI, 4.2 to 25.3; *P* = 0.0062) (Table 28). In Study 12, there was also a larger proportion of dapagliflozin 10 mg patients with an A1C of < 7% after 24 weeks, although no *P* value was reported (difference in proportions versus placebo, adjusted for baseline A1C, of 16.1%; 95% CI, 3.3 to 29.0) (Table 29). These differences between dapagliflozin and placebo appear to have been maintained in the extensions, to week 102 in each study.

In Study 5, which involved a sulfonylurea background, there was a statistically significant reduction in A1C in both the dapagliflozin 5 mg (adjusted mean difference −0.49%; 95% CI, −0.67 to −0.32; *P* < 0.0001) and the dapagliflozin 10 mg group versus placebo after 24 weeks (adjusted mean difference −0.68%; 95% CI, −0.86 to −0.51; *P* < 0.0001) (Table 30). There was also a larger proportion of dapagliflozin 5 mg patients versus placebo achieving an A1C < 7.0% after 24 weeks (difference versus placebo, adjusted for baseline, A1C 17.3%; 95% CI, 8.7 to 25.9; *P* = 0.0001) and dapagliflozin 10 mg patients versus placebo (difference versus placebo, adjusted for baseline A1C 18.7%, 95% CI, 9.9 to 27.4; *P* < 0.0001). The manufacturer performed a sensitivity analysis that included completers only (patients with non-missing baseline and week 24 values), and found a similar change in A1C when compared with the primary analysis, which imputed missing values using LOCF. These between-group differences appear to have been maintained in the extension to Study 5, to 48 weeks.

In Study 6, which includes an insulin background, there was a statistically significant reduction in A1C after 24 weeks in both the dapagliflozin 5 mg (adjusted mean difference –0.52%; 95% CI, –0.66 to –0.38; *P* < 0.0001) and the dapagliflozin 10 mg groups versus placebo (adjusted mean difference –0.60%; 95% CI, –0.74 to –0.45; *P* < 0.0001) (Table 31). There was also a larger proportion of patients on dapagliflozin 5 mg versus placebo achieving an A1C < 7% after 24 weeks (difference in proportions versus placebo, adjusted for baseline A1C, 11.1%; 95% CI, 4.6 to 17.6; *P* = 0.0009) and dapagliflozin 10 mg versus placebo (difference in proportions versus placebo, adjusted for baseline 12.8%; 95% CI, 5.9 to 19.8; *P* = 0.0003) (Table 31). These between-group differences appear to have been maintained in the extension to Study 6, to week 104.

The mean change from baseline in A1C was the primary outcome of Study 18; however, the primary analysis was between triple therapy (dapagliflozin plus saxagliptin plus metformin) and the two dual therapy groups (dapagliflozin plus metformin or saxagliptin plus metformin), and the two dual therapy groups were not formally compared. The adjusted mean change from baseline to 24 weeks in the dapagliflozin group was –1.20% (95% CI, –1.35 to –1.04) and in the saxagliptin group was –0.88% (95% CI, –1.03 to –0.72) (Table 32). The proportion of patients achieving an A1C < 7% after 24 weeks, adjusted for baseline A1C, was 22.2% (95% CI, 16.1 to 28.3) in the dapagliflozin group and 18.3% (95% CI, 13.0 to 23.5) in the saxagliptin group (Table 32).

The studies that had both approved doses of dapagliflozin were not designed to compare these two doses. There were no clear differences in A1C responses between the two doses in these studies.

In one of the network meta-analyses (NMAs) of second-line therapy with metformin (Appendix 7), dapagliflozin was found to provide a smaller decrease in A1C compared with empagliflozin, canagliflozin, exenatide, liraglutide, insulin glargine, glibenclamide, gliclazide, glimepiride, sitagliptin, pioglitazone, and rosiglitazone. In second-line therapy added to either sulfonylureas or insulin, comparisons were not conducted between SGLT-2 inhibitors. There was no difference in A1C-lowering effects between dapagliflozin and incretins on a sulfonylurea background, and with insulin (with or without metformin) background, there was also no difference between comparators, but sensitivity and subgroup analyses revealed a reduced ability of dapagliflozin to lower A1C compared with metformin.

In Study 4, there was no statistically significant interaction between subgroups based on baseline A1C (< 8%, ≥ 8% to < 9%, or ≥ 9% at baseline) (Table 39). There was a statistically significant interaction between subgroups based on baseline eGFR (Modification of Diet in Renal Disease), *P* = 0.0055 (Table 39). The reduction in A1C was numerically greater for dapagliflozin than glipizide in patients with normal renal function (adjusted mean difference between dapagliflozin and glipizide of –0.16; 95% CI, –0.32 to 0.00). However, as renal function decreased, the reduction in A1C was numerically smaller in the dapagliflozin group versus glipizide in patients with mild renal impairment (adjusted mean difference between dapagliflozin and glipizide of 0.11; 95% CI,–0.05 to 0.27). Although the sample size was small (N = 41 across groups, approximately 10% of the full analysis set), this difference grew larger in the patients with moderate renal impairment (adjusted mean difference between dapagliflozin and glipizide 0.56; 95% CI, 0.07 to 1.05). No *P* values were reported for between-group differences. Note that, according to the product monograph, dapagliflozin is contraindicated for use in patients with moderate renal impairment.

In the placebo-controlled studies, in patients with a background of metformin, there was no statistically significant interaction among subgroups in Study 14 based on baseline A1C (< 8%, ≥ 8% to < 9% at baseline), and no subgroup analysis was conducted based on eGFR (Table 40). In Study 12, the primary outcome was change in body weight, and subgroup analyses performed based on baseline A1C and renal function found no statistically significant interaction (Table 41). In patients on a sulfonylurea background (Study 5), there was no statistically significant interaction between subgroups based on baseline A1C; however, there was a statistically significant interaction for subgroups based on eGFR (*P* = 0.0115; Table 42). The largest difference between dapagliflozin groups and placebo was in patients with normal renal function, in the dapagliflozin 5 mg group (adjusted mean difference versus placebo–0.75; 95% CI, –1.06 to –0.45) and between dapagliflozin 10 mg and placebo (adjusted mean difference versus placebo–0.90; 95% CI, –1.21 to –0.59). In patients with mild renal impairment, the differences were smaller in both the dapagliflozin 5 mg (adjusted mean difference versus placebo –0.39; 95% CI, –0.62 to –0.16) and the dapagliflozin 10 mg (adjusted mean difference versus placebo –0.57; 95% CI, –0.80 to –0.34) groups. Although the sample size was small (N = 11 in each of the dapagliflozin groups and N = 24 with placebo), there was a notable difference in response based on dose in patients with moderate renal impairment. The difference between dapagliflozin 5 mg and placebo (adjusted mean difference versus placebo –0.04; 95% CI, –0.57 to 0.50) was smaller than the difference between dapagliflozin 10 mg and placebo (adjusted mean difference versus placebo –0.56; 95% CI, –1.10 to –0.03). Finally, in Study 6, with patients on a background of insulin, there was a statistically significant interaction reported in the subgroup based on baseline A1C (7.5% to 9%, or > 9%), *P* = 0.0023 (Table 43). At the lower baseline A1C, the differences between dapagliflozin 5 mg and placebo (adjusted mean difference versus placebo –0.43; 95% CI, –0.60 to –0.27; *P* < 0.0001) and dapagliflozin 10 mg and placebo (adjusted

mean difference versus placebo –0.48; 95% CI, –0.65 to –0.32; *P* < 0.0001) were smaller than at the higher baseline A1C (dapagliflozin 5 mg –0.76; 95% CI, –1.06 to –0.45; *P* < 0.0001; dapagliflozin 10 mg –0.94; 95% CI, –1.25 to –0.62; *P* < 0.0001). No interaction *P* value was reported for the subgroup based on baseline eGFR. There was a pattern, similar to that of the other studies, of an attenuation in response in patients with progressively worse renal impairment; however, without a *P* value no conclusions can be drawn regarding an interaction.

3.6.5 Fasting Plasma Glucose

In Study 4, dapagliflozin reduced FPG to a numerically greater extent than glipizide after 52 weeks; however, this difference was not statistically significant (adjusted mean change versus glipizide –0.2 mmol/L; 95% CI, –0.4 to 0.0; *P* = 0.1159) (Table 27). This difference continued into the extension to 104 weeks, although no statistical analysis was provided.

In the studies with background metformin, in Study 14, after 24 weeks, there was a statistically significant reduction in FPG versus placebo in both the dapagliflozin 5 mg (adjusted mean change versus placebo of –0.9 mmol/L; 95% CI, –1.3 to –0.4; *P* < 0.0001) and dapagliflozin 10 mg (adjusted mean change versus placebo of –1.0 mmol/L; 95% CI, –1.4 to –0.6; *P* < 0.0001) groups (Table 28). In Study 12, after 24 weeks there was a statistically significant reduction in FPG versus placebo in the dapagliflozin 10 mg group (adjusted mean change versus placebo of –0.9 mmol/L; 95% CI, –1.3 to –0.6; *P* < 0.0001) (Table 29). There was no dapagliflozin 5 mg group in this study.

In the study with background sulfonylurea, Study 5, after 24 weeks there was a statistically significant reduction in FPG versus placebo in both the dapagliflozin 5 mg (adjusted mean change versus placebo of –1.1 mmol/L; 95% CI, –1.5 to –0.7; *P* < 0.0001) and dapagliflozin 10 mg (adjusted mean change versus placebo of –1.5 mmol/L; 95% CI, –1.9 to –1.1; *P* < 0.0001) groups (Table 30).

In the study with background insulin, Study 6, after 24 weeks there was a statistically significant reduction in FPG versus placebo in both the dapagliflozin 5 mg (adjusted mean change versus placebo of –1.2 mmol/L; 95% CI, –1.7 to –0.7; *P* < 0.0001) and dapagliflozin 10 mg (adjusted mean change versus placebo of –1.1 mmol/L; 95% CI, –1.8 to –0.4; *P* < 0.0001) groups (Table 31).

The studies that had both approved doses of dapagliflozin were not designed to compare the two doses. In these studies, there was no clear or consistent difference between these two doses with respect to FPG when compared with placebo.

3.6.6 Body Weight

In Study 4, there was a greater reduction in body weight for dapagliflozin versus glipizide after 52 weeks (adjusted mean change versus glipizide of –4.65 kg; 95% CI, –5.14 to –4.17; *P* < 0.0001), and this difference was statistically significant (Table 27). There was a statistically greater proportion of patients treated with dapagliflozin versus glipizide who achieved a reduction in weight of at least 5% from baseline to 52 weeks (adjusted mean difference achieving 5% change of 31%; 95% CI, 26% to 36%; *P* < 0.0001) (Table 27).

In all studies, regardless of dose studied (dapagliflozin 5 mg or dapagliflozin 10 mg), the reduction in weight was statistically significantly larger for dapagliflozin than for placebo, whether on a background of metformin, a sulfonylurea, or insulin.

In the studies with background metformin, in Study 14, after 24 weeks there was a statistically significant reduction in weight versus placebo in both the dapagliflozin 5 mg (adjusted mean change versus placebo of –2.16 kg; 95% CI, –2.81 to –1.50; *P* < 0.0001) and dapagliflozin 10 mg (adjusted mean change versus placebo of –1.97 kg; 95% CI, –2.63 to –1.31; *P* < 0.0001) groups (Table 28). Body weight was the primary outcome of Study 12, and after 24 weeks there was a statistically significant reduction in weight versus placebo in the dapagliflozin 10 mg group (adjusted mean change versus placebo of –2.08 kg; 95% CI, –2.84 to –1.31; *P* < 0.0.0001) (Table 29). These differences appear to have remained into the extension to 102 weeks in Study 12, and further losses may have been achieved through week 102 in the extension to Study 14, although no statistical analysis was planned in either Study.

In Study 5, on a sulfonylurea background, after 24 weeks there was a statistically significant reduction in body weight versus placebo in both the dapagliflozin 5 mg (adjusted mean change versus placebo of –0.84 kg; 95% CI, –1.47,–0.21; *P* = 0.0091) and dapagliflozin 10 mg (adjusted mean change versus placebo of –1.54 kg; 95% CI, –2.17,–0.92; *P* < 0.0001) (Table 30). These differences appear to have remained into the extension to 48 weeks, although no statistical analysis was planned.

In Study 6, on an insulin background, after 24 weeks there was a statistically significant reduction in body weight versus placebo in both the dapagliflozin 5 mg (adjusted mean change versus placebo of –1.00 kg; 95% CI, –1.50 to –0.50; *P* < 0.0001) and dapagliflozin 10 mg (adjusted mean change versus placebo of –1.68 kg; 95% CI, –2.19 to –1.18; *P* < 0.0001) groups (Table 31). Further losses may have been achieved through week 104 in the extension to Study 6, although no statistical analysis was planned in this study.

The studies that had both approved doses of dapagliflozin were not designed to compare the two doses; however, there was no clear or consistent indication of dose–response effect, with a maximum difference between doses of well below 1 kg.

Study 18 was not planned to compare dapagliflozin plus metformin to saxagliptin plus metformin, and no statistical analysis was completed. However, there was a reduction in body weight in the dapagliflozin group from baseline to week 24 (adjusted mean change versus baseline of –2.4 kg; 95% CI, –2.9 to –1.9) but not in the saxagliptin group (adjusted mean change versus baseline of 0 kg; 95% CI, –0.5 to 0.5) (Table 32).

3.6.7 Blood Pressure

SBP was reduced to a greater extent with dapagliflozin than with glipizide (adjusted mean difference of –5.0 mm Hg; 95% CI, –6.7 to –3.4; *P* < 0.001), and this difference was statistically significant. DBP was also reduced to a greater extent with dapagliflozin than with glipizide (adjusted mean difference of –1.2 mm Hg; 95% CI, –2.3 to –0.2; *P* = 0.0179), and this difference was statistically significant (Table 27). The clinical significance of these changes in blood pressure is questionable.

In the placebo-controlled studies, statistical analysis for mean change in blood pressure was not reported in all studies. After 24 weeks in Study 12, on a metformin background, there was no difference in change in SBP or DBP between dapagliflozin 10 mg and placebo (Table 29). There was no dapagliflozin 5 mg group in this study. In Study 5 (sulfonylurea background), there was a statistically significant reduction in SBP at both dapagliflozin 5 mg and 10 mg doses, but not for DBP at either dose, versus placebo (Table 30). On an insulin background, the reduction in SBP was statistically significantly greater only at the higher dapagliflozin 10 mg dose versus placebo, and there was no statistically significant difference at either of the dapagliflozin doses for DBP (Table 31).

In Study 18 (metformin background), which was not designed to compare dapagliflozin with saxagliptin, the proportion of patients achieving a SBP of less than 130 mm Hg and a DBP of less than 80 mm Hg was reported. The proportions were 40% of dapagliflozin patients and 39% of saxagliptin patients (Table 32).

3.6.8 Other Efficacy Outcomes

Health care resource utilization was an "other" outcome of interest for this review; however, none of the included studies identified this as an efficacy outcome.

TABLE 27: KEY EFFICACY OUTCOMES (ADD-ON TO METFORMIN, VERSUS SULFONYLUREA)

	Study 4		Study 4-LT1 (Week 104)	
	Dapagliflozin N = 400	**Glipizide N = 401**	**Dapagliflozin**	**Glipizide**
Mortality				
Patients, n (%)	0	3 (1)	2	5
Reason		MI Mesenteric infarct Sudden death	Renal failure Septic shock	MI (2) Mesenteric infarct Sudden death MVA
Quality of Life (DTSQc Total Score)	N = 312	N = 303	N = 231	N = 205
Mean (SD) baseline	30.9 (5.41)	31.5 (5.01)		
Adjusted mean (SE) change, week 52[a]	14.3 (0.288)	13.6 (0.292)		
Adjusted mean change vs. glipizide [95% CI]	0.7 [–0.1 to 1.5], *P* = 0.0797			
Blood Glucose (FPG), mmol/L				
Mean (SD) baseline	9.0 (2.1)	9.1 (2.3)		
Adjusted mean (SE) change, week 52[a]	–1.2 (0.1)	–1.0 (0.1)		
Adjusted mean (SE) change, week 104[a]			–1.1 (0.1)	–0.6 (0.1)
Adjusted mean change vs. glipizide [95% CI]	–0.2 [–0.4 to 0.0], *P* = 0.1159		–0.4 [–0.7 to –0.1]	
A1C, %			N = 233	N = 208
Mean (SD) baseline	7.69 (0.86)	7.74 (0.89)		
Adjusted mean (SE) change at week 52[a]	–0.52 (0.0403)	–0.52 (0.0402)		
Adjusted mean (SE) change at week 104[a]			–0.29 (0.0532)	–0.12 (0.0546)
Adjusted mean change vs. glipizide [95% CI]	0.00 [–0.11 to 0.11]		–0.18 [–0.33 to –0.03]	
P value for non-inferiority[b]	Upper limit [95% CI]: 0.11, *P* < 0.0001			
Patients with A1C < 7.0% at week 52[c], n (%)	110 (27.5)	128 (31.9)		
Patients with A1C < 7.0% at week 104[c], n (%)			70/316 (22.2)	65/323 (20.1)
Adjusted mean % (SE)[95% CI][a]	27.4 (2.231)	32.0 (2.326)	21.8 [17.3 to 26.3]	20.4 [16.1 to 24.7]
Adjusted mean change vs. glipizide [95% CI]	–4.6 [–10.9 to 1.7], *P* = 0.1542		1.4 [–4.7 to 7.6]	
Body Weight, kilograms			N = 234	N = 211
Mean (SD) baseline	88.4 (16.3)	87.6 (17.0)		
Adjusted mean (SE) change at week 52[a]	–3.22 (0.1756)	1.44 (0.1754)		
Adjusted mean (SE) change at week 104[a]			–3.89 (0.2428)	1.18 (0.2498)
Adjusted mean change vs. glipizide [95% CI]	–4.65 [–5.14 to –4.17], *P* < 0.0001		–5.06 [–5.72 to –4.40]	
Patients with ↓weight of ≥ 5% by week 52, n (%)	133 (33)	10 (3)		

	Study 4		Study 4-LT1 (Week 104)	
	Dapagliflozin N = 400	**Glipizide N = 401**	**Dapagliflozin**	**Glipizide**
Patients with ↓weight of ≥ 5% by week 104, n (%)			95/400 (24)	11/401 (3)
Adjusted % (SE)	33.3 (2.354)	2.5 (0.779)	23.8 (2.128)	2.8 (0.815)
Adjusted mean change vs. glipizide [95% CI]	30.8 [26.0 to 35.7], *P* < 0.0001		21.0 [16.5 to 25.5]	
Blood Pressure (SBP), mm Hg			N = 234	N = 211
Mean (SD) baseline	132.8 (14.9)	133.8 (14.7)		
Adjusted mean [95% CI] change at week 52[a]	–4.3 [–5.4 to –3.1]	0.8 [–0.4 to 1.9]		
Adjusted mean [95% CI] change at week 104[a]			–3.0 (–4.6,–1.4)	0.9 (–0.8 to 2.6)
Adjusted mean change versus glipizide [95% CI]	–5.0 [–6.7 to –3.4], *P* < 0.0001		–3.9 [–6.1 to –1.7]	
Blood Pressure (DBP), mm Hg			N = 234	N = 211
Mean (SD) baseline	80.6 (8.4)	80.6 (8.5)		
Adjusted mean [95%CI] change at week 52[a]	–1.6 [–2.3 to –0.9]	–0.4 [–1.1 to 0.3]		
Adjusted mean [95%CI] change at week 104[a]			–2.0 (–3.0 to –1.0)	–1.6 (–2.5 to –0.6)
Adjusted mean change vs. glipizide [95% CI]	–1.2 [–2.3 to –0.2], *P* = 0.0179		–0.5 [–1.8 to 0.9]	

A1C = glycated hemoglobin; CI = confidence interval; DBP = diastolic blood pressure; DTSQc = Diabetes Treatment Satisfaction Questionnaire change version; FPG = fasting plasma glucose; MI = myocardial infarction; MVA = motor vehicle accident; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; vs. = versus.

[a] Analysis of continuous outcomes based on separate ANCOVA models with treatment group as effect and baseline value as a covariate for each end point.

[b] Primary end point is significantly (alpha = 0.025 one-sided) non-inferior if upper limit of 95% CI is < 0.35%.

[c] Logistic regression based on the methodology of Zhang, Tsiatis, and Davidian, and of Tsiatis, Davidian, Zhang, and Lu, with adjustment for baseline value. In case of less than five events per treatment group on average, the exact method is used.

Source: Clinical Study Report for Study 4.[1]

TABLE 28: KEY EFFICACY OUTCOMES (ADD-ON TO METFORMIN, VERSUS PLACEBO)

	Study 14			Study 14 (Extension to Week 102)		
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**	**Dapa 5 mg**	**Dapa 10 mg**	**Placebo**
Mortality						
Patients, n	0	0	0	0	0	1
Reason						Malignant lung neoplasm
Blood glucose (FPG), mmol/L				N = 45	N = 53	N = 25
Mean (SD) baseline	9.4 (2.7)	8.7 (2.1)	9.2 (2.6)			
Adjusted mean (SE) change, week 24[a]	–1.2 (0.1)	–1.3 (0.2)	–0.3 (0.1)			
Adjusted mean (SE) change, week 102[a]				–1.5 (0.2)	–1.4 (0.1)	–0.6 (0.2)
Adjusted mean change vs. placebo [95% CI][b]	**5 mg:** –0.9 [–1.3 to –0.4], *P* < 0.0001 **10 mg:** –1.0 [–1.4 to –0.6], *P* < 0.0001			**5 mg:** –0.9 [–1.4 to –0.4] **10 mg:** –0.8 [–1.3 to –0.3]		
A1C, %				N = 47	N = 57	N = 28

	Study 14			Study 14 (Extension to Week 102)		
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**	**Dapa 5 mg**	**Dapa 10 mg**	**Placebo**
Mean (SD) baseline	8.17 (0.96)	7.92 (0.82)	8.11 (0.96)			
Adjusted mean (SE) change at week 24[a]	–0.70 (0.07)	–0.84 (–0.07)	–0.30 (–0.07)			
Adjusted mean (SE) change at week 102[a]				–0.58 (0.10)	–0.78 (0.09)	0.02 (0.11)
Adjusted mean change vs. placebo [95% CI][b]	**5 mg:** –0.41 [–0.61 to –0.21], *P* < 0.0001 **10 mg:** –0.54 [–0.74 to –0.34], *P* < 0.0001			**5 mg:** –0.60 [–0.89 to –0.31] **10 mg:** –0.80 [–1.08 to –0.52]		
Patients with A1C < 7.0% at week 24, adjusted for baseline A1C, % [95% CI]	37.5 (30.0 to 45.1)	40.6 (32.9 to 48.3)	25.9 (19.1 to 32.6)			
Patients with A1C < 7.0% at week 24, adjusted for baseline A1C, % [95% CI]				26.4[c] (19.4 to 33.4)	31.5[c] (23.7 to 39.3)	15.4[c] (9.5 to 21.3)
Difference [95% CI] vs. placebo, %	**5 mg:** 11.7 [1.3,22.1], *P* = 0.0275 **10 mg:** 14.7 [4.2 to 25.3], *P* = 0.0062			**5 mg:** 11.0 [1.7 to 20.2] **10 mg:** 16.1 [6.2 to 25.9]		
Body Weight, kilograms				N = 90	N = 95	N = 73
Mean (SD) baseline	84.7 (16.3)	86.3 (17.5)	87.7 (19.2)			
Adjusted mean (SE) change at week 24[a]	–3.04 (0.24)	–2.86 (0.24)	–0.89 (0.24)			
Adjusted mean (SE) change at week 102[a]				–1.70 (0.40)	–1.74 (0.39)	1.36 (0.42)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –2.16 [–2.81 to –1.50], *P* < 0.0001 **10 mg:** –1.97 [–2.63 to –1.31], *P* < 0.0001			**5 mg:** –3.06 [–4.21 to –1.92] **10 mg:** –3.10 [–4.24 to –1.96]		
Blood Pressure (SBP), mm Hg						
Mean (SD) baseline	126.9 (14.3)	126.0 (15.9)	127.7 (14.6)	NR	NR	NR
Mean (SE) change at week 24	–4.3 (1.3)	–5.1 (1.3)	–0.2 (1.2)	NR	NR	NR
Adjusted mean (SE) change at week 24	NR	NR	NR			
Adjusted mean (SE) change at week 102				NR	NR	NR
Blood Pressure (DBP), mm Hg						
Mean (SE) baseline	80.8 (8.5)	79.0 (10.2)	80.9 (9.0)	NR	NR	NR
Mean (SE) change at week 24	–2.5 (0.8)	–1.8 (0.8)	–0.1 (0.7)	NR	NR	NR
Adjusted mean (SE) change at week 24	NR	NR	NR			
Adjusted mean (SE) change at week 102				NR	NR	NR

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; DBP = diastolic blood pressure; DTSQ = diabetes treatment satisfaction questionnaire; FPG = fasting plasma glucose; NR = not reported; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; vs. = versus.

[a] Analysis of covariance (ANCOVA) model with treatment group as an effect and baseline value as a covariate.

[b] The primary end point is tested at alpha = 0.019, applying the Dunnett adjustment. The primary analysis excluded data after rescue for all outcomes

[c] Percentages in the extension used the original intention-to-treat set in the denominator.

