Common Drug Review
Clinical Review Report

April 2016

Drug	Dapagliflozin (Forxiga)
Indication	For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.
Listing request	For the treatment of patients with type 2 diabetes mellitus to improve glycemic control when added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.
Dosage form(s)	5 mg and 10 mg oral tablets
NOC date	December 2, 2015
Manufacturer	AstraZeneca Canada Inc.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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ABBREVIATIONS

A1C	glycated hemoglobin
ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
CDA	Canadian Diabetes Association
CDR	CADTH Common Drug Review
CI	confidence interval
DB	double-blind
DBP	diastolic blood pressure
DIC	deviance information criterion
DM	diabetes mellitus
DPP-4	dipeptidyl-peptidase 4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	Diabetes Treatment Satisfaction Questionnaire change version
DTSQs	Diabetes Treatment Satisfaction Questionnaire original status version
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol 5-Dimensions Questionnaire
FAS	full analysis set
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
HRQoL	health-related quality of life
IDC	indirect comparison
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention-to-treat
IWQOL-Lite	Impact of Weight on Quality of Life–Lite questionnaire
LOCF	last observation carried forward
MCID	minimal clinically important difference
NMA	network meta-analysis
RCT	randomized controlled trial
SAE	serious adverse event
SBP	systolic blood pressure
SGLT-2	sodium-glucose cotransporter-2
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TZD	thiazolidinedione
VAS	visual analogue scale

EXECUTIVE SUMMARY

Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels, on both microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral vascular disease, cardiovascular disease) levels. There are two main subtypes of DM: type 1 (T1DM), in which the primary problem is a lack of adequate insulin secretion from pancreatic beta cells, and type 2 (T2DM), in which cells are unresponsive to insulin followed by a lack of insulin production in later stages. Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT-2) inhibitor, and by inhibiting the glucose transporter in the kidney, increases the excretion of glucose, providing an antihyperglycemic effect. Secondary effects may include an osmotic diuresis, which may reduce weight and lower blood pressure.

Indication under review
For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.
Listing criteria requested by sponsor
For the treatment of patients with type 2 diabetes mellitus to improve glycemic control when added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.

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 who have experienced inadequate glycemic control on combination therapy with metformin and a sulfonylurea.

Results and interpretation

Included studies

One international, multi-centre, manufacturer-sponsored, placebo-controlled, double-blind (DB), randomized controlled trial (RCT) met inclusion criteria for this review. Study 5 (N = 218) had a 24-week DB period and a 28-week site- and patient-blind extension period that evaluated the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM who had inadequate glycemic control (7.0% ≤ glycated hemoglobin [A1C] ≤ 10.5%) on a combination therapy of metformin ≥ 1,500 mg/day and ≥ 50% the maximum dose of a sulfonylurea. Patients were randomized in a 1:1 ratio to either dapagliflozin 10 mg or placebo (with a background of metformin and a sulfonylurea) after an eight-week single-blind, placebo lead-in period. The primary outcome was the change from baseline in A1C at week 24. Key secondary outcomes included the change in fasting plasma glucose (FPG) and total body weight from baseline at week 24, the proportion of patients achieving A1C < 7.0% at week 24, and the change in seated systolic blood pressure (SBP) from baseline at week 8. Health-related quality of life (HRQoL) was evaluated using the EuroQol 5-Dimensions Questionnaire (EQ-5D) and the Impact of Weight on Quality of Life–Lite (IWQOL-Lite) questionnaire as secondary and exploratory outcomes. Efficacy outcomes at the end of the 28-week extension (52 weeks) were exploratory and are not highlighted in the review due to different statistical methods used from the 24-week analysis.

The main limitations of Study 5 included the unsuccessful randomization procedure that led to unbalanced baseline characteristics between the dapagliflozin and placebo groups, including gender, the distribution of time since diagnosis, and baseline FPG levels. Once the integrity of randomization has been compromised, the impact of measured and unmeasured confounders on the outcomes of interest is uncertain and exposes the study to a high risk of bias. In addition, modelling the proportion of patients who achieved target A1C rather than using the observed data is of questionable validity. Study 5 was relatively small and was not designed to assess key clinical outcomes such as morbidity, mortality, and HRQoL.

Generalizability to the Canadian population is limited due to the dosing regimen used for dapagliflozin. At 10 mg once daily, this does not adhere to the Health Canada–recommended starting dose of 5 mg once daily before increasing to 10 mg in patients requiring additional glycemic control, nor adhere to what would occur in clinical practice, according to the clinical expert consulted by CADTH. Generalizability is also limited due to dose ranges of background therapy that were not consistent with the maximum Health Canada–approved doses.

Efficacy

No deaths were reported during the 24-week DB period and the 28-week extension period. Morbidity was not specifically assessed in this study, and would be difficult to assess given the relatively short duration of the study. Health resource utilization was not assessed in this study.

The primary efficacy end point of Study 5 was the change in A1C from baseline to week 24. There was a statistically significant reduction from baseline in A1C at week 24 in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo [95% confidence interval (CI)] of –0.69 [–0.89 to –0.49], $P < 0.0001$). The proportion of patients achieving A1C < 7% at week 24 was a key secondary end point in Study 5, and was statistically significantly greater in the dapagliflozin group compared with the placebo group (33.3% versus 10.2%; adjusted mean difference versus placebo 20.7; 95% CI, 10.7 to 30.6; $P < 0.0001$). The cut-off of 7% would be considered a standard threshold for achieving glycemic control in Canada for most patients.

Subgroup analyses of change from baseline in A1C at week 24 suggested a statistically significant interaction ($P = 0.0038$), with patients with a higher baseline A1C (≥ 9%) having a larger reduction in A1C with dapagliflozin compared with placebo (adjusted mean change versus placebo –0.82; 95% CI, –1.17 to –0.47) when compared with patients with a baseline A1C ≥ 8% and < 9% (adjusted mean change versus placebo –0.64; 95% CI, –0.87 to –0.41) and when compared with patients with a baseline A1C < 8% (adjusted mean change versus placebo –0.36; 95% CI, –0.59 to –0.14). These data might suggest that dapagliflozin may play a more important role in difficult-to-treat patients; however, these findings are from only one relatively small study, with no active comparator. There was no statistically significant interaction from the subgroup analysis based on baseline estimated glomerular filtration rate (eGFR). However, patients with moderate renal impairment (eGFR 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2) had a smaller reduction in A1C with dapagliflozin compared with placebo (adjusted mean change versus placebo –0.40; 95% CI, –0.83 to 0.02) when compared with patients with normal renal function (eGFR ≥ 90 mL/min/1.73m^2) (adjusted mean change versus placebo –0.74; 95% CI, –1.02 to –0.47). This is expected, as the mechanism of action of dapagliflozin is dependent on renal function.

There was a statistically significantly greater reduction from baseline in FPG at week 24 in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo –1.86 mmol/L; 95% CI, –2.39 to –1.32; $P < 0.0001$). However, baseline FPG levels were not balanced between

groups, with the placebo group having a higher baseline mean FPG compared with the dapagliflozin group (10.0 mmol/L versus 9.3 mmol/L). The clinical expert consulted for this review noted that it would be more difficult to see a decrease in FPG when starting from a lower baseline level, so this would have biased against dapagliflozin. However, the extent and direction of bias is uncertain, and the unbalanced baseline characteristics between treatment groups are a concern and limits the internal validity of the study.

There was a statistically significant greater reduction from baseline in body weight at week 24 in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo –2.07 kg; 95% CI, –2.79 to –1.35; $P < 0.0001$). Although these reductions in weight are relatively small, they should be considered in the context of a disease where weight gain is a contributor to pathophysiology, and where many of the key interventions can cause weight gain.

There was a statistically significantly greater reduction from baseline in SBP at week 8 in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo –3.76 mm Hg; 95% CI, –7.05 to –0.48; $P = 0.0250$). This difference was maintained at week 24 (adjusted mean change versus placebo –4.00 mm Hg; 95% CI, –7.14 to –0.87; $P = 0.0125$), although this end point was not included in the testing hierarchy. Medication for high blood pressure was not allowed to change in the first eight weeks of DB study medication, after which adjustments were permitted to manage blood pressure. The change from baseline in diastolic blood pressure (DBP) at week 24 was statistically significantly greater in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo –2.20 mm Hg; 95% CI, –3.99 to –0.42; $P = 0.0158$), although this end point was not included in the testing hierarchy. The reductions in blood pressure overall, both SBP and DBP, would be considered small and of limited clinical significance, particularly when compared with an antihypertensive drug.

Quality of life was assessed using the EQ-5D instrument, and there were no statistically significant differences in mean change from baseline between the dapagliflozin and placebo groups in both the EQ-5D visual analogue scale (VAS) and the EQ-5D index score at week 24. There was a slightly greater increase in Diabetes Treatment Satisfaction Questionnaire original status version (DTSQs) score from baseline at week 24 in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo 1.4; 95% CI, 0.1 to 2.8; $P = 0.0393$). No differences were seen in change from baseline at week 24 in IWQOL-Lite total score between the dapagliflozin and placebo groups, and in the individual dimensions of physical function, self-esteem, sexual life, and work. The dimension of public distress showed a slight increase in the dapagliflozin group compared with placebo (adjusted mean change versus placebo 4.7; 95% CI, 0.8 to 8.7; $P = 0.0178$). As patient-reported outcomes were considered exploratory, the study may not have been appropriately powered to detect differences in these outcomes. These outcomes were also not included in the study's hierarchy, which limits the validity of statistical comparison between groups.

Since there were no head-to-head comparisons of dapagliflozin with other therapies used for third-line treatment for T2DM, the manufacturer submitted a network meta-analysis (NMA) that assessed the efficacy and safety of third-line therapies for T2DM in combination with metformin and a sulfonylurea. Based on the results of the NMA, dapagliflozin 10 mg showed similar efficacy in change from baseline in A1C and SBP to dipeptidyl-peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, thiazolidinediones (TZDs), and insulin analogues. Dapagliflozin had a statistically significant greater reduction in weight from baseline compared with the other drug classes except for GLP-1 analogues, for which there was no significant difference. For the proportion of patients with hypoglycemia, there was

no difference with dapagliflozin in the odds of hypoglycemic events compared with the other treatments, though the definition of hypoglycemia varied across trials. There was considerable heterogeneity identified in trials of certain pairwise comparisons, which may have been due to baseline characteristics of patients, treatment duration, and dosing regimen and ranges, between drug differences within classes. This limits the confidence in the results.

Harms

A total of 48.6% of patients in the dapagliflozin group and 51.4% of patients in the placebo group reported an adverse event (AE) during the 24-week DB period, with the most common AEs with dapagliflozin being bronchitis, urinary tract infection, and pharyngitis. During the 24-week DB period, the proportion of patients reporting a serious adverse event (SAE) was 0.9% in the dapagliflozin group and 5.5% in the placebo group. There was no clear pattern of reason for discontinuing due to an AE in any group. During the 24-week DB phase, the proportion of patients discontinuing study treatment due to an AE was 1.8% in the dapagliflozin group and 2.8% in the placebo group. There was no clear pattern of reason for discontinuing due to an AE in any group.

Patients indicated that daily fluctuations in blood glucose were the most important aspect of diabetes to control during the day and overnight, as fluctuations affect patients' ability to work and interactions with friends and family, and are a source of stress. During the 24-week DB period, there were a greater proportion of patients in the dapagliflozin group who had a confirmed AE of hypoglycemia than in the placebo group (12.8% versus 2.8%). Although the proportion of patients experiencing a confirmed hypoglycemic event had increased by the end of extension, the difference in proportions between groups was similar to the 24-week DB phase. Most hypoglycemia episodes were minor, with a plasma glucose level between 3.0 mmol/L and 3.5 mmol/L.

During the 24-week DB period, genital infections were more common with dapagliflozin than placebo (5.5% versus 0%), urinary tract infections were balanced between groups (6.4%), renal impairment was reported in two patients (1.8%) in the dapagliflozin group, and bone fractures were reported in one patient (0.9%) in the placebo group.

Conclusions

One international, multi-centre, manufacturer-sponsored, placebo-controlled, 24-week DB RCT with a 28-week site- and patient-blind extension met inclusion criteria for this review. Study 5 (N = 218) evaluated the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM who had inadequate glycemic control on a combination therapy of metformin and a sulfonylurea. Results from Study 5 suggest that dapagliflozin 10 mg once daily is associated with a statistically significant reduction in A1C, FPG, and weight compared with placebo after 24 weeks. Study 5 was not designed to assess the effect of dapagliflozin on morbidity or mortality due to its relatively short duration and small sample size. Results at the end of the 28-week extension (52 weeks) suggest that effects are maintained from 24 weeks. Several significant limitations introduce a high risk of bias to the trial. Randomization was not successful at evenly distributing baseline characteristics between groups, and large differences were observed at baseline in measured characteristics such as FPG, gender, time since diagnosis, and use of angiotensin-converting enzyme (ACE) inhibitors. Statistical methodology used for the proportion of patients achieving A1C < 7% and outcomes at 52 weeks is of questionable validity, and there is a high proportion of missing data that is not evenly distributed between groups. Generalizability to the Canadian population is limited by the dosing of dapagliflozin and background metformin and sulfonylurea therapy.

The difference in weight reduction was a mean of 2 kg, which could be considered clinically significant in T2DM patients, as other therapies may cause weight gain. In addition, there was a statistically significant reduction in SBP with dapagliflozin compared with placebo after eight weeks, during which antihypertensive therapies were not adjusted, and after 24 weeks. However, this decrease was relatively small (4 mm Hg) and of uncertain clinical significance. HRQoL was assessed using EQ-5D and IWQOL-Lite, and no significant differences were seen in change from baseline to week 24 between the dapagliflozin and placebo groups. AE data were generally balanced between groups.

There was a greater proportion of patients in the dapagliflozin group who reported hypoglycemia episodes and genital infections. Although only two patients in the dapagliflozin group reported a renal impairment, serum creatinine levels were increased and eGFR was decreased compared with baseline at week 24 in the dapagliflozin group, while the opposite was seen in the placebo group.

There was a lack of direct comparative data of dapagliflozin versus other third-line therapies for T2DM, but a manufacturer-submitted NMA suggests that dapagliflozin had similar A1C and SBP responses compared with other drug classes, and had an increased weight reduction compared with other drug classes with a background of metformin and a sulfonylurea. Long-term safety data and impact on microvascular and macrovascular complications of diabetes remain uncertain.

TABLE 1: SUMMARY OF RESULTS

	Study D1693C00005 (Study 5)	
	24-week DB period	
	Dapa 10 mg (n = 108)	Placebo (n = 108)
Mortality		
Deaths, n (%)	0	0
A1C, %		
Baseline mean (SD)	8.08 (0.91)	8.24 (0.87)
Adjusted mean change (SE), week 24	–0.86 (0.07)	–0.17 (0.07)
Adjusted mean change vs. placebo (95% CI)[a]	–0.69 (–0.89 to –0.490), *P* < 0.0001	
Patients with A1C < 7.0%, n (%)	36 (33.3)	11 (10.2)
Adjusted mean difference vs. placebo (95% CI)	20.7 (10.7 to 30.6), *P* < 0.0001	
FPG, mmol/L		
Baseline mean (SD)	9.29 (2.40)	10.02 (2.40)
Adjusted mean change (SE), week 24	–1.90 (0.19)	–0.04 (0.19)
Adjusted mean change vs. placebo (95% CI)[b]	–1.86 (–2.39 to –1.32), *P* < 0.0001	
Body weight, kg		
Baseline mean (SD)	88.57 (17.58)	90.07 (16.18)
Adjusted mean change (SE), week 24	–2.65 (0.26)	–0.58 (0.26)
Adjusted mean change vs. placebo (95% CI)[b]	–2.07 (–2.79 to –1.35), *P* < 0.0001	
SBP, mm Hg		
Baseline mean (SD)	134.70 (12.69)	136.31 (14.37)
Adjusted mean change (SE), week 8	–4.04 (1.18)	–0.27 (1.18)
Adjusted mean change vs. placebo (95% CI)[b]	–3.76 (–7.05 to –0.48), *P* = 0.0250	
Adjusted mean change (SE), week 24	–5.30 (1.12)	–1.29 (1.13)
Adjusted mean change vs. placebo (95% CI)[b]	–4.00 (–7.14 to –0.87), *P* = 0.0125	
DBP, mm Hg		
Baseline mean (SD)	80.39 (9.17)	81.75 (7.75)
Adjusted mean change (SE), week 24	–2.92 (0.64)	–0.72 (0.64)
Adjusted mean change vs. placebo (95% CI)[b]	–2.20 (–3.99 to –0.42), *P* = 0.0158	
Harms		
Patients with > 0 AEs, N (%)	53 (48.6)	56 (51.4)
Patients with > 0 SAEs, N (%)	1 (0.9)	6 (5.5)
Patients with > 0 WDAEs, N (%)	2 (1.8)	3 (2.8)
Notable harms, n (%)		
Hypoglycemia	14 (12.8)	4 (3.7)
Genital infection	6 (5.5)	0
Urinary tract infection	7 (6.4)	7 (6.4)
Renal impairment	2 (1.8)	0
Bone fractures	0	1 (0.9)

A1C = glycated hemoglobin; AE = adverse event; ANCOVA = analysis of covariance; Dapa = dapagliflozin; DB = double-blind; DBP = diastolic blood pressure; FPG = fasting plasma glucose; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Longitudinal repeated measures analysis with fixed categorical effects of treatment, week, treatment-by-week interaction, and the continuous fixed covariates of baseline and baseline-by-week interaction.

[b] ANCOVA model with treatment group as an effect and baseline value as a covariate.

Source: Clinical Study Reports.[1,2]

1. INTRODUCTION

1.1 Disease prevalence and incidence

Diabetes mellitus (DM) is a metabolic disease characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels, on both microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral artery disease, cardiovascular disease) levels. There are two main subtypes of DM: type 1 (T1DM), in which the primary problem is a lack of adequate insulin secretion from pancreatic beta cells, and type 2 (T2DM), in which cells are unresponsive to insulin. T2DM is more common than T1DM, accounting for approximately 90% of cases of DM.[3] The etiology of T1DM is unknown, although onset is typically early in life. In contrast, onset of T2DM 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 T2DM.[4] There is overlap between the two subtypes; most notably, patients with type 2 diabetes who, in the initial stages of their disease are able to secrete insulin, or may be hyperinsulinemic, progress to a stage where insulin secretion is reduced, similar to T1DM.

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.[5] 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.[6] 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.[7]

1.2 Standards of therapy

There are many classes of antidiabetic drugs used in treating T2DM, including insulin. The drugs 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 similar manner to sulfonylureas; and alpha-glucosidase inhibitors, which have a simple mechanism (block glucose absorption) and are typically used in combination with other drugs. Insulin and insulin analogues can be used in rapid-acting, intermediate, or longer-acting forms, and are all administered by injection.

1.2.1 Drug

Dapagliflozin is a selective inhibitor of the renal sodium-glucose cotransporter-2 (SGLT-2) and has an antihyperglycemic effect by reducing renal glucose reabsorption, leading to increased urinary glucose excretion. This excretion of glucose contributes to reduced body weight through calorie loss, and lower blood pressure through osmotic diuresis. Dapagliflozin is available as 5 mg or 10 mg oral tablets. The recommended dose is 5 mg once daily, and can be increased to 10 mg once daily for those who require additional glycemic control. Other SGLT2 inhibitors approved in Canada include empagliflozin and canagliflozin.

