Common Drug Review
Clinical Review Report

September 2017

Drug	Empagliflozin and Metformin Fixed-Dose Combination (Synjardy)
Indication	SYNJARDY (empagliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on: • metformin • sulfonylurea in combination with metformin • pioglitazone in combination with metformin • insulin in combination with metformin Or in patients already being treated and achieving glycemic control with: • metformin and empagliflozin as separate tablets • sulfonylurea in combination with metformin and empagliflozin as separate tablets • pioglitazone in combination with metformin and empagliflozin as separate tablets • insulin in combination with metformin and empagliflozin as separate tablets
Reimbursement request	As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus already stabilized on therapy with metformin and empagliflozin, to replace the individual components of metformin and empagliflozin in these patients.
Dosage form	5 mg / 500 mg, 5 mg / 850 mg, 5 mg /1,000 mg, 12.5 mg / 500 mg, 12.5 mg / 850 mg, 12.5 mg / 1,000 mg, tablets for oral administration
NOC Date	July 29, 2016
Manufacturer	Boehringer Ingelheim (Canada) Ltd.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in Endocrinology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

AE	adverse event
AIC	glycated hemoglobin
ANCOVA	analysis of covariance
BMI	body mass index
CDA	Canadian Diabetes Association
CDR	CADTH Common Drug Review
CI	confidence interval
CV	cardiovascular
CVD	cardiovascular disease
DB	double-blind
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EMPA	empagliflozin
EQ-5D	EuroQol 5-Dimensions Questionnaire
FAS	full analysis set
FDC	fixed-dose combination
FPG	fasting plasma glucose
GLIM	glimepiride
HRQoL	health-related quality of life
ITT	intention-to-treat
LOCF	last observation carried forward
MCID	minimal clinically important difference
MET	metformin
OL	open-label
PIO	pioglitazone
PPG	postprandial glucose
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SGLT2	sodium-glucose cotransporter-2
SU	sulfonylurea
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Diabetes mellitus is a metabolic disorder characterized by persistent elevations in blood glucose (hyperglycemia) and impaired glycemic control, which, if prolonged, may result in damage to blood vessels, and consequently causes dysfunction and failure of various organs including heart, brain, kidneys, retina, and lower limbs. Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of cases of diabetes. Diabetes is one of the most common chronic diseases in Canada. The Canadian Diabetes Association estimated that there were 3.4 million people (9.3% of the population) with diabetes in 2015, and by 2025 this number will increase to five million people (12.1%). The economic burden of diabetes in Canada is heavy.

Empagliflozin (EMPA) is an inhibitor of sodium-glucose cotransporter-2 (SGLT2), which has an antihyperglycemic effect by reducing renal reabsorption of filtered glucose and which lowers the renal threshold for glucose, leading to increased urinary glucose excretion. SGLT2 inhibitors are also generally associated with weight loss and lower blood pressure.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of EMPA/metformin (MET) fixed-dose combination (Synjardy) for the treatment of adults with T2DM who have experienced inadequate glycemic control on MET alone or on combination therapy of MET and other glucose-lowering products, or who are already being treated with EMPA and MET co-administered as separate tablets.

(**Note:** EMPA/MET [Synjardy] was submitted to the CADTH Common Drug Review before issuance of a Health Canada Notice of Compliance, and the indication that the protocol and subsequent inclusion of studies was based on was the following:

Empagliflozin and metformin hydrochloride [Synjardy] is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus when:

- *treatment with both empagliflozin and metformin is appropriate*
- *inadequately controlled with metformin alone*
- *inadequately controlled with metformin in combination with other glucose-lowering products, including insulin*
- *already treated with empagliflozin and metformin co-administered as separate tablets.*

Late in the review process, the wording of the official indication changed to the following:

Empagliflozin and metformin hydrochloride [Synjardy] is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on:

- *metformin;*
- *sulfonylurea in combination with metformin;*
- *pioglitazone in combination with metformin;*
- *insulin in combination with metformin;*

Or in patients already being treated and achieving glycemic control with:

- *metformin and empagliflozin as separate tablets;*
- *sulfonylurea in combination with metformin and empagliflozin as separate tablets;*

- *pioglitazone in combination with metformin and empagliflozin as separate tablets;*
- *insulin in combination with metformin and empagliflozin as separate tablets.*

At the time of completion of this review, the Health Canada Reviewer's report was not available, and clarification as to the reason for the change in wording was therefore not available.)