Source: Clinical Study Report for Study 14.[2]

TABLE 29: KEY EFFICACY OUTCOMES (ADD-ON TO METFORMIN, VERSUS PLACEBO)

	Study 12		Study 12 Extension to 102 Weeks	
	Dapa 10 mg N = 89	**Placebo N = 91**	**Dapa 10 mg N = 89**	**Placebo N = 91**
Mortality				
Patients, n	1 (1)	0	No additional deaths	
Reason	GI bleed			
Quality of Life (EQ-5D)			N = 68	N = 70
VAS scores, mean (SD) baseline	72.8 (19.39)	73.7 (15.49)		
Adjusted mean (SE) change, week 24[a]	4.2 (1.216)	4.8 (1.200)		
Adjusted mean (SE) change, week 102[a]			6.7 (1.461)	5.4 (1.349)
Adjusted mean change vs. placebo [95% CI]	–0.6 [–3.9 to 2.8], *P* = 0.7449		1.2 [–2.6 to 5.0]	
Index scores, mean (SD) baseline	0.85 (0.163)	0.82 (0.154)		
Adjusted mean (SE) change, week 24[a]	0.03 (0.014)	0.04 (0.014)		
Adjusted mean (SE) change, week 102[a]			0.00 (0.019)	0.01 (0.018)
Adjusted mean change vs. placebo [95% CI]	–0.01 [–0.05 to 0.03], *P* = 0.4929		–0.01 [–0.06 to 0.04]	
Blood Glucose (FPG), mmol/L			N = 58	N = 49
Mean (SD) baseline	8.2 (1.4)	8.3 (1.4)		
Adjusted mean (SE) change, week 24[a]	–0.8 (0.1)	0.1 (0.1)		
Adjusted mean (SE) change, week 102[a]			–1.0 (0.1)	0.0 (0.1)
Adjusted mean change vs. placebo [95% CI]	–0.9 [–1.3 to –0.6], *P* < 0.0001		–0.9 [–1.3 to –0.6]	
A1C, %			N = 60	N = 49
Mean (SD) baseline	7.19 (0.444)	7.16 (0.531)		
Adjusted mean (SE) change at week 24[a]	–0.39 (0.049)	–0.10 (0.048)		
Adjusted mean (SE) change, week 102[a]			–0.30 (0.069)	0.12(0.072)
Adjusted mean change vs. placebo [95% CI]	–0.28 [–0.42 to –0.15], *P* < 0.0001		–0.42 [–0.62 to –0.22]	
Patients with A1C < 7.0% at week 24, % (SE)	63.3 (4.99)	47.1 (4.73)		
Patients with A1C < 7.0% at week 102, % (SE)			50.0 (5.23)	33.4 (4.84)
Difference [95% CI] vs. placebo, %	16.1% [3.3 to 29.0]		16.5% [2.8 to 30.2] [c]	
Body Weight, kilograms			N = 69	N = 71
Mean (SD) baseline	92.06 (14.13)	90.91 (13.72)		
Adjusted mean (SE) change at week 24[a,b]	–2.96 (0.2766)	–0.88 (0.2746)		
Adjusted mean (SE) change at week 102[a]			–4.54 (0.45)	–2.12 (0.43)
Adjusted mean change vs. placebo [95% CI]	–2.08 (–2.84 to –1.31), *P* < 0.0001		–2.42 (–3.64 to –1.21)	
Patients with ↓weight of ≥ 5% by week 24, n (%)	27 (30)	4 (4)		
Patients w ↓weight of ≥ 5% by week 102, n (%)			24 (27)	15 (17)
Adjusted % (SE)	30.5 (4.929)	4.3 (2.148)	27.1 (4.699) [c]	16.5 (3.888) [c]
Adjusted mean change vs. placebo [95% CI]	26.2% [15.6 to 36.7], *P* < 0.0001		10.6% [–1.3 to 22.6]	
Blood Pressure (SBP), mm Hg			N = 69	N = 71
Mean (SD) baseline	135.9 (13.92)	133.3 (13.66)		

	Study 12		Study 12 Extension to 102 Weeks	
	Dapa 10 mg N = 89	**Placebo N = 91**	**Dapa 10 mg N = 89**	**Placebo N = 91**
Adjusted mean (SE) change at week 24[a]	–2.7 (1.088)	0.1 (1.071)		
Adjusted mean (SE) change at week 102[a]			–2.0 (1.307)	0.2 (1.233)
Adjusted mean change vs. placebo [95% CI]	–2.8 [–5.9 to 0.2,] *P* = 0.0637		–2.3 [–5.7 to 1.2]	
Blood Pressure (DBP), mm Hg			N = 69	N = 71
Mean (SE) baseline	80.6 (8.09)	80.4 (8.25)		
Adjusted mean (SE) change at week 24[a]	–0.7 (0.720)	0.3 (0.709)		
Adjusted mean (SE) change at week 102[a]			–2.8 (0.720)	0.3 (0.671)
Adjusted mean change vs. placebo [95% CI]	–1.0 [–2.9 to 1.0], *P* = 0.3458		–3.0 [–4.9 to –1.1]	

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; DBP = diastolic blood pressure; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; FPG = fasting plasma glucose; GI = gastrointestinal; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; VAS = visual analogue scale; vs. = versus.
[a] Analysis of continuous outcomes based on separate analysis of covariance (ANCOVA) models with treatment group and stratum as effect and baseline value as a covariate for each end point.
[b]Primary outcome. Logistic regression based on the methodology of Zhang, Tsiatis, and Davidian, and of Tsiatis, Davidian, Zhang, and Lu, with adjustment for baseline total body weight and stratum. In case of less than five events per treatment group on average, the exact method is used. The primary analysis for the primary outcome included data after rescue therapy, while the secondary outcomes change in A1C and FPG excluded data after rescue, and SBP/DBP and EQ-5D included data after rescue.
[c] Percentages in the extension used the original intention-to-treat set in the denominator.
Source: Clinical Study Report for Study 12.[3]

TABLE 30: KEY EFFICACY OUTCOMES (ADD-ON TO SULFONYLUREA, VERSUS PLACEBO)

	Study 5			Study 5 (Extension to Week 48)		
	Dapa 5 mg N = 142	**Dapa 10 mg N = 151**	**Placebo N = 145**	**Dapa 5 mg N = 142**	**Dapa 10 mg N = 151**	**Placebo N = 145**
Mortality						
Patients, n	0	1	0	No additional deaths		
Reason		PE				
Blood Glucose (FPG), mmol/L				N = 90	N = 107	N = 55
Mean (SE) baseline	9.7 (2.1)	9.6 (2.0)	9.6 (2.1)			
Adjusted mean (SE) change, week 24[a]	–1.2 (0.1)	–1.6 (0.1)	–0.1 (0.1)			
Adjusted mean (SE) change, week 48[a]				–0.9 (0.2)	–1.6 (0.2)	0.1 (0.2)
Adjusted mean change vs. placebo [95% CI][a]	**5 mg:** –1.1 [–1.5 to –0.7], *P* < 0.0001 **10 mg:** –1.5 [–1.9 to –1.1], *P* < 0.0001			**5 mg:** –1.1 [–1.6 to –0.5] **10 mg:** –1.7 [–2.2 to –1.2]		
Quality of Life (DTSQ Total)				N = 90	N = 105	N = 55
Mean (SD) baseline	27.4 (5.9)	27.6 (6.4)	28.3 (7.1)			
Adjusted mean (SE) change, week 24[a]	2.7 (0.4)	3.2 (0.4)	2.6 (0.5)			
Adjusted mean (SE) change, week 48[a]				4.6 (6.5)[b]	4.4 (6.9)[b]	2.2 (6.3)[b]
Adjusted mean change vs. placebo [95% CI]	**5 mg:** 0.1 [–1.1 to 1.3], *P* = 0.8695 **10 mg:** 0.6 [–0.6 to 1.8], *P* = 0.3575			NR		
A1C, %				N = 90	N = 107	N = 55
Mean (SD) baseline	8.12 (0.78)	8.07 (0.79)	8.15 (0.74)			

	Study 5			Study 5 (Extension to Week 48)		
	Dapa 5 mg N = 142	**Dapa 10 mg N = 151**	**Placebo N = 145**	**Dapa 5 mg N = 142**	**Dapa 10 mg N = 151**	**Placebo N = 145**
Adjusted mean (SE) change at week 24[a]	−0.63 (0.06)	−0.82 (0.06)	−0.13 (0.06)			
Adjusted mean (SE) change at week 48[a]				–0.56 (0.08)	–0.73 (0.07)	–0.04 (0.09)
Adjusted mean change vs. placebo [95% CI][a]	**5 mg:** −0.49 [−0.67, −0.32], *P* < 0.0001 **10 mg:** −0.68 [−0.86, −0.51], *P* < 0.0001			**5 mg:** –0.53 [–0.75 to –0.30] **10 mg:** –0.70 [–0.92 to –0.47]		
% Patients (SE) achieving A1C < 7%[a]	30.3 (3.5)	31.7 (3.6)	13.0 (2.7)			
% Patients (SE) achieving A1C < 7%[a]				28.2 (3.6)	29.6 (3.6)	10.6 (2.5)
Difference [95% CI] vs. placebo, %	**5 mg:** 17.3 [8.7 to 25.9], *P* = 0.0001 **10 mg:** 18.7 [9.9 to 27.4], *P* < 0.0001			**5 mg:** 17.6 [9.1 to 26.1] **10 mg:** 19.0 [10.5 to 27.6]		
Body Weight, kilograms				N = 90	N = 107	N = 55
Mean (SD) baseline	81.0 (18.6)	80.6 (17.9)	80.9 (15.8)			
Adjusted mean (SE) change at week 24[a]	–1.56 (0.23)	–2.26 (0.22)	–0.72 (0.23)			
Adjusted mean (SE) change at week 48[a]				–1.54 (0.29)	–2.41 (0.28)	–0.77 (0.33)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –0.84 [–1.47,–0.21], *P* = 0.0091 **10 mg:** –1.54 [–2.17,–0.92], *P* < 0.0001			**5 mg:** –0.76 [–1.63 to 0.11] **10 mg:** –1.64 [–2.48 to –0.79]		
Blood Pressure (SBP), mm Hg				N = 90	N = 107	N = 55
Mean (SD) baseline	130.9 (15.1)	132.4 (13.7)	133.3 (13.9)			
Adjusted mean (SE) change at week 24[a]	–4.0 (0.96)	–5.0 (0.93)	–1.2 (0.95)			
Adjusted mean (SE) change at week 48[a]				–3.0 (1.21)	–4.2 (1.12)	1.81 (1.51)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –2.8 [–5.5,–0.2], *P* = 0.0352 **10 mg:** –3.8 [–6.4 to –1.2], *P* = 0.0047			**5 mg:** –4.81 [–8.62 to –1.01] **10 mg:** –6.02 [–9.71 to –2.32]		
Blood Pressure (DBP), mm Hg				N = 90	N = 107	N = 55
Mean (SD) baseline	77.9 (8.5)	78.7 (8.2)	79.8 (7.8)			
Adjusted mean (SE) change at week 24[a]	–1.7 (0.60)	–2.8 (0.59)	–1.4 (0.60)			
Adjusted mean (SE) change at week 48[a]				–1.41 (0.77)	–2.15 (0.71)	0.79 (0.96)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –0.3 [–1.9 to 1.4], *P* = 0.7478 **10 mg:** –1.4 [–3.0 to 0.3], *P* = 0.0993			**5 mg:** –2.20 [–4.62 to 0.22] **10 mg:** –2.94 [–5.29 to –0.59]		

A1C = glycated hemoglobin; CI = confidence interval; DBP = diastolic blood pressure; DTSQ = Diabetes Treatment Satisfaction Questionnaire; FPG = fasting plasma glucose; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; vs. = versus.

[a] Primary end point is tested at alpha = 0.019 applying the Dunnett adjustment, and secondary end points are tested following a sequential testing procedure at alpha = 0.05. Logistic regression analysis of responses are based on the methodology of Zhang, Tsiatis, and of Davidian and Tsiatis, Davidian, Zhang, and Lu, with adjustment for baseline value. In case of less than five events per treatment group on average, the exact method is used. Analysis of continuous outcomes based on separate analysis of covariance (ANCOVA) models with treatment group as an effect and baseline value as a covariate for each end point. All primary analyses of efficacy outcomes were carried out excluding data after rescue.

Source: Clinical Study Report for Study 5.[4]

TABLE 31: KEY EFFICACY OUTCOMES (ADD-ON TO INSULIN, VERSUS PLACEBO)

	Study 6			Study 6 Extension to Week 104		
	Dapa 5 mg N = 211	**Dapa 10 mg N = 194**	**Placebo N = 193**	**Dapa 5/10 mg**	**Dapa 10 mg**	**Placebo**
Mortality						
Patients, n (%)	1	0	0	2 (0.9)	1 (0.5)	0
Reason	Cardiogenic shock			Cardiogenic shock MI	Angina pectoris	
Blood Glucose (FPG), mmol/L				N = 87	N = 96	N = 48
Mean (SE) baseline	10.3 (3.3)	9.6 (3.0)	9.4 (3.2)			
Adjusted mean (SE) change, week 24	–1.0 (0.2)	–1.2 (0.2)	0.2 (0.2)			
Adjusted mean (SE) change, week 104				–1.7 (0.2)	–1.0 (0.2)	–0.6 (0.3)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –1.2 [–1.7 to –0.7], *P* < 0.0001 **10 mg:** –1.1 [–1.8 to –0.4], *P* < 0.0001			**5 mg:** –1.1 [–1.8 to –0.4] **10 mg:** –0.4 [–1.1 to 0.3]		
A1C, %				N = 89	N = 100	N = 50
Mean (SD) baseline	8.61 (0.89)	8.58 (0.82)	8.46 (0.76)			
Adjusted mean (SE) change at week 24	–0.82 (0.05)	–0.90 (0.05)	–0.30 (0.05)			
Adjusted mean (SE) change at week 104				–0.71 (0.08)	–0.71 (0.08)	–0.06 (0.10)
Adjusted mean change vs. placebo [95% CI] [a]	**5 mg:** –0.52 [–0.66 to –0.38], *P* < 0.0001 **10 mg:** –0.60 [–0.74 to –0.45], *P* < 0.0001			**5 mg:** –0.65 [–0.90 to –0.41] **10 mg:** –0.65 [–0.90 to –0.41]		
% patients achieving A1C < 7% adjusted for baseline [95% CI]	19.8 (14.8 to 24.9)	21.5 (16.0 to 27.1)	8.7 (4.7 to 12.8)			
% patients achieving A1C < 7% adjusted for baseline [95% CI]				11.3[b] (7.3 to 15.4)	6.9[b] (3.4 to 10.4)	4.6[b] (1.6 to 7.5)
Difference [95% CI] versus placebo, %	**5 mg:** 11.1% [4.6 to 17.6], *P* = 0.0009 **10 mg:** 12.8% [5.9 to 19.8], *P* = 0.0003			**5 mg:** 6.8% [1.7 to 11.8] **10 mg:** 2.3% [–2.3 to 6.9]		
Body Weight, kilograms				N = 128	N = 141	N = 107
Mean (SD) baseline	93.2 (17.4)	94.6 (16.8)	94.2 (19.5)			
Adjusted mean (SE) change at week 24	–0.98 (0.17)	–1.67 (0.18)	0.02 (0.18)			
Adjusted mean (SE) change at week 104				–0.95 (0.37)	–1.40 (0.36)	1.79 (0.39)
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –1.00 [–1.50 to –0.50], *P* < 0.0001 **10 mg:** –1.68 [–2.19 to –1.18], *P* < 0.0001			**5 mg:** –2.74 [–3.80 to –1.69] **10 mg:** –3.19 [–4.24 to –2.14]		
Blood Pressure (SBP), mm Hg				N = 128	N = 140	N = 103
Mean (SD) baseline	137.8 (16.2)	140.6 (16.7)	136.1 (17.2)			
Adjusted mean (SE) change at week 24	–6.0 (0.87)	–6.9 (0.91)	–3.9 (0.93)			
Adjusted mean (SE) change at week 104				–4.5 (1.10)	–6.4 (1.08)	–2.44 (1.21)

	Study 6			Study 6 Extension to Week 104		
Adjusted mean change vs. placebo [95% CI]	**5 mg:** –2.1 [–4.6 to 0.4], *P* = 0.0962 **10 mg:** –3.0 [–5.5 to –0.4], *P* = 0.0228			**5 mg:** –2.07 [–5.29 to 1.14] **10 mg:** –3.98 [–7.18 to –0.78]		
Blood Pressure (DBP), mm Hg				N = 128	N = 140	N = 103
Mean (SD) baseline	81.1 (8.9)	79.9 (9.3)	80.0 (9.6)			
Adjusted mean (SE) change at week 24	–2.8 (0.50)	–3.0 (0.52)	–1.9 (0.53)			
Adjusted mean (SE) change at week 104				–2.6 (0.64)	–3.9 (0.63)	–1.90 (0.70)
Adjusted mean change vs. placebo [95% CI][f]	**5 mg:** –0.9 [–2.3 to 0.6], *P* = 0.2356 **10 mg:** –1.1 [–2.5 to 0.4], *P* = 0.1489			**5 mg:** –0.74 [–2.61 to 1.13] **10 mg:** –2.04 [–3.88 to –0.19]		

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; DBP = diastolic blood pressure; FPG = fasting plasma glucose; MI = myocardial infarction; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; vs. = versus.
[a] Primary end point is tested at alpha = 0.019 applying the Dunnett adjustment, and secondary end points are tested following a sequential testing procedure at alpha = 0.05. Logistic regression analysis of responses are based on the methodology of Zhang, Tsiatis, and Davidian, and of Tsiatis, Davidian, Zhang, and Lu, with adjustment for baseline value and stratum. In case of less than five events per treatment group on average, the exact method is used. Analysis of continuous outcomes based on separate analysis of covariance (ANCOVA) models with treatment group and stratum as effect and baseline value as a covariate for each end point.
[b] Percentages in the extension used the original intention-to-treat set in the denominator.
Source: Clinical Study Report for Study 6.[5]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Appendix 4 for detailed harms data.

3.7.1 Adverse Events

There was a similar proportion of dapagliflozin and glipizide patients who reported an adverse event (AE) in Study 4: 78% in each group (Table 33). The proportions were also similar in the extension: 88% with dapagliflozin and 87% with glipizide. The most common AE was nasopharyngitis, affecting 11% of dapagliflozin patients and 15% of glipizide patients.

Across the placebo-controlled studies, there was no clear or consistent difference in the proportion of patients with an AE between dapagliflozin and placebo groups, or between the dapagliflozin 5 mg and 10 mg groups. The largest difference in proportions was in Study 14 (metformin background), in which 73% of dapagliflozin 10 mg and 64% of placebo patients experienced an AE (Table 34). In the other study with metformin as a background, Study 12, the proportion of patients in the dapagliflozin 10 mg group with an AE was 43% versus 40% with placebo (Table 35). Because this numerical difference in AEs was observed only in one of two placebo-controlled studies with a metformin background, one cannot conclude that the type of background therapy influences the risk of an AE.

In Study 18, 49% of dapagliflozin patients and 53% of saxagliptin patients reported an AE (Table 38).

TABLE 32: KEY EFFICACY OUTCOMES (ADD-ON TO METFORMIN, TRIPLE THERAPY VERSUS DUAL THERAPY)

	Study 18		
	Dapa/Saxa N = 179	**Dapa N = 179**	**Saxa N = 176**
Mortality			
Patients, n	0	0	0
Blood Glucose (FPG), mmol/L			
Mean (SD) baseline	10.0 (2.5)	10.3 (2.6)	10.7 (2.5)
Adjusted mean (SE) change, week 24	–2.1 [–2.4 to –1.8]	–1.8 [–2.1 to –1.5]	–0.8 [–1.1 to –0.5]
Adjusted mean change, dapagliflozin vs. saxagliptin [95% CI]	Not evaluated		
A1C, %			
Mean (SD) baseline	8.93 (1.19)	8.87 (1.17)	9.03 (1.05)
Adjusted mean (SE) change at week 24	–1.47 [–1.62 to –1.31]	–1.20 [–1.35 to –1.04]	–0.88 [–1.03 to –0.72]
Adjusted mean change, dapagliflozin vs. saxagliptin [95% CI]	Not evaluated		
Patients with A1C < 7.0% at week 24, adjusted [b] for baseline A1C, % [95% CI]	41.4 [34.5 to 48.2]	22.2 [16.1 to 28.3]	18.3 [13.0 to 23.5]
Difference [95% CI], dapagliflozin vs. saxagliptin, %	Not evaluated		
Body Weight, kilograms			
Mean (SD) baseline	87.1 (18.0)	86.3 (18.6)	88.0 (18.7)
Adjusted mean (SE) change at week 24	–2.1 [–2.5 to –1.6]	–2.4 [–2.9 to –1.9]	0 [–0.5 to 0.5]
Adjusted mean change, dapagliflozin vs. saxagliptin [95% CI]	Not evaluated		
Blood Pressure			
Patients achieving SBP < 130 and DBP < 80 mm Hg, n (%)	70/179 (39)	72/179 (40)	70/179 (39)
Mean change, dapagliflozin vs. saxagliptin [95% CI]	Not evaluated		

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; FPG = fasting plasma glucose; Saxa = saxagliptin; SD = standard deviation; SE = standard error; vs. = versus.
Source: Clinical Study Report for Study 18.[6]

3.7.2 Serious Adverse Events

In Study 4, 9% of dapagliflozin patients and 11% of glipizide patients experienced a serious adverse event (SAE), and in the extension the proportions were 19% and 20%, respectively (Table 33). The largest difference in proportion of specific SAEs between dapagliflozin and glipizide involved events of anemia, which did not occur in any dapagliflozin patients and in 1% of glipizide patients. SAEs of hypoglycemia also occurred in no dapagliflozin patients and 1% of glipizide patients.

Among the placebo-controlled studies, the largest difference in proportion of patients with an SAE was in Study 12 (metformin background), in which 7% of dapagliflozin 10 mg patients and 1% of placebo patients had an SAE after 24 weeks (Table 35). There was no dapagliflozin 5 mg group in this study. In the other studies, there was no more than a 2% difference in proportion of patients with an SAE between dapagliflozin and placebo. Because this numerical difference in SAEs was observed only in one of two placebo-controlled studies with a metformin background, one cannot conclude that the type of background therapy influences the risk of an SAE.

In Study 18 (metformin background), 1% of dapagliflozin patients and 3% of saxagliptin patients had an SAE (Table 38).

3.7.3 Withdrawals Due to Adverse Events

There was no difference between dapagliflozin and glipizide groups with respect to withdrawals due to serious adverse events (WDSAEs) in Study 4, 2% in each group in the core study, and 3% in each group in the extension (Table 33). The proportion of patients who withdrew due to an AE was 9% with dapagliflozin and 6% with glipizide in the core study, and 13% versus 11% in the extension study (Table 33).

Study 12 had the largest difference between dapagliflozin 10 mg and placebo with respect to withdrawals due to AEs (WDAEs) or WDSAEs, a total of 5% of patients on dapagliflozin 10 mg and none of those on placebo, and in the extension, 19% of patients on dapagliflozin 10 mg and 4% of those on placebo (Table 35). There was no dapagliflozin 5 mg group in this study. In the other included studies, there was no more than a 2% difference between groups in the proportion of patients who discontinued due to an AE or SAE. Because this numerical difference in WDAE and WDSAEs was observed only in one of two placebo-controlled studies with a metformin background, one cannot conclude that the type of background therapy influences the risk of a WDAE or WDSAE.

In Study 18 (metformin background), one patient on dapagliflozin discontinued due to an AE, and none discontinued in the saxagliptin group (Table 38).

3.7.4 Notable Harms

In Study 4, the proportion of patients experiencing hypoglycemia was a pre-specified analysis outcome, and there was a lower proportion of patients with an event of hypoglycemia after 52 weeks with dapagliflozin versus glipizide (adjusted mean difference between groups –37%; 95% CI, –42% to –32%; $P < 0.0001$), and this difference was statistically significant (Table 33). There were numerically more genital infections with dapagliflozin than with glipizide (12% versus 3%) and numerically more urinary tract infections in females (14% versus 9%). There were numerically more patients in the dapagliflozin group with events of renal impairment or failure than with glipizide (6% versus 3% of patients). There were no clear differences in risk of other notable harms between dapagliflozin and glipizide.

Across the placebo-controlled studies, the proportion of patients with urogenital infections was consistently numerically higher with dapagliflozin than with placebo. There were no clear indications of difference in risk based on background therapy, although no statistical analyses were performed and the studies were not powered to carry out such analyses. The risk of hypoglycemia was similar between dapagliflozin groups and placebo in the studies with the metformin background, slightly numerically higher with dapagliflozin in the study with a sulfonylurea background (Study 5) and numerically higher with an insulin background (Study 6) in the core study for dapagliflozin 5 mg versus placebo (45% versus 35%), but no obvious difference in the extension. For other notable harms, there were no clear or consistent differences between dapagliflozin groups and placebo.

When compared with saxagliptin in Study 18, the only notable harm for which there was a numerical difference was genital infection, with a numerically higher proportion of patients on dapagliflozin than saxagliptin experiencing an event (6% versus 1%) (Table 38). Once again, this study was not designed to compare dapagliflozin and saxagliptin

TABLE 33: HARMS (ADD-ON TO METFORMIN, VERSUS SULFONYLUREA)

	Study 4		Study 4 Extension to Week 208	
Adverse Events	**Dapagliflozin N = 400**	**Glipizide N = 401**	**Dapagliflozin N = 400**	**Glipizide N = 401**
Subjects with > 0 AEs, n (%)	318 (78)	318 (78)	356 (88)	355 (87)
Most common AEs, n (%)				
Nasopharyngitis	43 (11)	61 (15)	70 (17)	76 (19)
Hypertension	30 (7)	35 (9)	44 (11)	62 (15)
Influenza	30 (7)	30 (7)	50 (12)	45 (11)
SAEs				
Subjects with > 0 SAEs, n (%)	35 (9)	46 (11)	75 (19)	81 (20)
Most common SAEs, n (%)				
MI	1 (< 1)	3 (1)	1 (< 1)	4(1)
Prostate cancer	3 (1)	1 (< 1)	4 (1)	3 (1)
Hypoglycemia	0	3 (1)	0	3 (1)
Anemia	0	2 (1)	0	4 (1)
WDAEs				
WDSAEs, n (%)	9 (2)	8 (2)	12 (3)	13 (3)
WDAEs, n (%)	37 (9)	24 (6)	54 (13)	46 (11)
Hypoglycemia, n (%)	0	6 (2)	0	7 (2)
Notable harms				
Hypoglycemia, n (%)	14 (4)	162 (40)	22 (5)	210 (52)
Hypoglycemia, adjusted[a] %, mean (SE)	3.5% (0.92)	40.8% (2.40)		
Mean difference vs. glipizide [95% CI]	–37.2% [–42.3 to –32.2], *P* < 0.0001			
Renal impairment/failure, n (%)	24 (6)	14 (3)	35 (9)	31 (8)
Mean (SE) change from baseline in eGFR, mL/min/1.73 m^2	–0.5 (0.787)	–5.4 (0.75)		
Hepatic disorder, n (%)	10 (3)	6 (2)	13 (3)	9 (2)
Genital infection, n (%)	50 (12)	11 (3)	66 (16)	17 (4)
UTI, n (%)	44 (11)	26 (6)	65 (16)	44 (11)
UTI female, n (%)	26/180 (14)	17/185 (9)	40/180 (22)	28/185 (15)
Left ventricular failure	2 (1)	0	2 (1)	0
Cardiac failure	0	2 (1)	1 (< 1)	2 (1)
Congestive cardiac failure	0	1 (< 1)	0	2 (1)
Acidosis	0	0		
Lipids: Adjusted[b] mean % change from baseline, vs. glipizide (95% CI) [mmol/L]				
Total cholesterol	2.10 [–0.12 to 4.27], *P* = 0.0643			
HDL	6.05 [4.01 to 8.13], *P* < 0.0001			
LDL-C	0.44 [–2.84 to 3.83], *P* = 0.7958			
TG	–0.34 [–4.96 to 4.51], *P* = 0.8893			

AE = adverse event; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; SAE = serious adverse event; SE = standard error; TG = triglycerides; UTI = urinary tract infection; WDAE = withdrawal due to adverse event; WDSAE = withdrawal due to serious adverse event.

[a] Logistic regression analysis of responses are based on the methodology of Zhang, Tsiatis, and Davidian, and of Tsiatis, Davidian, Zhang, and Lu, with adjustment for baseline value. In case of less than five events per treatment group on average, the exact method is used.

[b] Based on a separate ANCOVA model for (log (week 52 value) – log (baseline value)) for each end point with treatment group as effect and log (baseline value) as a covariate.

Source: Clinical Study Report for Study 4.[1]

TABLE 34: HARMS (ADD-ON TO METFORMIN, VERSUS PLACEBO)

	Study 14			Study 14 (Extension to Week 102)		
Adverse Events	**Dapa 5 mg N = 137**	**Dapa 10 mg N = 135**	**Placebo N = 137**	**Dapa 5 mg N = 137**	**Dapa 10 mg N = 135**	**Placebo N = 137**
Subjects with > 0 AEs, n (%)	95 (69)	98 (73)	88 (64)	111 (81)	111 (82)	111 (81)
Most common AEs, n (%)						
Nasopharyngitis	4 (3)	8 (6)	11 (8)	8 (6)	12 (9)	12 (9)
Headache	10 (7)	11 (8)	6 (4)	13 (10)	15 (11)	8 (6)
Hypertension	4 (3)	5 (4)	6 (4)	8 (6)	7 (5)	13 (10)
Influenza	13 (10)	8 (6)	10 (7)	20 (15)	17 (13)	15 (11)
SAEs						
Subjects with > 0 SAEs, n (%)	4 (3)	4 (3)	5 (4)	9 (7)	14 (10)	14 (10)
Most common SAEs, n (%)						
Acute myocardial infarction	0	0	2 (2)	0	0	3 (2)
WDAEs						
WDSAEs, n (%)	0	0	3 (2)	1 (1)	2 (2)	6 (4)
WDAEs, n (%)	3 (2)	4 (3)	5 (4)	5 (4)	6 (4)	9 (7)
Hypoglycemia	0	0	0	0	0	0
Notable harms, n (%)						
Hypoglycemiaa	5 (4)	5 (4)	4 (3)	7 (5)	7 (5)	8 (6)
major	0	0	0	0	0	0
minor	2 (2)	1 (1)	0	2 (2)	1 (1)	1 (1)
other	3 (2)	4 (3)	4 (3)	6 (4)	6 (4)	8 (6)
Renal impairment/failure	3 (2)	1 (1)	1 (1)	4 (3)	2 (2)	2 (2)
Mean (SE) change from baseline in eGFR, mL/min/m2	2.03(0.95)	1.12 (1.0)	0.89 (0.99)			
Hepatobiliary disorder	1 (1)	0	3 (2)	3 (2)	4 (3)	3 (2)
Genital infection	18 (13)	12 (9)	7 (5)	20 (15)	17 (13)	7 (5)
UTI	10 (7)	11 (8)	11 (8)	12 (9)	18 (13)	11 (8)
UTI female	6 (9)	9 (16)	5 (8)	7 (10)	13 (22)	5 (8)
Cardiac failure congestive	0	0	0	0	0	1 (1)
Left ventricular hypertrophy	0	0	0	0	1 (1)	0
Acidosis	0	0	0	0	0	0
Lipids: Adjustedb mean % change from baseline, vs. placebo (95% CI) [mmol/L]						
Total cholesterol	5 mg: –0.50 [–3.93 to 3.06] 10 mg: 1.49 [–2.05 to 5.15]					
HDL	5 mg: 2.89 [–0.96 to 6.89] 10 mg: 4.06 [0.12 to 8.14]					

	Study 14			Study 14 (Extension to Week 102)		
Adverse Events	**Dapa 5 mg N = 137**	**Dapa 10 mg N = 135**	**Placebo N = 137**	**Dapa 5 mg N = 137**	**Dapa 10 mg N = 135**	**Placebo N = 137**
LDL-C	5 mg: –0.42 [–6.34 to 5.88] 10 mg: 5.75 [–0.61 to 12.5]					
TG	5 mg: –8.10 [–16.6 to 1.23] 10 mg: –8.14 [–16.67 to 1.26]					

AE = adverse events; CI = confidence interval; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SAE = serious adverse event; SE = standard error; TG = triglycerides; UTI = urinary tract infection; WDAE = withdrawal due to adverse event; WDSAE = withdrawal due to serious adverse event; vs. = versus.

[a] Major hypoglycemic episode was defined as a symptomatic episode requiring third-party assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value < 3 mmol/L and prompt recovery after glucose or glucagon administration. Minor episode defined as either a symptomatic episode with a capillary or plasma glucose measurement below 3.5 mmol/L regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement below 3.5 mmol/L that does not qualify as a major episode. Other episode of hypoglycemia defined as suggestive episode reported but not meeting the criteria for major or minor episodes.

[b] Based on a separate analysis of covariance (ANCOVA) model for (log (week 24 value) – log (baseline value)) for each end point with treatment group as an effect and log (baseline value) as a covariate.