Dapagliflozin is indicated for use in patients with T2DM to improve glycemic control in combination with: metformin; a sulfonylurea; metformin and a sulfonylurea; or insulin (alone or with metformin), when the existing therapy, along with diet and exercise, does not provide adequate glycemic control. Dapagliflozin in combination with metformin, a sulfonylurea, or insulin (alone or with metformin) has

previously been reviewed by the CADTH Common Drug Review (CDR) and received a recommendation to "list with clinical criteria" (see CADTH Canadian Drug Expert Committee [CDEC] final recommendation, November 20, 2015).[8] Dapagliflozin in combination with metformin and a sulfonylurea is the focus of this review.

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Listing criteria requested by sponsor
For the treatment of patients with type 2 diabetes mellitus to improve glycemic control when added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.

TABLE 2: KEY CHARACTERISTICS OF SGLT-2 INHIBITORS, METFORMIN, AND SULFONYLUREAS

	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]	In T2DM: • 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 drugs does not provide adequate glycemic control • in combination with metformin and either a sulfonylurea or pioglitazone[b] when diet, exercise, and dual therapy (with metformin plus either a sulfonylurea or pioglitazone) do not provide adequate glycemic control • combination therapy	T2DM 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	T2DM in adults, alone or in combination with other antihyperglycemic drugs as an adjunct to exercise and diet

	SGLT-2 Inhibitors	Biguanides (Metformin)	Sulfonylureas
	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	Canagliflozin: 100 mg to 300 mg once daily Dapagliflozin: 5 mg to 10 mg once daily Empagliflozin: 10 mg to 25 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 (canagliflozin and empagliflozin) or 60 mL/min/1.73 m^2 (dapagliflozin), 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

eGFR = estimated glomerular filtration rate; LDL-C = low–density lipoprotein cholesterol; SGLT2 = sodium-glucose cotransporter 2; T2DM = type 2 diabetes mellitus.
[a] Health Canada indication.
[b] Health Canada–approved combination for canagliflozin and empagliflozin, but not dapagliflozin.
Source: Product monographs from the electronic edition of the *Compendium of Pharmaceuticals and Specialties* (e-CPS).[9]

TABLE 3: 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: T2DM in combination with metformin or metformin and a sulfonylurea, when these drugs, with diet and exercise, do not provide adequate glycemic control T2DM in combination with metformin and a basal insulin, when liraglutide and metformin, with diet and exercise, do not provide adequate glycemic control	T2DM that cannot be adequately controlled by diet and exercise alone May be used as monotherapy or in combination with a sulfonylurea or metformin when monotherapy fails to adequately control blood glucose	Saxagliptin: T2DM in combination with metformin or a sulfonylurea, or insulin (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: T2DM 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: T2DM as monotherapy or in combination with metformin or a sulfonylurea, or	Patients with DM who require insulin for control of hyperglycemia

	GLP-1 Analogues	Thiazolidinediones (Pioglitazone)	DPP-4 Inhibitors	Insulin/Insulin Analogues
			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 mg to 1.8 mg once daily	15 mg 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: • DKA Warnings/precautions: • heart failure • pancreatitis • immune suppression	Serious warnings and precautions: • hypoglycemia • immune responses

DKA = diabetic ketoacidosis; DM = diabetes mellitus; DPP-4=dipeptidyl-peptidase 4; FFA = free fatty acids; GLP-1 = glucagon-like peptide-1; PPAR = peroxisome proliferator-activated receptor; PR = period from the onset of atrial depolarization to the onset of ventribular depolarization; T2DM = type 2 diabetes mellitus.

[a] Health Canada indication.

Source: Product monographs from the electronic edition of the *Compendium of Pharmaceuticals and Specialties* (e-CPS).[9]

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 T2DM who have experienced inadequate glycemic control on combination therapy with metformin and a sulfonylurea.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with T2DM who have experienced inadequate glycemic control on combination therapy with metformin and a sulfonylurea **Subgroups:** baseline A1C, eGFR, T2DM duration
Intervention	Dapagliflozin at a dose of 5 mg once daily, in combination with metformin and a sulfonylurea • dose can be increased to 10 mg once daily for those tolerating and needing additional glycemic control
Comparators	SGLT-2 inhibitors Incretins (DPP-4 inhibitors, GLP-1 analogues) Thiazolidinediones Meglitinides Insulin or insulin analogues Alpha-glucosidase inhibitors or Placebo In combination with metformin and a sulfonylurea
Outcomes	**Key efficacy outcomes**[a] • 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** • AEs, SAEs, WDAEs • notable harms: hypoglycemia; urogenital adverse events; renal adverse events; lipid abnormalities, heart failure, ketoacidosis, bone AEs
Study Design	Published and unpublished phase 3 DB RCTs ≥ 12 weeks' duration

A1C = glycated hemoglobin; AE = adverse event; DB = double-blind; DPP-4 = dipeptidyl-peptidase 4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; FPG = fasting plasma glucose; RCT = randomized controlled trial; SAE = serious adverse event; SGLT-2 = sodium-glucose cotransporter 2; T2DM = type 2 diabetes mellitus; WDAE = withdrawal due to adverse event.

[a] Bolded outcomes represent those identified by patients as important in patient-group submission.

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 and daily updates via Ovid; Embase (1974–) 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 Forxiga and dapagliflozin.

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 October 7, 2015. Regular alerts were established to update the search until the CDEC meeting on February 17, 2016. 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 CADTH 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); 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 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 5; there were no excluded studies.

3. RESULTS

3.1 Findings from the literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 2 and described in Section 3.2. There were no excluded studies.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

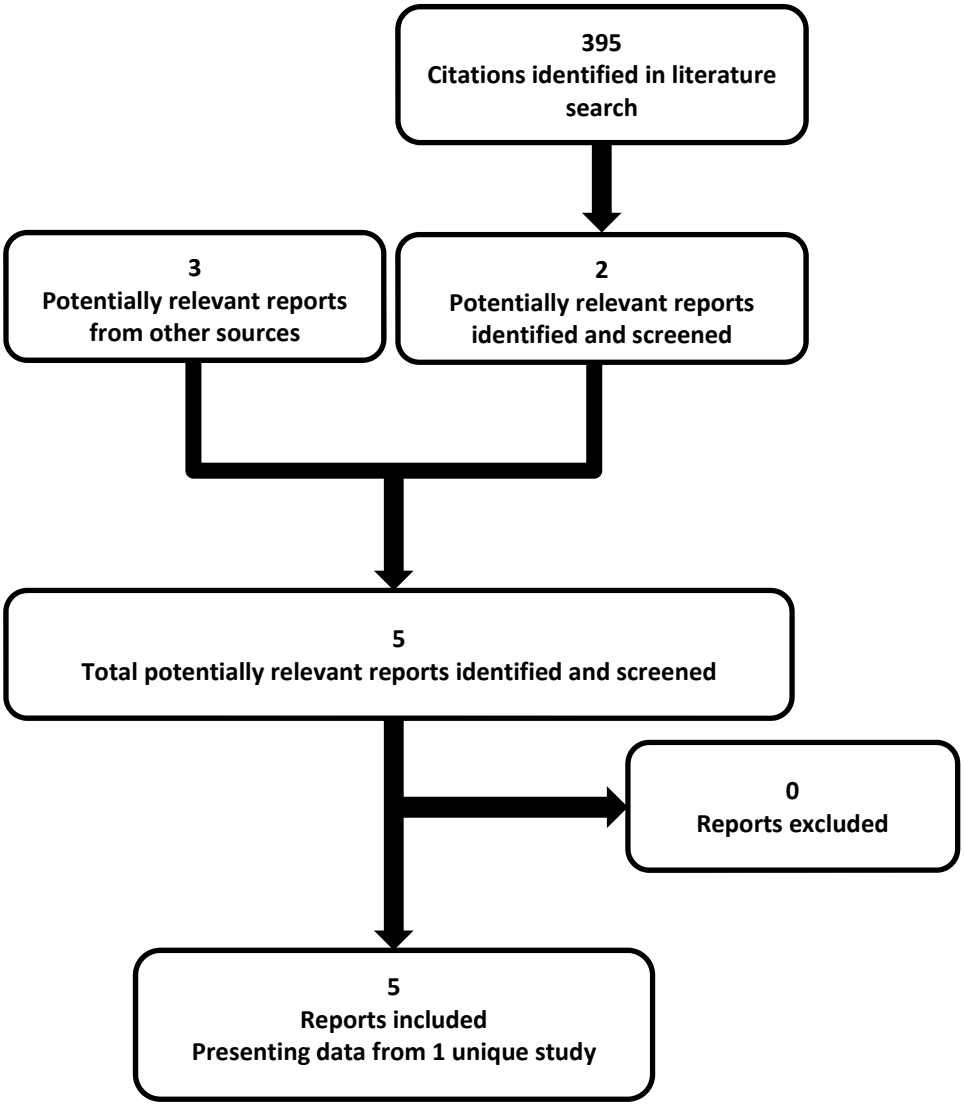


TABLE 5: DETAILS OF INCLUDED STUDIES

		Study D1693C00005 (Study 5)
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	46 centres in 6 countries: Canada (13), Europe
	Randomized (N)	218
	Inclusion Criteria	Adults ≥ 18 years with T2DM; 7.7% ≤ A1C ≤ 11.0% at screening and 7.0% ≤ A1C ≤ 10.5% at randomization; BMI ≤ 45 kg/m^2 at screening; and a stable dose combination therapy of metformin ≥ 1,500 mg/day and a maximum tolerated dose at least half the maximum dose of sulfonylurea ≥ 8 weeks prior to enrollment.
	Exclusion Criteria	T1DM; FPG > 15 mmol/L; history of diabetic ketoacidosis; symptoms of poorly controlled diabetes (e.g., marked polyuria, polydipsia, > 10% weight loss during 3 months prior to enrollment); recent cardiovascular events (e.g., ACS, unstable angina, acute MI, acute stroke, TIA) within 2 months prior to enrollment, congestive heart failure NYHA class IV; SBP ≥ 170 mm Hg and/or DBP ≥ 110 mm Hg at enrollment, SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg at randomization; renal function that precluded treatment with metformin (serum creatinine value ≥ 133 µmol/L for males, ≥ 124 µmol/L for females); severe hepatic insufficiency and/or significant abnormal liver function as defined by AST or ALT > 3x ULN; use of weight loss medication or systemic glucocorticoids within 30 days prior to enrollment; use of antihyperglycemic medications other than metformin or sulfonylurea during the 10 weeks prior to enrollment
DRUGS	**Intervention**	Dapagliflozin 10 mg PO once daily + Metformin ≥ 1,500 mg/day + A sulfonylurea at maximum tolerated dose and ≥ 50% of maximum recommended dose
	Comparator(s)	Placebo + Metformin ≥ 1,500 mg/day + A sulfonylurea at maximum tolerated dose and ≥ 50% of maximum recommended dose
DURATION	**Phase**	
	Single-blind, placebo lead-in	8 weeks
	DB	24 weeks
	Site- and patient-blind extension	28 weeks
	Follow-up	3 weeks
OUTCOMES	**Primary End Point**	Change in A1C from baseline at week 24
	Other End Points	Key secondary: Change in FPG from baseline at week 24 Change in total body weight from baseline at week 24 Proportion of patients achieving A1C < 7.0% at week 24 Change in seated SBP from baseline at week 8

		Study D1693C00005 (Study 5)
		Other secondary: Change in waist circumference from baseline at week 24 EQ-5D scores at baseline and week 24 DTSQ scores at baseline and week 24 Exploratory: SHIELD-WQ-9 scores at week 24 IWQOL-Lite scores at baseline and week 24 Outcomes at week 52
NOTES	**Publications**	Matthaei et al. 2015 (24 weeks)[10] Matthaei et al. 2015 (52 weeks)[11]

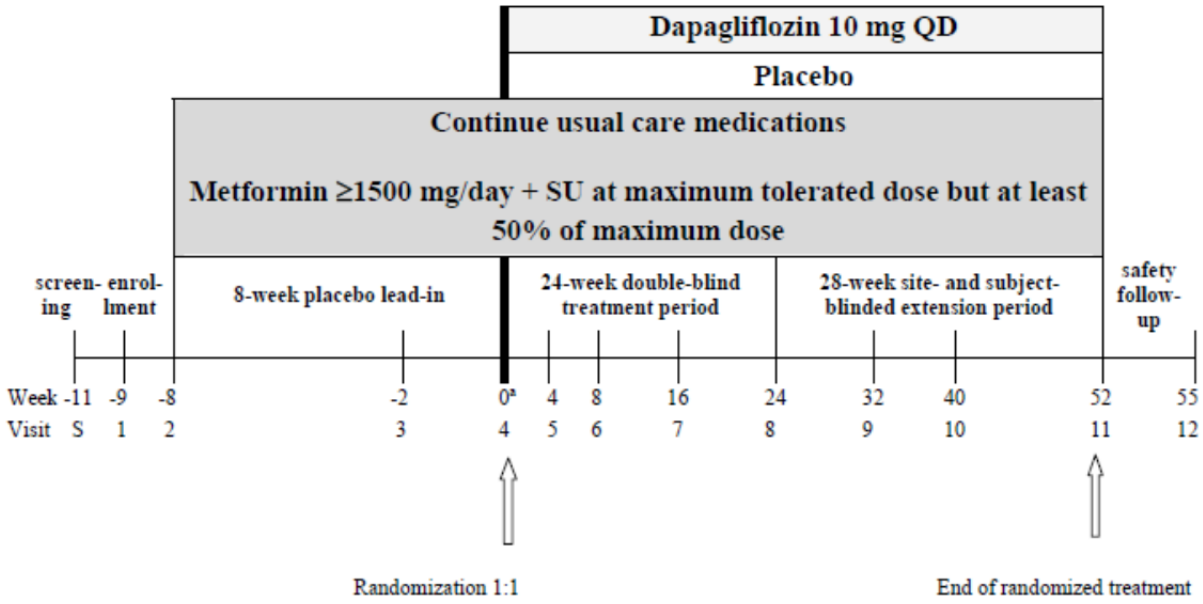
A1C = glycated hemoglobin; ACS = acute coronary syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DB = double-blind; DBP = diastolic blood pressure; DTSQ = Diabetes Treatment Satisfaction Questionnaire; EQ-5D = EuroQoL 5-Dimensions Questionnaire; FPG = fasting plasma glucose; IWQOL-Lite = Impact of Weight on Quality of Life–Lite questionnaire; MI = myocardial infarction; NYHA = New York Heart Association; PO = orally; RCT = randomized controlled trial; SBP = systolic blood pressure; SHIELD-WQ-9 = Study to Help Improve Early Evaluation and Management of Risk Factors Leading to Diabetes Weight Questionnaire–9 items; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; ULN = upper limit of normal.
Source: 24-week and 52-week Clinical Study Reports.[1,2]
Note: One additional report was included (manufacturer's submission).[3]

3.2 Included studies

3.2.1 Description of studies

Study D1693C00005 (Study 5) was an international, multi-centre, placebo-controlled, randomized controlled trial (RCT) with a 24-week double-blind (DB) period and a 28-week site- and patient-blind extension period evaluating the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes mellitus (T2DM) who had inadequate glycemic control (7.0% ≤ glycated hemoglobin [A1C] ≤ 10.5%) on a combination therapy of ≥ 1,500 mg/day metformin and ≥ 50% the maximum dose of a sulfonylurea. In Study 5, patients were randomized in a 1:1 ratio to either dapagliflozin 10 mg or placebo (with a background of metformin and a sulfonylurea) after an eight-week, single-blind, placebo lead-in period. After the 28-week extension period, there was a three-week safety follow-up period.

FIGURE 2: SCHEMATIC FOR STUDY 5



QD = once daily.
Source: 24-week and 52-week Clinical Study Reports.[1,2]

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients were included if they had a diagnosis of T2DM and were on a stable dose of at least 1,500 mg once-daily metformin and a maximum tolerated dose at least half the maximum dose of a sulfonylurea (according to local label) for at least eight weeks prior to enrollment. Patients had to have an A1C value between 7.7% and 11.0% at screening, and between 7.0% and 10.5% at randomization. Patients were excluded if they had symptoms of poorly controlled diabetes, a recent history of cardiovascular events (acute coronary syndrome, unstable angina, myocardial infarction, stroke, or transient ischemic attack) within two months prior to enrollment, and renal function that precluded treatment with metformin (serine creatinine value ≥ 133 µmol/L for males, ≥ 124 µmol/L for females).

b) Baseline characteristics

The mean age of patients was 61 years and the majority (> 90%) of patients were Caucasian (Table 6). There was a greater proportion of males in the placebo group than in the dapagliflozin group (55.6% versus 42.6%). Physical characteristics such as weight and blood pressure were similar between groups. With regards to time since diagnosis, a higher proportion of patients in the dapagliflozin group had a time since diagnosis of three to 10 years compared with those in the placebo group (58.3% versus 50.0%), and a higher proportion of patients in the placebo group had a time since diagnosis greater than 10 years compared with the dapagliflozin group (39.8% versus 34.3%). Patients in the placebo group had a higher fasting plasma glucose (FPG) reading compared with the dapagliflozin group (10.0 mmol/L versus 9.3 mmol/L).

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	Study D1693C00005 (Study 5)	
	Dapagliflozin 10 mg (n = 108)	Placebo (n = 108)
Demographics		
Age, years (SD)	61.1 (9.7)	60.9 (9.2)
Male, n (%)	46 (42.6)	60 (55.6)
Caucasian, n (%)	104 (96.3)	102 (94.4)
Physical characteristics		
Weight, kg (SD)	88.6 (17.6)	90.1 (16.2)
BMI, kg/m^2 (SD)	31.9 (4.8)	32.0 (4.6)
Seated SBP, mm Hg (SD)	134.5 (12.6)	136.4 (14.2)
Seated DBP, mm Hg (SD)	80.4 (9.2)	81.6 (7.9)
Uncontrolled BP (SBP ≥ 130 mm Hg and/or DBP ≥ 80 mm Hg), n (%)	24 (22.2)	23 (21.3)
Disease characteristics		
Time since diagnosis, years (SD) [range]	9.3 (6.5) [0.5 to 32.1]	9.6 (6.2) [0.2 to 27.7]
< 3 years, n (%)	8 (7.4)	11 (10.2)
3 to 10 years, n (%)	63 (58.3)	54 (50.0)
> 10 years, n (%)	37 (34.3)	43 (39.8)
A1C, % (SD)	8.1 (0.9)	8.2 (0.9)
< 8.0%, n (%)	49 (45.4)	42 (38.9)
8.0% to < 9.0%, n (%)	41 (38.0)	46 (42.6)
≥ 9.0%, n (%)	18 (16.7)	20 (18.5)
FPG, mmol/L (SD)	9.3 (2.4)	10.0 (2.4)
eGFR, mL/min/1.73 m^2 (SD)	79.3 (18.1)	81.9 (18.8)
History of CVD, n (%)	91 (84.3)	95 (88.0)
Hypertension only, n (%)	61 (56.5)	63 (58.3)

A1C = glycated hemoglobin; BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; SBP = systolic blood pressure; SD = standard deviation.
Note: Values are means unless otherwise specified.
Source: 24-week and 52-week Clinical Study Reports.[1,2]

3.2.3 Interventions

Patients were randomized 1:1 to dapagliflozin 10 mg or placebo, administered orally once daily. The treatment groups had a background combination therapy regimen of metformin and a sulfonylurea. Patients were to be on a stable dose of background combination therapy for at least eight weeks prior to enrollment, with a metformin dose of at least 1,500 mg/day and a maximum tolerated dose at least half the maximum recommended dose of a sulfonylurea. An eight-week placebo lead-in period was implemented before randomization to dapagliflozin and placebo.