Results and interpretation

Included studies

No randomized controlled trials (RCT) of Synjardy were identified from the literature search. Three international, multi-centre, placebo-controlled, double-blind (DB) RCTs were submitted by the manufacturer and included in this review. All three studies had a 24-week treatment period that evaluated the efficacy and safety of EMPA 10 mg or 25 mg once daily in patients with T2DM who had inadequate glycemic control (glycated hemoglobin [A1C] ≥ 7.0% and ≤ 10%) on a background therapy of MET alone (Study 1245.23$_{MET}$, N = 638), MET and a sulfonylurea (SU; Study 1245.23$_{MET+SU}$, N = 669), or MET and pioglitazone (PIO; Study 1245.19, N = 499). The doses of the background medications were ≥ 30 mg per day for PIO, ≥ 1,500 mg per day for MET, ≥ 50% the maximum dose of an SU, or the maximum tolerated dose, or maximum dose according to local label for each of these medications. Patients were randomized in a 1:1:1 ratio to EMPA 10 mg per day, EMPA 25 mg per day, or placebo add-on to the background therapy after a two-week open-label (OL), placebo lead-in period. The primary outcome was the change from baseline in level of A1C at week 24. Key secondary outcomes included the change in fasting plasma glucose (FPG) and body weight from baseline at week 24. Other efficacy outcomes included the change in blood pressure from baseline at week 24, health-related quality of life (HRQoL) measured with the EuroQol 5-Dimensions Questionnaire (EQ-5D), and safety outcomes outside of a testing hierarchy.

The clinical efficacy and safety of EMPA 10 mg or 25 mg once daily in patients with T2DM who had inadequate glycemic control on a background therapy of MET alone or on combination therapy of MET + SU or MET + PIO are summarized below.

Efficacy

Outcomes are presented in the order pre-specified in the review protocol (Table 3).

Mortality: In total, three patients in the EMPA 10 mg or 25 mg groups and one patient in the placebo group died during the 24-week DB treatment period. The deaths were not considered to be related to the study drugs. Diabetes-related morbidity was not assessed in the included studies.

Glycemic control: EMPA 10 mg or 25 mg once daily is associated with a statistically and clinically significant greater reduction in A1C compared with placebo after 24 weeks (Table 1). The between-group differences in change in A1C from baseline ranged from –0.48% to –0.61%, –0.57% to –0.64%, and –0.59% to –0.64% for EMPA versus placebo when added on to MET + PIO, MET alone, or MET + SU, respectively. EMPA as an add-on to the background therapy was also associated with a statistically and clinically significant greater reduction in FPG.

HRQoL: Change in EQ-5D was descriptively analyzed, and statistical comparisons between treatment groups were not performed. Change in EQ-5D from baseline was small and similar across all the studies and treatment groups. These results suggest that 24-week treatment with EMPA can provide additional

glycemic control and weight benefit when added to a background of MET monotherapy or combination therapy of MET + PIO or MET + SU, in a population with inadequate glycemic control.

Change in body weight: EMPA was associated with a statistically significant greater weight loss in the study population after 24 weeks of treatment in all three studies. The magnitude of the reduction in body weight ranged from 1.63 kg to 2.16 kg versus placebo, depending on the dose of EMPA and the background therapy (Table 1); however, these differences versus placebo were not considered clinical significant.