Source: Clinical Study Report for Study 14.[2]

TABLE 35: HARMS (ADD-ON TO METFORMIN, VERSUS PLACEBO)

	Study 12		Study 12 (Extension to Week 102)	
Adverse Events	**Dapa 10 mg N = 89**	**Placebo N = 91**	**Dapa 10 mg N = 89**	**Placebo N = 91**
Subjects with > 0 AEs, N (%)	39 (43)	36 (40)	65 (71)	63 (69)
Most common AEsa				
Nasopharyngitis	6 (7)	5 (6)	12 (13)	8 (9)
Hypertension	4 (4)	4 (4)	5 (6)	7 (8)
SAEs				
Subjects with > 0 SAEs, N (%)	6 (7)	1 (1)	16 (18)	14 (15)
Most common SAEs				
Pneumonia	2 (2)	0	3 (3)	1 (1)
WDAEs				
WDSAEs, N (%)	1 (1)	0	4 (4)	0
WDAEs, N (%)	4 (4)	0	14 (15)	4 (4)
Notable harms				
Hypoglycemiaa	2 (2)	3 (3)	4 (4)	5 (6)
major	0	0	0	0
minor	2 (2)	2 (2)	4 (4)	4 (4)
other	0	1 (1)	0	2 (2)
Renal impairment/failure	0	0	3 (3)	1 (1)
Mean (SE) change from baseline in eGFR, mL/min/m2	2.1(1.069)	1.9(1.060)		
Hepatic disorder	2 (2)	1 (1)	3 (3)	1 (1)

	Study 12		Study 12 (Extension to Week 102)	
Adverse Events	**Dapa 10 mg N = 89**	**Placebo N = 91**	**Dapa 10 mg N = 89**	**Placebo N = 91**
Genital infection	3 (3)	0	3 (3)	2 (2)
UTI	6 (7)	2 (2)	9 (10)	7 (8)
UTI female	5	2	4	6
Heart failure	0	0	0	0
Left ventricular hypertrophy	0	0	0	0
Acidosis	0	0	0	0
Lipids: Total cholesterol	NR			
HDL	NR			
LDL-C	NR			
TG	NR			

AE = adverse event; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NR = not reported; SE = standard error; SAE = serious adverse event; TG = triglycerides; UTI = urinary tract infection; WDAE = withdrawal due to adverse event; WDSAE = withdrawal due to serious adverse event.
[a] Major hypoglycemic episode was defined as a symptomatic episode requiring third-party assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value < 3 mmol/L and prompt recovery after glucose or glucagon administration. Minor episode defined as either a symptomatic episode with a capillary or plasma glucose measurement below 3.5 mmol/L regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement below 3.5 mmol/L that does not qualify as a major episode. Other episode of hypoglycemia defined as suggestive episode reported but not meeting the criteria for major or minor episodes.
Source: Clinical Study Report for Study 12.[3]

TABLE 36: HARMS (ADD-ON TO SULFONYLUREA, VERSUS PLACEBO)

	Study 5			Study 5 (Extension to Week 48)		
Adverse Events	**Dapa 5 mg N = 145**	**Dapa 10 mg N = 151**	**Placebo N = 146**	**Dapa 5 mg N = 145**	**Dapa 10 mg N = 151**	**Placebo N = 146**
Subjects with > 0 AEs, N (%)	70 (48)	76 (50)	69 (47)	88 (61)	89 (59)	81 (56)
Most common AEs, n (%)						
Nasopharyngitis	8 (6)	5 (3)	4 (3)	11 (8)	10 (7)	10 (7)
Hypertension	2 (1)	2 (1)	6 (4)	5 (3)	3 (2)	10 (7)
SAEs						
Subjects with > 0 SAEs, N (%)	10 (7)	9 (6)	7 (5)	16 (11)	13 (9)	13 (9)
Most common SAEs, n (%)						
Cardiac failure	0	0	1 (1)	0	0	1 (1)
Coronary artery stenosis	0	0	1 (1)	0	0	3 (2)
Angina pectoris	1 (1)	0	0	2 (1)	0	0
WDAEs						
WDSAEs, N (%)	1 (1)	1 (1)	2 (1)	1 (1)	1 (1)	3 (2)
WDAEs, N (%)	5 (3)	4 (3)	3 (2)	5 (3)	4 (3)	5 (3)
Hypoglycemia	0	0	0			
Notable harms, n (%)						
Hypoglycemia	10 (7)	12 (8)	7 (5)	15 (10)	17 (11)	10 (7)
major	0	0	0	0	0	0
minor	8 (6)	10 (7)	3 (2)	12 (8)	13 (9)	4 (3)

	Study 5			Study 5 (Extension to Week 48)		
Adverse Events	**Dapa 5 mg N = 145**	**Dapa 10 mg N = 151**	**Placebo N = 146**	**Dapa 5 mg N = 145**	**Dapa 10 mg N = 151**	**Placebo N = 146**
other	3 (2)	3 (2)	5 (3)	5 (3)	5 (3)	7 (5)
Renal impairment/failure	1 (1)	0	2 (1)	1 (1)	0	5 (3)
Mean (SE) change from baseline in eGFR, mL/min/m2	–0.1 (1.02)	–1.2 (1.03)	0.0 (0.94)			
Hepatic disorder	2 (1)	1 (1)	0	3 (2)	2 (1)	0
Genital infection	9 (6)	10 (7)	1 (1)	9 (6)	13 (9)	2 (1)
UTI	10 (7)	8 (5)	9 (6)	11 (8)	12 (8)	11 (8)
UTI female	6	6	9	7	8	10
Cardiac failure	0	1 (1)	1 (1)	0	1 (1)	1 (1)
Left ventricular hypertrophy	0	0	1 (1)	0	0	1 (1)
Acidosis	0	0	0			
Lipids: Adjustedb mean % change from baseline, vs. placebo (95% CI) [mg/dL]						
Total cholesterol	5 mg: 0.69 [–2.90 to 4.42], *P* = 0.7094 10 mg: –0.45 [–3.95,3.17], *P* = 0.8047			NR		
HDL	5 mg: 2.07 [–1.36 to 5.61], *P* = 0.2393 10 mg: 2.78 [–0.61 to 6.28], *P* = 0.1089			NR		
LDL-C	5 mg: 0.11 [–5.61 to 6.19], *P* = 0.9700 10 mg: 1.66 [–4.04 to 7.70], *P* = 0.5754			NR		
TG	5 mg: –4.27 [–11.68 to 3.76], *P* = 0.2876 10 mg: –10.82 [–17.61 to –3.47], *P* = 0.0046			NR		

AE = adverse event; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NR = not reported; SAE = serious adverse event; SE = standard error; TG = triglycerides; UTI = urinary tract infection; WDAE = withdrawal due to adverse event; WDSAE = withdrawal due to serious adverse event; vs. = versus.

[a] Major hypoglycemic episode was defined as a symptomatic episode requiring third-party assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value < 3 mmol/L and prompt recovery after glucose or glucagon administration. Minor episode defined as either a symptomatic episode with a capillary or plasma glucose measurement below 3.5 mmol/L regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement below 3.5 mmol/L that does not qualify as a major episode. Other episode of hypoglycemia defined as suggestive episode reported but not meeting the criteria for major or minor episodes.

[b] Based on a separate analysis of covariance (ANCOVA) model for (log (week 24 value) – log (baseline value)) for each end point with treatment group as an effect and log (baseline value) as a covariate.

Source: Clinical Study Report for Study 5.[4]

TABLE 37: HARMS (ADD-ON TO INSULIN, VERSUS PLACEBO)

	Study 6			Study 6 (Extension to Week 104)		
Adverse Events	**Dapa 5 mg N = 212**	**Dapa 10 mg N = 196**	**Placebo N = 197**	**Dapa 5/10 mg N = 212**	**Dapa 10 mg N = 196**	**Placebo N = 197**
Subjects with > 0 AEs, n (%)	139 (66)	132 (67)	127 (65)	166 (78)	157 (80)	154 (78)
Most common AE, n (%)						
Nasopharyngitis	29 (14)	17 (9)	22 (11)	39 (18)	33 (17)	27 (14)
Hypertension	13 (6)	7 (4)	16 (8)	21 (10)	19 (10)	23 (12)
SAEs						
Subjects with > 0 SAEs, n (%)	10 (5)	14 (7)	14 (7)	32 (15)	36 (18)	39 (20)
Most common SAEs, n (%)						
Pneumonia	0	2(1)	0	0	2(1)	2 (1)
TIA	0	0	2 (1)	0	1(1)	3 (2)
Positional vertigo	0	0	2 (1)	0	0	2 (1)
Hypoglycemia	2 (1)	0	0	2 (1)	0	0
WDAEs						
WDSAEs, N (%)	3 (1)	4 (2)	3 (2)	5 (2)	5 (3)	5 (3)
WDAEs, N (%)	12 (6)	8 (4)	8 (4)	20 (9)	11 (6)	13 (6)
Hypoglycemia	0	0	0	0	0	0
Notable harms						
Hypoglycemia	96 (45)	83 (42)	69 (35)	130 (61)	119 (61)	122 (62)
Major	1 (1)	1 (1)	1 (1)	3 (1)	3 (2)	2 (1)
Renal impairment/failure	5 (2)	2 (1)	2 (1)	6 (3)	6 (3)	4 (2)
Mean (SE) change from baseline in eGFR, mL/min/m^2	–0.9 (0.740)	–0.8 (0.824)	–0.6 (0.777)			
Hepatic disorder	2 (1)	2 (1)	0	3 (1)	4 (2)	4 (2)
Genital infection	16 (8)	18 (9)	4 (2)	27 (13)	28 (14)	6 (3)
UTI	19 (9)	17 (9)	8 (4)	28 (13)	27 (14)	11 (6)
UTI female, n/N (%)	15/112(13)	14/108(13)	6/99 (6)	21/112(19)	21/108(19)	7/99 (7)
Cardiac failure	0	0	1 (1)	3 (1)	0	3 (2)
Chronic cardiac failure	0	0	1 (1)	0	0	1 (1)
Cardiac failure congestive	0	0	0	0	0	2 (1)
Diabetic ketoacidosis	0	0	0	0	1 (1)	0
Lipids: Adjusted[a] mean % change from baseline, vs. placebo (95% CI) [mg/dL]						
Total cholesterol	**5 mg:** –0.94 [–4.45 to 2.70], *P* = 0.6087 **10 mg:** 0.31 [–3.31 to 4.06], *P* = 0.8696					
HDL	**5 mg:** 5.78 [2.15 to 9.54], *P* = 0.0017 **10 mg:** 2.70 [–0.89 to 6.42], *P* = 0.1420					
LDL-C	**5 mg:** –1.74 [–6.93 to 3.74], *P* = 0.5254 **10 mg:** –0.38 [–5.75 to 5.30], *P* = 0.8937					

	Study 6			Study 6 (Extension to Week 104)		
Adverse Events	**Dapa 5 mg N = 212**	**Dapa 10 mg N = 196**	**Placebo N = 197**	**Dapa 5/10 mg N = 212**	**Dapa 10 mg N = 196**	**Placebo N = 197**
TG	**5 mg:** –1.78 [–9.30 to 6.36], *P* = 0.6573 **10 mg:** –0.51 [–8.24 to 7.88], *P* = 0.9017					

AE = adverse event; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SAE = serious adverse event; SE = standard error; TG = triglycerides; TIA = transient ischemic attack; UTI = urinary tract infection; WDAE = withdrawal due to adverse event; WDSAE = withdrawal due to serious adverse event; vs. = versus.

[a] Based on a separate analysis of covariance (ANCOVA) model for (log (week 24 value) – log (baseline value)) for each end point with treatment group as an effect and log (baseline value) as a covariate.

Source: Clinical Study Report for Study 6.[5]

TABLE 38: HARMS (ADD-ON TO METFORMIN, TRIPLE THERAPY VERSUS DUAL THERAPY)

	Study 18		
Adverse Events	**Dapagliflozin/ saxagliptin N = 179**	**Dapagliflozin N = 179**	**Saxagliptin N = 176**
Subjects with > 0 AEs, N (%)	87 (49)	87 (49)	93 (53)
Most common AEs			
Nasopharyngitis	7 (4)	7 (4)	8 (5)
SAEs			
Subjects with > 0 SAEs, N (%)	2 (1)	2 (1)	6 (3)
Most common SAEs[a]			
AMI			
WDAEs			
WDSAEs, N (%)	0	0	0
WDAEs, N (%)	1 (1)	1 (1)	0
Hypoglycemia			
Notable harms			
Hypoglycemia[a]	2 (1)	2 (1)	2 (1)
major	0	0	0
minor	1 (1)	1 (1)	0
other	1 (1)	1 (1)	1 (1)
eGFR decrease	3 (2)	0	1 (1)
Renal impairment	0	0	1 (1)
Renal failure	0	0	1 (1)
Genital infection	0	10 (6)	1 (1)
UTI	1 (1)	7 (5)	9 (5)
UTI female	NR	NR	NR
Cardiac failure congestive	0	0	0
Left ventricular hypertrophy	0	1	1
Acidosis	0	0	0
Lipids: Total cholesterol	NR		
HDL	NR		

	Study 18		
Adverse Events	**Dapagliflozin/ saxagliptin N = 179**	**Dapagliflozin N = 179**	**Saxagliptin N = 176**
LDL-C	NR		
TG	NR		

AE = adverse event; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SAE = serious adverse event; TG = triglycerides; UTI = urinary tract infection; WDAE = withdrawal due to adverse event; WDSAE = withdrawal due to serious adverse event.

[a] Major hypoglycemic episode defined as a symptomatic episode requiring external (third-party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value < 3 mmol/L (< 54 mg/dL) and prompt recovery after glucose or glucagon administration. Minor episode defined as either a symptomatic episode with a capillary or plasma glucose measurement below 3.5 mmol/L (63 mg/dL), regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement below 3.5 mmol/L (63 mg/dL) that does not qualify as a major episode. Other episode of hypoglycemia defined as suggestive episode reported but not meeting the criteria for major or minor episodes. Percentages reported are based on the total number of subjects in each treatment group.

Source: Clinical Study Report for Study 18.[6]

4. DISCUSSION

4.1 Summary of Available Evidence

Six manufacturer-sponsored multinational DB RCTs met the inclusion criteria for this review. All of the included studies enrolled patients with type 2 diabetes inadequately controlled on a regimen of lifestyle modifications as well as background therapy with an antidiabetes drug. Dapagliflozin was added to these background therapies. In four of the included studies, the background therapy was metformin (Studies 4, 12, 14, and 18), Study 5 employed a sulfonylurea as background, and Study 6 employed insulin as background. There were only two studies with an active control, and only one of these studies (Study 4) was designed to compare dapagliflozin with an active control. The other study, Study 18, compared triple therapy (dapagliflozin, saxagliptin and metformin) with dual therapy (dapagliflozin or saxagliptin andmetformin). In this study, there were numerically greater reductions in A1C, FPG, and body weight for dapagliflozin compared with saxagliptin. However, as no comparisons were planned between dapagliflozin and saxagliptin in this study, its findings must be considered hypothesis-generating, and no conclusions can be drawn about the relative efficacy of dapagliflozin versus gliptins at this time. In Study 4, dapagliflozin was non-inferior to glipizide in reducing A1C from baseline after 52 weeks. Among key secondary outcomes, there was no statistically significant difference in reduction in FPG after 52 weeks, and no difference in quality of life based on DTSQ. Dapagliflozin reduced weight compared with glipizide over 52 weeks, a difference between groups of about 5 kg that was maintained in the extension to 104 weeks. Dapagliflozin also reduced both SBP and DBP versus glipizide after 52 weeks. Dapagliflozin consistently elicited statistically significant reductions in A1C, FPG, and weight after 24 weeks when compared with placebo, regardless of the background regimen. Reductions in blood pressure were more inconsistent, and SBP was more likely to see a statistically significant improvement than DBP. There were no clear differences in the overall risk of AEs, SAEs, or WDAEs for dapagliflozin versus either glipizide or placebo; however, these studies were not powered to make such comparisons. Among notable harms, Study 4 was designed to assess risk of hypoglycemia, and there was a statistically significant reduction in risk of hypoglycemia with dapagliflozin compared with glipizide. The risk of both genital infections and urinary tract infections appeared numerically higher with dapagliflozin than with glipizide or with placebo; however, again, these studies were not powered for such analyses. The proportion of patients experiencing other notable harms such as renal impairment/failure, hepatic disorders, heart failure or diabetic ketoacidosis (DKA) were low, with no obvious differences between dapagliflozin and glipizide or placebo.

4.2 Interpretation of Results

4.2.1 Efficacy

Data from the included studies suggest that dapagliflozin, when added to metformin, a sulfonylurea, or insulin, reduces A1C versus placebo, and when added to metformin, to the same extent as glipizide. This suggests that dapagliflozin can provide additional glycemic control when added to a background of metformin or a sulfonylurea, or insulin, in a population with inadequate glycemic control. The relatively short follow-up, even considering the extension, does not allow for assessment of key clinical outcomes in type 2 diabetes such as morbidity and mortality, although this would be a common limitation of studies of antidiabetes drugs. SGLT-2 inhibitors may therefore present a complementary mechanism to that of insulin sensitizers such as metformin and secretagogues such as sulfonylureas in the management of type 2 diabetes. What is not currently known is how the three SGLT-2 inhibitors compare with each other, and whether any represents an advantage (or disadvantage) to another. One of the three NMAs summarized in Appendix 7, which analyzed dapagliflozin with a background of metformin, suggested that there was a smaller reduction in A1C with dapagliflozin than with

empagliflozin or canagliflozin, or compared with a number of other antidiabetes drugs, including sulfonylureas. This NMA was sponsored by a manufacturer that is a competitor to dapagliflozin, with results that were favourable to that manufacturer's drug, and a sensitivity analysis performed by the authors failed to find statistically significant differences between SGLT-2 inhibitors. The NMAs featuring antidiabetes drugs as add-on to sulfonylureas or to insulin (with or without metformin) did not attempt to compare SGLT-2 inhibitors with each other. The NMA with sulfonylureas as background found no difference between dapagliflozin and DPP-4 inhibitors or GLP-1 analogues. The NMA with insulin as background did not find any differences between dapagliflozin and comparators but, in a sensitivity analysis, did find less of an improvement in A1C compared with metformin.

Another issue of note in the included studies was the persistence of A1C-lowering effects. Study 4 had the longest duration of follow-up of any of the included studies, 52 weeks compared with 24 weeks for the other studies, with an extension to 104 weeks and then 208 weeks. The 208-week efficacy results represent less than half of the intention-to-treat population, and are therefore not useful for drawing conclusions; however, the 104-week data suggest an attenuation in A1C response, with both dapagliflozin and glipizide. Focusing on the 52-week data, which is the more complete data set, looking at response over time, it is evident that in the final analysis at 52 weeks, the A1C response for dapagliflozin was essentially identical to that of glipizide. However, there was considerable variation in the A1C responses with glipizide over time, with a peak effect at 18 weeks, and less variability with dapagliflozin (Figure 9 in Appendix 4). Therefore, although an attenuation in A1C responses appears to occur after 108 weeks of treatment in the extension, data from the 52-week core phase suggest that dapagliflozin responses may be less variable over time than responses to glipizide.

Dapagliflozin, similar to other SGLT-2 inhibitors, appears to consistently elicit weight loss in patients with type 2 diabetes. The weight loss appears to be between 1 kg and 3 kg, on average, with the 1 to 2 kg loss observed in the 24-week studies and the 3 kg loss in the 52-week study. Although these weight reductions are not large, this must be considered with the fact that many of the current oral antidiabetes drugs tend to lead to weight gain. Patients also identified weight gain as an important issue in their input to CDR. The weight loss appeared to persist into the extensions, although due to significant attrition, it is difficult to draw any conclusions about this longer-term data. In the NMAs reviewed in Appendix 7, in combination with metformin, both dapagliflozin and the GLP-1 analogues elicited statistically significant reductions in weight. The decrease in weight with dapagliflozin was statistically significant compared with changes in weight with sulfonylureas, thiazolidinediones, DPP-4 inhibitors, and insulin glargine. When combined with sulfonylureas, there was a statistically significant decrease in body weight for dapagliflozin versus DPP-4 inhibitors, and when combined with insulin, with or without metformin, there was a statistically significant decrease in weight versus DPP-4 inhibitors and pioglitazone. It is not clear whether there are differences in the extent of weight loss between the SGLT-2 inhibitors.

The effects of dapagliflozin on blood pressure are more variable and are small when compared with an antihypertensive. There was a more consistent reduction in SBP than in DBP; however, there were studies in which no statistically significant reduction in SBP versus placebo was observed. With the exception of metformin as background, there was only one study each of dapagliflozin with sulfonylurea as background and with insulin as background. Therefore, at present, one cannot conclude that background therapy plays a role in the blood pressure response. While patients providing input to CDR did not explicitly single out cardiovascular disease as a major concern with type 2 diabetes, they did allude to the fear associated with living with the disease, and their expectation that dapagliflozin lowers blood pressure. Hypertension is a significant contributor to the cardiovascular events associated with

type 2 diabetes, and it was identified as a common manifestation of cardiovascular disease among baseline characteristics. Dapagliflozin and other SGLT-2 inhibitors cause an osmotic diuresis through increased glucose excretion in the urine, and this appears to contribute to a modest antihypertensive effect, at least for SBP. Therefore, it is not clear whether this modest blood pressure–lowering effect of dapagliflozin will meet patient expectations. Dapagliflozin elicited a statistically significant reduction in SBP versus glipizide, although there was some variation in its ability to cause a statistically significant reduction in SBP versus placebo, depending on the drugs it was combined with. One cannot conclude that there is currently any difference in blood pressure–lowering effects among the SGLT-2 inhibitors. The only consistent observation is that the blood pressure reduction is most consistent for SBP rather than DBP and is small and of questionable clinical significance.

The SGLT-2 inhibitors work by inhibiting glucose transporters at the level of the nephron; therefore, patients with impaired renal function may have a reduced response to drugs in this class. In the subgroup analysis based on baseline eGFR, there was some evidence of a reduction in A1C responses with increasing renal impairment, although this subgroup interaction was not statistically significant in all studies. The product monograph for dapagliflozin states that it is contraindicated in patients with moderate to severe renal impairment (eGFR less than 60 mL/min/m^2). The product monograph for canagliflozin states it is contraindicated in patients with an eGFR less than 45 mL/min/m^2. The product monographs for dapagliflozin and canagliflozin go on to state that, in these patients with impaired renal function, glycemic control was not improved and adverse reactions were more frequent. Therefore, there appears to be some variation in the directions for use of the SGLT-2 inhibitors in patients with renal impairment. However, it is not clear whether this is due to a different effect of the drugs, or whether it is simply a function of the number and design of studies on which to base analyses.

4.2.2 Harms

In the post-marketing period, there have been cases of DKA with the SGLT-2 inhibitors, including euglycemic DKA, reported in patients with type 1 diabetes or with type 2 diabetes, and safety warnings have been issued by both Health Canada and the US Food and Drug Administration (FDA).[33,34] No cases of euglycemic DKA were reported in the studies included in this review, although one case of DKA was reported. In its response to the draft CDR report, the manufacturer provided additional details, stating that there has been one case of DKA out of 5,936 patients treated with dapagliflozin. The FDA safety warning stated that 20 cases of DKA, ketoacidosis, or ketosis were found in a search of their AE database from March 2013 (first approval of an SGLT-2 inhibitor) to June 2014. Most of these cases involved patients with type 2 diabetes. The median time to onset of symptoms was two weeks, although there was a wide range (i.e., 1 to 175 days). It was noted that, in some of these reports, patients exhibited only mild elevations in blood glucose.[34] A case series published in June 2015 reviewed 13 events of euglycemic DKA, occurring in patients with type 1 diabetes (seven patients) and type 2 diabetes (two patients).[35] All patients in this case series were on canagliflozin. Normally, DKA occurs in the setting of hyperglycemia, and cases of euglycemic DKA, characterized by a lack of marked hyperglycemia, are considered to be relatively rare and more likely to occur in type 1 diabetes. There have been a number of proposed mechanisms for these cases, reviewed in Taylor et al.,[36] one of the more obvious being that patients taking insulin reduce their dose of insulin while on SGLT-2 inhibitors in order to avoid hypoglycemia. The reduced insulin could lead to generation of ketones by a number of mechanisms. This mechanism is more likely to be a risk in the setting of type 1 diabetes, where insulin use is more common, although dapagliflozin is approved for use with insulin therapy (whereas empagliflozin is not approved for use with insulin at present). Mechanistically, SGLT-2 is expressed on pancreatic alpha cells, promoting secretion of glucagon, which would in turn lead to generation of ketones. SGLT may also promote excretion of ketones; therefore, inhibition of this transporter may lead to accumulation of

ketone bodies, and thus to ketosis. A key clinical issue is that ketoacidosis without markedly elevated hyperglycemia may go undetected, as clinicians are accustomed to DKA patients presenting with marked hyperglycemia.

The product monographs for all the SGLT-2 inhibitors describe warnings and precautions related to renal function. There were few renal AEs in the included studies in this review, too few to determine whether there was an elevated risk of such events with dapagliflozin over placebo. When compared with glipizide, on a metformin background in Study 4, there were 6% of dapagliflozin patients versus 3% of glipizide patients with an AE of renal impairment or failure. Again, none of these studies were powered to assess harms outcomes such as this; therefore, these data should be considered hypothesis-generating. There was no difference between dapagliflozin and glipizide in renal AEs in the extension to 208 weeks (9% versus 8% of patients with an event, respectively). There was some evidence of a numerical reduction in eGFR for dapagliflozin versus placebo; however, this was not consistent across studies, and the studies were not powered to assess such differences.

Patients describe the daily fluctuations in blood glucose as a major contributor to the stress associated with their disease. Hypoglycemia is likely a major contributor to this stress and is considered one of the major limiting factors to a number of the key drugs used in type 2 diabetes management. When compared with a sulfonylurea, there was a statistically significant reduction in risk of hypoglycemia with dapagliflozin, when each was added to metformin therapy. The insulin secretagogues, most notably sulfonylureas, and insulin are most associated with hypoglycemia. When combined with a sulfonylurea in Study 5, there was no obvious increase in risk of hypoglycemia with dapagliflozin compared with placebo; however, this study was not powered to assess safety outcomes. When combined with insulin, there appeared to be a numerical increase in risk of hypoglycemia with dapagliflozin compared with placebo; however, once again, this study was not designed to assess this outcome. In the NMAs (Appendix 7), when combined with metformin, dapagliflozin had a lower risk of hypoglycemia compared with sulfonylureas, insulin glargine, or nateglinide. No clear conclusion could be drawn regarding risk of hypoglycemia in combination with sulfonylureas, and there was no statistically significant difference when combined with insulin versus other comparators.

As a glucose transporter inhibitor, SGLT-2 inhibitors are expected to elicit glycosuria, and the excess sugar provides a favourable environment for bacterial growth, leading to increased risk of urinary tract and genital infections. The included studies were not designed to assess harms such as these; however, there was some evidence of an elevated risk of urinary tract infections (particularly in female patients) and genital infections. However, particularly for urinary tract infections, elevated risk with dapagliflozin was not clear in every study. The product monograph for dapagliflozin notes the elevated risk of genital mycotic infections, particularly in patients with a previous history of mycotic infections.

4.3 Potential Place in Therapy[1]

The indication in Canada is for combination use with any of metformin, a sulfonylurea, and/or insulin in patients for whom those therapies do not achieve adequate glycemic control. Off-label use in type 2 diabetes as monotherapy or in combination with other classes of diabetes drugs is possible. Off-label use in type 1 diabetes is also possible.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Metformin is widely considered first-line monotherapy, and all other classes as potential second-line pharmacotherapy, based on a variety of patient- and disease-specific factors. Dapagliflozin would be considered among these second-line agents. Clinical experience suggests A1C lowering in a range comparable to other agents, with low hypoglycemic potential. The profile of the medications suggests that prescription is likely when an oral agent is desired and goals of therapy include some weight loss, and a neutral or slightly improved effect on blood pressure. The patient population most likely to receive SGLT-2 medications are those with type 2 diabetes, high BMI or hypoglycemia potential, in whom sulfonylureas or insulin are likely to promote weight gain or hypoglycemia.

5. CONCLUSIONS

Six manufacturer-sponsored multinational DB RCTs met the inclusion criteria for this review. All studies enrolled patients who had inadequate glycemic control on current therapies and lifestyle modifications, who were on a background of metformin (four studies), a sulfonylurea (one study), or insulin (one study). One of the studies with metformin background compared triple therapy (dapagliflozin, saxagliptin, and metformin) with dual therapy (dapagliflozin plus metformin or saxagliptin plus metformin); however, due to the study design, no formal comparisons between dapagliflozin and saxagliptin in patients on a metformin background were made. The other active-controlled study with a metformin background, Study 4, found dapagliflozin to be non-inferior to glipizide in reducing A1C after 52 weeks of therapy. The same study found that dapagliflozin elicited statistically significant weight loss and reduction in blood pressure versus glipizide. The reduction in blood pressure is modest and of questionable clinical significance. Dapagliflozin also consistently improved A1C and weight at both approved doses, regardless of whether it was added to metformin, a sulfonylurea, or insulin with or without metformin. The risk of hypoglycemia was lower with dapagliflozin than with glipizide, and this difference was statistically significant. Dapagliflozin was numerically more likely to cause urogenital infections compared with glipizide and with placebo, although the included studies were not powered to assess harms such as these. The incidence of other notable harms was low, with no clear differences in risk between groups.