Background antihypertensive medications could not be increased between weeks 1 and 8 unless the patient had a confirmed systolic blood pressure (SBP) ≥ 160 mm Hg or diastolic blood pressure (DBP) ≥ 100 mm Hg. Antihypertensive medications could not be decreased during this time unless the patient had symptomatic hypotension or documented orthostatic hypotension during a study visit. After week 8, changes in antihypertensive medication could be made as needed for appropriate management.

Prohibited medications included antihyperglycemic medications other than metformin or sulfonylurea (unless rescue therapy was needed), weight loss medication, and glucocorticoid treatment.

Glycemic parameters were assessed from visit 5 (week 4) to visit 11 (week 52) to determine whether a patient required rescue therapy. From weeks 4 to 16, rescue therapy could be initiated only if a patient had a confirmed glucose level of > 13.2 mmol/L after an overnight fast. From weeks 16 to 24, rescue therapy could be initiated only if a patient had a confirmed glucose level of > 11.1 mmol/L after an overnight fast. From week 24 to 52, rescue medication could be initiated only if a patient had an A1C value of > 8.0%. Patients had to repeat their self-monitored glucose measurement on the same day and if both results were above the limit, they were to return to the study site within one week to have the parameters measured in the central laboratory to determine whether the patient met rescue criteria. Rescue therapy was administered on top of the study medication, and the first-choice rescue therapy was a dipeptidyl-peptidase 4 (DPP-4) inhibitor. If glycemic control was still inadequate (A1C > 8%) after six months of DPP-4 inhibitor treatment, or if DPP-4 inhibitors were poorly tolerated or unavailable in the country, insulin was considered as a rescue therapy. Patients who had inadequate glycemic control after six months despite a maximum tolerated dose of oral antihyperglycemic rescue therapy, and for whom insulin was considered but not utilized for investigator-determined reasons, had to be discontinued from the study. For patients receiving insulin as rescue medication, an up-titration step was considered instead of study discontinuation. During the 24-week double-blind period, a greater proportion of patients received rescue medication in the placebo group compared with the dapagliflozin group (9.3% versus 0%) (Table 7). During the 52-week period, a greater proportion of patients in the placebo group received rescue medication compared with the dapagliflozin group (44.4% versus 9.3%), with the most common rescue medication administered being a DPP-4 inhibitor (Table 8).

TABLE 7: USE OF RESCUE MEDICATION DURING 24-WEEK DOUBLE-BLING PERIOD

	Study D1693C00005 (Study 5)	
	Dapagliflozin 10 mg (n = 108)	Placebo (n = 108)
Rescue medication, n (%)	0	10 (9.3)

Source: 24-week Clinical Study Report.[2]

TABLE 8: USE OF RESCUE MEDICATION DURING 24-WEEK DOUBLE-BLIND PERIOD + 28-WEEK EXTENSION

	Study D1693C00005 (Study 5)	
	Dapagliflozin 10 mg (n = 108)	Placebo (n = 108)
Rescue medication, n (%)	10 (9.3)	48 (44.4)
DPP-4 inhibitor	9 (8.3)	39 (36.1)
Insulin	1 (0.9)	6 (5.6)
DPP-4 inhibitor + insulin	0	3 (2.8)

DPP-4 = dipeptidyl-peptidase 4.
Source: Clinical Study Report.[1]

3.2.4 Outcomes

a) Glycated hemoglobin and fasting plasma glucose

Patients were to visit the clinic on a fasting stomach in the morning and were instructed not to eat or drink anything except water for 12 hours before. Patients were also instructed not to take investigational product or concomitant medications that morning. Blood samples were taken and analyzed by a central laboratory according to procedures described in the Laboratory Manual that was

distributed to each study site. Change from baseline in A1C at week 24 was the primary efficacy end point. Change from baseline in FPG at week 24 was a key secondary end point.

b) Blood pressure

SBP and DBP measurements were to be taken after the patient had been sitting or resting for at least five minutes and before blood samples were taken. Blood pressure was to be measured three times each, two minutes apart on both arms, and all readings were recorded. The arm with the highest mean seated blood pressure readings was the one used for all subsequent readings. Change from baseline in SBP at eight weeks was assessed as a key secondary end point.

c) Health-related quality of life and patient satisfaction

Health-related quality of life (HRQoL) was assessed using the EuroQol 5-Dimensions Questionnaire (EQ-5D). The descriptive system of 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. This is completed by applying preference weights elicited from general population samples to health states. The scores can range from below 0 (worse than death) to 100%, with higher scores representing better perceived health. The second component of EQ-5D is a visual analogue scale (VAS), which asks patients to rate their health from 0 to 100 (0 represents worst imaginable health state and 100 represents best imaginable health). A minimal clinically important difference (MCID) specific to diabetes mellitus for EQ-5D has not been identified, but has ranged from 0.033 to 0.074 in other conditions (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). In Study 5, EQ-5D scores were assessed at baseline and after 24 weeks as a secondary outcome.

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was used to assess patient satisfaction with treatment and perception of change in hyperglycemia and hypoglycemia. The DTSQ has two versions that have eight items each: the DTSQ original status version (DTSQs) and the DTSQ change version (DTSQc). The DTSQc instructions and response options differ from those of the DTSQs, as the relative change in satisfaction is assessed instead of a measure of absolute satisfaction. Higher DTSQs scores indicate greater satisfaction with treatment (range 0 to 36). No MCID was identified for the DTSQs or DTSQc (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). In Study 5, the DTSQs was assessed at baseline and at week 24, and the DTSQc was used at week 52 (end of treatment). DTSQs scores at baseline and week 24 were assessed as a secondary outcome.

The Impact of Weight on Quality of Life–Lite questionnaire (IWQOL-Lite) is a 31-item measure assessing HRQoL in overweight or obese individuals. IWQOL-Lite consists of scores on five dimensions: physical function (11 items); self-esteem (seven items); sexual life (four items); public distress (five items); and work (four items). In addition, there is a global score that is the sum of scale scores. Patients rate items with respect to the past week from “never true” to “always true”. Scores range from 0 to 100, with higher scores indicating poorer quality of life. An MCID for IWQOL-Lite in patients with T2DM was not identified, but typically ranges from 7 to 12 in other conditions (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). IWQOL-Lite was assessed as an exploratory outcome at baseline, at week 24, and at week 52.

c) Hypoglycemic events

Patient self-monitoring of FPG was performed at least every second day between visit 2 and visit 8, and at least once a week between visit 8 and visit 11. A major hypoglycemic event was defined as a symptomatic event requiring external assistance due to severe impairment in consciousness or

behaviour, with a capillary or plasma glucose value < 3.0 mmol/L and prompt recovery after glucose or glucagon administration. A minor hypoglycemic event was defined as either a symptomatic episode with a capillary or plasma glucose measurement < 3.5 mmol/L regardless of the need for external assistance or an asymptomatic capillary or plasma glucose measurement < 3.5 mmol/L that does not quality as a major episode.

3.2.5 Statistical analysis

A sample size of 216 patients (108 patients per group) was planned to provide 90% power at a significance level of 0.050 to detect a difference of 0.5% between dapagliflozin versus placebo for mean change in A1C from baseline to week 24, assuming that 5% of patients would not be evaluable in the full analysis set. A standard deviation of 1.1% was selected based on a phase 2 dapagliflozin study and historical data from other diabetes programs.

The primary end point was the mean change in A1C from baseline to week 24. The statistical model used for the primary analysis was a longitudinal repeated measures analysis using "direct likelihood" with fixed categorical effects of treatment, week, treatment-by-week interaction, as well as the continuous fixed covariates of baseline and baseline-by-week interaction. Data for scheduled time points up to week 24 prior to rescue were included in the analysis. If a measurement was missing at week 24 for the primary end point, no imputation was performed. The treatment group comparison between dapagliflozin and placebo at week 24 was performed at the two-sided 0.05 confidence level. Results were summarized using least squares mean estimates, standard errors (SEs), and two-sided 95% confidence intervals (CIs). Other continuous variables were analyzed using an analysis of covariance (ANCOVA) model with treatment group as an effect and baseline value as a covariate. For the ANCOVA model, the last observation carried forward (LOCF) method was used to account for missing data in the full analysis set (FAS), where analyses were based on measurements available at the specified time point or the last post-baseline measurement prior to the time point, if no measurement was available. Unless otherwise specified, if a patient initiated rescue medication, the last value taken on or before the first rescue dose was used for analysis. The original protocol stated that all continuous variables were to be analyzed with an ANCOVA model, but the analyses for the primary end point were changed to a longitudinal repeated measures analysis before unblinding of study data, to align with the National Academy of Sciences 2010 recommendations for missing data report.[12]

A hierarchical closed testing procedure was used for primary and key secondary end points, testing each treatment comparison at a two-sided significance level of 0.050. If superiority of dapagliflozin versus placebo was demonstrated for the primary end point, key secondary end points were tested in the following order:

- change in FPG from baseline to week 24
- change in total body weight from baseline to week 24
- proportion of patients achieving A1C < 7.0% at week 24
- change in seated SBP from baseline to week 8.

At any step of the testing procedure, if the null hypothesis was not rejected, the testing was to stop.

To analyze the proportion of patients achieving A1C < 7.0%, the probability of response for each treatment group was modelled using a logistic regression model with A1C value at baseline as a covariate, if there were at least five responders on average by treatment group. Treatment group estimates of response rate were then obtained by integrating each group's modelled probability of response over the observed distribution of covariates (combined across groups). The difference in

response rate between treatment groups was presented along with the 95% CI. If there were fewer than five responders on average by treatment group, unadjusted proportions and difference between unadjusted proportions, exact 95% CIs, and *P* values from Fisher's exact test were provided.

Subgroup analyses for the primary efficacy end point (change from baseline to week 24 in A1C) were conducted for the following: gender, age, female sex, baseline body mass index (BMI), race, ethnicity, region, baseline A1C, and baseline estimated glomerular filtration rate (eGFR). Significant treatment-by-subgroup interaction was defined as $P < 0.05$. Subgroups were analyzed using the longitudinal repeated measures analysis model.

Efficacy outcomes at 52 weeks were considered exploratory. For the results presented at 52 weeks (end of the 28-week extension), the longitudinal repeated measures analysis was used for all continuous end points and missing data were not imputed and considered as not reported. Data for scheduled time points up to week 52 prior to rescue were included in the analysis. Unlike the week 24 analysis, ANCOVA with LOCF was not used for continuous variables.

a) Analysis populations

In Study 5, the following data sets were defined.

Full analysis set: All randomized patients who received at least one dose of study medication during the 24-week DB period who had a non-missing baseline value and at least one post-baseline value for at least one efficacy variable to be analyzed at week 24. Analyses were performed according to the treatment patients were randomized to receive.

Per-protocol analysis set: A subset of patients from the FAS who did not violate the terms of the protocol.

Safety analysis set: All randomized patients who received at least one dose of study medication during the 24-week DB period and who provided any safety records. Analyses were performed according to the treatment patients actually received.

3.3 Patient disposition

Discontinuations between the dapagliflozin and placebo groups were balanced, with the most common reason for discontinuation being an adverse event (AE) or incorrect enrollment, meaning patients did not meet all inclusion and exclusion criteria (Table 9).

TABLE 9: PATIENT DISPOSITION

	Study D1693C00005 (Study 5)			
	24-week DB period		28-week extension period	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
Enrolled, N	311			
Randomized, N	219[a]			
Treated, N (%)	109 (100)	109 (100)		
Discontinued, N (%)	8 (7.3)	8 (7.3)	5 (4.6)	4 (3.7)
Adverse event	1 (0.9)	3 (2.8)	1 (0.9)	0
Incorrect enrollment[b]	3 (2.8)	2 (1.8)	0	1 (0.9)
Non-compliance	0	0	1 (0.9)	0
Not meeting study criteria	0	0	2 (1.8)	0
Withdrew consent	2 (1.8)	0	0	1 (0.9)
Other	2 (1.8)	3 (2.8)	1 (0.9)	2 (1.8)
FAS, N	108 (99.1)	108 (99.1)	108 (99.1)	108 (99.1)
PP, N	105 (96.3)	107 (98.2)	-	-
Safety, N	109 (100)	109 (100)	109 (100)	109 (100)

DB = double-blind; FAS = full analysis set; PP = per-protocol.
[a] One patient died during the placebo lead-in phase.
[b] Patients did not meet all inclusion and exclusion criteria.
Source: 24-week and 52-week Clinical Study Reports.[1,2]

3.4 Exposure to study treatments

The extent of exposure was similar between groups in the 24-week DB phase and was consistent with the length of treatment (Table 10). Similar results were seen for the entire 52-week treatment period.

The doses of metformin taken throughout the study were generally aligned with the requirement for a minimum dose of 1,500 mg/day, with mean daily doses exceeding 2,000 mg/day for both groups (Table 11). With regards to sulfonylurea dosing, the majority of patients were on gliclazide or glimepiride, and a smaller proportion of patients were on glyburide (Table 12). The dosing was generally consistent with study requirements, which specified that patients were to be on a dose that was at least half the recommended maximum dose.

Concomitant medication use was balanced between groups except for angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs), where a greater proportion of patients in the placebo group were using an ARB or ACEI compared with the dapagliflozin group during the 24-week DB period (76.1% versus 68.8%) (Table 12).

TABLE 10: EXTENT OF EXPOSURE TO STUDY DRUG — SAFETY ANALYSIS SET

	Study D1693C00005 (Study 5)		Study D1693C00005 (Study 5)	
	24-week DB period		24-week DB period + 28-week extension period	
	Dapagliflozin 10 mg (n = 109)	Placebo (n = 109)	Dapagliflozin 10 mg (n = 109)	Placebo (n = 109)
Mean exposure, days (SD)	161.9 (26.5)	159.3 (34.8)	337.3 (82.0)	332.3 (89.8)

DB = double-blind; SD = standard deviation.
Source: 24-week and 52-week Clinical Study Reports.[1,2]

TABLE 11: SUMMARY OF DOSES OF METFORMIN AND SULFONYLUREA — SAFETY ANALYSIS SET

Most Common Daily Dose, mg	Study D1693C00005 (Study 5)		Study D1693C00005 (Study 5)	
	24-week DB period		24-week DB period + 28-week extension period	
	Dapagliflozin 10 mg (n = 109)	Placebo (n = 109)	Dapagliflozin 10 mg (n = 109)	Placebo (n = 109)
Metformin				
Mean (SD)	2,177.9 (528.0)	2,147.7 (478.2)	2,170.1 (528.8)	2,147.7 (478.2)
Median [range]	2,000 [1,000 to 3,400]	2,000 [1,500 to 3,000]	2,000 [1,000 to 3,400]	2,000 [1,500 to 3,000]
Gliclazide				
N	41	51	41	51
Mean (SD)	116.5 (79.6)	114.7 (90.2)	115.0 (80.1)	114.7 (90.2)
Median [range]	90 [30 to 320]	60 [30 to 320]	90 [30 to 320]	60 [30 to 320]
Glimepiride				
N	52	46	52	46
Mean (SD)	4.2 (1.8)	4.2 (1.2)	4.2 (1.8)	4.2 (1.2)
Median [range]	4 [1 to 12]	4 [3 to 8]	4 [1 to 12]	4 [3 to 8]
Glyburide				
N	16	12	16	12
Mean (SD)	14.3 (6.5)	12.8 (5.0)	13.3 (6.7)	12.6 (5.2)
Median [range]	13.8 [5 to 30]	10.5 [7 to 23]	11.5 [5 to 30]	10.3 [7 to 23]

DB = double-blind; SD = standard deviation.
Source: 24-week and 52-week Clinical Study Reports.[1,2]

TABLE 12: SUMMARY OF CONCOMITANT MEDICATION USE — SAFETY ANALYSIS SET

Concomitant Medication, N (%)	Study D1693C00005 (Study 5)		Study D1693C00005 (Study 5)	
	24-week DB period		24-week DB period + 28-week extension period	
	Dapagliflozin 10 mg (n = 109)	Placebo (n = 109)	Dapagliflozin 10 mg (n = 109)	Placebo (n = 109)
Antihypertensives	89 (81.7)	95 (87.2)	90 (82.6)	97 (89.0)
ARB and/or ACEI	75 (68.8)	83 (76.1)	76 (69.7)	84 (77.1)
Lipid-lowering medication	74 (67.9)	72 (66.1)	75 (68.8)	74 (67.9)
Diuretics	51 (46.8)	47 (43.1)	51 (46.8)	48 (44.0)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DB = double-blind.
Source: 24-week and 52-week Clinical Study Reports.[1,2]

3.5 Critical appraisal

3.5.1 Internal validity

In Study 5, randomization was performed centrally using an interactive web or voice response system; no member of the extended study team had access to the randomization scheme except for the persons responsible for packaging study medication. Randomization was not stratified by any baseline variables. Despite randomization, baseline characteristics were not balanced between the dapagliflozin and placebo groups. There was a greater proportion of males in the placebo group compared with the dapagliflozin group (55.6% versus 42.6%), and there were differing proportions of patients in the time since diagnosis of T2DM of less than three years, three to 10 years, and more than 10 years. In addition, the proportion of patients taking a concomitant ARB or ACEI was higher in the placebo group compared with the dapagliflozin group (76.1% versus 68.8%), further highlighting the imbalance and suggesting that background treatment or severity of hypertension may be different between groups. The FPG levels at baseline were higher in the placebo group compared with the dapagliflozin group (10.0 mmol/L versus 9.3 mmol/L). As the change in baseline at week 24 in FPG was a key secondary end point, it is concerning that baseline values were not equal. The clinical expert consulted for this review noted that it would be more difficult to decrease plasma glucose levels at a lower baseline FPG, so this would have biased against dapagliflozin. Since randomization did not ensure balanced patient characteristics between treatment groups, Study 5 is at high risk of bias and all study results need to be interpreted with caution due to measured and unmeasured confounders that may have contributed to differences observed between groups. Any adjustments made would not be able to account for these differences.

A hierarchical testing procedure was used to account for multiple comparisons among 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. Outcomes outside of the testing hierarchy need to be interpreted with caution.

The primary analysis was based on an FAS, which included patients who received at least one dose of study medication during the 24-week DB period who have a non-missing baseline value and at least one post-baseline value for at least one efficacy variable to be analyzed at week 24. This is not a true intention-to-treat (ITT) analysis, where all patients assigned to a given group would have been included in the analysis, regardless of whether they had received study drug. However, few patients were excluded from the analysis using this approach, and therefore it was unlikely to have an impact on the results.