Change in blood pressure: EMPA was superior to placebo in reducing systolic blood pressure (SBP) at 24 weeks in all three studies. The magnitude of the reduction in SBP versus placebo ranged from 2.1 mm Hg to 4.8 mm Hg; these values were not considered clinically significant. EMPA was also superior to placebo in reducing diastolic blood pressure (DBP) at 24 weeks when added on to MET + PIO and to MET alone, but not when added on to MET + SU. None of the improvements in DBP were considered clinically significant.

Findings from an extension study (Study 1245.31) indicated that the improvement in A1C, body weight, SBP, and DBP observed in the 24-week core studies were maintained through the 76-week extension phase (0).

The bioequivalence of Synjardy to EMPA + MET co-administered as individual tablets was demonstrated in healthy individuals (0).

The main limitations of these studies included the lack of data regarding diabetes-related comorbidity (microvascular or macrovascular) and imbalanced baseline patient characteristics between the EMPA groups and the placebo group (such as gender, the proportion of patients with a history of hypertension, and the distribution of time since initial diagnosis of T2DM). According to the protocols, patients and investigators could review and discuss changes in glycemic parameters, body weight, blood pressure, and adverse events (AEs) during the studies. Some specific drug effects, such as weight loss and urogenital AEs, are known to be associated with the administration of SGLT2 inhibitor class drugs. This may have allowed certain patients (and/or investigators) to surmise that the patients were randomized to receive the active treatment. However, the primary outcome variable in all of the studies, change in A1C, is an objective (hard) outcome measure, which was determined by central laboratories; therefore, if unblinding occurred, it is unlikely that it had an important impact on the study results for the primary analysis. Results of the outcome measures outside of the testing hierarchy, such as change in blood pressure and patient-reported outcome, should be interpreted with caution. There was a lack of adjustment in multiple comparisons in the subgroup analyses; in addition, due to the smaller number of patients in the subgroups, the results of subgroup analyses should also be interpreted with caution.

Generalizability to the Canadian population is limited due to the restricted inclusion criteria of the studies. Based on the eligibility criteria of the included studies, patients with uncontrolled hyperglycemia, recent occurrence of cardiovascular (CV) events, severe renal impairment, or a number of other conditions were excluded. The recruited patient population had milder severity of the disease (close to normal level of A1C, normal renal function or mild renal impairment, and well-controlled blood pressure); therefore, the generalizability of the study results to a broader population with diabetes is uncertain. A lack of longer-term efficacy and safety data (beyond six months) was another limitation.

Harms

Overall, the proportion of patients reporting an AE was balanced between the EMPA and the placebo groups. Isolated cases of serious AEs (SAEs) and withdrawal due to AEs were reported across the studies and treatment groups. In the included studies, a higher proportion of patients in the EMPA group had a confirmed AE of hypoglycemia than the placebo group at 24 weeks. Renal impairment was rarely reported across the treatment groups. There were more patients in the EMPA groups who reported developing a genital infection during the 24-week period than in the placebo group. Ketoacidosis was not reported in any study; this may be because the patient population was at low risk of developing this AE, with the relatively mild conditions.

Longer-term safety was explored in an extension study (Study 1245.31). Findings from this study suggested that the overall frequency of AEs was generally similar across the treatment groups at week 76. The frequency and severity of the AEs during the extension phase were similar to those reported during the core studies.

Potential place in therapy

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

Patients with T2DM have an increasing choice of drugs with low risk of hypoglycemia and low or reduced risk of weight gain. SGLT2 inhibitors add to this choice, with additional benefits for blood pressure reduction. Like other members of this drug class, EMPA is a good choice for people who have hypertension and wish to avoid weight gain and hypoglycemia. EMPA is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM for whom MET is inappropriate owing to contraindications or intolerance, and as add-on therapy when MET used alone does not provide adequate glycemic control, in combination with MET, MET and an SU, PIO (alone or with MET), basal or prandial insulin (alone or with MET). The revised Canadian Diabetes Association guidelines also suggest EMPA as the first choice for the prevention of CV events as an adjunct to standard care therapy in patients with T2DM at high CV risk; however, MET remains the cornerstone of treatment, and it is to be expected that 60% of people prescribed EMPA will also be on MET. Combining the two in one pill is likely to reduce pill burden for patients and facilitate adherence to prescribed therapy. As other SGLT2 inhibitors are available in combination with MET, there will also be patient expectation that EMPA will be available in this way.