In a manufacturer-submitted NMA, there were no significant differences in A1C between dapagliflozin and DPP-4 inhibitors as dual therapy with either metformin or a sulfonylurea. However, a published NMA sponsored by the manufacturer of a competitor SGLT-2 inhibitor reported that dapagliflozin added to metformin was associated with statistically lower A1C reduction (by approximately 0.2%) than either canagliflozin or empagliflozin added to metformin.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Canadian Diabetes Association (CDA) provides education and services, advocates on behalf of people with diabetes, supports research, and translates research into practical applications. The CDA is supported in its efforts by a community-based network of volunteers, employees, health care professionals, researchers, and partners.

The CDA solicits and receives unrestricted educational grants from multiple manufacturers and vendors of medications, supplies, and devices for diabetes and its complications; these sources are listed in Figure 8. These funds are used to help the CDA support community programs and services for people with diabetes and to fund research and advocacy across Canada. The CDA declared no conflicts of interest in the preparation of this submission.

2. Condition-Related Information

The CDA solicited patient input through two surveys distributed through social media and email blasts. The first survey was conducted on 376 patients with type 2 diabetes and their caregivers to identify the impacts of diabetes and the aspects of diabetes they want medications to address. The second survey gathered information from 424 individuals (349 patients with diabetes and 75 caregivers) about their experiences with current drug therapies (including dapagliflozin) and their expectations of diabetes treatment. Approximately 23% (98 of 424) of respondents had taken dapagliflozin or cared for a patient who had taken dapagliflozin.

Type 2 diabetes is a chronic (progressive) condition that occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced. Common symptoms of diabetes include fatigue, thirst, and weight change. High blood glucose levels can cause long-term complications such as blindness, heart disease, kidney problems, nerve damage, and erectile dysfunction.

The majority of patients with type 2 diabetes indicated that daily fluctuations in blood sugar were the most important aspect of diabetes to control during the day and overnight. The fluctuations affect the ability to work and interact with friends and family, cause stress and worry, and impede the ability to participate in normal activities of daily living. Uncontrolled diabetes and the stigma associated with the disease can result in reduced quality of life. Respondents frequently emphasized the psychological and emotional impact of diabetes on their lives (effect on stress, anxiety, adjusting to changes in diet and lifestyle, medication and treatment management as well as relationships with family) as well as fatigue and lack of energy. A patient noted, “Having diabetes makes me useless. I have no energy or strength to enjoy life anymore. I can’t do partial jobs around the house. I can’t enjoy sports anymore. Diabetes has instill (sic) a fear in me.”

3. Current Therapy-Related Information

Management of diabetes includes lifestyle changes (diet, exercise, and stress management). Repeated monitoring of blood sugar levels over the course of the day and taking multiple medications can be very stressful. A large proportion of people with type 2 diabetes fail to achieve optimal glycemic control, which places patients at risk for both acute and chronic diabetes complications. Initial therapy is most

often with metformin, but over time, most patients will require the addition of a second or third drug to reach glycemic targets. Many of the currently available second-line therapies cause significant weight gain, while their ability to achieve optimal glycemic control may be limited by hypoglycemia. As one patient reported, "The most distressing side effect of all of the diabetes drugs is they make you gain weight or prevent weight loss. It is annoying to be told to lose weight then handed a drug that prevents weight loss."

The majority of respondents (63%; n = 218 of 397) stated that they were satisfied or very satisfied with their current therapies, whereas 18% indicated dissatisfaction. Patients indicated that current therapies were better or much better at maintaining target blood glucose and glycated hemoglobin (A1C) levels. However, 38% of respondents responded that they found avoiding low blood sugar with current therapies "the same", "worse", or "much worse". More than 90% of respondents indicated that keeping blood sugar at satisfactory levels and avoiding low blood sugar throughout the day and overnight were "quite important" or "very important".

At least half of the patients surveyed reported that several side effects were "the same", "worse", or "much worse" with current therapies, including weight gain (52% of respondents), gastrointestinal effects (57% of respondents), dehydration (59% of respondents), and urinary tract or yeast infection (55% of respondents). The vast majority of respondents indicated that avoiding these side effects and reducing high blood pressure are important to them.

4. Expectations About the Drug Being Reviewed

Dapagliflozin belongs to a new class of drugs that lowers blood glucose and also causes a reduction in blood pressure and weight loss through inhibition of sodium glucose cotransporter-2 (SGLT-2). Of 349 diabetes patients and 75 caregivers who participated in the second survey, 98 respondents had experience with dapagliflozin. In addition, 47 patients reported experience with other drugs from the same class (i.e., canagliflozin [Invokana] or empagliflozin [Jardiance]).

Patients and caregivers who reported experience with dapagliflozin noted its effectiveness in lowering blood sugar levels and blood pressure relative to other medications. Several patients who successfully achieved target blood sugar levels on dapagliflozin remarked that they had previously had difficulty lowering their blood sugar on other medications, or they noticed a positive change despite being on dapagliflozin for a very short time (four days to a month). Some patients also experienced "significant" and "dramatic" weight loss and/or reduced the amount of insulin or other medications (e.g., for blood pressure or depression) they took after being treated with dapagliflozin. In addition, respondents generally did not describe serious side effects; some who did experience side effects such as frequent urination, dehydration, and increased appetite described them as "manageable." As a result, patients reported improved quality of life, feeling more energetic and exercising more, feeling happier, more self-confident, more in control of their current condition, and optimistic about improving their health in the long-term. One patient called dapagliflozin an "absolute game-changer," and another said, "I feel more like my old self."

Most patients reported a positive experience with dapagliflozin; however, some have not experienced the same benefits and have found side effects challenging. Some patients did not achieve stabilization of blood sugar levels or weight loss after up to two months of treatment. Two respondents discontinued this medication because of a rash and facial swelling and "concerns about bladder cancer." A few patients reported experiencing repeated vaginal yeast infections, urinary tract infections, and

constipation. Others mentioned episodes of bowel incontinence, increased blood pressure, and an "annoying pang in my chest." One patient stated, "I have never felt so ill in my life."

More than 90% of respondents (n = 84 of 93) who have taken dapagliflozin indicated that its availability is "important" or "very important" to people living with type 2 diabetes. Among respondents who are on diabetes medications, 70% (n = 225 out of 321) indicated it is important for dapagliflozin to be available. The reasons cited included aforementioned benefits such stabilizing blood glucose levels, weight loss, and minimal side effects compared with other medications. Some patients emphasized the importance of giving patients options, particularly if other medications are not effective or tolerable. Others were concerned about not being able to afford dapagliflozin after the end of their participation in a clinical trial and supported coverage of this drug so that "other Canadians can benefit like I have."

FIGURE 8: ORGANIZATIONS AND FOUNDATIONS THAT MADE DONATIONS TO THE CANADIAN DIABETES ASSOCIATION BETWEEN SEPTEMBER 2012 AND AUGUST 2013[37]

593123 Alberta Ltd.
A. Lassonde Inc.
Abbott Laboratories, Ltd.
Aecon Group Inc.
Affinity Credit Union
Agway Metals Inc.
Amgen Canada Inc.
Amor Da Patria Community Centre of Toronto
Animas Canada
AstraZeneca Canada Inc.
Balmoral Office Group Inc.
Bayer HealthCare – Diabetes Care Division
Bayshore Home Health
BD Medical – Diabetes Care
BHP Billiton Matched Giving Program
Blistex Corporation
Boehringer Ingelheim (Canada) Ltd.
Brian & Susan Thomas Foundation
Bristol-Myers Squibb/ AstraZeneca Canada Allianance
Cal LeGrow Foundation
Cal Wenzel Family Foundation
Cameco Corporation
Canadian Footwear Ltd.
Canadian National Railway Company
Canola Info/Canola Council of Canada
Cenovus Energy – Employee Foundation
Chadi & Company
Chartwell Retirement Residences
Children's Hospital Aid Society
Chippendale Foundation
CIBC
Clifford & Lily Fielding Foundation
CMG Computer Modelling Group Ltd.
Community Foundation of Ottawa
Community Initiatives Fund
Compass Pharmacies
Conexus Credit Union
Co-operators/CUMIS
Covidien Canada
Dauphin Clinic Pharmacy
Donors Choice – Killarney & Area
E-L Financial Corporation Ltd.
Eli Lilly Canada Inc.
Eli Lilly Canada Inc./ Boehringer Ingelheim Alliance
Excelleris Technologies LP
Flame Of Hope Golf Classic London
General Mills Canada Corporation
Genzyme Canada Inc.
GlaxoSmithKline Inc.
Glenn's Helping Hand Foundation Inc.
Gold Bond Ultimate
Government of Canada – Province of New Brunswick
Grand Court Order of The Amaranth
Great-West Life, London Life & Canada Life
Green Shield Canada
Guelph Community Foundation
Home Hardware Stores Ltd.
Honeybush Health Ltd.
HOPE Ottawa Carleton Inc.
Husky Energy Inc.
Information Services Corporation (ISC)
Janssen Inc.
Janzen's Pharmacy Ltd.
Jarrod Oils Ltd.
Jewish Foundation of Manitoba
John Ung-Ling Ting Professional Corporation
John Zubick Ltd.
Johnson & Johnson Inc.
Kiwanis Club of Vancouver
KPMG
Kraft Canada Inc.
Lagniappe Foundation
Lawson Foundation
Leon's Furniture Ltd.
LifeScan Canada Ltd.
Lions Clubs of Canada
Loblaw Companies Ltd.
Loyal Protestant Association
Manitoba Association of Health Care Professionals
Manulife Financial
Mark's Work Wearhouse
Masonic Foundation of Ontario
Masons
McNeil Consumer Healthcare
Medavie Health Foundation
MEDEC
MedicAlert
Medisys Health Group
Medtronic of Canada Ltd.
Merck Canada
MLF Consulting Ltd.
National Bank of Canada
Nestlé Health Science
Newfound Foundation
Novartis Pharmaceuticals Canada Inc.
Novo Nordisk Canada Inc.
Order Of The Eastern Star – Grand Chapter of NS & PEI
Pacific Blue Cross Health Foundation
Performance Boat Club Charities
Pfizer Canada Inc.
Pharmasave Central
Progressive Foods Inc.
Project Read Literacy Network
Raymond James Canada Foundation
RBC Foundation
Realty Executives Western Canada
Regina Capital Cosmopolitan Club
Regina Queen City Kinsmen
Rexall Foundation
Roche Diagnostics Canada
Rubicon/ Pharmasave
Rx&D, Canada's Research-Based Pharmaceutical Companies
Sandra & Leo Kolber Foundation
Sanofi Aventis Canada Inc.
Saskatchewan Indian Gaming Authority
Saskatoon Community Foundation
Saskatoon Subway
Shaw Communications Inc.
Shopease Foods Inc.
Silver Hills Bakery
South Saskatchewan Community Foundation Inc.
Stickling's Specialty Bakery Ltd.
Storck Canada Inc.
Strategic Charitable Giving Foundation
Subway Franchisee Advertising
Sudbury Rocks Running Club
Sun Life Financial
Sunrise Soya Foods
Sure Flow Equipment Inc.
Takeda Canada Inc.
TD Waterhouse
TELUS
The Arthur J E Child Foundation
The Calgary Foundation
The Cash Store Financial Services Inc.
The Charles Norcliffe Baker & Thelma Scott Baker Foundation
The Chastell Foundation
The Community Foundation of Prince Edward Island
The John & Judy Bragg Family Foundation
The Kinsmen Club of Saskatoon
The London & District Concrete Forming Contractors Assoc.
The Lome & Evelyn Johnson Foundation
The North West Company Inc.
The Poker For Diabetes Foundation
The Toronto Star Fresh Air Fund
The Toronto-Dominion Bank
The Winnipeg Foundation
TransCanada Pipelines Ltd.
Unilever Canada Inc.
Union 52 Benevolent Society
United Way Newfoundland & Labrador
Wellington Laboratories Inc.
Williamsburg Arms

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 28 2015
Alerts:	Biweekly search updates until 21 October 2015
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

Line #	Search Strategy	Results
1	(dapagliflozin* or Forxiga* or Farxiga* or BMS 512148 or BMS512148 or BMS–512148 or UNII1ULL0QJ8UC or UNII–1ULL0QJ8UC).ti,ab,rn,nm,sh,hw,ot.	1053
2	(461432–26-8 or "461432268" or 461432 26 8 or 46143226 8 or 461432 268).rn,nm.	559
3	1 or 2	1053
4	3 use pmez	227
5	*dapagliflozin/	378
6	(dapagliflozin* or Forxiga* or Farxiga* or BMS 512148 or BMS512148 or BMS–512148 or UNII1ULL0QJ8UC or UNII–1ULL0QJ8UC or UNII 1ULL0QJ8UC).ti,ab.	718
7	5 or 6	740
8	conference abstract.pt.	1858285
9	7 not 8	527
10	9 use oemezd	300
11	4 or 10	527
12	remove duplicates from 11	333

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Date of Search:	May 28, 2015
Keywords:	Forxiga, Farxiga, dapagliflozin, type 2 diabetes mellitus
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Clinical Study Report: MB102009. A pilot study of the efficacy and safety of BMS–512148 on glycemic control in subjects with type 2 diabetes treated aggressively but not controlled on combination antihyperglycemic therapy with metformin and/or thiazolidinedione (TZD) and insulin. [**CONFIDENTIAL** internal manufacturer's report]. New York (NY): Bristol-Myers Squibb; 2008 Mar 31. Wilding JP, et al. Diabetes Care. 2009 Sep;32(9):1656–62. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2732143 Mudaliar S, et al. Diabetes Technol Ther. 2014 Mar;16(3):137–44.	**Phase 2b**
List JF. Kidney Int [Internet]. 2014 [cited 2015 Jun 9];85(4):962–71. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3973038/pdf/ki2013356a.pdf	**Monotherapy**
Jabbour SA, et al. Diabetes Care [Internet]. 2014 [cited 2015 Jun 9];37(3):740–50. Available from: http://care.diabetesjournals.org/content/37/3/740.full.pdf+html	**Wrong background (DPP-4)**
Schumm-Draeger PM, et al. Diabetes Obes Metab [Internet]. 2015 Jan [cited 2015 Jun 9];17(1):42–51. Available from: http://onlinelibrary.wiley.com/doi/10.1111/dom.12387/epdf	**Wrong dose (twice daily)**
Leiter LA, et al. J Am Geriatr Soc. 2014 Jul;62(7):1252–62.	**Wrong background (usual care)**
Rosenstock J, et al. Diabetes Care [Internet]. 2012 Jul [cited 2015 Jun 9];35(7):1473-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3379599/pdf/1473.pdf	**Wrong background (glitazone)**
Cefalu WT, et al. Diabetes Care. 2015 Apr 7.	**Wrong background (any)**
Strojek K, et al. Dtsch Med Wochenschr. 2013 Apr;138 Suppl 1:S16-S26. German. Wilding JP, et al. Dtsch Med Wochenschr. 2013 Apr;138 Suppl 1:S27-S38.	**German**

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 39: SUBGROUP ANALYSES FOR A1C (ADD-ON TO METFORMIN, VERSUS SULFONYLUREA)

	Study 4	
	Dapagliflozin N = 400	**Glipizide N = 401**
A1C: Mean Change From Baseline		
A1C < 8%		
Mean (SD) baseline	7.18 (0.415)	7.16 (0.439)
N	262	246
Mean (SD) change from baseline	–0.25 (0.591)	–0.31 (0.877)
Adjusted mean (SE)	–0.25 (0.0511)	–0.31 (0.0528)
Adjusted mean [95% CI] difference from glipizide	0.06 [–0.09 to 0.20]	
A1C ≥ 8% to < 9%		
Mean (SD) baseline	8.40 (0.264)	8.31 (0.261)
N	103	104
Mean (SD) change from baseline	–0.88 (0.695)	–0.72 (1.085)
Adjusted mean (SE)	–0.88 (0.0816)	–0.72 (0.0812)
Adjusted mean [95% CI] difference from glipizide	–0.16 [–0.39 to 0.06]	
A1C ≥ 9%		
Mean (SD) baseline	9.46 (0.516)	9.38 (0.353)
N	35	51
Mean (SD) change from baseline	–1.29 (0.914)	–1.19 (1.151)
Adjusted mean (SE)	–1.29 (0.1399)	–1.19 (0.1159)
Adjusted mean [95% CI] difference from glipizide	–0.10 [–0.46 to 0.25]	
Interaction P value[a]	***P = 0.2038***	
Baseline eGFR (MDRD) [mL/min/1.73 m²]:		
≥ 90 mL/min/1.73 m² (normal)		
Mean (SD) baseline	7.72 (0.857)	7.78 (0.887)
N	183	196
Mean (SD) change from baseline	–0.54 (0.804)	–0.41 (1.098)
Adjusted mean (SE)	–0.53 (0.0589)	–0.37 (0.0570)
Adjusted mean [95% CI] difference from glipizide	–0.16 [–0.32 to 0.00]	
60 to < 90 mL/min/1.73 m² (mild impairment)		
Mean (SD) baseline	7.65 (0.851)	7.67 (0.867)
N	198	181
Mean (SD) change from baseline	–0.48 (0.698)	–0.59 (0.923)
Adjusted mean (SE)	–0.50 (0.0567)	–0.61 (0.0593)
Adjusted mean [95% CI] difference from glipizide	0.11 [–0.05 to 0.27]	
30 to < 60 mL/min/1.73 m² (moderate impairment)		
Mean (SD) baseline	7.73 (0.758)	7.90 (0.938)
N	18	23

	Study 4	
Mean (SD) change from baseline	–0.47 (0.655)	–1.10 (0.776)
Adjusted mean (SE)	–0.46 (0.1879)	–1.02 (0.1663)
Adjusted mean [95% CI] difference from glipizide	0.56 [0.07 to 1.05]	
Interaction P value [b]	***P = 0.0055***	

A1C = glycated hemoglobin; CI = confidence interval; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet In Renal Disease; SD = standard deviation; SE = standard error.
[a] *P* value for the treatment-by-subgroup interaction based on continuous baseline A1C (one degree of freedom).
Based on an analysis of covariance (ANCOVA) model with terms for treatment group, baseline A1C category, and the interaction between treatment group and baseline A1C category.
[b] *P* value for the treatment-by-subgroup interaction. Based on an analysis of covariance (ANCOVA) model controlling for treatment, baseline A1C, subgroup variable and treatment-by-subgroup interaction
Source: Clinical Study Report for Study 4.[1]

TABLE 40: SUBGROUP ANALYSES FOR A1C (ADD-ON TO METFORMIN, VERSUS PLACEBO)

	Study 14		
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**
A1C < 8%			
Mean (SD) baseline	7.37 (0.380)	7.39 (0.378)	7.33 (0.465)
N	67	82	63
Mean (SD) change from baseline	–0.30 (0.654)	–0.60 (0.618)	–0.02 (0.860)
Adjusted mean (SE)	–0.30 (0.1016)	–0.60 (0.0918)	–0.02 (0.1047)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.28 [–0.56 to 0.01] **10 mg:** –0.57 [–0.85 to –0.30]		
A1C ≥ 8% to < 9%			
Mean (SD) baseline	8.44 (0.227)	8.44 (0.285)	8.41 (0.261)
N	32	32	49
Mean (SD) change from baseline	–1.07 (0.714)	–1.03 (0.961)	–0.59 (0.973)
Adjusted mean (SE)	–1.07 (0.1469)	–1.03 (0.1469)	–0.59 (0.1188)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.47 [–0.84 to –0.10] **10 mg:** –0.44 [–0.81 to –0.07]		
Test for interaction[a]	*P* = 0.0681		
Baseline eGFR (MDRD) [mL/min/1.73 m^2]: ≥ 90 (normal)	NR		

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet In Renal Disease; NR = not reported; SD = standard deviation; SE = standard error.
[a] *P* value for the treatment-by-subgroup interaction based on continuous baseline A1C (one degree of freedom).
Based on an analysis of covariance (ANCOVA) model with terms for treatment group, baseline A1C category, and the interaction between treatment group and baseline A1C category.
Source: Clinical Study Report for Study 14.[2]

TABLE 41: SUBGROUP ANALYSES FOR A1C (ADD-ON TO METFORMIN, VERSUS PLACEBO)

	Study 12	
	Dapa 10 mg N = 89	**Placebo N = 91**
A1C: Mean Change From Baseline		
A1C < 7%		
Mean (SD) baseline	6.74 (0.179)	6.67 (0.208)
N	28	40
Mean (SD) change from baseline	–0.13 (0.313)	0.09 (0.448)
Adjusted mean (SE)	–0.13 (0.086)	0.09 (0.072)
Adjusted mean [95% CI] difference from placebo	–0.22 [–0.44 to 0.00]	
A1C ≥ 7% to < 8%		
Mean (SD) baseline	7.34 (0.284)	7.42 (0.265)
N	55	43
Mean (SD) change from baseline	–0.47 (0.512)	–0.23 (0.469)
Adjusted mean (SE)	–0.47 (0.0618)	–0.22 (0.0699)
Adjusted mean [95% CI] difference from placebo	–0.24 [–0.43 to –0.06]	
A1C ≥ 8%		
Mean (SD) baseline	8.18 (0.110)	8.18 (0.167)
N	5	8
Mean (SD) change from baseline	–1.10 (0.570)	–0.36 (0.262)
Adjusted mean (SE)	NR	NR
Adjusted mean difference from placebo	NR	
Interaction P value[a]	***P = 0.3710***	
Baseline eGFR (MDRD) [mL/min/1.73 m^2]:		
≥ 90 mL/min/1.73 m^2 (normal)		
Mean (SD) baseline	7.14 (0.487)	7.05 (0.541)
N	34	30
Mean (SD) change from baseline	–0.38 (0.45)	–0.16 (0.35)
Adjusted mean (SE)	–0.39 (0.077)	–0.21 (0.082)
Adjusted mean [95% CI] difference from placebo	–0.18 [–0.40 to 0.04]	
60 to < 90 mL/min/1.73 m^2 (mild impairment)		
Mean (SD) baseline	7.22 (0.418)	7.24 (0.534)
N	53	56
Mean (SD) change from baseline	–0.43 (0.54)	–0.06 (0.54)
Adjusted mean (SE)	–0.41 (0.062)	–0.03 (0.060)
Adjusted mean (SE) difference from placebo	–0.39 [–0.55 to –0.22]	
30 to < 60 mL/min/1.73 m^2 (moderate impairment)		
Mean (SD) baseline	7.50	6.88 (0.23)
N	1	5
Mean (SD) change from baseline	0.70	–0.24 (0.21)
Adjusted mean (SE)	NR	NR

	Study 12	
	Dapa 10 mg N = 89	**Placebo N = 91**
Adjusted mean [95% CI] difference from placebo	NR	
Interaction P value[b]	***P = 0.5139***	

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; NR = not reported; SD = standard deviation; SE = standard error.
[a] *P* value for treatment-by-subgroup interaction based on continuous baseline A1C (one degree of freedom). ANCOVA model with terms for treatment group, baseline A1C category and interaction between treatment group and baseline A1C category.
[b] *P* value for the treatment-by-subgroup interaction based on continuous baseline eGFR (one degree of freedom). ANCOVA model controlling for treatment group, stratum, baseline eGFR, subgroup and treatment-by-subgroup interaction

Source: Clinical Study Report for Study 12.[3]

TABLE 42: SUBGROUP ANALYSES FOR A1C (ADD-ON TO SULFONYLUREA, VERSUS PLACEBO)

	Study 5		
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**
A1C < 8%			
Mean (SD) baseline	7.39 (0.356)	7.41 (0.447)	7.45 (0.300)
N	61	70	61
Mean (SD) change from baseline	–0.38 (0.719)	–0.58 (0.597)	0.08 (0.615)
Adjusted mean (SE)	–0.38 (0.0970)	–0.58 (0.0906)	0.08 (0.0970)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.47 [–0.74 to –0.20] **10 mg:** –0.66 [–0.92 to –0.40]		
A1C ≥ 8% to < 9%			
Mean (SD) baseline	8.39 (0.280)	8.39 (0.279)	8.39 (0.301)
N	57	61	58
Mean (SD) change from baseline	–0.65 (0.847)	–0.84 (0.815)	–0.24 (0.846)
Adjusted mean (SE)	–0.65 (0.1004)	–0.84 (0.0970)	–0.24 (0.0995)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.41 [–0.69 to –0.13] **10 mg:** –0.60 [–0.88 to –0.33]		
A1C ≥ 9%			
Mean (SD) baseline	9.34 (0.273)	9.44 (0.386)	9.33 (0.238)
N	24	19	24
Mean (SD) change from baseline	–1.21 (0.921)	–1.50 (0.790)	–0.51 (0.870)
Adjusted mean (SE)	–1.21 (0.1547)	–1.50 (0.1739)	–0.51 (0.1547)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.70 [–1.13 to –0.27] **10 mg:** –0.99 [–1.45 to –0.53]		
Test for interaction[a]	***P = 0.2546***		
By baseline eGFR (MDRD) [mL/min/1.73 m²]:			
≥ 90 mL/min/1.73 m² (normal)			
Mean (SD) baseline	8.23 (0.809)	8.17 (0.791)	8.23 (0.791)
N	51	47	42
Mean (SD) change from baseline	–0.79 (0.687)	–0.91 (0.921)	–0.03 (0.759)
Adjusted mean (SE)	–0.75 (0.1043)	–0.89 (0.1086)	0.01 (0.1149)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.75 [–1.06 to –0.45]		

	Study 5		
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**
	10 mg: –0.90 [–1.21 to –0.59]		
60 to < 90 mL/min/1.73 m² (mild impairment)			
Mean (SD) baseline	8.12 (0.747)	8.03 (0.807)	8.15 (0.711)
N	80	92	77
Mean (SD) change from baseline	–0.62 (0.928)	–0.77 (0.624)	–0.24 (0.795)
Adjusted mean (SE)	–0.62 (0.083)	–0.80 (0.078)	–0.23 (0.085)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.39 [–0.62 to –0.16] **10 mg:** –0.57 [–0.80 to –0.34]		
[mL/min/1.73 m²]: 30 to < 60 (moderate impairment)			
Mean (SD) baseline	7.68 (0.806)	7.96 (0.687)	8.02 (0.756)
N	11	11	24
Mean (SD) change from baseline	0.05 (0.671)	–0.58 (1.136)	–0.04 (0.800)
Adjusted mean (SE)	–0.11 (0.2251)	–0.63 (0.2245)	–0.07 (0.1520)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.04 [–0.57 to 0.50] **10 mg:** –0.56 [–1.10 to –0.03]		
Test for interaction[b]	***P = 0.0115***		

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; SD = standard deviation; SE = standard error.
[a] *P* value for the treatment-by-subgroup interaction based on continuous baseline A1C (one degree of freedom). Based on an analysis of covariance (ANCOVA) model with terms for treatment group, baseline A1C category, and the interaction between treatment group and baseline A1C category.
[b] *P* value for the treatment-by-subgroup interaction based on continuous baseline eGFR (one degree of freedom). ANCOVA model with terms for treatment group, baseline eGFR category and the interaction between treatment group and baseline eGFR category.
Source: Clinical Study Report for Study 5.[4]

TABLE 43: SUBGROUP ANALYSES FOR A1C (ADD-ON TO INSULIN, VERSUS PLACEBO)

	Study 6		
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**
A1C ≥ 7.5% to < 9%			
Mean (SD) baseline	8.20 (0.389)	8.21 (0.394)	8.19 (0.428)
N	122	121	128
Mean (SD) change from baseline	–0.69 (0.584)	–0.75 (0.577)	–0.26 (0.737)
Adjusted mean (SE)	–0.69 (0.0597)	–0.74 (0.0600)	–0.26 (0.0583)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.43 [–0.60 to –0.27], *P* < 0.0001 **10 mg:** –0.48 [–0.65 to –0.32], *P* < 0.0001		
A1C ≥ 9%			
Mean (SD) baseline	9.62 (0.485)	9.57 (0.410)	9.48 (0.456)
N	73	60	48
Mean (SD) change from baseline	–1.25 (0.910)	–1.41 (0.835)	–0.45 (0.810)
Adjusted mean (SE)	–1.23 (0.0974)	–1.41 (0.1069)	–0.47 (0.1199)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.76 [–1.06 to –0.45], *P* < 0.0001 **10 mg:** –0.94 [–1.25 to –0.62], *P* < 0.0001		
Test for interaction[a]	***P = 0.0023***		

	Study 6		
	Dapa 5 mg N = 137	**Dapa 10 mg N = 135**	**Placebo N = 137**
Baseline eGFR (MDRD) [mL/min/1.73 m²]:			
≥ 90 mL/min/1.73 m² (normal)			
Mean (SD) baseline	8.70 (0.731)	8.73 (0.772)	8.55 (0.760)
N	46	59	58
Mean (SD) change from baseline	–0.98 (0.810)	–1.03 (0.790)	–0.27 (0.748)
Adjusted mean (SE)	–0.92 (0.1048)	–0.96 (0.0926)	–0.26 (0.0931)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.66 [–0.94 to –0.39] **10 mg:** –0.70 [–0.96 to –0.44]		
60 to < 90 mL/min/1.73 m² (mild impairment)			
Mean (SD) baseline	8.61 (0.949)	8.48 (0.777)	8.48 (0.761)
N	122	103	103
Mean (SD) change from baseline	–0.93 (0.771)	–0.90 (0.803)	–0.31 (0.813)
Adjusted mean (SE)	–0.90 (0.0642)	–0.92 (0.0699)	–0.33 (0.0699)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.57 [–0.76 to –0.38] **10 mg:** –0.59 [–0.78 to –0.40]		
[mL/min/1.73 m²]: 30 to < 60 (moderate impairment)			
Mean (SD) baseline	8.54 (0.898)	8.59 (1.007)	8.21 (0.762)
N	42	30	27
Mean (SD) change from baseline	–0.49 (0.632)	–0.72 (0.624)	–0.16 (0.587)
Adjusted mean (SE)	–0.49 (0.1096)	–0.70 (0.1298)	–0.27 (0.1368)
Adjusted mean [95% CI] difference from placebo	**5 mg:** –0.22 [–0.56 to 0.13] **10 mg:** –0.42 [–0.79 to –0.05]		
Test for interaction[b]	***P = 0.0819***		

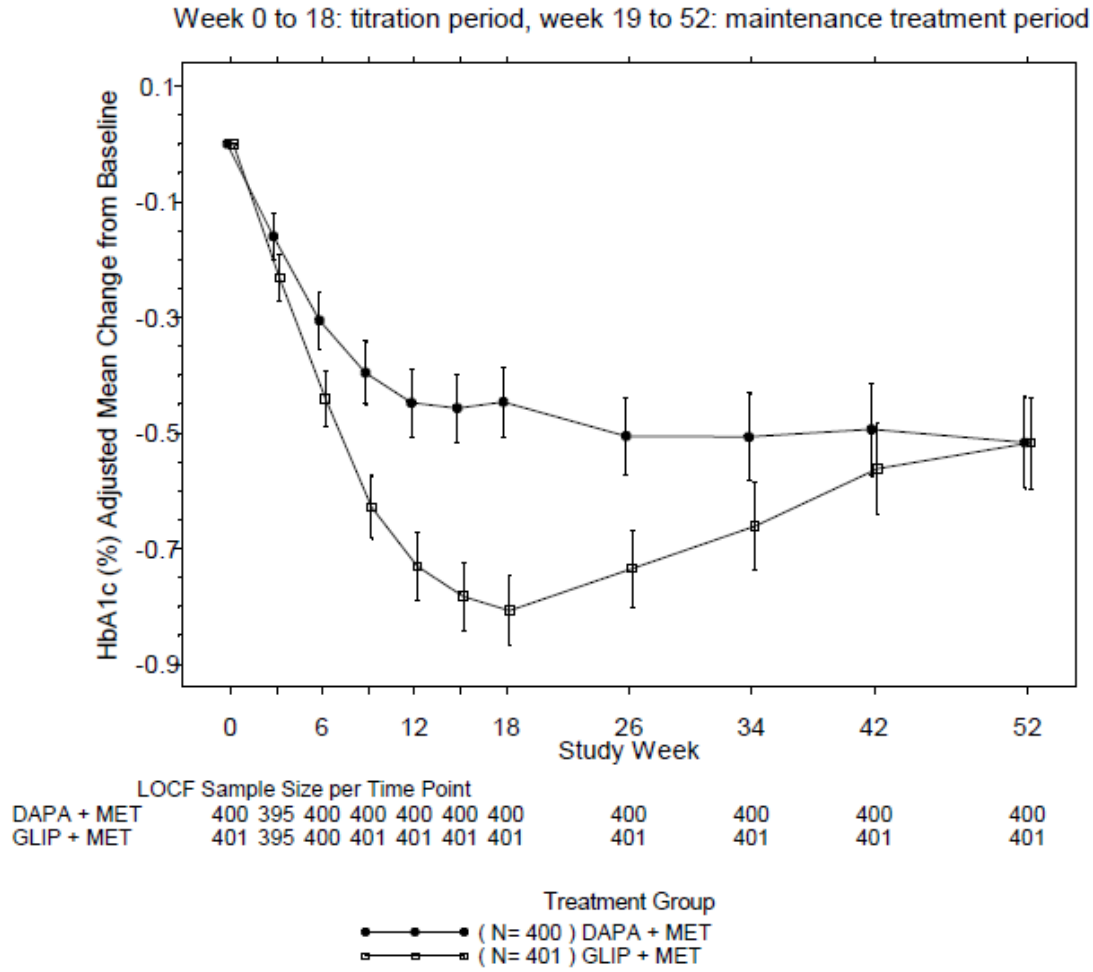
A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; SD = standard deviation; SE = standard error.