A longitudinal repeated mixed model (LRMM) was used for the primary end point, change from baseline in A1C at 24 weeks, and all continuous end points at 52 weeks. In the LRMM, only patients in the FAS with non-missing baseline and week 24 or week 52 values were included in the analysis and data after rescue was excluded. As more patients in the placebo group received rescue than in the dapagliflozin group, there were fewer patients contributing to the model in the placebo group than in the dapagliflozin group. The potential impact of missing data during scheduled time points on the overall study results is uncertain. A LOCF method was used to impute missing data for continuous outcomes at 24 weeks other than the primary efficacy outcome, including all four key secondary end points. This is a conservative method, but may still lead to introduction of bias. The manufacturer did conduct sensitivity analyses using observed data, and confirmed the findings of the primary analysis.

Modelling of the proportion of patients achieving A1C < 7%, as opposed to using the actual values observed in the study period, is of questionable validity and may have biased the study results for this specific end point.

The included studies were not powered to assess key outcomes such as weight, FPG, blood pressure, or for harms outcomes such as hypoglycemia.

Subgroup analyses were presented for a number of subgroups, and analyses of results versus placebo were presented; however, there does not appear to have been an adjustment made for multiple comparisons. Therefore, no conclusions should be drawn from such analyses, as they are prone to type 1 error; they should be considered as hypothesis-generating only.

3.5.2 External validity

There was only one included study in this review, with a relatively small sample size (N = 218). Although Study 5 was adequately powered to achieve its primary outcome, this was still a relatively small study considering how common T2DM is, how many patients struggle to achieve adequate glycemic control, and the rarity of some of the key AEs. There were no studies with an active comparator, making it difficult to assess the relative efficacy and harms of dapagliflozin versus other comparators.
The dosing regimen used for dapagliflozin was 10 mg once daily, which was selected based on safety, efficacy, and pharmacokinetic data from phase 1 and 2 studies. In the Health Canada–approved product monograph, the recommended starting dose of dapagliflozin is 5 mg once daily, which can be increased to 10 mg once daily for patients requiring additional glycemic control. The clinical expert consulted for this review noted that patients would be started on a 5 mg dose first, as per the product monograph. Therefore, the dosing regimen used in Study 5 may not be reflective of what is done in clinical practice. In addition, the doses of metformin and sulfonylureas used by some patients were on the high end and may have exceeded the maximum recommended dosing regimen in Canada, which would limit the generalizability of the study results. Specifically, the maximum recommended daily dose for the background therapies are as follows: metformin 2,550 mg; gliclazide 320 mg; glimepiride 8 mg; and glyburide 20 mg.[13-16] The maximum doses taken of background therapies in Study 5 were as follows: metformin 3,400 mg; gliclazide 320 mg; glimepiride 12 mg; and glyburide 30 mg.

Baseline characteristics were representative of a population with advanced disease. Thirteen of the 46 study centres were from Canada, with the remaining centres from European countries. This may limit generalizability of the results to the Canadian population, as the majority of patients were European. Due to restricted inclusion criteria, patients with impaired renal function and recent cardiovascular events were excluded, limiting generalizability of results to this patient population. The eight-week placebo run-in phase may have excluded additional patients, resulting in a selective population that may

not be as generalizable to the broader T2DM population. As well, most patients with cardiovascular disease had only hypertension, suggesting the vast majority of patients were free of a history of major cardiovascular events.

Another impact on the generalizability to the Canadian population includes the dosing of the background therapies. The high end of doses used in the trials of metformin, gliclazide, and glimepiride all exceed the Health Canada–approved dosage maximum. Only the maximum dose of glyburide used in the study is consistent with the Health Canada–approved maximum dose. As well, the trial does not differentiate modified-release preparations of gliclazide with immediate-release preparations, which are dosed differently.

Study 5 was not designed to assess key clinical outcomes such as morbidity and mortality due to its relatively small size and short follow-up. A1C is a widely used surrogate marker for glycemic control, and was therefore used as the primary end point of Study 5.

Study 5 was not powered to assess quality of life, and reported these only as exploratory outcomes. Patient input indicated that quality of life is an important issue with type 2 diabetes.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 4). See APPENDIX 3: DETAILED OUTCOME DATA for detailed efficacy data. Efficacy outcomes at the end of the 28-week extension (52 weeks) were exploratory and are presented descriptively in Table 17 and Table 18, but are not highlighted in this section due to different statistical methods used from the 24-week analysis.

3.6.1 Mortality

No deaths were reported during the 24-week DB period and the 28-week extension period. One patient died suddenly during the eight-week placebo lead-in phase of the study

3.6.2 Morbidity

Morbidity was not specifically assessed in this study.

3.6.3 Glycated hemoglobin

The primary efficacy end point of Study 5 was the change in A1C from baseline to week 24. There was a statistically significant reduction from baseline in A1C at week 24 in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo –0.69; 95% CI, –0.89 to –0.49; $P < 0.0001$) (Table 13). Sensitivity analyses were performed including data after rescue, using ANCOVA methodology with baseline value as a covariate, and including only patients with non-missing baseline and week 24 values, and results were similar to the primary analysis.

The proportion of patients achieving A1C < 7% at week 24 was a key secondary end point in Study 5, and was statistically significantly greater in the dapagliflozin group compared with the placebo group (33.3% versus 10.2%; adjusted mean difference versus placebo 20.7; 95% CI, 10.7 to 30.6; $P < 0.0001$).

Subgroup analyses of primary end point

Subgroup analyses of change from baseline in A1C at week 24 suggested a statistically significant interaction ($P = 0.0038$). Patients with a higher baseline A1C (≥ 9%) had a larger reduction in A1C with dapagliflozin compared with placebo (adjusted mean change versus placebo –0.82; 95% CI, –1.17 to

–0.47) when compared with patients with a baseline A1C ≥ 8% and < 9% (adjusted mean change versus placebo –0.64; 95% CI, –0.87 to –0.41) and when compared with patients with a baseline A1C < 8% (adjusted mean change versus placebo –0.36; 95% CI, –0.59 to –0.14) (Table 15).

There was no statistically significant interaction from the subgroup analysis based on baseline eGFR (Table 15). However, patients with moderate renal impairment (eGFR 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2) had a smaller reduction in A1C with dapagliflozin compared with placebo (adjusted mean change versus placebo –0.40; 95% CI, –0.83 to 0.02), compared with patients with normal renal function (eGFR ≥ 90 mL/min/1.73m^2) (adjusted mean change versus placebo –0.74; 95% CI, –1.02 to –0.47). Other subgroup analyses that demonstrated a statistically significant interaction (P < 0.05) included age (greater reduction in younger patients) and region (greater reduction in patients from North America). No subgroup analysis was performed based on duration of disease.

3.6.4 Fasting plasma glucose

The change in FPG from baseline to week 24 was a key secondary end point in Study 5. There was a statistically significantly greater reduction from baseline in FPG at week 24 in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo –1.86 mmol/L; 95% CI, –2.39 to –1.32; P < 0.0001) (Table 13).

3.6.5 Body weight

The change in body weight from baseline to week 24 was a key secondary end point in Study 5. There was a statistically significantly greater reduction from baseline in body weight at week 24 in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo –2.07 kg; 95% CI, –2.79 to –1.35; P < 0.0001) (Table 13).

3.6.6 Blood pressure

The change in seated SBP from baseline to week 8 was a key secondary end point in Study 5. Medication for high blood pressure was not allowed to change in the first eight weeks of DB study medication. There was a statistically significantly greater reduction from baseline in SBP at week 8 in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo –3.76 mm Hg; 95% CI, –7.05 to –0.48; P = 0.0250) (Table 13). This difference was maintained at week 24 (adjusted mean change versus placebo –4.00 mm Hg; 95% CI, –7.14 to –0.87; P = 0.0125), though this was a secondary end point not included in the testing hierarchy.

The change from baseline in DBP at week 24 was statistically significantly greater in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo –2.20 mm Hg; 95% CI, –3.99 to –0.42; P = 0.0158), though this end point was not included in the testing hierarchy.

3.6.7 Quality of life

Patient-reported outcomes reported at 24 weeks were considered exploratory analyses and not included in the statistical hierarchy. Quality of life was assessed using EQ-5D, and there were no statistically significant differences in mean change from baseline between the dapagliflozin and placebo groups in both the EQ-5D VAS and the EQ-5D index score at week 24 (Table 16).

DTSQs was used to assess patient satisfaction with treatment and perception of change in hyperglycemia and hypoglycemia, with higher scores indicating greater satisfaction with treatment (range 0 to 36). There was a slightly greater increase in DTSQs score from baseline at week 24 in the dapagliflozin group compared with the placebo group (adjusted mean change versus placebo 1.4; 95%

CI, 0.1 to 2.8; P = 0.0393), but the clinical importance of this change is uncertain, and as this was not part of the hierarchical testing, the statistical significance is also uncertain.

IWQOL-Lite was another questionnaire used to assess quality of life in Study 5. Higher scores indicate poorer quality of life (range 0 to 100). No differences were seen in change from baseline at week 24 in IWQOL-Lite Total Score between the dapagliflozin and placebo groups, and in the individual dimensions of physical function, self-esteem, sexual life, and work. The dimension of public distress showed a slight increase in the dapagliflozin group compared with placebo (adjusted mean change versus placebo 4.7; 95% CI, 0.8 to 8.7; *P* = 0.0178), but the clinical and statistical significance of this is uncertain.

3.6.8 Other efficacy outcomes

Health resource utilization was not assessed in this study.

TABLE 13: KEY EFFICACY OUTCOMES — FULL ANALYSIS SET

	Study D1693C00005 (Study 5)	
	24-week DB period	
	Dapa 10 mg (n = 108)	Placebo (n = 108)
Mortality		
Deaths, n (%)	0	0
A1C, %		
Baseline mean (SD)	8.08 (0.91)	8.24 (0.87)
N[a]	100	93
Adjusted mean change (SE), week 24	–0.86 (0.07)	–0.17 (0.07)
Adjusted mean change vs. placebo (95% CI)[b]	–0.69 (–0.89 to –0.49)	
P value	< 0.0001	
Patients with A1C < 7.0%, n (%)	36 (33.3)	11 (10.2)
Adjusted mean % difference vs. placebo (95% CI)	20.7 (10.7 to 30.6)	
P value	< 0.0001	
FPG, mmol/L		
Baseline mean (SD)	9.29 (2.40)	10.02 (2.40)
N[c]	108	107
Adjusted mean change (SE), week 24	–1.90 (0.19)	–0.04 (0.19)
Adjusted mean change vs. placebo (95% CI)[d]	–1.86 (–2.39 to –1.32)	
P value	< 0.0001	
Body weight, kg		
Baseline mean (SD)	88.57 (17.58)	90.07 (16.18)
N[c]	108	108
Adjusted mean change (SE), week 24	–2.65 (0.26)	–0.58 (0.26)
Adjusted mean change vs. placebo (95% CI)[d]	–2.07 (–2.79 to –1.35)	
P value	< 0.0001	
SBP, mm Hg		
Baseline mean (SD)	134.70 (12.69)	136.31 (14.37)
N[c]	105	105
Adjusted mean change (SE), week 8	–4.04 (1.18)	–0.27 (1.18)
Adjusted mean change vs. placebo (95% CI)[d]	–3.76 (–7.05 to –0.48)	

	Study D1693C00005 (Study 5)	
	24-week DB period	
	Dapa 10 mg (n = 108)	Placebo (n = 108)
P value	0.0250	
N[c]	108	106
Adjusted mean change (SE), week 24	–5.30 (1.12)	–1.29 (1.13)
Adjusted mean change vs. placebo (95% CI)[d]	–4.00 (–7.14 to –0.87)	
P value	0.0125	
DBP, mm Hg		
Baseline mean (SD)	80.39 (9.17)	81.75 (7.75)
N[c]	108	106
Adjusted mean change (SE), week 24	–2.92 (0.64)	–0.72 (0.64)
Adjusted mean change vs. placebo (95% CI)[d]	–2.20 (–3.99 to –0.42)	
P value	0.0158	

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; Dapa = dapagliflozin; DB = double-blind; DBP = diastolic blood pressure; FAS = full analysis set; FPG = fasting plasma glucose; LOCF = last observation carried forward; SD = standard deviation; SE = standard error; SBP = systolic blood pressure; vs. = versus.
[a] Number of patients in FAS with non-missing baseline and week 24 values.
[b] Longitudinal repeated measures analysis with fixed categorical effects of treatment, week, treatment-by-week interaction, and the continuous fixed covariates of baseline and baseline-by-week interaction.
[c] Number of patients in FAS with non-missing baseline and week 24 (LOCF) values.
[d] ANCOVA model with treatment group as an effect and baseline value as a covariate.
Source: Clinical Study Reports.[1,2]

3.7 Harms

Only those harms identified in the review protocol are reported below (see Section 2.2., Table 4). See APPENDIX 3: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse events

A total of 48.6% of patients in the dapagliflozin group and 51.4% of patients in the placebo group reported an AE during the 24-week DB period (Table 14). The most common AEs with dapagliflozin were bronchitis, urinary tract infection, and pharyngitis. Over the entire 52-week study period, a total of 69.7% of patients in the dapagliflozin group and 73.4% of patients in the placebo group reported an AE, the most common AE with dapagliflozin being nasopharyngitis.

3.7.2 Serious adverse events

During the 24-week DB period, the proportion of patients reporting a serious adverse event (SAE) was 0.9% in the dapagliflozin group and 5.5% in the placebo group. Over the 52-week study period, 6.4% of patients in the dapagliflozin group and 7.3% of patients in the placebo group reported a SAE. There was no clear pattern of specific SAEs occurring more frequently in any of the groups.

3.7.3 Withdrawals due to adverse events

During the 24-week DB phase, the proportion of patients discontinuing study treatment due to an AE was 1.8% in the dapagliflozin group and 2.8% in the placebo group. During the 28-week extension period, two additional patients discontinued study treatment due to an AE in the placebo group. There was no clear pattern of reason for discontinuing due to an AE in any group.

a) Notable harms

During the 24-week DB period, there was a greater proportion of patients in the dapagliflozin group who had a confirmed AE of hypoglycemia than in the placebo group (12.8% versus 2.8%). Although the proportion of patients experiencing a confirmed hypoglycemic event had increased by the end of extension, the difference in proportions between groups was similar to the 24-week DB phase. Most hypoglycemia episodes were minor, with a plasma glucose level between 3.0 mmol/L and 3.5 mmol/L.

During the 24-week DB period, genital infections were more common with dapagliflozin than placebo (5.5% versus 0%), urinary tract infections were balanced between groups (6.4%), renal impairment was reported in two patients (1.8%) in the dapagliflozin group, and bone fractures were reported in one patient (0.9%) in the placebo group. There was a slight decrease in eGFR in the dapagliflozin group from baseline at weeks 24 and 52, while the placebo group showed a slight increase from baseline. This was accompanied by a slight increase from baseline in serum creatinine levels in the dapagliflozin group at weeks 24 and 52, while the placebo group showed a slight decrease form baseline. The creatinine clearance showed a greater decrease from baseline in the dapagliflozin group at weeks 24 and 52 compared with placebo.

TABLE 14: HARMS — SAFETY ANALYSIS SET

	Study D1693C00005 (Study 5)			
	24-week DB period		24-week DB period + 28-week extension period	
	Dapa 10 mg (n = 109)	Placebo (n = 109)	Dapa 10 mg (n = 109)	Placebo (n = 109)
AEs				
Patients with > 0 AEs, N (%)	53 (48.6)	56 (51.4)	76 (69.7)	80 (73.4)
Common AEs, N (%)				
Bronchitis	5 (4.6)	1 (0.9)	9 (8.3)	3 (2.8)
Urinary tract infection	5 (4.6)	7 (6.4)	8 (7.3)	10 (9.2)
Pharyngitis	3 (2.8)	2 (1.8)	4 (3.7)	3 (2.8)
Nasopharyngitis	2 (1.8)	3 (2.8)	11 (10.1)	7 (6.4)
Hypertension	1 (0.9)	4 (3.7)	5 (4.6)	7 (6.4)
Dizziness	2 (1.8)	2 (1.8)	3 (2.8)	4 (3.7)
SAEs				
Patients with > 0 SAEs, N (%)	1 (0.9)	6 (5.5)	7 (6.4)	8 (7.3)
Common SAEs, N (%)				
COPD	1 (0.9)	0	1 (0.9)	0
WDAEs				
Patients with > 0 WDAEs, N (%)	2 (1.8)	3 (2.8)	2 (1.8)	4 (3.7)
Notable Harms, N (%)				
Hypoglycemia	14 (12.8)	4 (3.7)	17 (15.6)	9 (8.3)
Major episode (requiring external assistance or PG < 3 mmol/L)	0	0	0	0
Minor episode (PG < 3.5 mmol/L)	14 (12.8)	4 (3.7)	17 (15.6)	9 (8.3)
Other episode	0	1 (0.9)	0	1 (0.9)
Cardiac disorder[a]	0	2 (1.8)	0	2 (1.8)
Genital infection[b]	6 (5.5)	0	11 (10.1)	1 (0.9)

	Study D1693C00005 (Study 5)			
	24-week DB period		24-week DB period + 28-week extension period	
	Dapa 10 mg (n = 109)	Placebo (n = 109)	Dapa 10 mg (n = 109)	Placebo (n = 109)
Females	5 (4.6)	0	9 (8.3)	1 (0.9)
UTI[c]	7 (6.4)	7 (6.4)	11 (10.1)	12 (11.0)
Females	4 (3.7)	6 (5.5)	8 (7.3)	11 (10.1)
Renal impairment[d]	2 (1.8)	0	2 (1.8)	0
Mean (SD) change from baseline in eGFR, mL/min/1.73 m^2	–0.5 (1.3)	0.8 (1.2)	–1.3 (1.2)	1.0 (1.2)
Mean (SD) change from baseline in serum creatinine, µmol/L	0.6 (1.2)	–0.7 (0.9)	1.3 (1.0)	–0.7 (1.1)
Mean (SD) change from baseline in creatinine clearance (mL/min)	–4.4 (1.6)	–0.4 (1.4)	–6.4 (1.5)	–0.3 (1.4)
Bone fractures[e]	0	1 (0.9)	0	3 (2.8)
Fasting lipids – adjusted mean per cent change from baseline versus placebo (95% CI), mg/dL				
Total cholesterol	6.65 (1.65 to 11.86)		1.95 (–3.56 to 7.78)	
LDL	13.08 (4.18 to 22.74)		3.86 (–5.98 to 14.73)	
HDL	5.04 (0.95 to 9.29)		6.33 (0.67 to 12.31)	
TG	–7.51 (–16.48 to 2.43)		–10.64 (–22.69 to 3.28)	

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; Dapa = dapagliflozin; DB = double-blind; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PG = plasma glucose; SAE = serious adverse event; SD = standard deviation; TG = triglycerides; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] Included aortic valve stenosis and arrhythmia.

[b] Included vulvovaginal candidiasis, balanitis candida, genital infection, vaginal infection, and vulvovaginitis.

[c] Included UTI, cystitis, and chronic pyelonephritis.

[d] Decreased creatinine renal clearance.

[e] Included facial fracture, foot fracture, and rib fracture.