Conclusions

No phase III RCTs evaluating the efficacy and safety of EMPA/MET fixed-dose combination (Synjardy) were available. Instead, three international, multi-centre, placebo-controlled, DB RCTs with a 24-week treatment period met inclusion criteria for this review. The efficacy and safety of EMPA 10 mg or 25 mg once daily was evaluated in patients with T2DM who had inadequate glycemic control on MET monotherapy, or on a combination therapy of MET and an SU, or MET and PIO.

Results from the three studies suggest that EMPA 10 mg or 25 mg once daily is associated with a statistically and clinically significant reduction in A1C and FPG compared with placebo after 24 weeks. Diabetes-related morbidity was not assessed in any of the studies. The use of EMPA was also related to non–clinically significant reductions in body weight and blood pressure, but its effect on patient-reported quality of life (measured with EQ-5D) was minimal. Longer-term efficacy and safety data suggested that, by week 76, the treatment effect of EMPA on A1C, FPG, body weight, and blood

pressure was maintained. The safety profile at week 76 was similar to that reported in the core studies. Imbalances in the baseline characteristics of the EMPA and placebo groups were noted, which may represent a failure of the randomization methods; however, there was no apparent evidence or strong clinical reason for these imbalances to have a clinically relevant impact on the primary study results. Additional limitations of the studies included a lack of long-term comparative efficacy and safety data, and limited generalizability of the study results to a typical Canadian T2DM patient population. Statistical methodology for some secondary outcomes is of questionable validity.

Findings from bioequivalence studies demonstrated that Synjardy is bioequivalent to the individual components administered separately. Data from other non-pivotal phase III DB RCTs suggested that EMPA was superior to glimepiride for improving glycemic control outcomes, decreasing blood pressure, and reducing weight. EMPA was also superior to placebo in glycemic control, body weight reduction, and insulin usage reduction in patients on a background therapy of MET combined with insulin.

AE data were generally similar between groups. Isolated cases of SAEs and withdrawal due to AEs were reported in the included studies. There was a greater proportion of patients in the EMPA group who reported hypoglycemic episodes and genital infections. Ketoacidosis was not reported in any studies.