[a] *P* value for the treatment-by-subgroup interaction based on continuous baseline A1C (one degree of freedom). Based on an analysis of covariance (ANCOVA) model with terms for treatment group, baseline A1C category and the interaction between treatment group and baseline A1C category.

[b] *P* value for the treatment-by-subgroup interaction based on continuous baseline eGFR (one degree of freedom). ANCOVA model with terms for treatment group, stratum, baseline eGFR category, subgroup and treatment-by-subgroup interaction

Source: Clinical Study Report for Study 6.[5]

FIGURE 9: CHANGES IN A1C OVER TIME, STUDY 4 (52-WEEK PHASE)



DAPA = dapagliflozin; GLIP = glipizide; HBA1c = glycated hemoglobin; LOCF = last observation carried forward; MET = metformin.
Source: Clinical Study Report for Study 4.[1]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D)
- Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Findings

TABLE 44: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Validated	MCID	References
EQ-5D	EQ-5D is a general, non–disease-specific, health-related quality of life questionnaire.	Yes	Unknown	Rabin 2001[38]
DTSQs DTSQc	Both forms of the DTSQ are eight-item, diabetes-specific measures of patient satisfaction with treatment.	Yes	Unknown	Bradley et al. 2007[39]

DTSQc = Diabetes Treatment Satisfaction Questionnaire change version; DTSQs = Diabetes Treatment Satisfaction Questionnaire status version; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; MCID = minimal clinically important difference.

EuroQol Five-Dimension Health-Related Quality of Life Questionnaire

The EQ-5D questionnaire is a generic, non–disease-specific measure of health status.[38] The tool is based on self-report of five domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. There are three levels per domain in the original version: 1 – no problems, 2 – some or moderate problems, and 3 – extreme problems. Each combination of the five domains and three levels creates a unique health state description (243 in total). The index score is calculated by applying a country-specific, utility function-based scoring algorithm to the EQ-5D health states. This algorithm attaches weights reflecting that society's preferences for each health state.[40] The EQ-5D is also accompanied by a visual analogue scale (VAS) to provide a self-rating of overall health, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[38]

In a systematic review of studies using EQ-5D in adults with type 2 diabetes with or without comorbidities, EQ-5D was found to demonstrate construct validity and adequately capture the burden of disease of type 2 diabetes.[41] A range of index and VAS scores for different populations with various levels of disease severity was provided; patients with newly diagnosed diabetes and good A1C levels demonstrated high EQ-5D index and VAS scores of 0.88 and 80, respectively, while those with severe diabetic peripheral neuropathic pain had lower index and VAS scores of 0.20 and 45, respectively.[41] However, some studies included in the review suggested that the EQ-5D may not be able to capture the impact of multiple complications and lacked discriminative power in patients with mild disease. In support of its convergent and discriminative validity, the EQ-5D was shown to correlate well with several other generic and disease-specific health status measures. It also demonstrated predictive validity for complications of diabetes, good to excellent test-retest reliability, and responsiveness (except in one study of long-term management of diabetic peripheral neuropathic pain).[41]

A more recent study examined the construct validity and responsiveness of the EQ-5D in community-based patients with type 2 diabetes.[42] The EQ-5D demonstrated convergent validity with the Short Form Health Survey – Six Dimensions (SF-6D) generic preference measure and significantly discriminated between patients with and without diabetes-related health problems with a high overall effect size

(0.74). However, the EQ-5D displayed a low level of responsiveness to change over time, indicating a ceiling effect at baseline and follow-up. The authors suggested that a new, five-level version of this instrument, the EQ-5D-5L, may increase the sensitivity to change over time.[42] The original EQ-5D is now referred to as EQ-5D-3L.

One study was identified that compared the measurement properties of the EQ-5D-5L and the EQ-5D-3L in patients with eight different chronic conditions, including diabetes.[43] Construct validity of the EQ-5D-5L was established through a known-groups comparison and demonstration of convergent validity with the EQ-5D-3L and the WHO-5 Well-Being Index. Furthermore, the authors reported a reduced ceiling effect with the EQ-5D-5L compared with the EQ-5D-3L for patients with diabetes, from 33.9% to 28.3%.[43]

A minimal clinically important difference (MCID) for the EQ-5D in patients with diabetes was not identified.

Diabetes Treatment Satisfaction Questionnaire

The DTSQ is a diabetes-specific measure of patient satisfaction with treatment.[39] The original "status" version, the DTSQs, contains eight items: six items measure treatment satisfaction (satisfaction with current treatment, convenience, flexibility, satisfaction with own understanding of diabetes, and likelihood of continuing on or recommending current treatment), and two items measure perceived frequency of hyperglycemia and frequency of hypoglycemia. The items are scored on seven-point response scales ranging from "very satisfied" to "very unsatisfied". The psychometric properties of different language versions of the DTSQs were assessed in a study of patients with type 1 and type 2 diabetes treated with insulin or poorly controlled on sulfonylureas who then started insulin treatment.[44] The DTSQs was shown to be consistently reliable in all languages studied and significantly sensitive to change in patients with type 1 diabetes at weeks 8, 20, 24, and at last available visit.[44]

However, it has also been observed that, because patients tend to report satisfaction with current treatment in the absence of experience with alternatives for comparison, the DTSQs often exhibits a ceiling effect.[39] The DTSQc was developed to better capture change in treatment satisfaction and address the ceiling effect for those patients who have high scores on the DTSQs at baseline.[39] The DTSQc also contains eight items that ask about current satisfaction relative to preceding treatment, and is scored on a seven-point scale with responses ranging from "much more satisfied now" to "much less satisfied now."[45] Psychometric analyses of the DTSQc in patients with type 1 and type 2 diabetes showed that the six-item treatment satisfaction component was highly reliable, with a Cronbach's alpha of 0.92.[39] This study also found that the DTSQc identified significantly greater improvement in treatment satisfaction than the DTSQs, particularly when patients had high baseline DTSQs scores; this suggests a reduction in ceiling effect and better responsiveness to change with the DTSQc. The authors recommended using the DTSQc in conjunction with the DTSQs to adequately capture changes in treatment satisfaction over the course of a clinical trial.[39]

An MCID for the DTSQ in patients with type 2 diabetes was not identified.

Conclusion

The EQ-5D is a widely used generic health status measure consisting of five self-reported health domains with three levels per domain. This questionnaire has demonstrated construct validity in patients with diabetes; however, its responsiveness may be limited by a ceiling effect. A newer version with five levels (EQ-5D-5L), rather than the original three-level version (EQ-5D-3L), may provide greater sensitivity to change over time. The DTSQs and DTSQc are measures of patient satisfaction with current treatment at baseline and changes in treatment satisfaction over time, respectively. Both questionnaires have been shown to be reliable in several languages for patients with type 1 and type 2 diabetes, and should be used in conjunction to reduce the ceiling effect observed with the DTSQs alone. MCIDs for patients with type 2 diabetes were not identified for either the EQ-5D or the DTSQ.

APPENDIX 6: SUMMARY OF INDIRECT COMPARISONS

Background

Studies that were included in the systematic review did not provide head-to-head comparisons of dapagliflozin with all the relevant drugs used as add-on therapies for type 2 diabetes in combination with metformin monotherapy, sulfonylurea monotherapy, or insulin (alone or in combination with metformin). The objective of this review is to summarize the objective, methods, and results, and to conduct a critical appraisal of the indirect evidence comparing the efficacy, tolerability and safety of dapagliflozin with other drugs used for treatment of type 2 diabetes.

Methods

Five network meta-analyses (NMAs) were provided by the manufacturer in the submission, of which three were prepared for the submission[46–48] and two were published.[49,50] Also, the CADTH Common Drug Review (CDR) literature search results were reviewed to identify any additional published relevant indirect comparisons (IDCs).[51]

Description of Indirect Comparisons Identified

All five manufacturer-submitted IDCs were relevant for the present review. One additional relevant published IDC was identified in the literature search. The characteristics of IDCs for each sub-indication are detailed in Table 45, Table 46, and Table 47.

TABLE 45: CHARACTERISTICS OF INCLUDED INDIRECT COMPARISONS FOR ANTIDIABETES DRUGS AS AN ADD-ON THERAPY TO METFORMIN

	Orme 2015[46]	Goring et al. 2013[49]	Mearns et al. 2015[51]
Study Designs	RCTs	RCTs	RCTs
Population	Adult with type 2 diabetes who have inadequate glycemic control on metformin monotherapy	Adult with type 2 diabetes who have inadequate glycemic control on metformin monotherapy	Adult with type 2 diabetes who showed inadequate response to stable, optimized metformin monotherapy
Interventions and Comparators	• placebo • SGLT-2 inhibitors: dapagliflozin, canagliflozin, empagliflozin, and ipragliflozin • GLP-1 analogues: lixisenatide, exenatide, liraglutide, dulaglutide • TZD: pioglitazone • DPP-4 inhibitors: linagliptin, alogliptin, saxagliptin, sitagliptin, vildagliptin • sulfonylureas • All in combination with metformin	• placebo • dapagliflozin • GLP-1 analogues • DPP-4 inhibitors • TZDs • sulfonylureas • meglitinides All in combination with metformin	Any FDA or EMA-approved antidiabetes drug therapy compared with another antidiabetes therapy or placebo
Outcomes	Efficacy: A1C, body weight, systolic blood pressure Safety: Hypoglycemic events End points: at 24 weeks ± 6 weeks	Efficacy: A1C, body weight, systolic blood pressure Safety: Hypoglycemia End points: 52 weeks ± 6 weeks	Efficacy: A1C, body weight, systolic blood pressure Safety: Hypoglycemia, urinary tract infections,

	Orme 2015[46]	Goring et al. 2013[49]	Mearns et al. 2015[51]
	and at 52 weeks		genital tract infections End points: from 12 to 52 weeks
N of Included Studies	53 RCTs	6 RCTs	62 RCTs
N of Included Patients	NR	7,861 patients	32,185 patients
Sponsor	Funded by AstraZeneca	Funded by AstraZeneca and Bristol-Myers Squibb	Funded by Boehringer Ingelheim

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; EMA = European Medicine Agency; FDA = Food and Drug Administration; GLP-1 = glucagon-like peptide-1; NR = not reported; RCT = randomized controlled trial; SGLT-2 = sodium glucose cotransporter-2; TZD = thiazolidinedione.

TABLE 46: CHARACTERISTICS OF INCLUDED INDIRECT COMPARISONS FOR ANTIDIABETES DRUGS AS AN ADD-ON THERAPY TO SULFONYLUREAS

	Orme 2015[47]	Orme et al. 2014[50]
Study Designs	RCTs	RCTs
Population	Adults with type 2 diabetes on a stable dose of a sulfonylurea monotherapy, where sulfonylureas with diet and exercise do not provide adequate glycemic control	Adults with type 2 diabetes on a stable dose of a sulfonylurea monotherapy, where sulfonylureas with diet and exercise do not provide adequate glycemic control
Intervention and Comparators	Placebo SGLT-2 inhibitors: dapagliflozin GLP-1 analogues: exenatide DPP-4 inhibitors: alogliptin, linagliptin, sitagliptin and vildagliptin	Placebo SGLT-2 inhibitors: dapagliflozin GLP-1 analogues: exenatide DPP-4 inhibitors: linagliptin, sitagliptin, vildagliptin
Outcomes	Efficacy: A1C, body weight Safety: Hypoglycemia Endpoints: 24 weeks ± 6 weeks	Efficacy: A1C, body weight Safety: Hypoglycemia Endpoints: 24 weeks ± 6 weeks
N of Included Studies	7 RCTs	5 RCTs
N of Included Patients	NR	1,946 patients
Sponsor	Funded by AstraZeneca	Funded by AstraZeneca and Bristol-Myers Squibb

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; NR = not reported; RCT = randomized controlled trial; SGLT-2 = sodium glucose cotransporter-2.

TABLE 47: CHARACTERISTICS OF INCLUDED INDIRECT COMPARISONS FOR ANTIDIABETES DRUGS AS AN ADD-ON THERAPY TO INSULIN ALONE OR IN COMBINATION WITH METFORMIN

	Orme 2015[48]
Study Designs	RCTs
Population	Adults with type 2 diabetes who have inadequate glycemic control with insulin monotherapy or in combination with up to two oral antidiabetes drugs
Interventions and Comparators	Placebo SGLT-2 inhibitors: dapagliflozin GLP-1 analogues: lixisenatide, exenatide, DPP-4 inhibitors: linagliptin, saxagliptin, sitagliptin, vildagliptin

	Orme 2015[48]
	TZD: pioglitazone Metformin In addition to insulin or insulin + metformin
Outcomes	Efficacy: A1C, body weight Safety: hypoglycemia Endpoints: 24 weeks ± 6 weeks
N of Included Studies	16 studies
Sponsor	Funded by AstraZeneca

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; RCT = randomized controlled trial; SGLT-2 = sodium glucose cotransporter-2; TZD = thiazolidinedione.

Review and Appraisal of Indirect Comparisons

Review of Manufacturer's Indirect Comparisons #1

Objectives and Rationale

The purpose of this document was to assess the relative efficacy and safety of sodium glucose cotransporter (SGLT)-2, with a special focus on dapagliflozin, as add-on therapy to metformin, when this latter drug, along with diet and exercise, does not provide adequate glycemic control. Although two others studies with an IDC were included, our analysis will focus on the document[46] provided by the manufacturer.

Methods

***Study Eligibility and Selection Process*:** To be included in the IDC, studies had to meet the inclusion criteria listed in Table 48. The criteria were pre-specified and were aligned with the funding request currently reviewed.

TABLE 48: STUDY ELIGIBILITY

	Inclusion Criteria
Study designs	RCTs
Population	Adults with type 2 diabetes who have inadequate glycemic control on metformin monotherapy
Intervention	All antidiabetes pharmacological therapies that would be added to metformin in clinical practice when metformin does not provide adequate glycemic control
Comparators	Placebo or dual therapy with drugs and doses licensed in the US, in combination with metformin
Outcomes	Efficacy: A1C, body weight, systolic blood pressure Safety: Hypoglycemic events Endpoints: 24 weeks ± 6 weeks or long-term results
Exclusion criteria	Uncontrolled open-label extensions Populations with moderate to severe renal impairment

A1C = glycated hemoglobin; RCT = randomized controlled trial.
Source: Manufacturer's indirect comparison document.[46]

The search for the systematic review was originally conducted in May 2011 but it was updated in 2013 and in September 2014. Cochrane Central, MEDLINE, and Embase databases were searched. Conference proceedings of the American Diabetes Association and the European Association for the Study of Diabetes, as well as the clinical trials registry, were searched. The detailed search strategy was provided.

The process of study selection and data extraction was conducted by two independent reviewers. Citations were screened based on titles and abstracts and rescreened for eligibility with full-text review. Disagreements on study eligibility were decided by a third reviewer. The list of included and excluded studies was provided. Data were extracted and verified by a second reviewer.

Data Extraction: A total of 32 studies were included for the 24 weeks (± 6 weeks) end point. Five more studies, which provided borderline time points (24 weeks ± 8 weeks) or had quality issues, were included in the sensitivity analysis. The evidence networks are displayed in Figure 10 (A1C), Figure 11 (body weight), Figure 12 (SBP), and Figure 13 (hypoglycemia). The included studies randomized 168 to 1,284 patients. Comparators included placebo, SGLT-2 inhibitors (dapagliflozin, empagliflozin, canagliflozin, and ipragliflozin), dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 analogues, and pioglitazone, all as add-on therapy to metformin (≥ 1.5 g per day for all trials, except two where the dose of metformin was 500 mg, 750 mg, and 1.0 g). Five studies reported on dapagliflozin. The mean age of patients was 55.2 years (ranged from 49.5 to 60.8 across treatment groups) and, in terms of gender, 47.5% (ranged from 33.7% to 61.6% across treatment groups) were female. The mean glycated hemoglobin (A1C) was 8.12% (ranged from 7.2% to 9.3% across treatment groups), the mean body mass index (BMI) ranged from 25.3 kg/m^2 to 34 kg/m^2 across treatment groups, and the mean duration of diabetes was 6.3 years (ranged from 0.5 to 8.4 years across treatment groups). Fasting plasma glucose concentration ranged from 7.7 to 11.2 mmol/L across treatment groups. Studies were generally homogeneous for baseline characteristics. The two studies reported by Derosa in 2012 (in sensitivity analysis) enrolled patients with a notably lower duration of diabetes compared with other studies. Also, studies in Asian populations generally reported a lower mean baseline BMI for their patients.

Twelve studies reported outcomes at 52 weeks (± 6 weeks). Eight more studies, which had quality issues, were included in the sensitivity analysis. The networks of evidence are shown in Figure 14 (A1C), Figure 15 (body weight), Figure 16 (systolic blood pressure), and Figure 17 (hypoglycemia). The included studies randomized from 549 to 2,789 patients. Comparators included placebo, sulfonylureas, SGLT-2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin), DPP-4 inhibitors, GLP-1 analogues, and pioglitazone, all as add-on therapy to metformin (≥ 1.5 g/d for all trials, except one that allowed doses between 500 mg and 3 g). Baseline characteristics of patients were similar to patients included in the trials reporting data at 24 weeks and had a similar homogeneity.

Comparators: The choice of comparators was based on drugs and doses licensed (or licence pending) in the United States. Studies reporting on the use of sulfonylurea at 24 weeks were excluded, but those providing data at 52 weeks were included. Efficacy results for sulfonylureas at 24 weeks were excluded for three reasons: 1) The short-term efficacy of sulfonylureas does not persist for longer durations of follow-up; 2) the effect size of sulfonylureas is not constant during the 24 ± 6 weeks period; and 3) sulfonylurea dose may be titrated during this period, often for up to 18 weeks. Also, insulin added to metformin was not included, as insulin was not considered relevant at this stage of the treatment pathway, in practice.

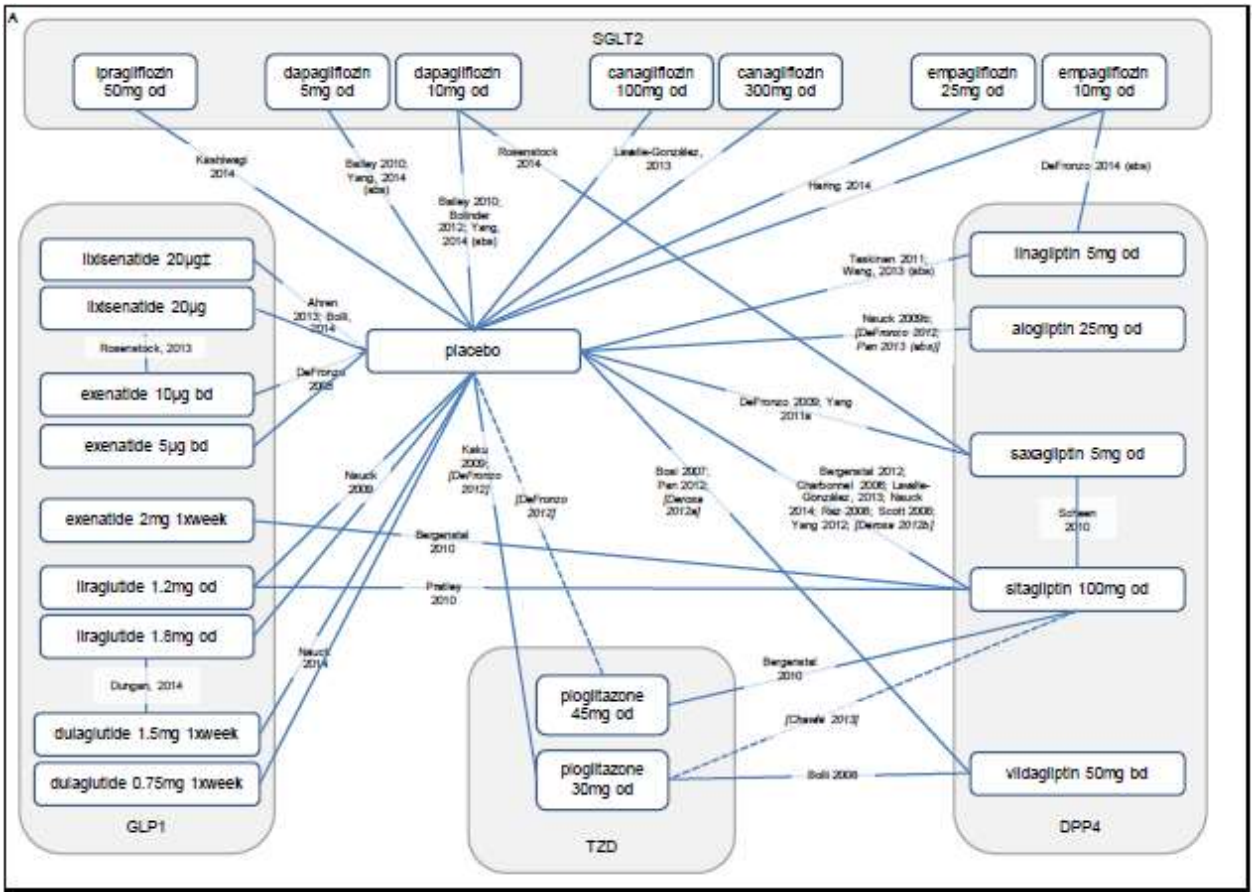
In comparisons with CDR review protocol, meglitinides, alpha-glucosidase inhibitors, and insulin and its analogues were not included in the search conducted by the manufacturer. Sulfonylureas were also excluded from the analysis at 24 weeks.

Outcomes: Outcomes of interest were A1C, body weight, systolic blood pressure, and hypoglycemic events at 24 weeks ± 6 weeks and at 52 weeks ± 6 weeks. These evaluated the most common surrogate outcomes for diabetes. However, more specific safety outcomes for SGLT-2 inhibitors such as genitourinary tract infections, renal adverse events, or ketoacidosis were not assessed and would have been of interest for this review. Clinical efficacy outcomes such as major cardiovascular events, mortality, and microvascular complications of diabetes were not assessed. Heart failure and bladder cancer would also be harms of interest, but were not assessed. The CDR review protocol for dapagliflozin includes these outcomes as well as quality of life.

Quality Assessment of Included Studies: The authors used the Cochrane Collaboration's tool for assessing risk of bias, and the assessment was reported. Overall, included studies were of high quality. Of the 32 studies reporting end points at 24 weeks, five had fair risks of bias, and three were reported only in conference abstracts and therefore could not be fully appraised. Of the 12 studies reporting on end points at 52 weeks, one study had high risk of bias, and five were at risk of reporting incomplete data. The other studies had low risk of bias.