Source: 24-week Clinical Study Report.[2]

4. DISCUSSION

4.1 Summary of available evidence

One international, multi-centre, manufacturer-sponsored, placebo-controlled DB RCT met inclusion criteria for this review. Study 5 (N = 218) had a 24-week DB period and a 28-week site- and patient-blind extension period that evaluated the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM who had inadequate glycemic control (7.0% ≤ A1C ≤ 10.5%) on a combination therapy of ≥ 1,500 mg/day metformin and ≥ 50% the maximum dose of a sulfonylurea. Patients were randomized in a 1:1 ratio to either dapagliflozin 10 mg or placebo (with a background of metformin and a sulfonylurea) after an eight-week, single-blind, placebo lead-in period. The primary outcome was the change from baseline in A1C at week 24. Key secondary outcomes included the change in FPG and total body weight from baseline at week 24, the proportion of patients achieving A1C < 7.0% at week 24, and the change in seated SBP from baseline at week 8. HRQoL was evaluated using EQ-5D and IWQOL-Lite as secondary and exploratory outcomes outside of a testing hierarchy.

The main limitations of Study 5 included the unsuccessful randomization procedure that caused unbalanced baseline characteristics between the dapagliflozin and placebo groups, including gender, the distribution of time since diagnosis, and baseline FPG levels. Once the integrity of randomization has been compromised, the impact of measured and unmeasured confounders on the outcomes of interest is uncertain and exposes the study to a high risk of bias. In addition, modelling the proportion of patients who achieved target A1C rather than using the observed data is of questionable validity. Study 5 was relatively small and was not designed assess key clinical outcomes such as morbidity, mortality, and HRQoL.

Generalizability to the Canadian population is limited due to the dosing regimen used for dapagliflozin. At 10 mg once daily, this does not adhere to the Health Canada–recommended starting dose of 5 mg once daily before increasing to 10 mg in patients requiring additional glycemic control, nor what would occur in clinical practice, according to the clinical expert consulted by CADTH. Generalizability is also limited due to dose ranges of background therapy that were not consistent with the maximum Health Canada–approved doses.

4.2 Interpretation of results

4.2.1 Efficacy

Results from Study 5 suggest that dapagliflozin 10 mg once daily is associated with a greater reduction in A1C compared with placebo after 24 weeks. These results suggest that dapagliflozin is able to provide additional glycemic control when added to a background of metformin and a sulfonylurea in a population with inadequate glycemic control. The relatively short duration of the trial, including the extension period, limits the ability to assess key clinical outcomes such as mortality and morbidity. As this was a placebo-controlled trial, there is a lack of data regarding the comparative efficacy and safety of dapagliflozin versus other treatments for T2DM inadequately controlled with metformin and a sulfonylurea. The manufacturer submitted a network meta-analysis (NMA) comparing dapagliflozin 10 mg with other drug classes, including DPP-4 inhibitors, glucagon-like peptide-1 (GLP-1) analogues, thiazolidinediones (TZDs), and insulin analogues (see APPENDIX 5: SUMMARY OF INDIRECT COMPARISONS). Despite heterogeneity among the included trials, results from the NMA found no statistically significant differences between dapagliflozin 10 mg and the other drug classes for change in A1C. However, within-class differences were not assessed in the submitted NMA, nor were comparisons to specific drugs.

The mechanism of dapagliflozin depends on filtration of glucose at the glomerulus, therefore it is expected that with reduced renal function, dapagliflozin will be less effective. Subgroup analysis of the primary end point based on renal impairment found that patients with moderate renal impairment (eGFR 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2) had a smaller reduction in A1C with dapagliflozin compared with placebo, when compared with patients with normal renal function (eGFR ≥ 90 mL/min/1.73m^2). However, the test for interaction was not statistically significant. In a long-term study of patients with T2DM and moderate renal impairment, dapagliflozin was found to reduce weight and blood pressure, but not improve glycemic control.[17] In the Health Canada–approved product monograph, it states that dapagliflozin is contraindicated in patients with moderate to severe renal impairment (eGFR < 60 mL/min/1.73m^2).[18]

The dapagliflozin group also showed a statistically significant decrease in FPG levels compared with placebo at week 24 on a background of metformin and a sulfonylurea. However, baseline FPG levels were not balanced between groups, with the placebo group having a higher baseline mean FPG compared with the dapagliflozin group (10.0 mmol/L versus 9.3 mmol/L). The clinical expert consulted for this review noted that it would be more difficult to see a decrease in FPG when starting from a lower baseline level, so this could have biased results against dapagliflozin. However, it is unclear whether this would actually be the case, and considerable caution should be used to interpret these results due to unbalanced baseline characteristics between treatment groups.

The dapagliflozin group showed a statistically significant reduction in weight after 24 weeks compared with placebo, which corresponded to a mean difference of 2.07 kg. This weight difference was maintained until week 52 (1.98 kg). According to the patients, weight gain is associated with several second-line therapies for T2DM (see APPENDIX 1: PATIENT INPUT SUMMARY). Weight loss appears to be a class effect of SGLT2 inhibitors, and has been observed with other SGLT2 inhibitors including canagliflozin and empagliflozin.[19] Results from the manufacturer-submitted NMA suggested that dapagliflozin and GLP-1 analogues were associated with statistically significant reductions in weight compared with placebo, while TZDs and insulin showed statistically significant weight gains compared with placebo (see APPENDIX 5: SUMMARY OF INDIRECT COMPARISONS). In the NMA, dapagliflozin was associated with statistically significant reductions in weight to all drug classes in the network except GLP-1 analogues. As weight is a surrogate marker, there is a challenge in trying to assess the significance of weight loss. In Study 5, the impact of weight on quality of life was assessed using the IWQOL-Lite questionnaire as an exploratory outcome. No significant differences were seen between the dapagliflozin and placebo groups in change from baseline in IWQOL-Lite scores at week 24. EQ-5D was used to assess generic quality of life measures, and no differences were seen in the change from baseline in index score and VAS between groups at 24 weeks.

In Study 5, more than 80% of patients had a history of cardiovascular disease, with approximately 57% of patients having hypertension only. SGLT2 inhibitors increase glucose excretion in the urine, cause osmotic diuresis, and contribute to a modest antihypertensive effect. This was observed in Study 5 through a greater decrease in SBP with dapagliflozin compared with placebo at week 8 (key secondary end point) and week 24 (outside of testing hierarchy), and a smaller decrease in DBP (outside of testing hierarchy). In the manufacturer-submitted NMA, there were no significant differences in change from baseline in SBP with dapagliflozin compared with the other drugs except for bolus insulin, to which dapagliflozin was statistically superior. It is unclear whether the decrease in SBP seen with dapagliflozin will have an effect on cardiovascular outcomes. A study published in 2015 (EMPA-REG OUTCOME; N = 7,020) reported that patients who received empagliflozin had a lower rate of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

compared with patients who received placebo.[20] A multi-centre trial is currently in progress to evaluate the effect of dapagliflozin 10 mg compared with placebo on the incidence of cardiovascular events.[21]

Efficacy outcomes at 52 weeks were considered exploratory and not highlighted in this review due to different statistical methods used, the unbalance in patients contributing to the statistical model between groups. However, results at 52 weeks did not appear to differ from those at 24 weeks, suggesting that efficacy is maintained.

4.2.2 Harms

Overall, the proportion of patients reporting an AE or SAE was balanced between the dapagliflozin and placebo groups. Withdrawals due to adverse events (WDAEs) were low and balanced between groups.

Patients indicated that daily fluctuations in blood glucose were the most important aspect of diabetes to control during the day and overnight, as fluctuations impact their ability to work and interactions with friends and family, and are a source of stress (seeAPPENDIX 1: PATIENT INPUT SUMMARY). Hypoglycemia contributes to fluctuations in blood glucose, and current T2DM therapies including insulin and sulfonylureas are associated with hypoglycemia. As dapagliflozin is used in combination with a sulfonylurea and metformin, and given its mechanism in inhibiting glucose reabsorption, it is expected that there may be an increase in hypoglycemia with dapagliflozin. In Study 5, a higher proportion of patients in the dapagliflozin group had a confirmed AE of hypoglycemia than the placebo group at 24 weeks (12.8% versus 2.8%) and 52 weeks (15.6% versus 8.3%), with most being reported as minor episodes. The manufacturer-submitted NMA examined the incidence of hypoglycemia as a safety event, and there were no differences between dapagliflozin and the other drug classes, though credible intervals were wide and there was considerable heterogeneity in the studies, including differing definitions of hypoglycemia between studies (see APPENDIX 5: SUMMARY OF INDIRECT COMPARISONS).

The Health Canada–approved product monograph states that renal function abnormalities can occur after initiating dapagliflozin, and increases in serum creatinine and decreases in eGFR may also be observed. This was in line with what was observed in this study, though increases and decreases were small. In particular, there was a greater decrease in creatinine clearance from baseline with dapagliflozin compared with placebo at weeks 24 and 52. However, renal impairment was reported in only two patients in the dapagliflozin group.

SGLT2 inhibitors increase urinary glucose concentration, which may provide a favourable environment for the development of urogenital infections. In Study 5, there were six patients in the dapagliflozin group who reported developing a genital infection during the 24-week period, and this number increased to 11 patients over 52 weeks, while one patient developed a genital infection over 52 weeks. Most of these patients were female.

SGLT2 inhibitors have been reported to increase the frequency of bone fractures, with the risk of fracture increasing over time.[22] In Study 5, one patient in the placebo group reported a bone fracture. Bone AEs may not have been observed due to the duration of the study that did not extend beyond 52 weeks.

Post-market safety reviews have identified ketoacidosis as a potential safety issue with dapagliflozin and canagliflozin.[23] No cases of diabetic ketoacidosis were reported in Study 5.

4.3 Potential place in therapy[1]

Dapagliflozin is another drug to be considered as add-on therapy to metformin for type 2 diabetes.[24] However, there are other important therapeutic factors to consider before prescribing dapagliflozin, including renal function, the risk of genital or urinary infections, and any history of bladder cancer. Caution is required to avoid hypotension in patients on loop diuretics, and rarely, euglycaemic ketoacidosis. These factors may limit its usefulness in older patients with an eGFR less than 60 mL/min, a history of UTIs or falls, and who are on a diuretic. Those most likely to benefit are younger patients not on a diuretic whose blood pressure and A1C are over target, and for whom avoidance of weight gain and hypoglycemia are important outcomes, when cost is not a consideration. Given the rising number of younger people with diabetes, this is likely to be a sizable population of patients.

5. CONCLUSIONS

One international, multi-centre, manufacturer-sponsored, placebo-controlled, 24-week DB RCT with a 28-week site- and patient-blind extension met inclusion criteria for this review. Study 5 (N = 218) evaluated the efficacy and safety of dapagliflozin 10 mg once daily in patients with T2DM who had inadequate glycemic control on a combination therapy of metformin and a sulfonylurea. Results from Study 5 suggest that dapagliflozin 10 mg once daily is associated with a statistically significant reduction in A1C, FPG, and weight compared with placebo after 24 weeks. Study 5 was not designed to assess the effect of dapagliflozin on morbidity or mortality due to its relatively short duration and small sample size. Results at the end of the 28-week extension (52 weeks) suggest that effects are maintained from 24 weeks. Several significant limitations introduce a high risk of bias to the trial. Randomization was not successful at evenly distributing baseline characteristics between groups, and large differences were observed at baseline in measured characteristics such as FPG, gender, time since diagnosis, and use of angiotensin-converting enzyme (ACE) inhibitors. Statistical methodology used for the proportion of patients achieving A1C < 7% and outcomes at 52 weeks is of questionable validity, and there is a high proportion of missing data that is not evenly distributed between groups. Generalizability to the Canadian population is limited by the dosing of dapagliflozin and background metformin and sulfonylurea therapy.

The difference in weight reduction was a mean of 2 kg, which could be considered clinically significant in T2DM patients, as other therapies may cause weight gain. In addition, there was a statistically significant reduction in SBP with dapagliflozin compared with placebo after eight weeks, during which antihypertensive therapies were not adjusted, and after 24 weeks. However, this decrease was relatively small (4 mm Hg) and of uncertain clinical significance. HRQoL was assessed using EQ-5D and IWQOL-Lite, and no significant differences were seen in change from baseline to week 24 between the dapagliflozin and placebo groups. AE data were generally balanced between groups.

There was a greater proportion of patients in the dapagliflozin group who reported hypoglycemia episodes and genital infections. Although only two patients in the dapagliflozin group reported a renal impairment, serum creatinine levels were increased and eGFR was decreased compared with baseline at week 24 in the dapagliflozin group, while the opposite was seen in the placebo group.

[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.

There was a lack of direct comparative data of dapagliflozin versus other third-line therapies for T2DM, but a manufacturer-submitted NMA suggests that dapagliflozin had similar A1C and SBP responses compared with other drug classes, and had an increased weight reduction compared with other drug classes with a background of metformin and a sulfonylurea. Long-term safety data and impact on microvascular and macrovascular complications of diabetes remain uncertain.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared 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 elsewhere.[25] 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 glucose were the most important aspect of diabetes to control during the day and overnight. The fluctuations impact the ability to work and interactions 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 glucose 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 glucose with current therapies "the same", "worse", or "much worse". More than 90% of respondents indicated that keeping blood glucose at satisfactory levels and avoiding low blood glucose 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 glucose levels and blood pressure relative to other medications. Several patients who successfully achieved target blood glucose levels on dapagliflozin remarked that they had previously had difficulty lowering their blood glucose 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 glucose 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."

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:	October 7, 2015
Alerts:	Bi-weekly search updates until February 17, 2016
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
fs	Floating subheading
exp	Explode a 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
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.kw	Keywords
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.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 Xigduo* or BMS 512148 or BMS512148 or BMS-512148 or UNII1ULL0QJ8UC or 1ULL0QJ8UC or 461432-26-8 or "461432268" or 461432 26 8 or 46143226 8 or 461432 268).ti,ab,ot,kw,hw,rn,nm. use pmez	267
2	*dapagliflozin/ use oemezd	443
3	(dapagliflozin* or Forxiga* or Farxiga* or Xigduo* or BMS 512148 or BMS512148 or BMS-512148 or UNII1ULL0QJ8UC or 1ULL0QJ8UC or 461432-26-8 or "461432268" or 461432 26 8 or 46143226 8 or 461432 268).ti,ab. use oemezd	588
4	2 or 3	614
5	conference abstract.pt.	1992334
6	4 not 5	346
7	1 or 6	613

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

Dates for Search:	To October 7 2015
Keywords:	Forxiga; dapagliflozin; Diabetes
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: DETAILED OUTCOME DATA

TABLE 15: SUBGROUP ANALYSES FOR PRIMARY END POINT AT 24 WEEKS

Change From Baseline in A1C at Week 24, %	Study D1693C00005 (Study 5)	
	Dapa 10 mg (n = 108)	Placebo (n = 108)
Primary analysis		
Baseline mean (SD)	8.08 (0.91)	8.24 (0.87)
N[a]	100	93
Adjusted mean change (SE)	–0.85 (0.85)	–0.23 (0.80)
Adjusted mean change vs. placebo (95% CI)[b]	–0.69 (–0.89 to –0.49)	
A1C < 8%		
Baseline mean (SD)	7.32 (0.54)	7.44 (0.34)
N[c]	49	42
Adjusted mean change (SE)	–0.79 (0.11)	–0.42 (0.11)
Adjusted mean change vs. placebo (95% CI)[b]	–0.36 (–0.59 to –0.14)	
A1C ≥ 8% and < 9%		
Baseline mean (SD)	8.35 (0.30)	8.37 (0.27)
N[c]	41	46
Adjusted mean change (SE)	–0.68 (0.09)	–0.04 (0.08)
Adjusted mean change vs. placebo (95% CI)[b]	–0.64 (–0.87 to –0.41)	
A1C ≥ 9%		
Baseline mean (SD)	9.51 (0.43)	9.64 (0.52)
N[c]	18	20
Adjusted mean change (SE)	–0.64 (0.18)	0.18 (0.18)
Adjusted mean change vs. placebo (95% CI)[b]	–0.82 (–1.17 to –0.47)	
eGFR ≥ 90 mL/min/1.73 m^2		
Baseline mean (SD)	7.95 (0.91)	8.24 (0.82)
N[c]	29	35
Adjusted mean change (SE)	–0.84 (0.10)	–0.10 (0.09)
Adjusted mean change vs. placebo (95% CI)[b]	–0.74 (–1.02 to –0.47)	
eGFR 60 to < 90 mL/min/1.73 m^2		
Baseline mean (SD)	8.14 (0.87)	8.24 (0.94)
N[c]	67	59
Adjusted mean change (SE)	–0.67 (0.07)	–0.19 (0.07)
Adjusted mean change vs. placebo (95% CI)[b]	–0.49 (–0.68 to –0.29)	
eGFR 30 to < 60 mL/min/1.73 m^2		
Baseline mean (SD)	8.07 (1.18)	8.24 (0.70)
N[c]	12	14
Adjusted mean change (SE)	–0.61 (0.16)	–0.21 (0.15)

Change From Baseline in A1C at Week 24, %	Study D1693C00005 (Study 5)	
	Dapa 10 mg (n = 108)	Placebo (n = 108)
Adjusted mean change vs. placebo (95% CI)[b]	–0.40 (–0.83 to 0.02)	

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; eGFR = estimated glomerular filtration rate; FAS = full analysis set; SD = standard deviation; SE = standard error; vs. = versus.
[a] Number of patients in FAS with non-missing baseline and week 24 values.
[b] Longitudinal repeated measures analysis with fixed categorical effects of treatment, week, treatment-by-week interaction, and the continuous fixed covariates of baseline and baseline-by-week interaction.
[c] Number of patients in FAS with non-missing baseline and at least one post-baseline value.
Source: 24-week Clinical Study Report.[2]

TABLE 16: PATIENT-REPORTED OUTCOMES AT 24 WEEKS

	Study D1693C00005 (Study 5)	
	Dapa 10 mg (n = 108)	Placebo (n = 108)
EQ-5D VAS		
N[a]	105	97
Baseline mean (SD)	74.6 (20.1)	73.1 (20.5)
Adjusted mean change at end of period (SE)	4.2 (1.4)	3.2 (1.4)
Adjusted mean change vs. placebo (95% CI)[b]	0.9 (–2.9 to 4.8)	
P value	0.6315	
EQ-5D Index Score		
N[a]	105	97
Baseline mean (SD)	0.84 (0.16)	0.85 (0.16)
Adjusted mean change at end of period (SE)	–0.01 (0.01)	–0.02 (0.01)
Adjusted mean change vs. placebo (95% CI)[b]	0.01 (–0.03 to 0.05)	
P value	0.6835	
DTSQs Score		
N[a]	93	101
Baseline mean (SD)	30.5 (4.5)	29.6 (5.9)
Adjusted mean change at end of period (SE)	1.5 (0.5)	0.1 (0.5)
Adjusted mean change vs. placebo (95% CI)[b]	1.4 (0.1 to 2.8)	
P value	0.0393	
IWQOL-Lite Total Score		
N[a]	100	94
Baseline mean (SD)	83.5 (13.6)	81.1 (18.1)
Adjusted mean change at end of period (SE)	2.6 (1.3)	1.0 (1.3)
Adjusted mean change vs. placebo (95% CI)[b]	1.6 (–2.1 to 5.3)	
P value	0.3819	
IWQOL-Physical Function Score		
N[a]	104	96
Baseline mean (SD)	76.6 (18.3)	73.3 (22.5)
Adjusted mean change at end of period (SE)	2.5 (1.6)	1.4 (1.7)
Adjusted mean change vs. placebo (95% CI)[b]	1.1 (–3.6 to 5.8)	
P value	0.6441	