TABLE 1: SUMMARY OF RESULTS

Parameter	1245.19			1245.2$_{MET}$			1245.23$_{MET+SU}$		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d. (N = 217)**	**EMPA 25 mg q.d. (N = 213)**	**PL (N = 207)**	**EMPA 10 mg q.d. (N = 225)**	**EMPA 25 mg q.d. (N = 216)**	**PL (N = 225)**
	MET + PIO			*MET alone*			*MET + SU*		
Efficacy at Week 24									
Mortality, n									
	0	2	1	0	0	0	1	0	0
Change in A1C (%)									
Baseline, mean (SE)	8.1 (0.1)	8.1 (0.1)	8.2 (0.1)	7.9 (0.1)	7.9 (0.1)	7.9 (0.1)	8.1 (0.1)	8.1 (0.1)	8.2 (0.1)
Week 24, mean (SE)	7.5 (0.1)	7.4 (0.1)	8.0 (0.1)	7.2 (0.1)	7.1 (0.1)	7.8 (0.1)	7.3 (0.1)	7.3 (0.1)	8.0 (0.1)
Change from baseline, adjusted mean[a] (SE)	–0.59 (0.1)	–0.72 (0.1)	–0.11 (0.1)	–0.70 (0.1)	–0.77 (0.1)	–0.13 (0.1)	–0.82 (0.05)	–0.77 (0.05)	–0.17 (0.05)
Comparison vs. PL, adjusted mean[a] (97.5% CI), *P* value	–0.48 (–0.69 to –0.27) < 0.0001	–0.61 (–0.82 to –0.40) < 0.0001	NA	–0.57 (–0.72 to –0.42) < 0.0001	–0.64 (–0.79 to –0.48) < 0.0001	NA	–0.64(–0.79 to –0.49) < 0.0001	–0.59 (–0.74 to –0.44) < 0.0001	NA
Change in fasting plasma glucose (mmol/L)									
Baseline, mean	8.3 (SD 2.1)	8.6 (SD 2.1)	8.3 (SD 2.1)	8.6 (SE 0.1)	8.3 (SE 0.1)	8.7 (SE 0.2)	8.4 (SE 0.1)	8.7 (SE 0.1)	8.4 (SE 0.1)
Week 24, mean	7.5 (SD 2.1)	7.3 (SD 1.6)	9.0 (SD 2.6)	7.4 (SE 0.1)	7.2 (SE 0.1)	8.9 (SE 0.1)	7.1 (SE 2.1)	7.3 (SE 0.1)	8.8 (SE 0.2)
Change from baseline, adjusted mean[a] (SE)	–0.89 (0.17)	–1.23 (0.17)	0.57 (0.17)	–1.11 (0.09)	–1.24 (0.10)	0.35 (0.10)	–1.29 (0.11)	–1.29 (0.11)	0.31 (0.11)
Comparison vs. PL, adjusted mean[a] (97.5% CI), *P* value	–1.46 (–1.93 to –1.00)	–1.80 (–2.26 to –1.33)	NA	–1.47 (–1.74 to –1.20) < 0.0001	–1.59 (–1.86 to –1.32)	NA	–1.60 (–1.90 to –1.30) < 0.0001	–1.60 (–1.91 to –1.29)	NA

Parameter	1245.19			1245.2$_{MET}$			1245.23$_{MET+SU}$		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d. (N = 217)**	**EMPA 25 mg q.d. (N = 213)**	**PL (N = 207)**	**EMPA 10 mg q.d. (N = 225)**	**EMPA 25 mg q.d. (N = 216)**	**PL (N = 225)**
	< 0.0001	< 0.0001			< 0.0001			< 0.0001	
Change in body weight (kg)									
Baseline, mean	79.4 (SD 19.6)	81.0 (SD 20.3)	79.5 (SD 21.2)	81.6 (SE 1.3)	82.2 (SE 1.3)	79.7 (SE 1.3)	77.1 (SE 1.2)	77.5 (SE 1.3)	76.2 (SE 1.1)
Week 24, mean	77.7 (SD 19.2)	79.4 (SD 20.0)	79.9 (SD 20.9)	79.5 (SE 1.2)	79.7 (SE 1.3)	79.3 (SE 1.3)	74.9 (SE 1.2)	75.1 (SE 1.3)	75.9 (SE 1.1)
Change from baseline, adjusted mean[a] (SE)	–1.71 (0.25)	–1.55 (0.25)	0.45 (0.25)	–2.08 (0.17)	–2.46 (0.17)	–0.45 (0.17)	–2.16 (0.15)	–2.39 (0.16)	–0.39 (0.15)
Comparison vs. PL, adjusted mean[a] (95% CI), *P* value	–2.16 (–2.84 to –1.47) < 0.0001	–2.00 (–2.68 to –1.31) < 0.0001	NA	–1.63 (–2.17 to –1.08) < 0.0001	–2.01 (–2.56 to –1.46) < 0.0001	NA	–1.76 (–2.25 to –1.28) < 0.0001	–1.99 (–2.48 to –1.50) < 0.0001	NA
Change in systolic blood pressure (mm Hg)									
Baseline, mean (SE)	126.5 (1.1)	126.0 (1.1)	125.7 (0.9)	129.6 (1.0)	130.0 (1.0)	128.6 (1.0)	128.7 (0.9)	129.3 (1.0)	128.8 (1.0)
Week 24, mean (SE)	123.3 (1.0)	121.9 (1.0)	126.6 (1.2)	125.0 (0.9)	124.6 (1.0)	128.5 (1.0)	124.7 (1.0)	125.7 (0.8)	127.4 (0.9)
Change from baseline, adjusted mean[a] (SE)	–3.14 (0.85)	–4.00 (0.84)	0.72 (0.85)	–4.5 (0.7)	–5.2 (0.7)	–0.4 (0.7)	–4.1 (0.7)	–3.5 (0.7)	–1.4 (0.7)
Comparison vs. PL, adjusted mean[a] (97.5% CI), *P* value	–3.86 (–6.23 to –1.50) = 0.0014	–4.73 (–7.08 to –2.37) < 0.0001	NA	–4.1 (–6.2 to –2.1) < 0.0001	–4.8 (–6.9 to –2.7) < 0.0001	NA	–2.7 (–4.6 to –0.8) = 0.0049	–2.1 (–4.0 to –0.2) = 0.0321	NA
Change in diastolic blood pressure (mm Hg)									
Baseline, mean (SE)	77.2 (0.7)	77.2 (0.6)	76.3 (0.7)	79.6 (0.5)	78.4 (0.6)	78.1 (0.6)	78.4 (0.6)	79.0 (0.6)	78.3 (0.6)
Week 24, mean	75.6 (0.6)	74.8	76.8 (0.7)	77.3 (0.5)	76.9	78.4 (0.6)	76.3 (0.6)	76.7	76.6 (0.6)