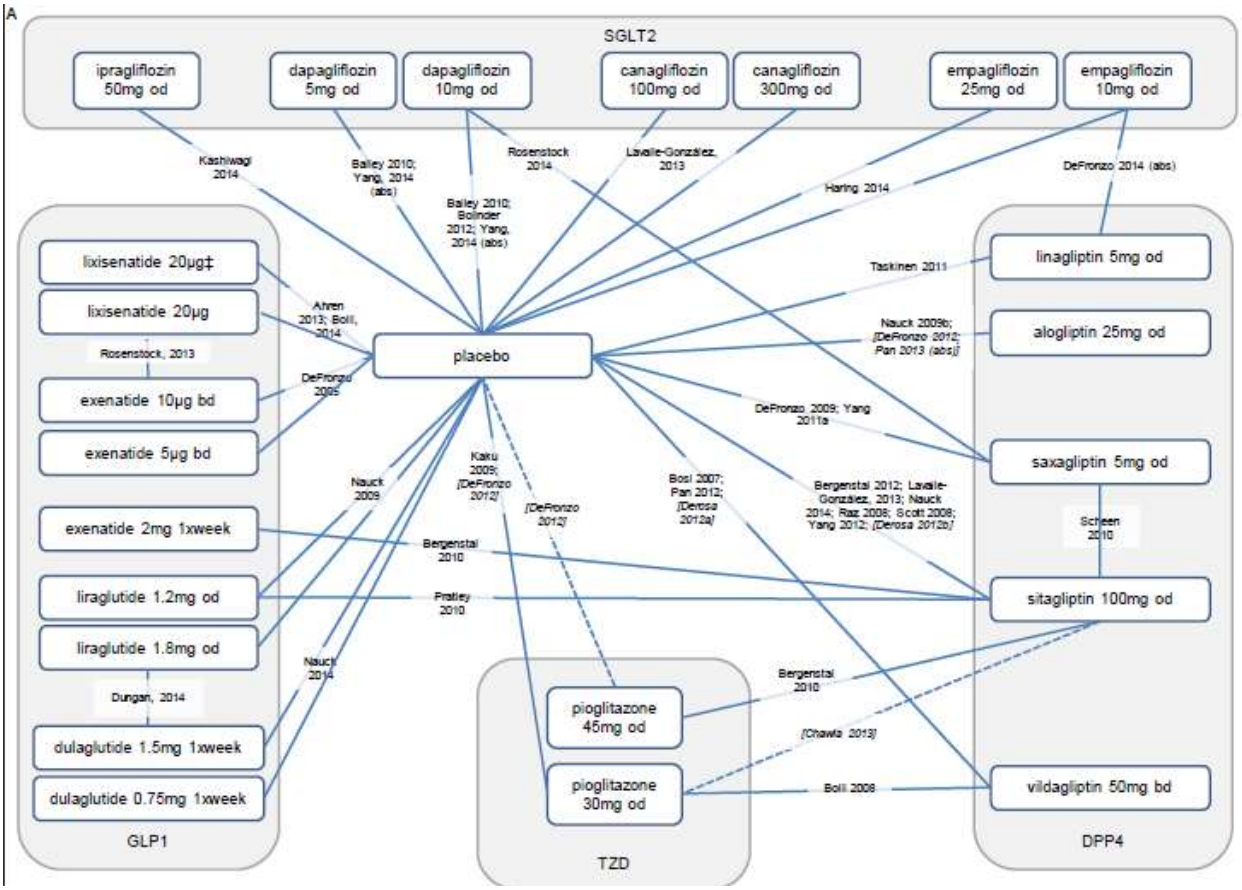
Evidence Network

FIGURE 10: EVIDENCE NETWORK FOR A1C AT 24 WEEKS



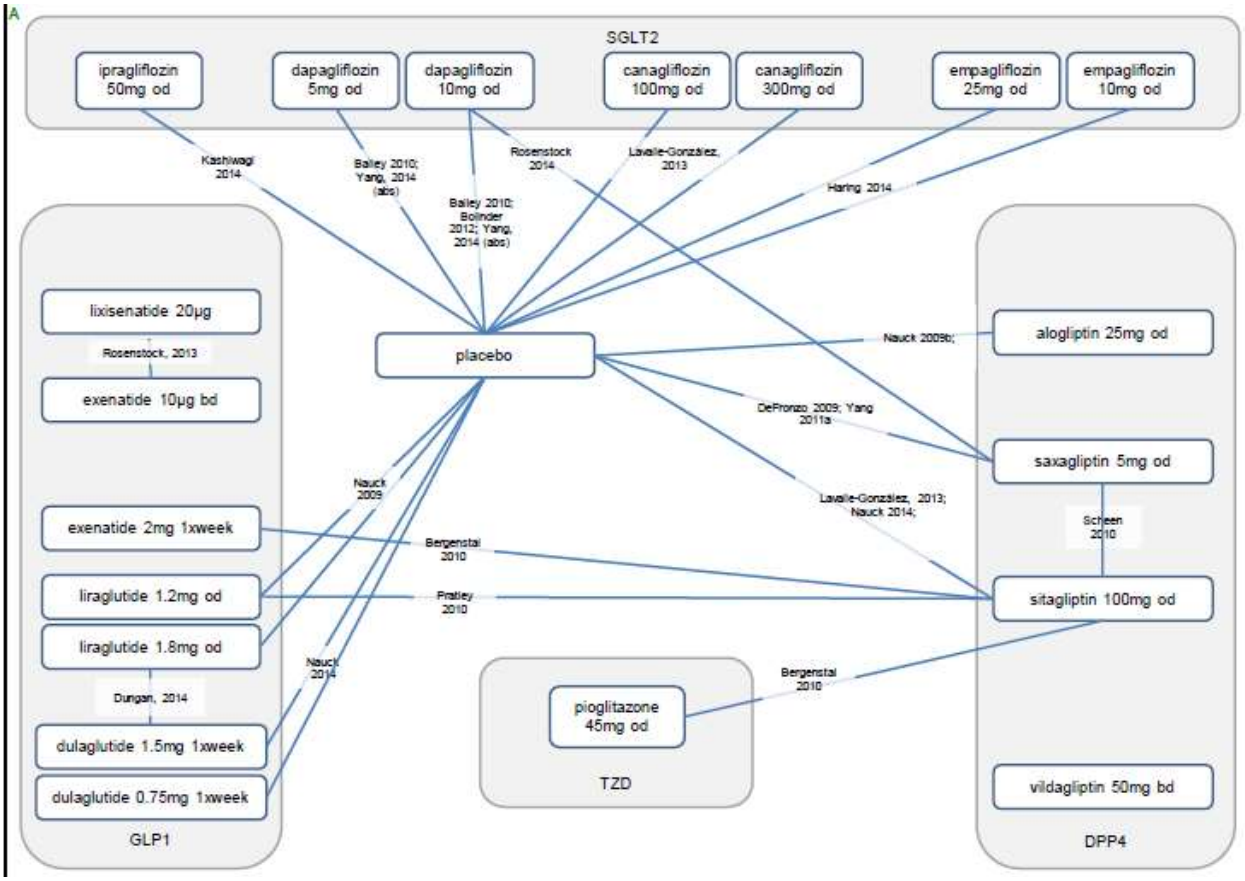
A1C = glycated hemoglobin; bd = twice daily; DPP4 = dipeptidyl peptidase–4 inhibitors; GLP-1 = glucagon-like peptide- 1 analogues; od = once daily; SGLT2 = sodium glucose cotransporter–2 inhibitors; TZD = thiazolidinedione.
Note: Studies included in the sensitivity analysis are displayed between brackets.
Source: Manufacturer's indirect comparison document.[46]

FIGURE 11: EVIDENCE NETWORK FOR BODY WEIGHT AT 24 WEEKS



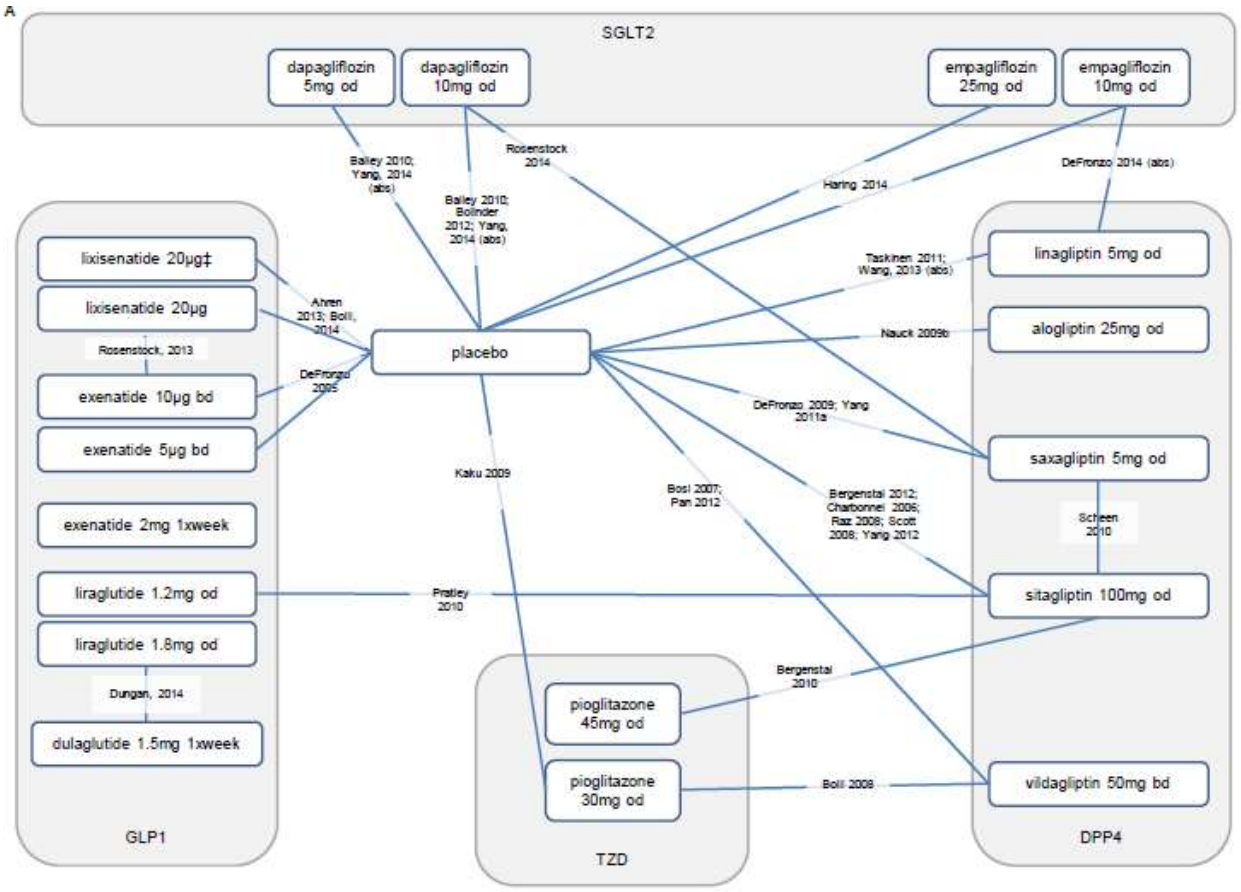
bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione.
Note: Studies included in the sensitivity analysis are displayed in parentheses.
Source: Manufacturer's indirect comparison document.[46]

FIGURE 12: EVIDENCE NETWORK FOR SYSTOLIC BLOOD PRESSURE AT 24 WEEKS



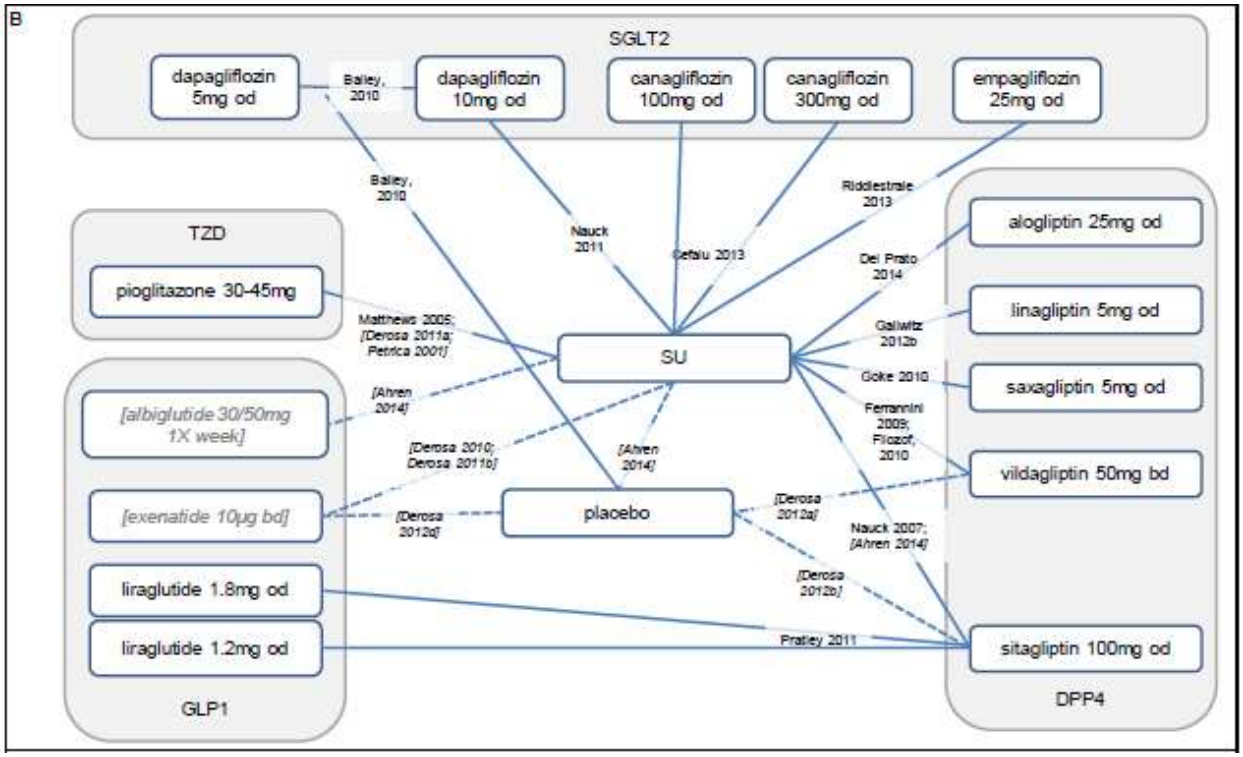
bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione.
Note: Studies included in the sensitivity analysis are displayed in parentheses.
Source: Manufacturer's indirect comparison document.[46]

FIGURE 13: EVIDENCE NETWORK FOR HYPOGLYCEMIA AT 24 WEEKS



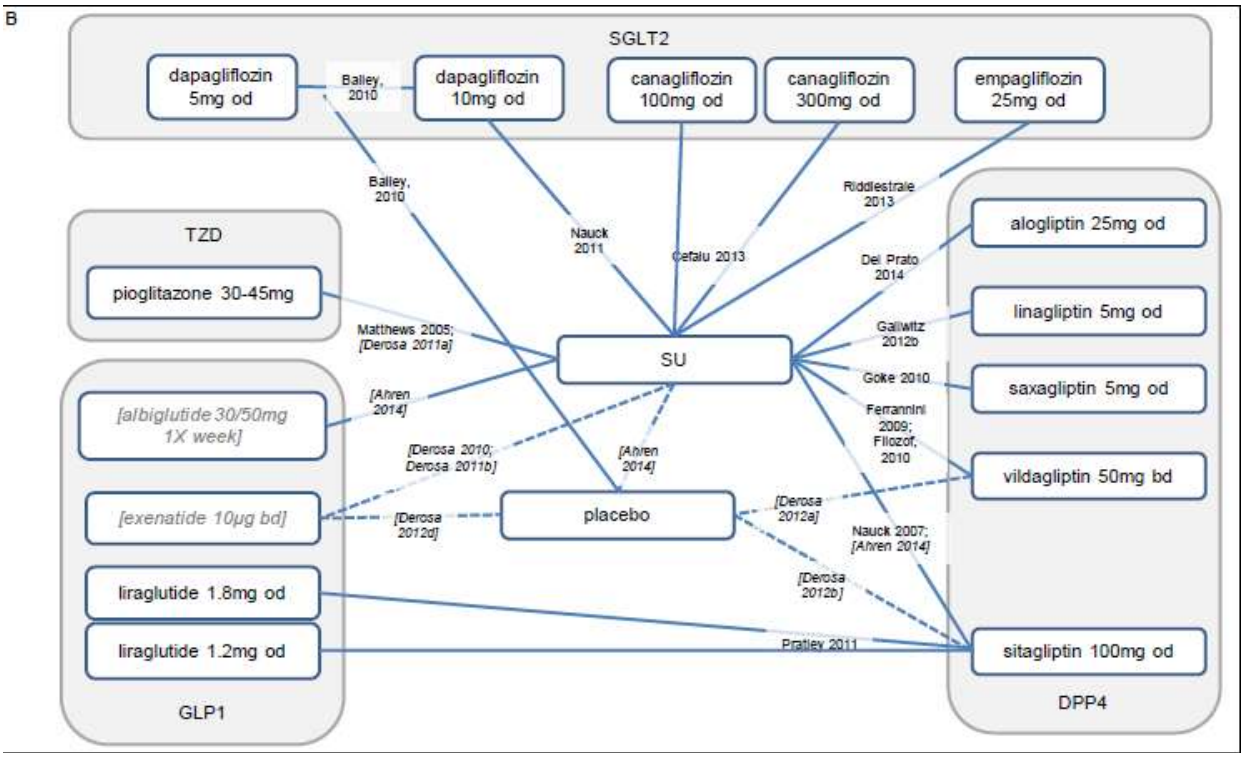
bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide- 1 analogues; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione.
Note: Studies included in the sensitivity analysis are displayed in parentheses.
Source: Manufacturer's indirect comparison document.[46]

FIGURE 14: EVIDENCE NETWORK FOR A1C AT 52 WEEKS



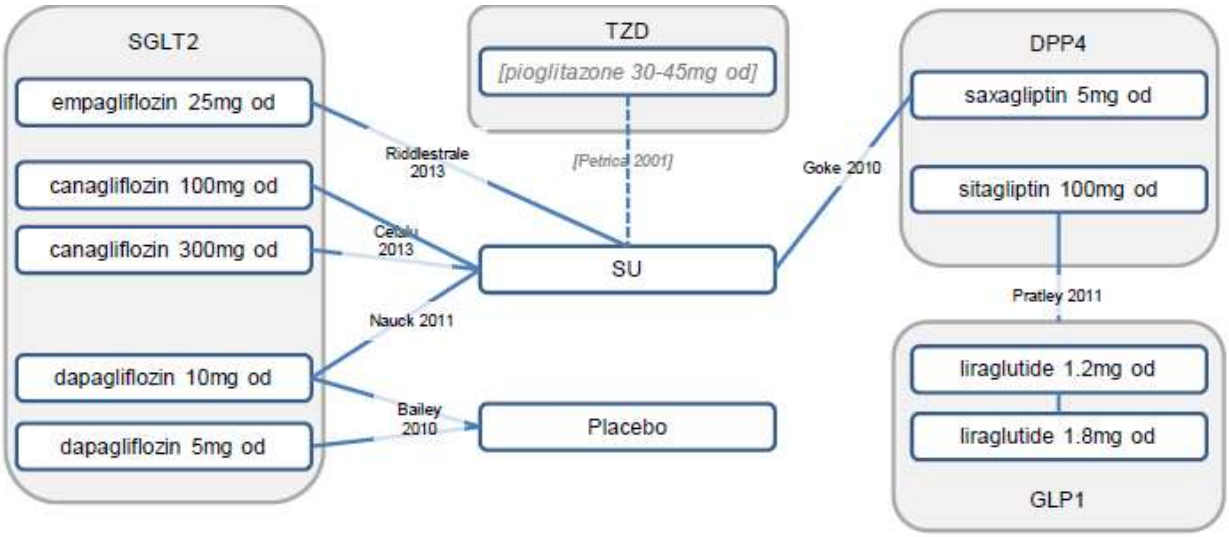
A1C = glycated hemoglobin; bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; SU = sulfonylureas; TZD = thiazolidinedione.
Source: Manufacturer's indirect comparison document.[46]

FIGURE 15: EVIDENCE NETWORK FOR BODY WEIGHT AT 52 WEEKS



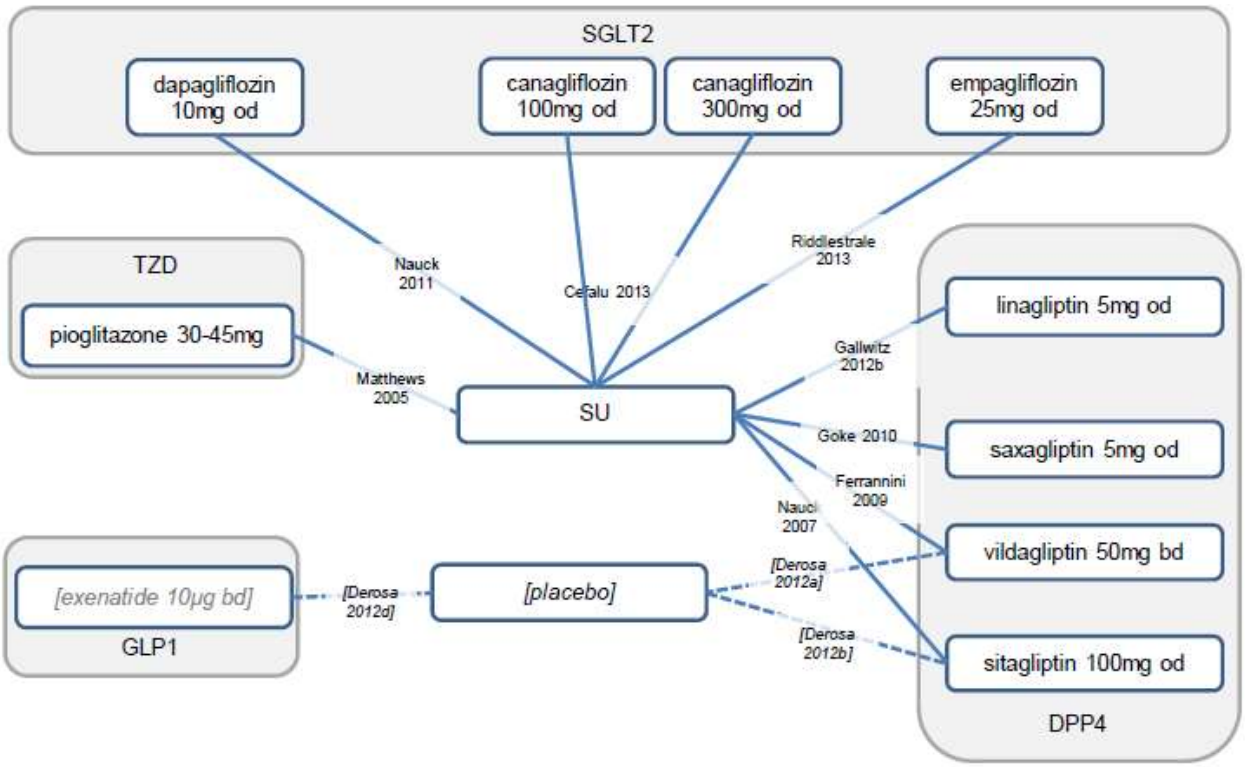
bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; SU = sulfonylureas; TZD = thiazolidinedione.
Source: Manufacturer's indirect comparison document.[46]

FIGURE 16: EVIDENCE NETWORK FOR SYSTOLIC BLOOD PRESSURE AT 52 WEEKS



DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; SU = sulfonylureas; TZD = thiazolidinedione.
Source: Manufacturer's indirect comparison document.[46]

FIGURE 17: EVIDENCE NETWORK FOR HYPOGLYCEMIA AT 52 WEEKS



bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; SU = sulfonylureas; TZD = thiazolidinedione.
Source: Manufacturer's indirect comparison document.[46]

Indirect Comparison Methods

The main analysis was based on a Bayesian NMA that models the probability of the most effective treatment among comparisons. In addition to the NMA, pairwise direct meta-analysis and indirect meta-analysis using the Bucher method were conducted.

For the pairwise direct meta-analysis, fixed and random effects models were used. The random effects model used the method of DerSimonian and Laird, with estimates of heterogeneity being taken from the fixed effects Mantel–Haenszel or inverse variance model.

The Bucher indirect comparisons were made using the Bucher method, and the pooled effects produced from the direct meta-analysis.

A random effects and fixed effects Bayesian NMA of continuous and dichotomous data were conducted for the main analysis. The NMA methodology was per the National Institute for Health and Care Excellence (NICE) Decision Support Unit recommendations. The models were fitted to the data via Bayesian Markov Chain Monte Carlo methods with Gibbs sampling. To ensure convergence, the models were run for a minimum of 100,000 iterations. Two subsequent chains of 100,000 were sampled to estimate the treatment effects. In random effects models, for the between-studies standard deviation, it was assumed the underlying expected differences between treatments would be uniformly distributed (uninformative prior). The model fit was appropriately assessed using the mean residual deviance and the deviance information criteria (DIC). The models with the best fit according to the DIC and the

average residual deviance were used. The pairwise direct estimates and Bucher indirect estimates were compared with estimates from the NMA as an informal assessment of consistency. If the estimates were not similar, a formal assessment of consistency was conducted by using the Bucher method.

For continuous end points and for binomial outcomes, weighted mean differences and odds ratios were reported, respectively.

The effect of potentially confounding baseline factors was explored for the A1C end point. Covariate analyses were done using A1C, weight, and age at baseline as covariates. An assessment of potential bias was conducted by plotting the study control groups in a funnel plot with the Egger's linear regression test of asymmetry.

A sensitivity analysis was performed by including studies which reported results at 24 weeks ± 8 weeks instead of ± 6 weeks. Studies with quality issues were also included in that analysis.

Results of Manufacturer's Indirect Comparison #1

Efficacy: Comparisons of efficacy outcomes were provided for SGLT-2 inhibitors, GLP-1 analogues, a thiazolidinedione (pioglitazone), and DPP-4 inhibitors as add-on therapies to metformin. Sulfonylureas were considered a valid comparator only at 52 weeks, and they were used as the reference treatment. Estimates of efficacy end points at 24 weeks are displayed in Table 49, and estimates at 52 weeks are shown in Table 50. Drugs and doses from a specific class were pooled together. Only dapagliflozin was analyzed separately from the SGLT-2 inhibitors class and compared with other classes of antidiabetes drugs.

For A1C, all antidiabetes classes provided a statistically significant improvement over placebo after 24 weeks. When other antidiabetes classes were compared with SGLT-2 inhibitors or specifically compared with dapagliflozin, no statistical difference was observed between classes.
For body weight, SGLT-2 inhibitors and GLP-1 analogues provided a statistically significant decrease; DPP-4 inhibitors did not provide a significant change; and pioglitazone statistically significantly increased weight after 24 weeks compared with placebo. SGLT-2 inhibitors led to a statistically significant decrease in weight compared with other classes. According to estimates for comparisons between drugs, dapagliflozin provided statistically significant benefits for weight compared with DPP-4 inhibitors and pioglitazone.

For systolic blood pressure, SGLT-2 inhibitors, GLP-1 analogues, and DPP-4 inhibitors had a statistically significant decrease in comparison with placebo after 24 weeks. SGLT-2s provided a statistically significant decrease in SBP compared with other classes. When more specifically compared with dapagliflozin, the reduction in SBP was only statistically significant versus GLP-1 analogues and DPP-4 inhibitors.

TABLE 49: ESTIMATED WEIGHTED MEAN DIFFERENCE IN EFFICACY OUTCOMES AFTER 24 WEEKS

Comparison		A1C (95% CrI)[a]	Weight (95% CrI)[b]	SBP (95% CrI)[c]
By class				
Difference vs. placebo				
SGLT-2		–0.69 (–0.85 to –0.53)[d]	–1.94 (–2.28 to –1.61)[d]	–4.62 (–5.58 to –3.62)[d]
GLP-1		–0.90 (–1.06 to –0.74)[d]	–1.37 (–1.75 to –0.98)[d]	–2.09 (–3.41 to –0.78)[d]
DPP-4		–0.62 (–0.74 to –0.50)[d]	0.19 (–0.08 to 0.46)	–1.66 (–2.75 to –0.56)[d]
TZD		–0.84 (–1.12 to –0.55)[d]	2.60 (1.95 to 3.27)[d]	–1.88 (–4.44 to 0.70)
Difference head-to-head				
SGLT-2	GLP-1	0.21 (–0.01 to 0.43)	–0.58 (–1.07 to –0.09)[d]	–2.52 (–4.02 to –1.05)[d]
SGLT-2	DPP-4	–0.07 (–0.23 to 0.09)	–2.13 (–2.51 to –1.76)[d]	–2.96 (–4.13 to –1.80)[d]
SGLT-2	TZD	0.15 (–0.16 to 0.45)	–4.54 (–5.27 to –3.83)[d]	–2.74 (–5.38 to –0.13)[d]
GLP-1	DPP-4	–0.28 (–0.45 to –0.11)[d]	–1.55 (–1.96 to –1.15)[d]	–0.41 (–1.62 to 0.73)
GLP-1	TZD	–0.06 (–0.36 to 0.23)	–3.96 (–4.68 to –3.27)[d]	–0.20 (–2.64 to 2.20)
DPP-4	TZD	0.21 (–0.06 to 0.48)	–2.41 (–3.06 to –1.77)[d]	0.22 (–2.17 to 2.65)
Dapagliflozin subgroup				
Difference vs. placebo				
DAPA		–0.64 (–0.88 to –0.41)[d]	–1.90 (–2.44 to –1.37)[d]	–4.59 (–6.15 to –3.00)[d]
GLP-1		–0.89 (–1.05 to –0.72)[d]	–1.38 (–1.78 to –0.97)[d]	–2.18 (–3.59 to –0.73)[d]
DPP-4		–0.62 (–0.74 to –0.49)[d]	0.17 (–0.13 to 0.47)	–1.74 (–2.92 to –0.46)[d]
TZD		–0.82 (–1.11 to –0.52)[d]	2.60 (1.90 to 3.32)[d]	–1.94 (–4.71 to 0.84)
Difference head-to-head				
DAPA	GLP-1	0.24 (–0.04 to 0.53)	–0.53 (–1.19 to 0.13)	–2.43 (–4.41 to –0.39)[d]
DAPA	DPP-4	–0.03 (–0.27 to 0.22)	–2.07 (–2.66 to –1.49)[d]	–2.85 (–4.68 to –1.06)[d]
DAPA	TZD	0.17 (–0.18 to 0.53)	–4.50 (–5.38 to –3.63)[d]	–2.65 (–5.70 to 0.47)
GLP-1	DPP-4	–0.27 (–0.44 to –0.09)[d]	–1.54 (–1.98 to –1.12)[d]	–0.44 (–1.73 to 0.80)
GLP-1	TZD	–0.07 (–0.37 to 0.24)	–3.97 (–4.73 to –3.23)[d]	–0.24 (–2.83 to 2.38)
DPP-4	TZD	0.20 (–0.08 to 0.48)	–2.43 (–3.13 to –1.75)[d]	0.20 (–2.33 to 2.84)

A1C = glycated hemoglobin; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 analogues; NMA = network meta-analysis; SBP = systolic blood pressure; SGLT-2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione.

[a] The random effects NMA model with 3 covariates (baseline A1C, weight, age) was used for A1C.

[b] The random effects NMA model was used for body weight.

[c] The random effects NMA model was used for systolic blood pressure.

[d] Statistically significant difference.

Source: Manufacturer's indirect comparison document.[46]

For A1C at 52 weeks, only GLP-1 analogues provided a statistically significant improvement over sulfonylureas (Table 50). GLP-1 analogues also offered increased benefits in A1C compared with SGLT-2 inhibitors or dapagliflozin.