	Study D1693C00005 (Study 5)	
	Dapa 10 mg (n = 108)	**Placebo (n = 108)**
IWQOL-Self-Esteem Score		
N[a]	104	96
Baseline mean (SD)	82.8 (20.9)	81.7 (22.6)
Adjusted mean change at end of period (SE)	3.4 (1.6)	2.4 (1.6)
Adjusted mean change vs. placebo (95% CI)[b]	1.1 (–3.4 to 5.6)	
P value	0.6358	
IWQOL-Sexual Life Score		
N[a]	93	89
Baseline mean (SD)	85.9 (22.2)	82.1 (27.9)
Adjusted mean change at end of period (SE)	1.9 (2.1)	1.2 (2.1)
Adjusted mean change vs. placebo (95% CI)[b]	0.7 (–5.2 to 6.7)	
P value	0.8097	
IWQOL-Public Distress Score		
N[a]	101	94
Baseline mean (SD)	93.2 (11.7)	91.6 (17.4)
Adjusted mean change at end of period (SE)	2.8 (1.4)	–2.0 (1.4)
Adjusted mean change vs. placebo (95% CI)[b]	4.7 (0.8 to 8.7)	
P value	0.0178	
IWQOL-Work Score		
N[a]	100	92
Baseline mean (SD)	90.4 (13.8)	89.3 (16.7)
Adjusted mean change at end of period (SE)	1.6 (1.3)	–1.5 (1.4)
Adjusted mean change vs. placebo (95% CI)[b]	3.2 (–0.7 to 7.0)	
P value	0.1059	

CI = confidence interval; Dapa = dapagliflozin; DTSQ = Diabetes Treatment Satisfaction Questionnaire; EQ-5D = EuroQoL 5-Dimensions Questionnaire; FAS = full analysis set; IWQOL = Impact of Weight on Quality of Life–Lite questionnaire; LOCF = last observation carried forward; SD = standard deviation; SE = standard error; VAS = visual analogue scale; vs. = versus.
[a] Number of patients in the FAS with non-missing baseline value and week 24 (LOCF) value, excluding data after rescue.
[b] Longitudinal repeated measures analysis with fixed categorical effects of treatment, week, treatment-by-week interaction, and the continuous fixed covariates of baseline and baseline-by-week interaction.
Source: 24-week Clinical Study Report.[2]

TABLE 17: EFFICACY OUTCOMES AT 52 WEEKS

	Study D1693C00005 (Study 5)	
	Dapa 10 mg (n = 108)	Placebo (n = 108)
Mortality		
Deaths, n (%)	0	0
A1C, %		
Baseline mean (SD)[a]	8.08 (0.91)	8.24 (0.87)
N[b]	84	48
Adjusted mean change (SE), week 52	–0.81 (0.09)	–0.08 (0.11)
Adjusted mean change vs. placebo (95% CI)[c]	–0.74 (–1.01 to –0.46)	
Patients with A1C < 7.0%, n (%)	31 (28.7)	11 (10.2)
Adjusted mean % difference vs. placebo (95% CI)	16.1 (6.3 to 25.9)	
FPG, mmol/L		
Baseline mean (SD)[a]	9.29 (2.41)	10.02 (2.40)
N[b]	83	48
Adjusted mean change (SE), week 52	–1.53 (0.21)	0.65 (0.26)
Adjusted mean change vs. placebo (95% CI)[c]	–2.18 (–2.83 to –1.53)	
Body weight, kg		
Baseline mean (SD)[a]	88.57 (17.58)	90.07 (16.18)
N[b]	86	48
Adjusted mean change (SE), week 52	–2.93 (0.36)	–0.96 (0.42)
Adjusted mean change vs. placebo (95% CI)[c]	–1.98 (–3.07 to –0.88)	
SBP, mm Hg		
Baseline mean (SD)[a]	134.70 (12.69)	136.31 (14.37)
N[b]	85	45
Adjusted mean change (SE), week 52	–1.0 (1.3)	1.1 (1.7)
Adjusted mean change vs. placebo (95% CI)[c]	–2.2 (–6.4 to 2.1)	
DBP, mm Hg		
Baseline mean (SD)[a]	80.39 (9.17)	81.75 (7.75)
N[b]	94	91
Adjusted mean change (SE), week 52	–1.7 (0.8)	–0.3 (0.7)
Adjusted mean change vs. placebo (95% CI)[c]	–1.3 (–3.4 to 0.7)	

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; DB = double-blind; DBP = diastolic blood pressure; FAS = full analysis set; FPG = fasting plasma glucose; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; vs. = versus.

[a] Baseline value was taken at the beginning of the 24-week DB period.

[b] Number of patients in FAS with non-missing baseline and week 52 values.

[c] Longitudinal repeated measures analysis with fixed categorical effects of treatment, week, treatment-by-week interaction, and the continuous fixed covariates of baseline and baseline-by-week interaction.

Source: Clinical Study Report.[1]

TABLE 18: PATIENT-REPORTED OUTCOMES AT 52 WEEKS

	Study D1693C00005 (Study 5)	
	Dapa 10 mg (n = 108)	Placebo (n = 108)
EQ-5D VAS		
Baseline mean (SD)[a]	75.12 (20.23)	72.83 (20.51)
N[b]	86	48
Adjusted mean change at end of period (SE)	3.87 (1.63)	2.77 (2.10)
Adjusted mean change vs. placebo (95% CI)[c]	1.10 (–4.16 to 6.37)	
EQ-5D Index Score		
Baseline mean (SD)[a]	0.85 (0.16)	0.85 (0.16)
N[b]	86	47
Adjusted mean change at end of period (SE)	0.01 (0.02)	–0.01 (0.02)
Adjusted mean change vs. placebo (95% CI)[c]	0.02 (–0.03 to 0.07)	
DTSQs Score		
Baseline mean (SD)[a]	30.41 (4.59)	29.80 (5.44)
N[b]	84	48
Adjusted mean change at end of period (SE)	1.53 (0.49)	1.48 (0.63)
Adjusted mean change vs. placebo (95% CI)[c]	0.04 (–1.54 to 1.63)	
IWQOL-Lite Total Score		
Baseline mean (SD)[a]	83.77 (13.47)	81.13 (18.21)
N[b]	81	46
Adjusted mean change at end of period (SE)	5.49 (1.18)	3.15 (1.51)
Adjusted mean change vs. placebo (95% CI)[c]	2.35 (–1.45 to 6.15)	
IWQOL-Physical Function Score		
Baseline mean (SD)[a]	77.02 (18.52)	73.42 (22.68)
N[b]	85	48
Adjusted mean change at end of period (SE)	6.74 (1.49)	4.04 (1.91)
Adjusted mean change vs. placebo (95% CI)[c]	2.70 (–2.10 to 7.50)	
IWQOL-Self-Esteem Score		
Baseline mean (SD)[a]	82.94 (21.29)	81.55 (22.71)
N[b]	85	48
Adjusted mean change at end of period (SE)	8.50 (1.46)	5.36 (1.85)
Adjusted mean change vs. placebo (95% CI)[c]	3.14 (–1.52 to 7.79)	
IWQOL-Sexual Life Score		
Baseline mean (SD)[a]	86.31 (22.15)	81.51 (28.36)
N[b]	75	44
Adjusted mean change at end of period (SE)	4.58 (2.31)	–1.81 (2.92)
Adjusted mean change vs. placebo (95% CI)[c]	6.39 (–0.99 to 13.77)	
IWQOL-Public Distress Score		
Baseline mean (SD)[a]	93.72 (10.97)	91.72 (17.57)
N[b]	83	46
Adjusted mean change at end of period (SE)	1.98 (1.39)	0.27 (1.83)
Adjusted mean change vs. placebo (95% CI)[c]	1.70 (–2.85 to 6.25)	

	Study D1693C00005 (Study 5)	
	Dapa 10 mg (n = 108)	Placebo (n = 108)
IWQOL-Work Score		
Baseline mean (SD)[a]	91.04 (12.95)	89.53 (16.68)
N[b]	81	45
Adjusted mean change at end of period (SE)	2.15 (1.37)	-1.03 (1.79)
Adjusted mean change vs. placebo (95% CI)[c]	3.18 (–1.29 to 7.64)	

CI = confidence interval; Dapa = dapagliflozin; DB = double-blind; DTSQ = Diabetes Treatment Satisfaction Questionnaire; EQ-5D = EuroQoL 5-Dimensions Questionnaire; FAS = full analysis set; IWQOL = Impact of Weight on Quality of Life–Lite questionnaire; SD = standard deviation; SE = standard error; VAS = visual analogue scale; vs. = versus.
[a] Baseline value was taken at the beginning of the 24-week DB period.
[b] Number of patients in the FAS with non-missing baseline value and week 52 value.
[c] Longitudinal repeated measures analysis with fixed categorical effects of treatment, week, treatment-by-week interaction, and the continuous fixed covariates of baseline and baseline-by-week interaction.
Source: Clinical Study Report.[1]

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- EuroQol 5-Dimensions Questionnaire (EQ-5D)
- Diabetes Treatment Satisfaction Questionnaire (DTSQ)
- Impact of Weight on Quality of Life–Lite questionnaire (IWQOL-Lite)

Findings

TABLE 19: 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	EuroQol Group[26]
DTSQs DTSQc	Both forms of the DTSQ are eight-item, diabetes-specific measures of patient satisfaction with treatment.	Yes	Unknown	Bradley et al. 2007[27]
IWQOL-Lite	IWQOL-Lite is a self-report instrument specifically developed to assess the effect of obesity on quality of life.	Yes	Unknown	Kolotkin et al. 2001[28]

DTSQc = Diabetes Treatment Satisfaction Questionnaire change version; DTSQs = Diabetes Treatment Satisfaction Questionnaire status version; EQ-5D = EuroQoL 5-Dimensions Questionnaire; IWQOL-Lite = Impact of Weight on Quality of Life–Lite questionnaire.

EuroQoL 5-Dimensions Questionnaire

EQ-5D is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments.[26] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged 12 years or older) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing “no problems”, “some problems”, and “extreme problems”, respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[26] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state”. Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. Hence, EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions, represented by a five-digit descriptor, such as 11121, 33211, etc.
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK

algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health", respectively.[26]

A minimal clinically important difference (MCID) for EQ-5D in patients with diabetes was not identified; however, in other conditions, it typically ranges from 0.033 to 0.074.[29]

Diabetes Treatment Satisfaction Questionnaire

The DTSQ is a diabetes-specific measure of patient satisfaction with treatment.[27] The original version, the DTSQ, 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 the sum of these items is taken to generate a DTSQ score. The remaining two items measure perceived frequency of hyperglycemia and frequency of hypoglycemia. The DTSQs is composed of six items and scored on seven-point response scales ranging from "very satisfied" (assigned a score of 6) to "very unsatisfied" (assigned a score of 0). Higher DTSQs scores indicate greater satisfaction with treatment (range 0 to 36). With respect to the two items measuring perceived frequency of hyperglycemia and frequency of hypoglycemia, the items are scored on seven-point response scales ranging from "most of the time" (assigned a score of 6) to "none of the time" (assigned a score of 0). In this case, the lower DTSQs scores indicate more ideal blood glucose levels. The psychometric properties of different language versions of the DTSQs were assessed in a study of type 1 and type 2 diabetes patients treated with insulin or poorly controlled on sulfonylureas who then started on insulin treatment.[30] The DTSQs was shown to be consistently reliable in all languages studied and significantly sensitive to change in type 1 diabetes patients at weeks 8, 20, 24, and at last available visit.[30]

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.[27] 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.[27] The DTSQc also contains six items that ask about current satisfaction relative to preceding treatment, and is scored on seven-point scale with responses ranging from "much more satisfied now" (assigned a score of +3) to "much less satisfied now" (assigned a score of –3).[27,31] Higher DTSQc scores indicate improved satisfaction with treatment (range –18 to +18); a score of 0 indicates no change.[27,31] With respect to the two items measuring perceived frequency of hyperglycemia and frequency of hypoglycemia, the items are scored on seven-point response scales ranging from "much more of the time now" (assigned a score of +3) to "much less of the time now" (assigned a score of –3).[27,31] In this case, lower DTSQs scores indicate more ideal blood glucose levels. 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.[27] This study also found that the DTSQc identified significantly more 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.[27]

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

Impact of Weight on Quality of Life–Lite questionnaire

IWQOL-Lite is a self-administered, disease-specific instrument that assesses quality of life in obesity.[28] It is a variant of the original Impact of Weight on Quality of Life (IWQOL) (74 items) questionnaire developed by Kolotkin et al. that was designed to alleviate the response burden. IWQOL-Lite is composed of five domains: physical function (11 items), self-esteem (seven items), sexual life (four items), public distress (five items), and work (four items) for a total of 31 items and the total IWQOL-Lite score. There are five levels to rate each item, ranging from "always true" to "never true". Each level is assigned a score from 1 to 5, where "usually true" is given a score of 5 and "never true" is given a score of 1.[28] The sum of scores for each item in its respective domain provides the domain score, and the sum of scores for each domain provides the total score, which ranges from 0 to 100. A higher score is associated to a poorer quality of life.[28]

A study by Kolotkin et al. assessed weight-related QoL in obese persons with type 2 diabetes using IWQOL-Lite.[32] The study involved (n = 1,197) obese people (of which n = 225 had type 2 diabetes) seeking weight loss treatment in a clinical trial comparing an obesity medication with gastric bypass surgery.[32] IWQOL-Lite demonstrated excellent internal consistency reliability, based on Cronbach's alpha, which was 0.981 and 0.980 for the total IWQOL-Lite score in diabetic and non-diabetic patients suffering from obesity, respectively.[32] Moderately strong correlations were identified between IWQOL-Lite and body mass index, and were comparable in both diabetic and non-diabetic patients suffering from obesity, suggesting concurrent validity of IWQOL-Lite.[32] Construct validity of the instrument was also assessed using confirmatory factor analysis; the factor structure between diabetic and non-diabetic patients was comparable, providing support of the scale structure, as well as the presence of a higher order (weight-related QoL).[32] However, IWQOL-Lite did not demonstrate significant discrimination in weight-related QoL between patients with and without diabetes.[32] Other limitations of this study include: convergent and discriminant validity were not measured against other measures such as the Short Form (36) Health Survey (SF-36) and the Rosenberg self-esteem scale; and no data were provided on comorbidities or complications due to diabetes, which may also impact some domains of QoL that are captured by IWQOL-Lite, such as physical function and work. Further, participants in this study were recruited from weight management programs instead of diabetes management programs.[32] However, there is likely considerable overlap between patients trying to manage diabetes and patients trying to manage obesity, given that 80% of patients with diabetes are obese.[32]

An MCID for IWQOL-Lite in patients with type 2 diabetes was not identified; however, in other conditions, it typically ranges from 7 to 12.[33]

Conclusion

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. 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. IWQOL-Lite is an obesity-specific quality of life measure composed of five domains and a total of 31 items. This instrument was demonstrated to be reliable and valid in obese persons with type 2 diabetes. The MCIDs for patients with type 2 diabetes were not identified for EQ-5D, DTSQ, or IWQOL-Lite.

APPENDIX 5: SUMMARY OF INDIRECT COMPARISONS

Introduction

Background

Studies included in the systematic review did not provide head-to-head comparisons of dapagliflozin with other relevant drugs used in third-line treatment of type 2 diabetes mellitus (T2DM). The objective of this review is to summarize and critically appraise indirect evidence comparing the efficacy, tolerability, and safety of dapagliflozin with other drugs used for third-line treatment of T2DM.

Methods

One network meta-analysis (NMA) was provided by the manufacturer in the submission.[34] The CADTH Common Drug Review (CDR) literature search results were also reviewed to identify any additional published relevant indirect evidence.

Description of indirect comparisons identified

One manufacturer-submitted NMA was relevant to the analysis of third-line therapies, in addition to metformin and a sulfonylurea, for T2DM. No additional published indirect treatment comparisons (IDCs) relevant to this review were identified. A summary of the characteristics of the NMA is presented in Table 20.

TABLE 20: CHARACTERISTICS OF INCLUDED NETWORK META-ANALYSIS

	Manufacturer-Submitted NMA for Third-Line Therapy[34]
Study designs	RCTs with minimal duration of treatment of 6 months
Population	Adult T2DM patients with inadequate glycemic control (A1C > 6.5%, FPG > 7 mmol/L or 2-h post-prandial glucose > 10 mmol/L) despite therapy with metformin and a sulfonylurea
N of included studies (base case)	24 RCTs
N of patients	10,897 patients

A1C = glycated hemoglobin; FPG = fasting plasma glucose; h = hour; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus.

Review and appraisal of indirect comparisons

Review of manufacturer's network meta-analysis for third-line treatment of Type 2 Diabetes Mellitus

Objectives and rationale

The primary objective for the IDC was to estimate the clinical efficacy of dapagliflozin in combination with metformin and a sulfonylurea, relative to other third-line drugs licensed in Canada for the treatment of T2DM for patients who fail to achieve adequate glycemic control on dual therapy with metformin and a sulfonylurea.

Methods

a) Study eligibility and selection process

Evidence for inclusion in the NMA was derived from a systemic literature review of third-line therapies for the treatment of T2DM conducted by CADTH (last search until March 1, 2013).[35,36] A supplemental search was conducted using a time frame from 1974 to September 9, 2013 in MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Embase, and Cochrane Central Register of Controlled Trials using the Ovid interface to identify randomized controlled trials (RCTs) for dapagliflozin, as this

intervention was not included in the CADTH search. Search updates were conducted in 2014 and 2015 (up until May 21, 2015). Ongoing clinical trials were searched in clinicaltrials.gov, and conference abstracts were also searched. Inclusion criteria for the systematic literature review are presented in Table 21. Studies where all patients had high cardiovascular risk, renal impairment, or hepatic impairment were excluded. In addition, studies where more than 15% of patients used a regimen other than combination therapy with metformin and a sulfonylurea at baseline were excluded.