Parameter	1245.19			1245.2$_{MET}$			1245.23$_{MET+SU}$		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d. (N = 217)**	**EMPA 25 mg q.d. (N = 213)**	**PL (N = 207)**	**EMPA 10 mg q.d. (N = 225)**	**EMPA 25 mg q.d. (N = 216)**	**PL (N = 225)**
(SE)		(0.7)			(0.6)			(0.5)	
Change from baseline, adjusted mean[a] (SE)	–1.49 (0.51)	–2.21 (0.51)	0.29 (0.51)	–2.0 (0.5)	–1.6 (0.5)	0 (0.5)	–2.1 (0.4)	–2.2 (0.4)	–1.8 (0.4)
Comparison vs. PL, adjusted mean[a] (97.5% CI), *P* value	–1.78 (–3.20 to –0.36) = 0.0144	–2.50 (–3.92 to –1.08) = 0.0006	NA	–1.9 (–3.3 to –0.6) = 0.0057	–1.6 (–2.9 to –0.2) = 0.0258	NA	–0.4 (–1.6 to 0.9) = 0.5566	–0.4 (–1.6 to 0.8) = 0.5343	NA
Harms at Week 24									
N	165	168	165	217	214	206	224	217	225
AEs, n (%)	111 (67.3)	120 (71.4)	120 (72.7)	124 (57.1)	106 (49.5)	121 (58.7)	152 (67.9)	139 (64.1)	141 (62.7)
SAEs, n (%)	7 (4.2)	6 (3.6)	7 (4.2)	7 (3.2)	5 (2.3)	7 (3.4)	11 (4.9)	1 (0.5)	14 (6.2)
WDAEs, n (%)	2 (1.2)	5 (3.0)	4 (2.4)	2 (0.9)	5 (2.3)	7 (3.4)	6 (2.7)	7 (3.2)	8 (3.6)

A1C = glycated hemoglobin; AE = adverse event; ANCOVA = Analysis of covariance; CI = confidence interval; EMPA = empagliflozin; MET = metformin; NA = not applicable; PIO = pioglitazone; PL = placebo; q.d. = once daily; SAE = serious adverse event; SD = standard deviation; SE = standard error; SU = sulfonylurea; vs. = versus; WDAE = withdrawal due to adverse event.