For body weight, SGLT-2 inhibitors, GLP-1 analogues, and DPP-4 inhibitors provided a statistically significant decrease in weight after 52 weeks in comparison with sulfonylureas. SGLT-2 inhibitors, as well as dapagliflozin (evaluated separately), showed statistically significant decreases in weight compared with DPP-4s and pioglitazone.

For systolic blood pressure, SGLT-2 inhibitors, GLP-1 analogues, and DPP-4 inhibitors had a statistically significant decrease in comparison with sulfonylureas after 52 weeks. No results for pioglitazone were available for this outcome at 52 weeks. SGLT-2 inhibitors, and dapagliflozin (separately), had similar effects on SBP compared with other classes.

TABLE 50: ESTIMATED WEIGHTED MEAN DIFFERENCE IN EFFICACY OUTCOMES AFTER 52 WEEKS

Comparison		A1C (95% CrI)[a]	Weight (95% CrI)[b]	SBP (95% CrI)[c]
By class				
Difference vs. sulfonylurea				
SGLT-2		–0.05 (–0.17 to 0.08)	–4.68 (–5.18 to –4.16)[d]	–5.01 (–5.96 to –4.06)[d]
GLP-1		–0.44 (–0.70 to –0.18)[d]	–4.07 (–5.16 to –2.99)[d]	–3.89 (–7.04 to –0.73)[d]
DPP-4		0.08 (–0.01 to 0.17)	–2.00 (–2.39 to –1.63)[d]	–2.89 (–4.93 to –0.87)[d]
TZD		0.02 (–0.24 to 0.28)	0.10 (–0.92 to 1.13)	NA
Difference head-to-head				
SGLT-2	GLP-1	0.39 (0.10 to 0.68)[d]	–0.61 (–1.79 to 0.60)	–1.12 (–4.42 to 2.16)
SGLT-2	DPP-4	–0.13 (–0.28 to 0.03)	–2.68 (–3.29 to –2.03)[d]	–2.12 (–4.36 to 0.13)
SGLT-2	TZD	–0.07 (–0.36 to 0.22)	–4.78 (–5.92 to –3.63)[d]	NA
GLP-1	DPP-4	–0.52 (–0.76 to –0.27)[d]	–2.07 (–3.08 to –1.05)[d]	–0.99 (–3.42 to 1.42)
GLP-1	TZD	–0.46 (–0.83 to –0.09)[d]	–4.17 (–5.66 to –2.69)[d]	NA
DPP-4	TZD	0.06 (–0.22 to 0.33)	–2.10 (–3.20 to –1.02)[d]	NA
Dapagliflozin subgroup				
Difference vs. sulfonylurea				
DAPA		0.00 (–0.30 to 0.30)	–4.66 (–5.93 to –3.38)[d]	–5.10 (–8.27 to –1.93)[d]
GLP-1		–0.44 (–0.76 to –0.13)[d]	–4.08 (–5.44 to –2.73)[d]	–3.90 (–7.06 to –0.75)[d]
DPP-4		0.08 (–0.04 to 0.20)	–2.01 (–2.54 to –1.50)[d]	–2.90 (–4.93 to –0.87)[d]
TZD		0.02 (–0.30 to 0.34)	0.10 (–1.23 to 1.45)	NA
Difference head-to-head				
DAPA	GLP-1	0.44 (0.00 to 0.87)[d]	–0.58 (–2.44 to 1.29)	–1.20 (–5.69 to 3.27)
DAPA	DPP-4	–0.08 (–0.40 to 0.24)	–2.65 (–4.02 to –1.26)[d]	–2.20 (–5.98 to 1.56)
DAPA	TZD	–0.02 (–0.46 to 0.41)	–4.76 (–6.61 to –2.92)[d]	NA
GLP-1	DPP-4	–0.52 (–0.81 to –0.23)[d]	–2.07 (–3.32 to –0.82)	–1.00 (–3.42 to 1.41)
GLP-1	TZD	–0.46 (–0.91 to –0.01)[d]	–4.18 (–6.10 to –2.29)	NA
DPP-4	TZD	0.06 (–0.28 to 0.40)	–2.11 (–3.56 to –0.69)	NA

A1C = glycated hemoglobin; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 analogues; NA = not available; NMA = network meta-analysis; SBP = systolic blood pressure; SGLT-2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione.

[a] The random effects NMA model was used for A1C.

[b] The random effects NMA model was used for body weight.

[c] The fixed effects NMA model was used for systolic blood pressure.

[d] Statistically significant difference.

Source: Manufacturer's indirect comparison document.[46]

Safety: For hypoglycemic events at 24 weeks, no differences in odds ratio were observed versus placebo or between classes or between dapagliflozin and other classes (Table 51). At 52 weeks, although no results for GLP-1 were available, all other classes provided reduced odds ratio versus sulfonylureas. No difference was observed for hypoglycemic events between SGLT-2 inhibitors and DPP-4 inhibitors or pioglitazone, nor between dapagliflozin and DPP-4 inhibitors or pioglitazone.

TABLE 51: ESTIMATED ODDS RATIOS FOR HYPOGLYCEMIA AFTER 24 AND 52 WEEKS

Comparison		24 Weeks[a]	52 Weeks
By class			
		OR vs. placebo (95% CrI)	OR vs. sulfonylurea (95% CrI)
SGLT-2		1.08 (0.51 to 2.34)	0.08 (0.04 to 0.13)[b]
GLP-1		1.32 (0.68 to 2.71)	NA
DPP-4		0.84 (0.49 to 1.43)	0.09 (0.06 to 0.14)[b]
TZD		0.39 (0.04 to 2.12)	0.09 (0.02 to 0.33)[b]
OR head-to-head (95% CrI)			
SGLT-2	GLP-1	0.82 (0.30 to 2.21)	NA
SGLT-2	DPP-4	1.29 (0.57 to 3.06)	0.86 (0.42 to 1.71)
SGLT-2	TZD	2.81 (0.44 to 28.61)	0.84 (0.21 to 4.03)
GLP-1	DPP-4	1.57 (0.78 to 3.33)	NA
GLP-1	TZD	3.41 (0.62 to 31.82)	NA
DPP-4	TZD	2.15 (0.41 to 19.43)	0.98 (0.25 to 4.64)
Dapagliflozin subgroup			
		OR vs. placebo (95% CrI)	OR vs. sulfonylurea (95% CrI)
DAPA		0.82 (0.32 to 2.11)	0.05 (0.01 to 0.19)[b]
GLP-1		1.32 (0.67 to 2.81)	NA
DPP-4		0.83 (0.47 to 1.47)	0.09 (0.05 to 0.17)[b]
TZD		0.39 (0.04 to 2.20)	0.09 (0.02 to 0.41)[b]
OR head-to-head (95% CrI)			
DAPA	GLP-1	0.62 (0.19 to 1.94)	NA
DAPA	DPP-4	0.99 (0.35 to 2.81)	0.57 (0.14 to 2.56)
DAPA	TZD	2.15 (0.29 to 22.33)	0.57 (0.08 to 4.81)
GLP-1	DPP-4	1.59 (0.77 to 3.46)	NA
GLP-1	TZD	3.44 (0.60 to 30.85)	NA
DPP-4	TZD	2.14 (0.39 to 18.41)	0.99 (0.19 to 5.85)

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 analogues; NA = not available; OR = odds ratio; SGLT-2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione; vs. = versus.
[a] The random effects NMA model was used at 24 weeks and at 52 weeks.
[b] Statistically significant difference.
Source: Manufacturer's indirect comparison document.[46]

Consistency: Some significant inconsistencies between direct and indirect evidence were observed in the network. For A1C at 24 weeks, a statistically significant difference between the indirect and direct estimate was observed when comparing dapagliflozin with DPP-4 inhibitors. The direct estimate suggests a statistically significant lower A1C for dapagliflozin compared with DPP-4, while the Bucher indirect comparison suggests the opposite. In the NMA, the difference between dapagliflozin and DPP-4 inhibitors is not statistically significant. This may be due to the NMA model, which takes into account the baseline A1C as a covariate. Inconsistencies have also been observed for A1C and SBP when comparing GLP-1 analogues with DPP-4 inhibitors.

Sensitivity Analyses: Five additional studies were included in the sensitivity analysis for the 24-weeks end point. The additional studies did not provide new data for systolic blood pressure and hypoglycemia. The results for A1C were similar to the base case, except that GLP-1 analogues provided a statistically significant better response compared with SGLT-2 inhibitors. For weight change, results in

the sensitivity analysis were similar to the base case. No specific comparison with dapagliflozin was made in the sensitivity analysis.

Eight additional studies were considered in the sensitivity analysis for the 52-weeks end point. These did not provide additional data for hypoglycemia and, as only one study of poor quality provided data on SBP, no further analysis was conducted for this outcome. The results for A1C were slightly different from the base case, as treatment with GLP-1 analogues is no longer different from sulfonylureas, and DPP-4 inhibitors caused an increase in A1C compared with sulfonylureas. Results for weight change were consistent with the base case.

Critical Appraisal

The critical appraisal was based on International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on indirect treatment comparisons.[52] The NMA document provided by the manufacturer was of high quality and adequately satisfied all the ISPOR criteria for the methods, although clinical limitations were observed.

Strengths: The manufacturer provided a very detailed document that comprehensively described the objectives, methods for the systematic review and analysis of evidence, literature search strategy, included and excluded studies, individual results of the studies, baseline characteristics of patients, quality appraisal of included studies, networks of evidence, and statistical models. The process of study selection and data extraction was conducted by two reviewers. Most studies were of relatively low risk of bias. The characteristics of patients were representative of patients with type 2 diabetes and fairly homogeneous. Long-term results were provided at 52 weeks. Statistical models were compared, and the model with the best fit was chosen. Sensitivity analyses were provided and were justified. Covariate analysis using A1C, weight, and age at baseline was justified. The evaluation of consistency has been provided. Publication biases were unlikely, as shown by funnel plots with Egger's linear regression of asymmetry.

Limitations: Sulfonylureas have been excluded from the analysis at 24 weeks, although they are the most common second-line treatment added on to metformin. The choice of comparators was based on drugs and doses licensed (or licence pending) in the United States, not in Canada. Ipragliflozin, lixisenatide, dulaglutide, glipizide, and vildagliptin were used as comparators but are not approved in Canada. Many comparators, including insulin and meglitinides, and clinical outcomes that were deemed relevant in the CDR review protocol, were not included in the literature search. The last literature search, conducted in September 2014, could have been updated. Data have been pooled across drug classes regardless of frequency or mode of administration. No difference could be made between different dosages of dapagliflozin. Estimates from the NMA were heterogeneous for some comparison of hypoglycemic events. Due to a lack of data, some comparisons were missing for systolic blood pressure and hypoglycemia at 52 weeks. Some inconsistencies were noted between direct and indirect estimates for dapagliflozin and DPP-4 inhibitors in terms of A1C at 24 weeks.

Review of Manufacturer's Indirect Comparison #2

Objectives and Rationale

The purpose of the manufacturer-submitted NMA was to assess the relative efficacy and safety of dapagliflozin as add-on therapy to sulfonylureas when sulfonylureas in monotherapy, with diet and exercise, do not provide adequate glycemic control. Although one more study with an IDC was included, our analysis will focus on the document[47] provided by the manufacturer.

Methods

Study Eligibility and Selection Process: In order to be included in the NMA, studies had to meet the inclusion criteria listed in Table 52. The criteria were pre-specified and were aligned with the funding request currently reviewed.

TABLE 52: STUDY ELIGIBILITY

	Inclusion Criteria
Study designs	RCTs
Population	• Adults with type 2 diabetes on a stable dose of sulfonylurea as monotherapy (at least 8 weeks, at half the maximum dose or maximum tolerable dose), as *first-line therapy* • Inadequate glycemic control on sulfonylurea monotherapy with diet and exercise
Intervention	All antidiabetes pharmacological therapies that would be added to sulfonylurea in clinical practice when sulfonylurea does not provide adequate glycemic control
Comparators	Placebo or dual therapy with drugs and doses licensed in the European Union, in combination with sulfonylurea
Outcomes	Efficacy: A1C, body weight, systolic blood pressure Safety: Hypoglycemic events End points: 24 weeks ± 6 weeks or long-term results
Exclusion criteria	Uncontrolled open-label extensions Studies with triple therapy Populations with moderate to severe renal impairment

A1C = glycated hemoglobin; RCT = randomized controlled trial.
Source: Manufacturer's indirect comparison document.[47]

The literature search conducted up to March 2015 covered the Cochrane Central, MEDLINE, and Embase databases. In addition, conference proceedings of the American Diabetes Association and of the European Association for the Study of Diabetes, as well as the clinical trials registry, were searched. The detailed search strategy and search results were provided.

The process of study selection and data extraction was conducted by two independent reviewers. Citations were screened based on titles and abstracts and rescreened for eligibility with full-text review. Disagreements on study eligibility were decided by a third reviewer. The list of included and excluded studies was provided. Data were extracted and verified by a second reviewer.

Data Extraction: A total of eight studies were eligible for inclusion in the systematic review. Seven of these were eligible for inclusion in the meta-analysis. The ineligible study was an abstract reporting on ipragliflozin, which is not currently licensed in Europe or Canada. Of the seven included studies, five reported on DPP-4 inhibitors, one on a GLP-1 analogue, and one on dapagliflozin. The network diagram is shown in Figure 18. The background sulfonylureas used in the studies were glimepiride (four studies) and glyburide (one study), but two studies did not specify the nature of the sulfonylurea.

The included studies randomized 212 to 597 patients. All included studies reported outcomes after 24 ± 6 weeks. Comparators were placebo, vildagliptin, sitagliptin, linagliptin, alogliptin, exenatide, and dapagliflozin, all as add-on therapies to sulfonylureas. The mean age of patients ranged from 54.4 to 60.3 years; the proportion of males ranged from 43.7% to 62.6%; the mean baseline A1C ranged from 8.07% to 8.7%; the mean BMI ranged from 24.8 kg/m^2 to 34 kg/m^2, although the Strojek et al. 2011 study did not report a mean; the mean baseline fasting plasma glucose levels ranged from 9.55 mmol/L to 10.8 mmol/L; and the mean duration of diabetes ranged from 5.7 to 8.0 years, although the Lewin

2012 study did not report a mean. Overall, the baseline characteristics of patients were similar across studies. Only the Yang 2015 study differed for its lower mean BMI at baseline (approximately 25.0 kg/m^2), but other parameters were similar to other studies.

Comparators: The comparators of interest were drugs and doses licensed in the European Union as add-on to sulfonylureas. Patients had to be on stable dose of a sulfonylurea monotherapy for at least eight weeks, at half the maximum dose or at the maximum dose.

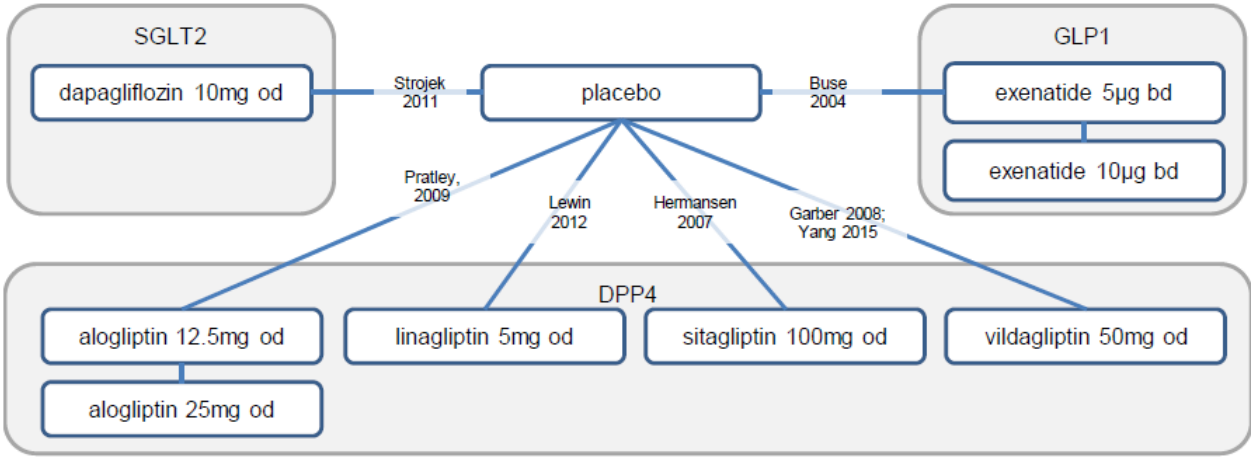
In comparisons with the CDR review protocol, meglitinides, alpha-glucosidase inhibitors, and insulin and its analogues were not included in the search conducted by the manufacturer.

Outcomes: Outcomes of interest were A1C, body weight, systolic blood pressure, and hypoglycemic events at 24 weeks ± 6 weeks. These evaluated the most common surrogate outcomes for diabetes. However, more specific safety outcomes for SGLT-2 inhibitors, such as genitourinary tract infections, renal adverse events, or ketoacidosis, were not assessed and would have been of interest for this review. Clinical efficacy outcomes such as major cardiovascular events, mortality, and microvascular complications of diabetes were not assessed. Heart failure and bladder cancer would also be harms of interest, but were not assessed. The CDR review protocol for dapagliflozin includes these outcomes as well as quality of life.

Quality Assessment: The authors used the Cochrane Collaboration's tool for assessing risk of bias, and the assessment was reported. Overall, the included studies were of good quality. Of note, the allocation method in the Garber 2008 study was at risk of not having preserved the randomization sequence. Also, the Buse 2004 study discarded data from one study site owing to non-compliance and had differences in discontinuations rates between groups.

Evidence Network

FIGURE 18: EVIDENCE NETWORK (A1C, WEIGHT, HYPOGLYCEMIA) FOR SECOND-LINE TREATMENT OF TYPE 2 DIABETES AS ADD-ON THERAPY TO A SULFONYLUREA



A1C = glycated hemoglobin; bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors.
Source: Manufacturer's indirect comparison document.[47]

Meta-analysis and Indirect Comparison
A direct meta-analysis, a Bucher indirect comparison, and a Bayesian NMA were conducted.

Direct Meta-analysis: The meta-analysis was conducted on a modified intention-to-treat basis, but for some studies, the efficacy set was further restricted to those with non-missing baseline and at least one follow-up efficacy result. Continuous outcomes were pooled as weighted mean differences (WMDs), and the binomial outcomes were pooled as odds ratios. For continuous end points, if the standard error was not reported, it was evaluated from the confidence interval or the standard deviation, or imputed from the observed standard errors.

Fixed and random effects models were used in Stata IC version 12.1. The random effects model used the method of DerSimonian and Laird, with estimates of heterogeneity being taken from the fixed effects Mantel–Haenszel or inverse variance model. For binomial outcomes, where a study had no observation, 0.5 was added by default to each cell of the trial.

Bucher Indirect Comparison: The Bucher indirect comparisons were made using the Bucher method, and the pooled effects produced from the direct meta-analysis.

Network Meta-analysis: A random and fixed effects Bayesian NMA of continuous and dichotomous data, which models the probability of the most effective treatment among comparisons, was conducted. The NMA methodology was as per NICE Decision Support Unit recommendations. The models were fitted to the data via Bayesian Markov Chain Monte Carlo methods with Gibbs sampling. To ensure convergence, the models were run for a minimum of 100,000 iterations. Two subsequent chains of 100,000 were sampled to estimate the treatment effects. Both random effects models and fixed effects models were tested. In random effects models, for the between-studies standard deviation, it was assumed the underlying expected differences between treatments would be uniformly distributed (uninformative prior). An estimate of the fit between the estimates and the observed dataset was provided by mean residual deviances. The model with the lowest DIC was deemed to have the best fit.

Other Analyses: An assessment of potential bias in study controls was conducted by plotting the study control groups in a forest plot.

Where feasible, the potentially confounding baseline factors were explored with a study-group level covariate analysis. These covariates were not further specified.

Results of Manufacturer's Indirect Comparison #2
Efficacy: The indirect evidence for efficacy was based on both the Bucher indirect comparison (Table 53 and Table 54) and the estimates from the NMA (Table 55). There were insufficient data to analyze the change in systolic blood pressure.

For A1C, dapagliflozin, DPP-4 inhibitors, and GLP-1 analogues all provided statistically significant improvement over placebo. The differences between dapagliflozin and DPP-4 inhibitors or between dapagliflozin and GLP-1 analogues were not statistically significant.

For body weight change, dapagliflozin and DPP-4 inhibitors showed a statistically significant decrease and increase, respectively, in body weight over placebo. In comparison with DPP-4 inhibitors, dapagliflozin provided a statistically significant decrease in body weight. Dapagliflozin showed a

numerical decrease in body weight in comparison with GLP-1 analogues, but it was not statistically significant.

Safety: For hypoglycemic events, only GLP-1 analogues showed a statistically significantly increased risk of hypoglycemia in comparison with placebo. When comparing dapagliflozin with GLP-1 analogues, the Bucher indirect comparison showed a statistically significant reduced risk for dapagliflozin, while the NMA estimate did not reach statistical significance.

TABLE 53: DIRECT AND BUCHER INDIRECT COMPARISONS OF DAPAGLIFLOZIN VERSUS DPP-4 INHIBITORS AT 24 WEEKS

Comparison	WMD (95% CI)	*P* value
Change in A1C		
Direct meta-analysis		
Dapagliflozin vs. placebo	–0.69 (–0.86 to –0.52)	< 0.01
DPP-4 vs. placebo	–0.55 (–0.67 to –0.41)	< 0.01
Bucher indirect comparisons		
Dapagliflozin vs. DPP-4	–0.15 (–0.35 to 0.06)	0.17
Change in weight		
Direct meta-analysis		
Dapagliflozin vs. placebo	–1.54 (–2.16 to –0.92)	< 0.01
DPP-4 vs. placebo	0.68 (0.30 to 1.05)	< 0.01
Bucher indirect comparisons		
Dapagliflozin vs. DPP-4	–2.22 (–2.94 to –1.49)	< 0.01
Hypoglycemia	**OR (95% CI)**	***P* value**
Direct meta-analysis		
Dapagliflozin vs. placebo	1.71 (0.66 to 4.48)	0.27
DPP-4 vs. placebo	1.39 (0.82 to 2.38)	0.22
Bucher indirect comparisons		
Dapagliflozin vs. DPP-4	1.23 (0.41 to 3.65)	0.71

A1C = glycated hemoglobin; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4 inhibitors; OR = odds ratio; WMD = weighted mean difference; vs. = versus.
Source: Manufacturer's indirect comparison document.[47]

TABLE 54: DIRECT AND BUCHER INDIRECT COMPARISONS OF DAPAGLIFLOZIN VERSUS GLP-1 ANALOGUES AT 24 WEEKS

Comparison	WMD (95% CI)	*P* value
Change in A1C		
Direct meta-analysis		
Dapagliflozin vs. placebo	–0.69 (–0.86 to –0.52)	< 0.01
GLP-1 vs. placebo	–0.79 (–1.03 to –0.55)	< 0.01
Bucher indirect comparisons		
Dapagliflozin vs. GLP-1	0.10 (–0.19 to 0.39)	0.51
Change in weight		
Direct meta-analysis		
Dapagliflozin vs. placebo	–1.54 (–2.16 to –0.92)	< 0.01
GLP-1 vs. placebo	–0.65 (–1.37 to 0.07)	0.08

Comparison	WMD (95% CI)	*P* value
Bucher indirect comparisons		
Dapagliflozin vs. GLP-1	–0.89 (–1.84 to 0.06)	0.07
OR of hypoglycemia	**OR (95% CI)**	***P* value**
Direct meta-analysis		
Dapagliflozin vs. placebo	1.71 (0.66 to 4.48)	0.27
GLP-1 vs. placebo	9.96 (3.57 to 27.83)	< 0.01
Bucher indirect comparisons		
Dapagliflozin vs. GLP-1	0.17 (0.04 to 0.70)	0.01

A1C = glycated hemoglobin; CI = confidence interval; GLP-1 = glucagon-like peptide-1 analogues; OR = odds ratio; WMD = weighted mean difference; vs. = versus.
Source: Manufacturer's indirect comparison document.[47]

TABLE 55: ESTIMATED WEIGHTED MEAN DIFFERENCE IN EFFICACY OUTCOMES FROM NMA AFTER 24 WEEKS

Comparison		A1C (95% CrI)	Weight (95% CrI)	Hypoglycemia (95% CrI)
By class				
Difference vs. placebo				OR vs. placebo
SGLT-2		–0.69 (–1.30 to –0.08)[a]	–1.54 (–2.17 to –0.92)[a]	1.77 (0.20 to 16.34)
GLP-1		–0.79 (–1.33 to –0.23)[a]	–0.65 (–1.37 to 0.07)	10.23 (1.41 to 82.19)[a]
DPP-4		–0.55 (–0.86 to –0.23)[a]	0.68 (0.30 to 1.05)[a]	1.57 (0.52 to 5.28)
Difference head-to-head				OR head-to-head
SGLT-2	GLP-1	0.10 (–0.74 to 0.91)	–0.89 (–1.84 to 0.06)	0.17 (0.01 to 3.39)
SGLT-2	DPP-4	–0.14 (–0.84 to 0.54)	–2.22 (–2.94 to –1.49)[a]	1.12 (0.09 to 13.03)
GLP-1	DPP-4	–0.25 (–0.87 to 0.40)	–1.32 (–2.14 to –0.51)[a]	6.51 (0.62 to 67.32)

A1C = glycated hemoglobin; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 analogues; NMA = network meta-analysis; OR = odds ratio; SGLT-2 = sodium glucose cotransporter-2 inhibitors.
Note: The random effects NMA models were used for A1C, body weight, and hypoglycemia.
[a] Statistically significant difference.
Source: Manufacturer's indirect comparison document.[47]

Critical Appraisal

The critical appraisal was based on ISPOR Task Force on indirect treatment comparisons.[52]

Strengths

The IDC document satisfied most of the ISPOR criteria. The manufacturer provided a very detailed document that comprehensively described the objectives, methods for the systematic review and analysis of evidence, literature search strategy, included and excluded studies, individual results of the studies, baseline characteristics of patients, quality appraisal of included studies, networks of evidence, and statistical models. The process of study selection and data extraction was conducted by two independent reviewers. The characteristics of patients were representative of patients with type 2 diabetes and were fairly homogeneous across studies. Statistical models were compared, and the model with the best fit was chosen. The consistency between direct and indirect estimates was good.

Limitations

Only a few studies were available. The limited availability of data increased the uncertainty in the treatment effect estimates. Two of the seven included studies were at risk of bias. No sensitivity analyses were provided. The choice of comparators was based on drugs and doses licensed in the European Union, not Canada. Vildagliptin is not approved in Canada. Different sulfonylurea background treatments were used, and their equivalency is uncertain. The differences from baseline of placebo

controls were compared for each outcome and each study. A1C levels for placebo controls appeared to have a certain heterogeneity among studies, indicating heterogeneity in background therapies. Covariate analyses were performed, but their results were not disclosed. Potential publication biases were not addressed. Many comparators and clinical outcomes that were deemed relevant in the CDR review protocol were not included in the literature search. Data have been pooled across drug classes, regardless of frequency or mode of administration. No difference could be made between different dosages of dapagliflozin.

Review of Manufacturer's Indirect Comparison #3

Objectives and Rationale

The purpose of the document was to assess the relative efficacy and safety of dapagliflozin as add-on therapy to insulin when insulin, with or without oral antidiabetes drugs, with diet and exercise, does not provide adequate glycemic control.

Methods

Study Eligibility and Selection Process: In order to be included in the IDC, studies had to meet the inclusion criteria listed in Table 56. The criteria were pre-specified and were aligned with the funding request currently reviewed.

TABLE 56: STUDY ELIGIBILITY

	Inclusion Criteria
Study designs	RCTs
Population	Adults with type 2 diabetes and inadequate glycemic control on insulin, with up to two oral antidiabetes drugs, with diet and exercise
Intervention	All antidiabetes pharmacological therapies that would be added to insulin in clinical practice when insulin does not provide adequate glycemic control (with or without up to two oral antidiabetes drugs)
Comparators	Placebo or dual therapy with drugs and doses licensed in the European Union and Canada, in combination with insulin
Outcomes	Efficacy: A1C, body weight, systolic blood pressure Safety: Hypoglycemic events Endpoints: 24 weeks ± 6 weeks
Exclusion criteria	Uncontrolled open-label extensions Populations with moderate to severe renal impairment

A1C = glycated hemoglobin; RCT = randomized controlled trial.

The original search for the systematic review was conducted in May 2011, but it was updated in July 2013 and once again in April 2015. The Cochrane Central, MEDLINE, and Embase databases were searched. Conference proceedings of the American Diabetes Association and the European Association for the Study of Diabetes, as well as the clinical trials registry, were searched. The detailed search strategy was provided.

The process of study selection and data extraction was conducted by two independent reviewers. Citations were screened based on titles and abstracts and rescreened for eligibility with full-text review. Disagreements on study eligibility were decided by a third reviewer. The lists of included and excluded studies were provided.

Data Extraction: A total of 13 studies were included in the analysis. Three more studies, which had an end point outside the 24 ± 6 weeks range, enrolled a different population or had quality issues, were included in the sensitivity analysis. The evidence networks are displayed in Figure 19 (A1C), Figure 20 (body weight), Figure 21 (systolic blood pressure), and Figure 22 (hypoglycemia). Seven were insulin-only studies. Eleven studies were stable background insulin trials, and five were "treat-to-target" background insulin trials. Comparators included placebo, dapagliflozin, DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin, and vildagliptin), GLP-1 analogues (lixisenatide and exenatide), pioglitazone, and metformin. Only one study (Wilding 2012) reported on dapagliflozin.