TABLE 21: INCLUSION CRITERIA FOR THE SYSTEMATIC LITERATURE REVIEW

Population	Adult patients with T2DM and inadequate glycemic control (A1C > 6.5%, FPG > 7 mmol/L or 2-h post-prandial glucose > 10 mmol/L) despite therapy with MET + SU
Interventions	• SGLT2 inhibitors: dapagliflozin, canagliflozin • DPP-4 inhibitors: saxagliptin, sitagliptin, linagliptin • GLP-1 analogues: liraglutide, exenatide • TZDs: pioglitazone • Insulin and insulin analogues Used in combination with MET + SU
Comparators	Placebo or other antidiabetic drug, in combination with MET + SU
Outcomes	• Mean change in A1C from baseline • Mean change in weight from baseline • Mean change in SBP from baseline • Proportion of patients with at least one hypoglycemic episode
Study design	Parallel-group RCTs > 4 weeks in duration

A1C = glycated hemoglobin; DPP-4 = dipeptidyl-peptidase 4; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; MET = metformin; SU = sulfonylurea; SGLT2 = sodium-glucose cotransporter 2; RCT = randomized controlled trial; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.
Source: Manufacturer-submitted network meta-analysis.[34]

In the CDR review, two reviewers jointly determined appropriate studies for inclusion. For the search updates, two reviewers independently determined whether articles met inclusion criteria; discrepancies were resolved by consensus and disputes were adjudicated by a third reviewer, who made the final decision. For data extraction from the CADTH reports, dapagliflozin search, and incremental search updates, one reviewer extracted relevant data and a second reviewer verified that the data had been correctly reproduced. For other data, two reviewers independently extracted data, and discrepancies were resolved by consensus.

b) Data extraction

For the base case, 24 RCTs reporting on 10,897 patients were included. The mean age of patients in the studies ranged from 50.9 years to 61.7 years, and the proportion of males ranged from 37.5% to 75.4%. The mean duration of disease at study entry ranged from five years to 12.3 years, and the mean baseline A1C ranged from 7.4% to 10.2%. Mean baseline weight across studies ranged from just above 65 kg to nearly 100 kg, and mean baseline systolic blood pressure (SBP) ranged from less than 130 mm Hg to more than 145 mm Hg. There appeared to be heterogeneity among the demographics and disease characteristics of patients across studies.

Interventions of studies were grouped according to drug class or insulin analogue: sodium-glucose cotransporter 2 (SGLT2) inhibitors (dapagliflozin, canagliflozin), dipeptidyl-peptidase 4 (DPP-4) inhibitors (saxagliptin, sitagliptin, linagliptin), thiazolidinedione (TZDs) (pioglitazone), glucagon-like peptide-1 (GLP-1) analogues (liraglutide, exenatide), basal insulin (insulin detemir, insulin glargine, neutral protamine

Hagedorn insulin), bolus insulin (insulin aspart), and biphasic insulin (biphasic insulin 70/30, biphasic insulin aspart 30/70). Dapagliflozin was the only SGLT2 inhibitor included in the base-case analysis. Three studies that used canagliflozin were included in a sensitivity analysis to examine the SGLT2 drug class effect. All therapies were added to a background of metformin plus a sulfonylurea. The dose of metformin administered was at least 1,500 mg/day in the studies that reported this information, and the dose of sulfonylurea administered was either the maximum tolerated dose or at least half of the maximum recommended dose in the majority of studies.

c) Comparators

The intervention of interest was dapagliflozin as add-on to metformin and a sulfonylurea. Canagliflozin was another SGLT2 inhibitor in the same class as dapagliflozin, but was only included in a sensitivity analysis to focus on the relative effect of dapagliflozin compared with other drug classes. Empagliflozin was not in Canada at the time the NMA was conducted and was therefore not included among the SGLT2 inhibitors. The comparators of interest included DPP-4 inhibitors, TZDs, GLP-1 analogues, and insulin analogues, as add-on to metformin plus a sulfonylurea (Table 21). Individual drugs within each drug class were restricted to drugs licensed in Canada for patients who have not achieved adequate glycemic control on a background therapy of metformin and a sulfonylurea.

d) Outcomes

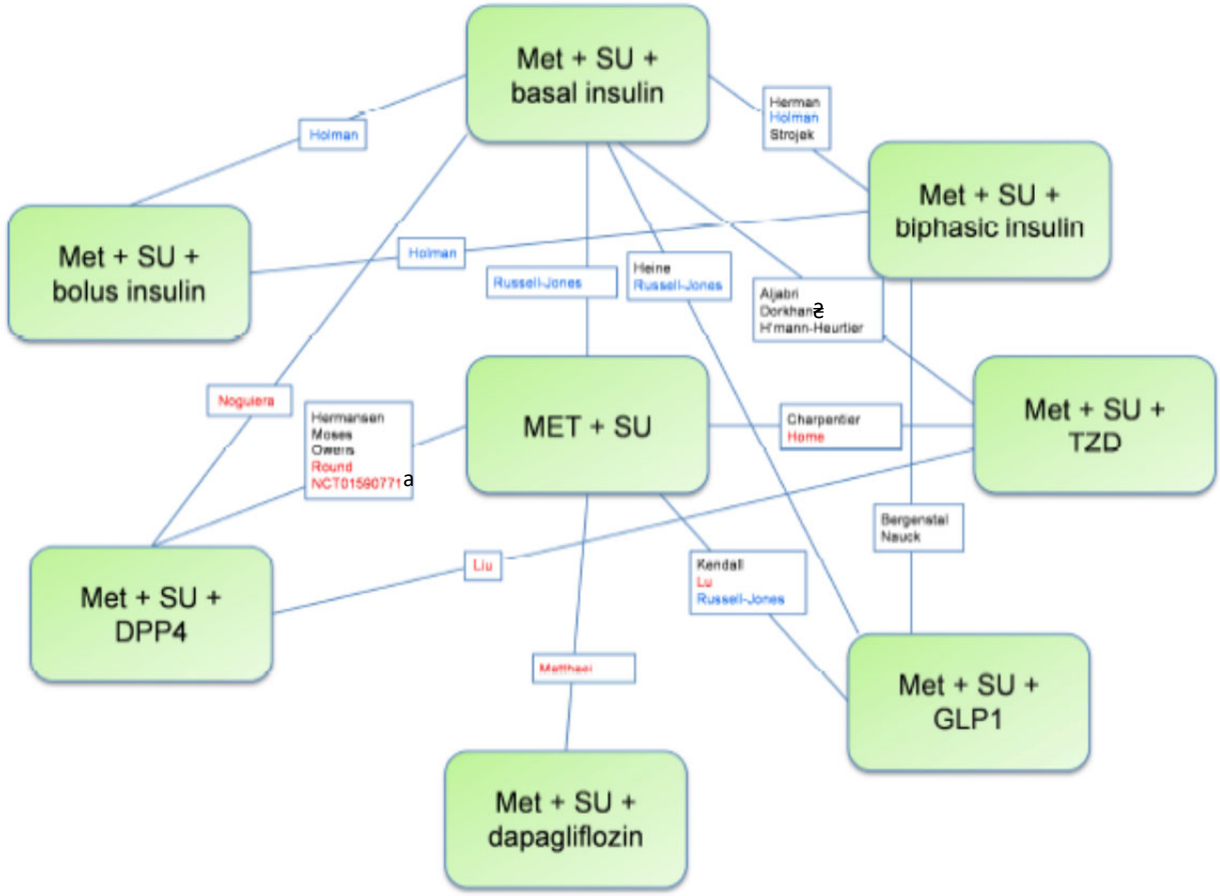
Efficacy outcomes of interest included A1C, weight, and SBP. The safety outcome of interest included the incidence of hypoglycemia. Efficacy outcomes included in the CDR review protocol such as mortality, morbidity, and quality of life, and safety outcomes such as adverse events (AEs), serious adverse events (SAEs), renal AEs, and genital infections were not investigated in the NMA.

e) Quality assessment of included studies

The Scottish Intercollegiate Guidelines Network (SIGN)-50 checklist for RCTs was used to assess the internal validity of the included studies.[37] Two independent reviewers performed the assessment and a third party resolved disagreement in the same manner as described for study selection.

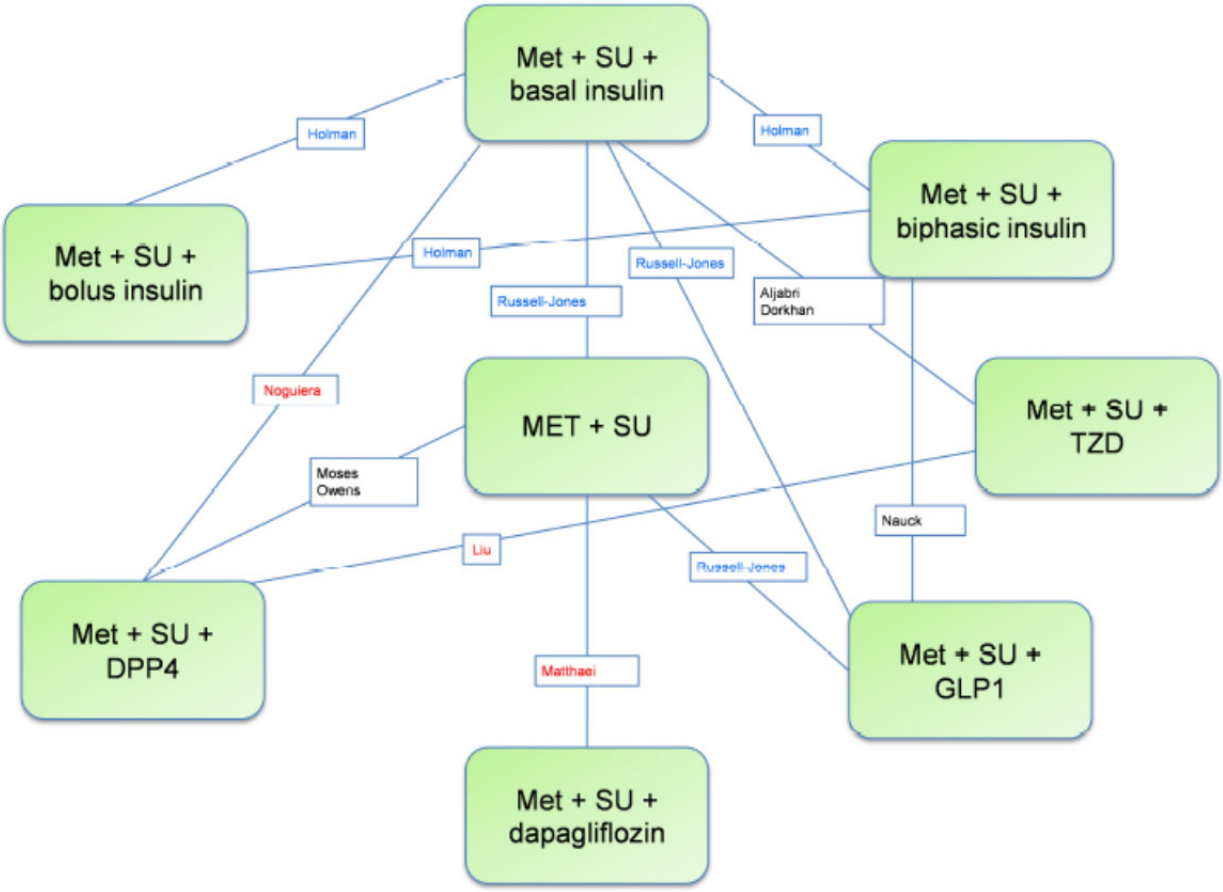
f) Evidence network

FIGURE 3: EVIDENCE NETWORK FOR GLYCATED HEMOGLOBIN AND BODY WEIGHT OUTCOMES



DPP4 = dipeptidyl-peptidase 4; GLP1 = glucagon-like peptide-1; MET = metformin; SU = sulfonylurea; TZD = thiazolidinedione.
[a] Study included in A1C network only.
Source: Manufacturer-submitted indirect comparison document.[34]

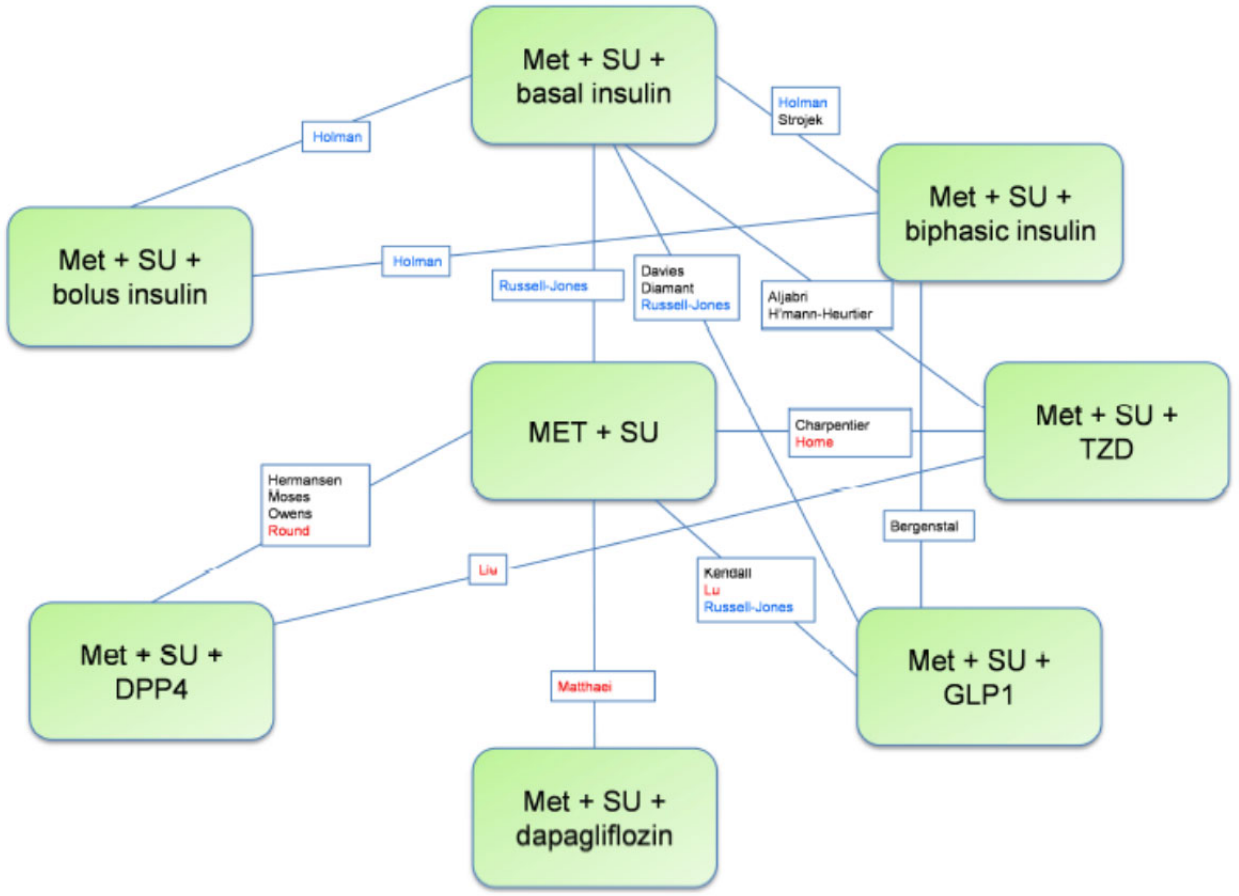
FIGURE 4: EVIDENCE NETWORK FOR SYSTOLIC BLOOD PRESSURE



DPP4 = dipeptidyl-peptidase 4; GLP1 = glucagon-like peptide-1; MET = metformin; SU = sulfonylurea; TZD = thiazolidinedione.
Source: Manufacturer-submitted indirect comparison document.[34]

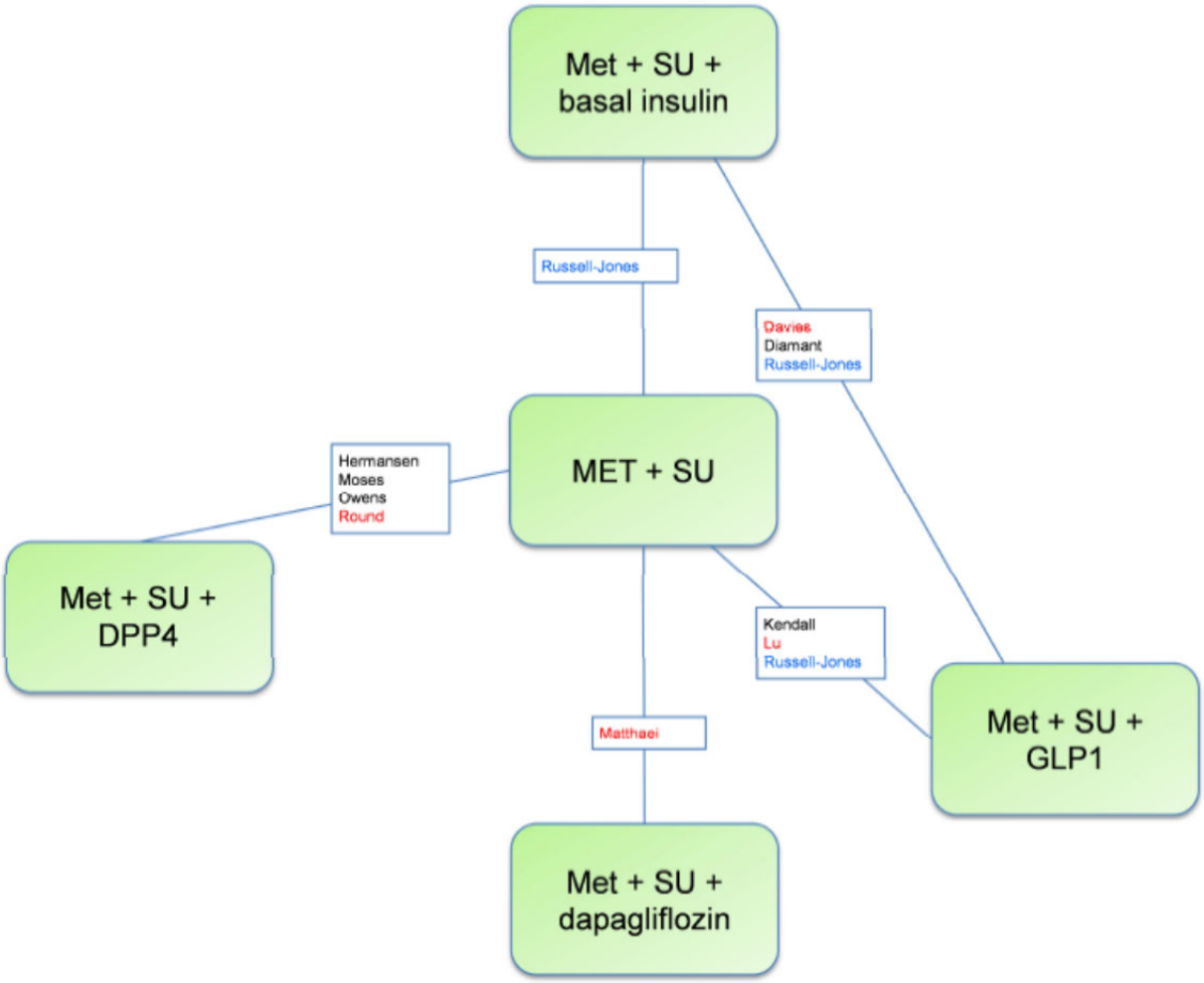
FIGURE 5: EVIDENCE NETWORKS FOR HYPOGLYCEMIA

FULL NETWORK



DPP4 = dipeptidyl-peptidase 4; GLP1 = glucagon-like peptide-1; MET = metformin; SU = sulfonylurea; TZD = thiazolidinedione.
Source: Manufacturer-submitted indirect comparison document.[34]

RESTRICTED NETWORK



DPP4 = dipeptidyl-peptidase 4; GLP1 = glucagon-like peptide-1; MET = metformin; SU = sulfonylurea; TZD = thiazolidinedione.
Source: Manufacturer-submitted indirect comparison document.[34]

Indirect comparison methods

A Bayesian NMA was performed for all outcomes using mean treatment difference for continuous outcomes (A1C, weight, SBP) and odds ratios for binary outcomes (hypoglycemia) with associated 95% credible intervals. The preferred point estimate was based on an intention-to-treat (ITT) population when data were available. Vague priors were used on all unknown parameters. Markov Chain Monte Carlo simulations were performed using at least 20,000 burn-in iterations followed by at least 100,000 update iterations. Convergence was assessed by visualizing the histories of the chains, of relevant parameters, against the iteration number.