[a] ANCOVA models were adopted in statistical analyses. Details of the models are described in the respective tables in section 3.6, Efficacy.

1. INTRODUCTION

1.1 Disease prevalence and incidence

Diabetes mellitus is a metabolic disorder characterized by persistent elevations in blood glucose (hyperglycemia).[1] When inadequately managed, diabetes is likely to result in poor glycemic control. Impaired glycemic control, if prolonged, may result in damage to blood vessels, on both a microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (peripheral artery disease and cardiovascular disease [CVD]) level, and consequently causes dysfunction and failure of various organs including heart, brain, kidneys, retina, and lower limbs.[1,2] There are two main subtypes of diabetes mellitus: 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 diabetes.[3] T1DM generally develops in childhood or adolescence. In contrast, onset of T2DM is typically later in life, although this is changing with the current epidemic of childhood obesity in Western societies. Family history of diabetes, unhealthy diet, and physical inactivity, and associated weight gain, are considered to be risk factors for T2DM.[4]

Diabetes has significant health impacts on individuals and societies. The prevalence of diabetes is increasing at a dramatic rate around the world. An estimated 422 million adults were living with diabetes globally in 2014, compared with 108 million in 1980, and this number is projected to increase to 642 million by 2040.[5,6] Diabetes is one of the most common chronic diseases in Canada. The Canadian Diabetes Association estimated that there were 3.4 million people (9.3% of the population) with diabetes in 2015, and, by 2025, this number will increase to five million people (12.1%).[7] People with diabetes are more likely to be hospitalized and to experience complications requiring specialist care. The economic burden of diabetes in Canada is expected to be about C$12.2 billion in 2010, and by 2020, the diabetes-associated costs to the Canadian health care system are estimated to increase to C$16.9 billion per year.[8]

1.2 Standards of therapy

Treatment regimens and therapeutic targets should be individualized in patients with T2DM. Treatment usually begins with lifestyle modification, including exercise and diet. When lifestyle interventions are not sufficient to control blood glucose levels, pharmacological treatment becomes necessary.[9,10] There are many classes of antidiabetic drugs used in treating T2DM, including insulin. Metformin (MET) is indicated for most patients and is considered to be the first-line drug of choice. When initial therapy with lifestyle intervention and MET monotherapy fails to achieve adequate glycemic control, a second or third drug can be added to MET. Several oral antidiabetic drugs can be used with MET, such as sulfonylureas (SUs), meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, and dipeptidyl peptidase-4 inhibitors. Injectable drugs (glucagon-like peptide-1 receptor agonists; insulin and insulin analogues in rapid-acting, intermediate, or longer-acting forms) can be added to MET when MET monotherapy fails, or patients are switched to insulin.[9] In deciding which drug to add after MET, multiple factors must be considered; for example, the drug's effectiveness at blood glucose and glycated hemoglobin (A1C) lowering, concerns regarding hypoglycemia, ability to reduce the risk of diabetic microvascular and/or macrovascular complications, and effect on body weight.[10]

1.3 Drug

Empagliflozin (EMPA) is an inhibitor of the sodium-glucose cotransporter-2 (SGLT2) and has an antihyperglycemic effect by reducing renal reabsorption of filtered glucose, and lowers the renal

threshold for glucose, leading to increased urinary glucose excretion.[11] In addition, previous research demonstrated that, in combination with MET, SGLT2 inhibitors are associated with weight loss and lower blood pressure.[12] A cardiovascular (CV) outcome trial of add-on therapy with EMPA (EMPA-REG OUTCOME) did not increase the risk of major CV adverse events (AEs) compared with standard of care in patients with T2DM and CVD.[13]

EMPA is available as 5 mg or 12.5 mg oral tablets. The recommended dose is one tablet twice daily. The maximum recommended daily dose is 25 mg EMPA and 2,000 mg of MET.[11] Other SGLT2 inhibitors approved in Canada include dapagliflozin and canagliflozin. Dapagliflozin, in combination with MET (Xigduo), and canagliflozin, in combination with MET (Invokamet), are currently under review by the CADTH Common Drug Review (CDR).