The included studies randomized 32 to 1,261 patients. The mean age of patients ranged from 47 to 60.9 years. The mean baseline A1C levels ranged from 8.3% to 9.1% in the stable dose studies and from 8.3% to 11% in the treat-to-target studies. Across treatment groups, the male ratios ranged from 28.6% to 69%; the fasting plasma glucose levels ranged from 8.0 mmol/L to 12.6 mmol/L; and BMI ranged from 28.9 kg/m^2 to 33.9 kg/m^2. The mean duration of diabetes ranged from 11.8 to 14.9 years in the stable dose studies and from 5.6 to 13.5 years in the treat-to-target studies. Baseline characteristics of patients were fairly homogeneous except for the Zib 2007 study, which enrolled patients who had high A1C levels (approximately 10.8%) and had had diabetes for approximately six years. The Aviles-Santa study also reported a higher A1C (approximately 9.0%) at baseline. Moreover, the Zib 2007 and the Hermann 2001 studies were small studies with sample sizes of 32 and 35 patients, respectively. More heterogeneity was observed for the gender ratio and ethnicity than for other baseline characteristics. Heterogeneity in the interventions was observed. Background insulin regimen, in terms of type of insulin and doses, differed across trials. Concomitant antidiabetes drugs other than metformin were used in some trials.

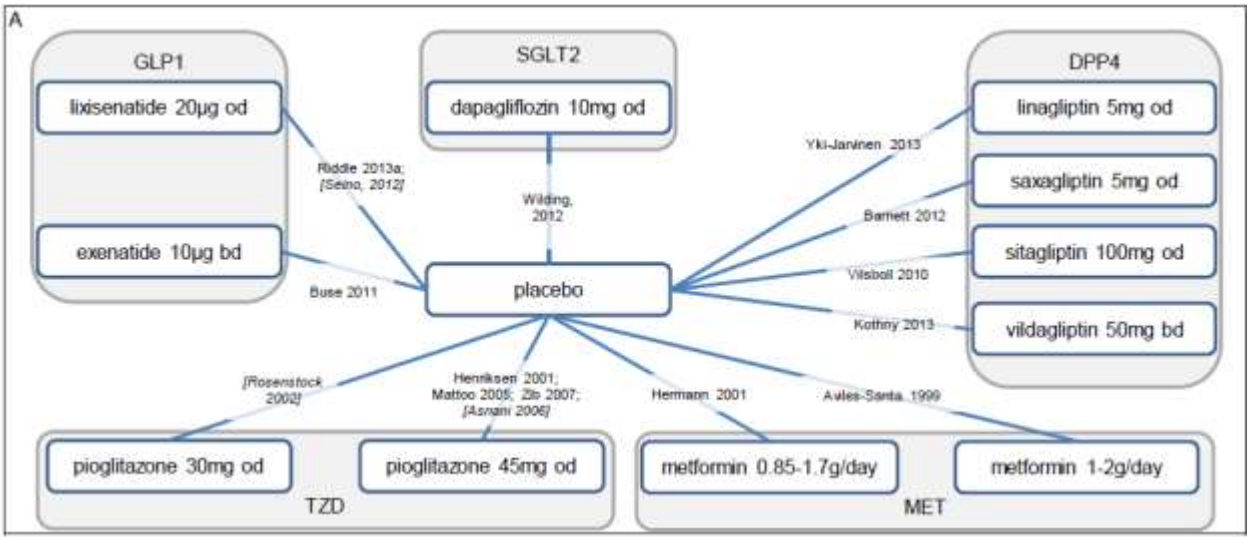
Comparators: The choice of comparators was based on drugs and doses licensed in the European Union and Canada. Up to two antidiabetes pharmacological therapies that would be added to insulin in clinical practice when insulin does not provide adequate glycemic control were considered. Indeed, the only concomitant medication to insulin that was specified in the indication was metformin. But some included trials allowed a background of non-metformin drugs with insulin.

Outcomes: Outcomes of interest were A1C, body weight, systolic blood pressure, and hypoglycemic events, which are common surrogate outcomes for diabetes. The only end point considered was at 24 ± 6 weeks. However, more specific safety outcomes for SGLT-2 inhibitors, such as genitourinary tract infections, renal adverse events, or ketoacidosis, were not assessed and would have been of interest for this review, as well as clinical efficacy outcomes such as major cardiovascular events, mortality, and microvascular complications of diabetes. Heart failure and bladder cancer would also be harms of interest, but were not assessed. The CDR review protocol for dapagliflozin includes these outcomes as well as quality of life.

Quality Assessment: The authors used the Cochrane Collaboration's tool for assessing risk of bias, and the assessment was reported. The authors observed no risks or unclear risk for random sequence generation, allocation concealment, blinding, and incomplete outcome data for all of the included studies except Zib 2007, which was an open-label study. Of the 13 studies included in the base-case analysis, four were deemed at risk of selective reporting, six were deemed at risk of bias from other sources, and the remaining studies were considered at low risk. The overall quality of the included studies was therefore deemed mediocre.

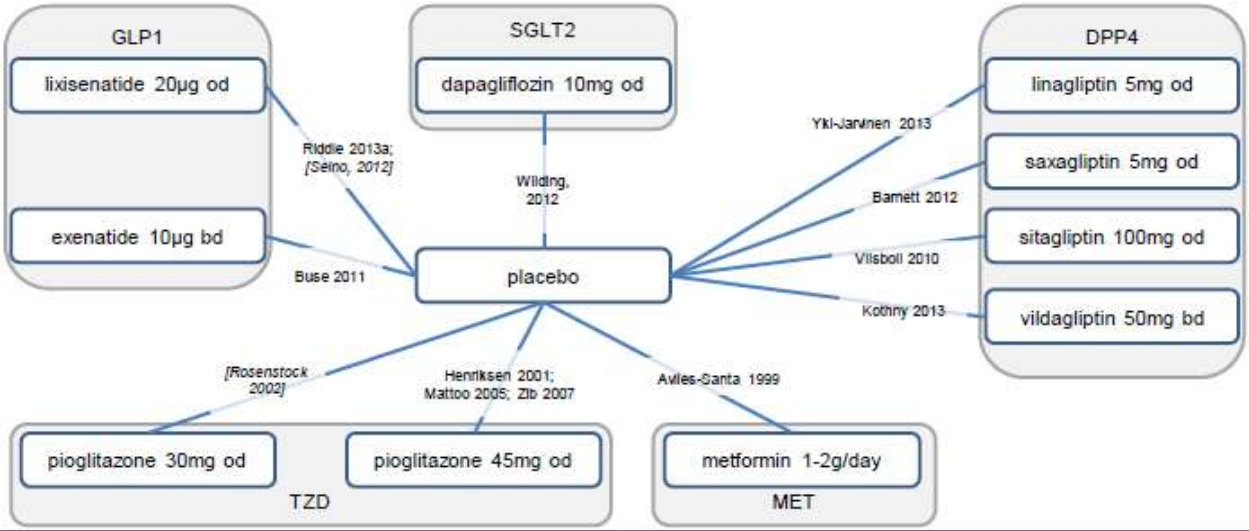
Evidence Network

FIGURE 19: EVIDENCE NETWORK FOR A1C INCLUDING ALL INSULIN TREATMENT REGIMENS



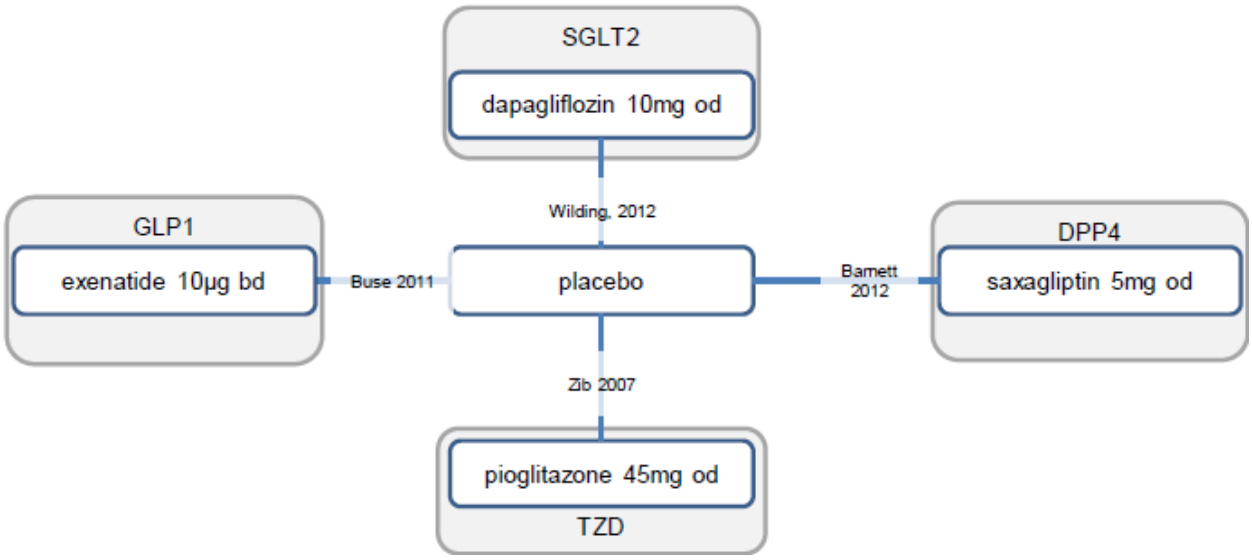
A1C = glycated hemoglobin; bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; MET = metformin; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione.
Note: Studies included in the sensitivity analysis are displayed between brackets.
Source: Manufacturer's indirect comparison document.[48]

FIGURE 20: EVIDENCE NETWORK FOR BODY WEIGHT INCLUDING ALL INSULIN TREATMENT REGIMENS



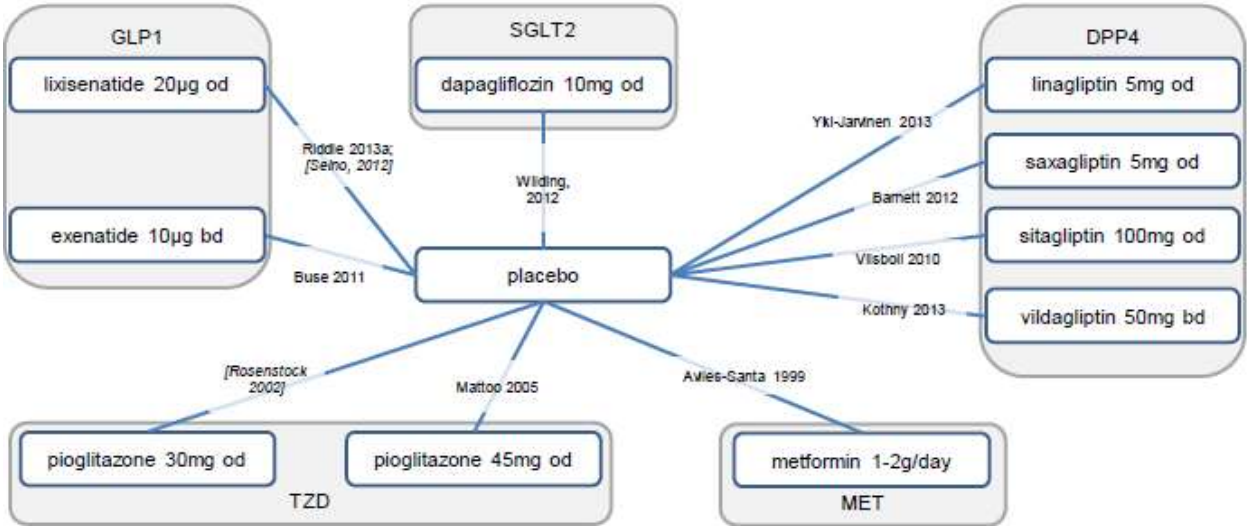
bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; MET = metformin; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione.
Note: Studies included in the sensitivity analysis are displayed between brackets.
Source: Manufacturer's indirect comparison document.[48]

FIGURE 21: EVIDENCE NETWORK FOR SYSTOLIC BLOOD PRESSURE INCLUDING ALL INSULIN TREATMENT REGIMENS



bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione.
Source: Manufacturer's indirect comparison document.[48]

FIGURE 22: EVIDENCE NETWORK FOR HYPOGLYCEMIA INCLUDING ALL INSULIN TREATMENT REGIMENS



bd = twice daily; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1 = glucagon-like peptide-1 analogues; MET = metformin; od = once daily; SGLT2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione.
Note: Studies included in the sensitivity analysis are displayed between brackets.
Source: Manufacturer's indirect comparison document.[48]

Meta-analysis and Indirect Comparison

A direct meta-analysis, a Bucher indirect comparison, and a Bayesian NMA were conducted. The main analysis was based on the NMA. The analyses were conducted on a modified intention-to-treat basis, but for some studies, the efficacy set was further restricted to those with non-missing baseline and at

least one follow-up efficacy result. Continuous outcomes were pooled as WMD, and the binomial outcomes were pooled as odds ratios. For continuous end points, if the standard error was not reported, it was evaluated from the confidence interval or the standard deviation, or imputed from the observed standard errors.

Direct Meta-analysis: Fixed and random effects models were used. The random effects model used the method of DerSimonian and Laird, with estimates of heterogeneity being taken from the fixed effects Mantel–Haenszel or inverse variance model. For binomial outcomes, where a study had no observation, 0.5 was added by default to each cell of the trial.

Bucher Indirect Comparison: The Bucher indirect comparisons were made using the Bucher method, and the pooled effects produced from the direct meta-analysis.

Network Meta-analysis: A random effects and fixed effects Bayesian NMA of continuous and dichotomous data were conducted for the main analysis, which models the probability of the most effective treatment among comparisons. The NMA methodology was per NICE Decision Support Unit recommendations. The models were fitted to the data via Bayesian Markov Chain Monte Carlo methods with Gibbs sampling. To ensure convergence, the models were run for a minimum of 100,000 iterations. Two subsequent chains of 100,000 were sampled to estimate the treatment effects. Both random effects models and fixed effects models were tested. In random effects models, for the between-studies standard deviation, it was assumed the underlying expected differences between treatments would be uniformly distributed (uninformative prior). The model fit was appropriately assessed using the mean residual deviance and the DIC. The models with the best fit according to the DIC and the average residual deviance were used.

The efficacy data for dapagliflozin came from the clinical study report, in which data were analyzed on an intention-to-treat basis with the last observation carried forward approach for missing data. In contrast, the published data (Wilding 2012) were based on the full analysis set with non-missing baseline and non-missing values for a given end point. This was presented in the publication as an alternative for the missing-at-random assumption, which some commentators considered to be a limitation of the last observation carried forward method.

Other Analyses:
Bias in the Study Controls: An assessment of potential bias in study controls was conducted by plotting the study control groups in a forest plot.

Subgroup Analysis: For the indication as add-on therapy to insulin alone, subgroup analyses were conducted on trials that had a stable insulin dose throughout the study and on trials in which insulin doses could be up-titrated in order to maintain glycemic control. For patients who were inadequately controlled on insulin plus one oral antidiabetes drug, the data were analyzed by drug classes using the subset of patients who had insulin plus the oral drug in the dapagliflozin study (Wilding 2012) and analyzed by individual drugs using the full population in the dapagliflozin study.

Covariate Analysis: Where feasible, the potentially confounding baseline factors were explored with a study-group level covariate analysis. These covariates were not further specified.

Sensitivity Analysis: A sensitivity analysis was performed by including studies that reported results at 24 weeks ± 8 weeks instead of ± 6 weeks. Studies with quality issues were also included in that analysis. In

addition, alternative data were used for the dapagliflozin study. Specifically, the data from the published article (available case analysis) was used instead of data from the clinical study report (intention-to-treat, last observation carried forward). Also, data for hypoglycemia excluded insulin up-titration.

Results of Manufacturer's Indirect Comparison #3

Efficacy: Based on estimates from the random effects base-case NMA model (see Table 57), DPP-4 inhibitors, pioglitazone, and metformin provided a statistically significant decrease in A1C compared with placebo (background therapy). Dapagliflozin did not show a statistical difference versus placebo for A1C, but did so in the stable insulin subgroup. In the base case, no statistically significant differences in A1C were observed between comparators and dapagliflozin. However, dapagliflozin showed an increased A1C compared with metformin in the stable insulin subgroup (WMD 1.33; 95% CI, 0.47 to 2.21). When comparing overall changes in A1C from baseline between the stable insulin and the treat-to-target subgroups, a lower absolute change was observed in the stable insulin studies. This indicated an important difference in A1C between placebo and baseline in treat-to-target studies.

For weight change, dapagliflozin and GLP-1 analogues resulted in statistically significant reductions, while pioglitazone resulted in a statistically significant increase, when compared with placebo in the base case. When comparing dapagliflozin with comparators, the SGLT-2 inhibitor provided statistically significant benefits over DPP-4 inhibitors and pioglitazone. Overall, results for weight change were similar in the stable insulin subgroup compared with the base case.

TABLE 57: ESTIMATED WEIGHTED MEAN DIFFERENCE IN EFFICACY OUTCOMES AFTER 24 WEEKS

Comparison		A1C (95% CrI)	Weight (95% CrI)
Difference vs. placebo			
SGLT-2		–0.60 (–1.31 to 0.11)	–1.69 (–3.19 to –0.18)[a]
GLP-1		–0.51 (–1.02 to 0.02)	–1.88 (–3.13 to –0.80)[a]
DPP-4		–0.53 (–0.86 to –0.21)[a]	0.06 (–0.66 to 0.85)
TZD		–0.85 (–1.35 to –0.35)[a]	4.07 (2.78 to 5.00)[a]
Metformin		–1.53 (–2.20 to –0.83)[a]	–2.74 (–6.06 to 0.61)
Difference head-to-head			
SGLT-2	GLP-1	–0.09 (–0.98 to 0.79)	0.19 (–1.62 to 2.18)
SGLT-2	DPP-4	–0.07 (–0.85 to 0.72)	–1.75 (–3.48 to –0.11)[a]
SGLT-2	TZD	0.25 (–0.62 to 1.12)	–5.76 (–7.43 to –3.69)[a]
SGLT-2	Metformin	0.94 (–0.08 to 1.88)	1.05 (–2.61 to 4.68)

A1C = glycated hemoglobin; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 analogues; SGLT-2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione; vs. = versus.
Note: The only SGLT-2 inhibitor included in the analysis was dapagliflozin. The random effects models were used.
[a] Statistically significant difference.
Source: Manufacturer's indirect comparison document.[48]

Safety: The odds of hypoglycemia for all the comparators were not different from placebo after 24 weeks (Table 58). Similarly, dapagliflozin did not show any statistical difference in odds ratio when compared with other comparators. Subgroup analyses were in agreement with the base case.

TABLE 58: ESTIMATED ODDS RATIOS FOR HYPOGLYCEMIA AFTER 24 WEEKS

Comparison		OR (95% CrI)
OR vs. placebo		
SGLT-2		1.117 (0.352 to 3.588)
GLP-1		1.100 (0.470 to 2.528)
DPP-4		1.073 (0.635 to 1.853)
TZD		1.673 (0.510 to 5.499)
Metformin		1.052 (0.130 to 8.904)
OR head-to-head		
SGLT-2	GLP-1	1.014 (0.245 to 4.352)
SGLT-2	DPP-4	1.041 (0.289 to 3.730)
SGLT-2	TZD	0.668 (0.128 to 3.524)
SGLT-2	Metformin	1.067 (0.095 to 11.451)

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 analogues; OR = odds ratio; SGLT-2 = sodium glucose cotransporter-2 inhibitors; TZD = thiazolidinedione; vs. = versus.
Note: The random effects models were used.
Source: Manufacturer's indirect comparison document.[48]

Consistency: Results of the Bucher indirect comparisons were consistent with estimates from the NMA.

Sensitivity Analyses: For A1C, results of the sensitivity analysis were similar to the base case. The only differences observed were that GLP-1 analogues had a statistical improvement compared with placebo (–0.64; 95%CrI, –1.00 to –0.26) and metformin had a statistical improvement (0.97; 95% CrI, 0.06 to 1.83) over dapagliflozin. Those two differences were very near to statistical significance in the base case. Of note, dapagliflozin was still not statistically different from placebo in the sensitivity analysis.

For change in body weight and odds of hypoglycemic events, the sensitivity analysis showed similar findings to the base case.

Subgrouping for patients who had an oral antidiabetes drug in addition to insulin as background therapy (as opposed to insulin alone) was also used as a sensitivity analysis. Overall, the findings were in line with the results presented for the base case.

Critical Appraisal

The critical appraisal was based on ISPOR Task Force on indirect treatment comparisons.[52] The NMA document provided by the manufacturer was of high quality and adequately satisfied all the ISPOR criteria for the methods, although other limitations were observed.

Strengths: The manufacturer provided a very detailed document that comprehensively described the objectives, methods for the systematic review and analysis of evidence, literature search strategy, included and excluded studies, individual results of the studies, baseline characteristics of patients, quality appraisal of included studies, networks of evidence, and statistical models. The process of study selection and data extraction was duplicated. Baseline characteristics of patients were representative of patients with type 2 diabetes, although heterogeneity was observed. Statistical models were compared, and the model with the best fit was chosen. Sensitivity analyses were provided and were justified. The evaluation of consistency was provided.

Limitations: The choice of comparators was based on drugs and doses licensed in various jurisdictions. As a result, lixisenatide and vildagliptin were included although they are not approved in Canada. There was some heterogeneity for the insulin background in terms of dosing target (stable insulin versus treat-to-target strategy) and type of insulin. This heterogeneity was evidenced by the subgroup analysis comparing the two dosing strategies. Of note, the variability and the magnitude of difference from baseline for placebo was higher in the treat-to-target studies compared with stable insulin studies. There was heterogeneity in the types of concomitant oral antidiabetes medications. Some of the combinations with insulin were not approved in the present indication reviewed. Most comparisons in the network diagram relied on a single study. This increased the uncertainty of treatment effect estimates and limited sensitivity analyses. Based on the author's assessment, many studies were at risk of bias, resulting in overall mediocre study quality. Also, some heterogeneity was observed between studies for baseline A1C, duration of diabetes, sample size, gender ratio, and ethnicity.

Discussion

For the utilization of antidiabetes drugs as second-line add-on therapies to metformin, three NMAs were available: one document provided by the manufacturer[46] and two published analyses.[49,51] Two were funded by the manufacturer of dapagliflozin,[46,49] and one was supported by a competitor.[51] Goring et al.[49] focused their analysis on end points at 52 weeks ± 6 weeks and used sulfonylureas as the common comparator. Only six studies were included in their primary analysis. No comparison with GLP-1 analogues and no data for systolic blood pressure were available in the primary analysis. Their conclusions were aligned with the analysis provided by the manufacturer at 52 weeks. Mearns et al.[51] included studies reporting data after 12 weeks through 52 weeks, but also included more drug classes, including alpha-glucosidase inhibitors, meglitinides, and the long-acting insulin glargine. Sixty-two trials were included. Each drug was analyzed separately. Pooling more time points and including more treatments led to discrepancies in the NMA results compared with the analysis provided by the manufacturer. Their analysis satisfied most of the ISPOR criteria. Major findings were:

- On A1C, dapagliflozin had a statistically significant weaker reduction (from 0.21% to 0.81%) than empagliflozin, canagliflozin, exenatide, liraglutide, insulin glargine, glibenclamide, gliclazide, glimepiride, sitagliptin, pioglitazone, and rosiglitazone. However, the lower 95% CrI for the estimates of dapagliflozin versus the other SGLT-2 inhibitors did not reach –0.3%, the a priori threshold for a clinically significant difference between treatments specified by Mearns et al.
- On body weight, dapagliflozin had a statistically significant better decrease (from 2.07 kg to 5.44 kg) than thiazolidinediones, sulfonylureas, DPP-4 inhibitors, insulin glargine, meglitinides, and acarbose.
- For systolic blood pressure, dapagliflozin had a statistically significant better decrease (from 4.76 mm Hg to 5.14 mm Hg) than glimepiride and saxagliptin.
- For hypoglycemia, dapagliflozin had statistically significantly lower risk (odds ratio from 0.1 to 0.2) than sulfonylureas, insulin glargine, and nateglinide.
- For urinary tract infections and genital tract infections, dapagliflozin was not statistically significantly different from other antidiabetes therapies approved in Canada.

The results of the NMAs were generally aligned with the therapeutic reviews conducted by CADTH on antihyperglycemic therapies in 2013.[53,54] These therapeutic reviews compared antidiabetes drugs as second-line add-on therapies with metformin[53] and as third-line add-on therapies with metformin and a sulfonylurea.[54] However, these therapeutic reviews did not include SGLT-2 inhibitors as comparators, because this class of antidiabetes drug was not approved in Canada at the time. Comparisons between other antidiabetes drugs showed only small differences between treatment options, especially for A1C.

For the utilization of antidiabetes drugs as second-line add-on therapy to sulfonylureas, two NMAs were available. One was provided from the manufacturer,[47] and one was published.[50] Both were funded by the manufacturer of dapagliflozin and were authored by the same person. The analysis conducted by Orme et al.[50] in 2014 was very similar to the one conducted by the manufacturer in 2015,[47] except that the 2015 analysis included two more studies. This update added a study reporting on vildagliptin (which is not approved in Canada) and on alogliptin.

For the utilization of antidiabetes drugs as add-on therapy to insulin, with or without metformin, only one NMA provided by the manufacturer was available.[48] More limitations were noted for this NMA than for the previous sub-indications. Heterogeneity in the interventions and risks of biases were among the concerns that increased the uncertainty of the findings.

For all three sub-indications, differences in A1C, body weight, and systolic blood pressure between dapagliflozin and its comparators were modest. Differences in A1C, body weight, and systolic blood pressure were less than 1.0% of A1C, less than 6 kg, and less than 6 mm Hg, respectively. Although no formal minimal clinically important differences were identified for these surrogate outcomes, the clinical relevance of those changes is uncertain. In terms of hypoglycemia, odds ratios for dapagliflozin were as low as 0.1 for some comparisons, especially sulfonylureas.

All the NMAs provided by the manufacturer analyzed a subpopulation of patients who did not have moderate to severe renal insufficiency, which may not represent the general population of patients with type 2 diabetes. Due to their mechanism of action, SGLT-2s are likely to lose their efficacy when renal impairment occurs.

Conclusion

For the evaluation of antidiabetes drugs as second-line add-on therapies to metformin, three NMAs were available. One of them provided a review with more comparators, more precise results, and decreased chances for conflicts of interest. When comparing drugs separately rather than comparing between classes, as analyzed by Mearns et al.,[51] dapagliflozin appeared to provide a smaller decrease in A1C than empagliflozin, canagliflozin, exenatide, liraglutide, insulin glargine, glibenclamide, gliclazide, glimepiride, sitagliptin, pioglitazone, and rosiglitazone. However, the effect of sulfonylureas on A1C appears to wane after 52 weeks. For body weight, dapagliflozin had a statistically significant greater decrease than thiazolidinediones, sulfonylureas, DPP-4 inhibitors, insulin glargine, meglitinides, and acarbose. For systolic blood pressure, dapagliflozin had a statistically significant greater decrease than glimepiride and saxagliptin. For hypoglycemia, dapagliflozin had statistically significantly lower risk than sulfonylureas, insulin glargine, and nateglinide. For urinary tract infections and genital tract infections risks, dapagliflozin was not statistically significantly different from other antidiabetes drugs approved in Canada.

For the evaluation of antidiabetes drugs as second-line add-on therapy to sulfonylureas, two NMAs were available, but the most recent was an update of the former. Results from the NMAs showed no statistically significant difference for A1C between dapagliflozin, DPP-4 inhibitors, and GLP-1 analogues. Dapagliflozin had a statistically significant decrease in body weight compared with DPP-4 inhibitors. The lower risk of hypoglycemia for dapagliflozin compared with GLP-1 drugs was unclear. For this sub-indication, the main limitation was the small number of studies available and a sparse network of evidence. This created high uncertainty regarding results between studies.

For the evaluation of antidiabetes drugs as add-on therapy to insulin, with or without metformin, only one NMA was available. In the base case, results from the NMA showed no statistically significant differences in A1C between the comparators and dapagliflozin. However, dapagliflozin showed an increased A1C compared with metformin in sensitivity and subgroup analyses. When comparing dapagliflozin with other drugs for body weight change, the SGLT-2 inhibitor provided statistically significant benefits over DPP-4 inhibitors and pioglitazone. For hypoglycemic events, dapagliflozin did not show a statistical difference in odds ratio when compared with other comparators. Limitations of this NMA were due to the available data. Background treatments, some of which were not part of the indication reviewed here, were heterogeneous. Most of the comparisons in the network diagram relied on a single study, thereby increasing the uncertainty on treatment effect estimates. Based on the author's assessment, many studies were at risk of bias, and the overall quality of studies was therefore mediocre. For all these reasons, the results for this sub-indication were less robust.

As efficacy outcomes were based on surrogates and the differences between treatments were relatively small, the clinical relevance of changes in A1C, body weight, and systolic blood pressure observed between dapagliflozin and its comparators is uncertain.

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