Though a random effects model was suggested to be the most appropriate to the heterogeneity across included studies, both random effects and fixed effects models were fitted and model fit was assessed using deviance information criterion (DIC) and total residual deviance. In addition, the between-studies standard deviation (compared against the prior distribution) was taken into consideration.

Sources of heterogeneity were summarized and inconsistency between direct and indirect evidence was evaluated. Statistical heterogeneity was estimated for pairwise comparisons based on the I^2 and Cochran's Q statistics. Closed loops within the network allowed for assessment of potential inconsistencies using the Bucher method approach. Meta-regression adjusting for baseline A1C and baseline duration of diabetes was conducted.

One sensitivity analysis was conducted, in which three studies that used canagliflozin as an intervention were also included to examine the class effect of SGLT2 inhibitors.

Results

A random effects model was determined a priori to be more suitable due to the heterogeneity between trials. In addition, the DIC suggested that a random effects model was a better fit than a fixed effects model. Only results from the random effects model are presented below. The results from the fixed effects model generated similar conclusions. No time points were specified for each outcome, and the timing of assessment depended on what was performed in the study. Generally, the quality of the included studies was good, and poor quality assessment was often due to inadequate reporting of methods to do with allocation concealment, ITT analyses, and definitions for hypoglycemia and AEs.

a) Change from baseline in A1C

A total of 22 trials (8,363 patients) informed the network for A1C. All drug classes were associated with statistically significant reductions in A1C compared with placebo (Table 22). No difference was observed when dapagliflozin was compared with the other treatment regimens. The sensitivity analysis that included canagliflozin trials reported similar results to the base case.

There was evidence of statistical heterogeneity in the pairwise meta-analysis of the five RCTs comparing DPP-4 inhibitor with placebo (I^2 = 60%), the two RCTs comparing GLP-1 analogues with basal insulin (I^2 = 67.8%), the three RCTs comparing biphasic insulin to basal insulin (I^2 = 81.9%), and the two RCTs comparing GLP-1 to biphasic insulin (I^2 = 90.8%). The effect sizes of change in A1C were in the same direction for all of these groups of studies, except for the RCTs comparing GLP-1 with biphasic insulin, where one study favoured biphasic insulin and the other study favoured GLP-1 analogues. Sources of heterogeneity included trial duration, baseline patient characteristics, and dosing.

Closed loops in the network were assessed for consistency, and evidence of inconsistency was found in the closed loop involving TZD, basal insulin, and placebo ($P < 0.01$).

TABLE 22: MEAN CHANGE FROM BASELINE IN GLYCATED HEMOGLOBIN (%)

	Base Case (Dapagliflozin Only in SGLT2 Class)		Sensitivity Analysis (Dapagliflozin and Canagliflozin in SGLT2 Class)	
Drug class	**Treatment vs. PBO (95% CrI)**	**Dapa vs. treatment (95% CrI)**	**Treatment vs. PBO (95% CrI)**	**SGLT2 vs. treatment (95% CrI)**
SGLT2 inhibitors	–0.69 (–1.17 to –0.21)	-	–0.80 (–1.03 to –0.56)	-
DPP-4 inhibitors	–0.68 (–0.87 to –0.49)	–0.01 (–0.53 to 0.50)	–0.64 (–0.81 to –0.47)	–0.16 (–0.42 to 0.12)
TZD	–0.94 (–1.19 to –0.65)	0.24 (–0.32 to 0.77)	–0.93 (–1.17 to –0.67)	0.13 (–0.22 to 0.46)
GLP-1 analogues	–1.04 (–1.32 to –0.76)	0.35 (–0.20 to 0.90)	–1.03 (–1.30 to –0.77)	0.23 (–0.12 to 0.59)
Biphasic insulin	–1.23 (–1.58 to –0.91)	0.54 (–0.03 to 1.13)	–1.22 (–1.55 to –0.91)	0.42 (0.03 to 0.83)
Basal insulin	–1.01 (–1.30 to –0.74)	0.32 (–0.22 to 0.89)	–1.00 (–1.28 to –0.74)	0.20 (–0.15 to 0.57)
Bolus insulin	–1.48 (–1.98 to –0.99)	0.78 (0.12 to 1.49)	–1.46 (–1.94 to –0.99)	0.66 (0.13 to 1.21)

CrI = credible interval; Dapa = dapagliflozin; DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; PBO = placebo; SGLT2 = sodium-glucose cotransporter 2; TZD = thiazolidinedione; vs. = versus.
Source: Manufacturer-submitted network meta-analysis.[34]

b) Change from baseline in weight

A total of 20 trials (7,948 patients) informed the network for weight. When compared with placebo, dapagliflozin and GLP-1 analogues were associated with statistically significant reductions in weight (Table 23). DPP-4 inhibitors demonstrated a non-significant difference in weight change compared with placebo. The TZD and insulin drug classes showed a statistically significant increase in weight from baseline compared with placebo. When compared with other treatments, dapagliflozin was associated with statistically significant reductions in weight to all regimens except GLP-1 analogues. The sensitivity analysis that included canagliflozin trials reported similar results to the base case.

There was evidence of statistical heterogeneity in the pairwise meta-analysis of the four RCTs comparing DPP-4 inhibitors with placebo (I^2 = 71.1%), the two RCTs comparing GLP-1 analogues with basal insulin (I^2 = 67.8%), and the three RCTs comparing biphasic insulin with basal insulin (I^2 = 92.7%). No statistically significant inconsistencies were detected in the network.

TABLE 23: MEAN CHANGE FROM BASELINE IN WEIGHT (KG)

	Base Case (Dapagliflozin Only in SGLT2 Class)		Sensitivity Analysis (Dapagliflozin and Canagliflozin in SGLT2 Class)	
Drug class	Treatment vs. PBO (95% CrI)	Dapa vs. treatment (95% CrI)	Treatment vs. PBO (95% CrI)	SGLT2 vs. treatment (95% CrI)
SGLT2 inhibitors	–2.07 (–3.93 to –0.20)	-	–1.67 (–2.54 to –0.78)	-
DPP-4 inhibitors	0.77 (–0.03 to 1.64)	–2.85 (–4.92 to –0.80)	0.75 (0.07 to 1.46)	–2.42 (–3.43 to –1.44)
TZD	3.64 (2.60 to 4.65)	–5.71 (–7.85 to –3.57)	3.65 (2.71 to 4.56)	–5.32 (–6.55 to –4.05)
GLP-1 analogues	–1.15 (–2.19 to –0.14)	–0.92 (–3.03 to 1.22)	–1.14 (–2.08 to –0.22)	–0.53 (–1.78 to 0.75)
Biphasic insulin	3.97 (2.69 to 5.26)	–6.05 (–8.28 to –3.76)	3.98 (2.79 to 5.14)	–5.65 (–7.08 to –4.17)
Basal insulin	2.62 (1.45 to 3.73)	–4.69 (–6.85 to –2.49)	2.62 (1.58 to 3.65)	–4.29 (–5.62 to –2.92)
Bolus insulin	5.68 (3.66 to 7.63)	–7.76 (–10.47 to –5.02)	5.69 (3.88 to 7.45)	–7.36 (–9.33 to –5.33)

CrI = credible interval; Dapa = dapagliflozin; DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; PBO = placebo; SGLT2 = sodium-glucose cotransporter 2; TZD = thiazolidinedione; vs. = versus.
Source: Manufacturer-submitted network meta-analysis.[34]

c) Change from baseline in systolic blood pressure

A total of 10 trials (3,511 patients) informed the network for SBP. Although the fixed effects DIC was lower than the random effects DIC, the difference did not exceed 3 points. There were no differences from placebo in SBP for any of the treatment regimens in the network (Table 24). When compared with the other treatment regimens, dapagliflozin was statistically superior to bolus insulin in change from baseline in SBP, but there were no differences compared to the other drugs. The sensitivity analysis that included canagliflozin trials reported similar results to the base case.

There was no evidence of statistical heterogeneity in the pairwise meta-analysis, but this may be due to the few trials available for any pairwise comparison (only two trials for DPP-4 versus placebo). No statistically significant inconsistencies were detected in the network.

TABLE 24: MEAN CHANGE FROM BASELINE IN SYSTOLIC BLOOD PRESSURE (MM HG)

	Base Case (Dapagliflozin Only in SGLT2 Class)		Sensitivity Analysis (Dapagliflozin and Canagliflozin in SGLT2 Class)	
Drug class	Treatment vs. PBO (95% CrI)	Dapa vs. treatment (95% CrI)	Treatment vs. PBO (95% CrI)	SGLT2 vs. treatment (95% CrI)
SGLT2 inhibitors	–3.49 (–9.00 to 2.06)	-	–3.74 (–6.21 to –1.16)	-
DPP-4 inhibitors	–0.23 (–3.47 to 3.30)	–3.26 (–9.84 to 3.02)	0.73 (–1.70 to 3.28)	–4.47 (–7.19 to –1.57)
TZD	0.14 (–4.49 to 6.03)	–3.63 (–11.95 to 3.22)	0.94 (–3.22 to 5.48)	–4.68 (–9.40 to –0.24)
GLP-1 analogues	–2.76 (–7.42 to 1.88)	–0.73 (–7.86 to 6.48)	–2.62 (–6.59 to 1.49)	–1.12 (–5.71 to 3.58)
Biphasic insulin	3.38 (–2.17 to 8.84)	–6.87 (–14.53 to 0.93)	3.54 (–1.23 to 8.28)	–7.28 (–12.48 to –1.89)
Basal insulin	1.50 (–2.73 to 5.62)	–4.99 (–11.70 to 1.95)	1.74 (–1.89 to 5.46)	–5.48 (–9.73 to –1.13)
Bolus insulin	5.48 (–0.92 to 11.73)	–8.97 (–17.31 to –0.46)	5.66 (0.14 to 11.26)	–9.40 (–15.30 to –3.37)

CrI = credible interval; Dapa = dapagliflozin; DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; PBO = placebo; SGLT2 = sodium-glucose cotransporter 2; TZD = thiazolidinedione; vs. = versus.
Source: Manufacturer-submitted network meta-analysis.[34]

d) Proportion of patients with hypoglycemia

A total of 18 trials (5,357 patients) informed the network for hypoglycemic episodes. All of the treatment regimens except for SGLT2 inhibitors (dapagliflozin) were associated with a statistically significant increase in the odds of hypoglycemic events compared with placebo (Table 25). There was a non-significant difference between dapagliflozin and placebo, which could be attributable to a wide 95% credible interval. There was no difference with dapagliflozin in the odds of hypoglycemic events compared with the other treatments. There were differences in the definition of hypoglycemia across included trials, which likely contributed to statistical heterogeneity and inconsistency in the analyses.

In an attempt to reduce heterogeneity and inconsistency, an analysis was conducted with a restricted network (10 trials; 3,829 patients), by reducing the trials to only the relevant comparisons (dapagliflozin, basal insulin, DPP-4 inhibitors, and GLP1 analogues versus placebo) and minimizing inconsistency from IDCs (Figure 5 and Table 26). Using the restricted network, no regimen (dapagliflozin, DPP-4 inhibitors, GLP-1 analogues, basal insulin) was associated with statistically significant increased odds of experiencing at least one hypoglycemic event compared with placebo. There was no statistically significant difference in the odds of experiencing at least one hypoglycemic event with dapagliflozin compared with the other drugs.

TABLE 25: MEAN ODDS RATIOS OF ANY HYPOGLYCEMIC EVENT (FULL NETWORK)

	Base Case (Dapagliflozin Only in SGLT2 Class)	
Drug class	Treatment vs. PBO (95% CrI)	Dapa vs. treatment (95% CrI)
SGLT2 inhibitors	4.20 (0.63 to 29.31)	-
DPP-4 inhibitors	3.15 (1.43 to 7.52)	1.34 (0.16 to 10.46)
TZD	2.64 (1.07 to 6.46)	1.59 (0.20 to 13.56)
GLP-1 analogues	3.51 (1.52 to 9.39)	1.20 (0.14 to 9.64)
Biphasic insulin	11.97 (3.56 to 45.97)	0.35 (0.03 to 3.41)
Basal insulin	5.61 (2.23 to 16.07)	0.75 (0.08 to 6.30)
Bolus insulin	39.58 (6.91 to 263.75)	0.11 (0.01 to 1.45)

CrI = credible interval; Dapa = dapagliflozin; DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; PBO = placebo; SGLT2 = sodium-glucose cotransporter 2; TZD = thiazolidinedione; vs. = versus.
Source: Manufacturer-submitted network meta-analysis.[34]

TABLE 26: MEAN ODDS RATIOS OF ANY HYPOGLYCEMIC EVENT (RESTRICTED NETWORK)

	Base Case (Dapagliflozin Only in SGLT2 Class)		Sensitivity Analysis (Dapagliflozin and Canagliflozin in SGLT2 Class)	
Drug class	Treatment vs. PBO (95% CrI)	Dapa vs. treatment (95% CrI)	Treatment vs. PBO (95% CrI)	SGLT2 vs. treatment (95% CrI)
SGLT2 inhibitors	4.30 (0.32 to 60.58)	-	2.91 (1.38 to 6.65)	-
DPP-4 inhibitors	3.30 (1.00 to 12.79)	1.30 (0.07 to 22.04)	2.87 (1.51 to 6.48)	1.01 (0.39 to 2.36)
GLP-1 analogues	3.01 (0.83 to 14.00)	1.43 (0.07 to 26.45)	2.64 (1.20 to 7.01)	1.1 (0.31 to 3.37)
Basal insulin	3.96 (0.78 to 26.21)	1.08 (0.04 to 22.92)	3.51 (1.28 to 11.75)	0.83 (0.20 to 3.01)

CrI = credible interval; Dapa = dapagliflozin; DPP-4 = dipeptidyl-peptidase 4; GLP-1 = glucagon-like peptide-1; PBO = placebo; SGLT2 = sodium-glucose cotransporter 2; vs. = versus.
Source: Manufacturer-submitted network meta-analysis.[34]

Critical appraisal

The quality of the manufacturer-submitted NMA was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on indirect treatment comparisons.[38] Details and commentary for each of the relevant items identified by ISPOR are provided in Table 27.

a) Strengths

The objectives of the IDC were clearly stated and a comprehensive systematic review was performed to identify all relevant literature. Comparators included third-line drugs licensed in Canada for the management of T2DM. The DIC was used to determine which statistical model had the best fit. One sensitivity analysis was performed to examine the class effect of SGLT2 inhibitors. For the hypoglycemia outcome, a restricted network was used to reduce heterogeneity from differing definitions of hypoglycemia.

b) Limitations

Although the list of included interventions was largely what is used in Canadian practice, therapies such as rosiglitazone (TZD) and acarbose were not included, which may also be used for third-line treatment of T2DM. Results were not analyzed by time point (e.g., 24 weeks) and trials of different duration were included. Although the majority of trials were 24 weeks to 26 weeks in duration, trials of 17 weeks and

52 weeks were also included, which may have contributed to the statistical heterogeneity that was observed. Treatment regimens were grouped according to class instead of analyzed by individual drug and dosing regimen. As different drugs within a class may have differences in efficacy and safety, this may not have been appropriate. Despite considerable heterogeneity between included trials (as determined by I^2 statistics), no sensitivity analyses were performed to address these differences. For the hypoglycemia analysis, the definition of hypoglycemia differed between studies and patients had different levels of baseline plasma glucose, which is problematic. Efficacy and safety outcomes that were included in the CDR protocol were not assessed in the NMA, including safety outcomes other than hypoglycemia.

TABLE 27: APPRAISAL OF INDIRECT COMPARISON USING ISPOR CRITERIA[38]

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an IDC and the study objectives were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCTs were stated. • Methods for selection process, data extraction were reported and the process was duplicated. • Validity of individual studies were assessed by the SIGN-50 checklist and reported.
3.	Are the outcome measures described?	• Outcomes assessed in the IDC were stated. Some outcomes in the CDR review protocol were not investigated.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the statistical model was provided. • The report states that the DIC was used to compare the fixed effects models with informative random effects models and non-informative random effects models. • Potential inconsistencies were assessed with the Bucher test, and results were reported.
5.	Are sensitivity analyses presented?	• One sensitivity analysis was conducted.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• Patient characteristics of individual studies were provided. • Network diagrams for each outcome were provided.
7.	Does the study describe an assessment of model fit?	• Fixed and random effects models were considered. A random effects model was chosen a priori, but confirmed using the DIC model fit measure. Results using each model were presented for comparison.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were reported for each outcome measure, including point estimates and 95% credible intervals as a measure of uncertainty.

ISPOR Checklist Item		Details and Comments
9.	Sensitivity/scenario analyses	• One sensitivity analysis including 3 studies that looked at canagliflozin was included to look at the class effect of SGLT2 inhibitors.

CDR = CADTH Common Drug Review; DIC = deviance information criterion; IDC = indirect comparison; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; RCT = randomized controlled trial.

Discussion

One manufacturer-submitted NMA was summarized and critically appraised. The NMA was based on a comprehensive systematic review that evaluated key efficacy outcomes such as A1C, weight, and blood pressure, but did not assess other important outcomes such as mortality, morbidity, or quality of life. The only safety outcome assessed was the proportion of patients with a hypoglycemia episode. There was considerable statistical heterogeneity in the included studies, which may have been due to the different inclusion criteria, baseline characteristics, and duration of studies, limiting the confidence in the results. The hypoglycemia analysis was limited by the use of different definitions of hypoglycemia across studies. One sensitivity analysis was performed to examine the class effect of SGLT2 inhibitors by including studies with canagliflozin, and yielded similar results to the base case.

The networks were grouped by class and did not differentiate based on dose or drug used, which makes the assumption that the effect of drug and dose of drug is uniform within class. This may have an impact on the validity of the comparison.

Conclusion

One manufacturer-submitted IDC that assessed the efficacy and safety of third-line therapies for T2DM in combination with metformin and a sulfonylurea was summarized. Based on the results of the network meta-analysis, dapagliflozin 10 mg did not show any statistically significant differences in change from baseline in A1C and SBP to DPP-4 inhibitors, GLP-1 analogues, TZDs, and insulin analogues. Dapagliflozin had a statistically significant greater reduction in weight from baseline compared with the other drug classes except for GLP-1 analogues, for which there was no significant difference. For the proportion of patients with hypoglycemia, there was no difference with dapagliflozin in the odds of hypoglycemic events compared with the other treatments, though the definition of hypoglycemia varied across trials. There was considerable heterogeneity identified in trials of certain pairwise comparisons, which may have been due to baseline characteristics of patients, treatment duration, and dosing regimen or ranges, or within-class differences between drugs. This limits the confidence in the results. One sensitivity analysis was conducted, including canagliflozin trials with dapagliflozin to examine the class effect of SGLT2 inhibitors, and the results were similar to the base case. No comparisons to the other two commercially available SGLT2 inhibitors were completed.

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