EMPA (Jardiance) received a Health Canada Notice of Compliance (NOC) in July 2015, as an adjunct to diet and exercise to improve glycemic control in patients with T2DM as a monotherapy, or as an add-on combination therapy when MET used alone does not provide adequate glycemic control. EMPA can be combined with MET; MET and an SU; pioglitazone (PIO, alone or with MET) or insulin (alone or with MET) (Table 2).[14] The EMPA/MET fixed-dose combination (FDC; Synjardy) is the focus of this review. Synjardy received a Health Canada NOC on July 29, 2016.

Indication under review
Health Canada indications: As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on: • metformin • sulfonylurea in combination with metformin • pioglitazone in combination with metformin • insulin in combination with metformin Or in patients already being treated and achieving glycemic control with: • metformin and empagliflozin as separate tablets • sulfonylurea in combination with metformin and empagliflozin as separate tablets • pioglitazone in combination with metformin and empagliflozin as separate tablets • insulin in combination with metformin and empagliflozin as separate tablets
Reimbursement criteria requested by sponsor
As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus already stabilized on therapy with metformin and empagliflozin, to replace the individual components of metformin and empagliflozin in these patients.

TABLE 2: KEY CHARACTERISTICS OF FIXED-DOSE COMBINATION OF SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITOR AND METFORMIN

	EMPA + MET (Synjardy)	CANA + MET (Invokamet)	DAPA + MET (Xigduo)
Mechanism of Action	Combines 2 antihyperglycemic drugs with complementary mechanisms of action.		
	EMPA: inhibitor of SGLT2 that reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion	CANA: inhibitor of SGLT2 that reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion, which decreases elevated plasma glucose concentrations by an insulin-independent mechanism in T2DM. It also reduces systolic blood pressure, results in a loss of calories and therefore a reduction in body weight.	DAPA: a reversible inhibitor of SGLT2 that improves glycemic control in patients with T2DM by reducing renal glucose reabsorption leading to urinary excretion of excess glucose
	MET: biguanide derivative that produces an antihyperglycemic effect only with existing insulin secretion. It decreases hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, improves peripheral glucose uptake and utilization by increasing insulin sensitivity, and decreases intestinal glucose absorption.		
Indication[a]	Adjunct to diet and exercise to improve glycemic control in adult patients with T2DM inadequately controlled on: • MET • an SU in combination with MET • PIO in combination with MET • insulin in combination with MET Or in patients already being treated and achieving glycemic control with: • MET and EMPA as separate tablets • an SU in combination with MET and EMPA as separate tablets • PIO in combination with MET and EMPA as separate tablets • insulin in combination with MET and EMPA as separate tablets	To improve glycemic control as an adjunct to diet and exercise in adult patients with T2DM inadequately controlled on MET, an SU in combination with MET, pioglitazone in combination with MET, or insulin in combination with MET In patients already being treated and achieving glycemic control with MET and CANA as separate tablets, a SU in combination with MET and CANA as separate tablets, PIO in combination with MET and CANA as separate tablets, or insulin in combination with MET and CANA as separate tablets	For use as an adjunct to diet and exercise in adults with T2DM who are already being treated with DAPA and MET as separate tablets and achieving glycemic control For use in combination with a SU (or sitagliptin, or insulin) as an adjunct to diet and exercise in adults with T2DM who are already achieving glycemic control with DAPA, MET, and a SU (or sitagliptin, or insulin)
Route of Administration	Oral		
Recommended Dose	One tablet twice daily Available tablet strengths:	One tablet twice daily with meals	One tablet twice daily with meals

	EMPA + MET (Synjardy)	CANA + MET (Invokamet)	DAPA + MET (Xigduo)
	EMPA 5 mg/MET 500 mg EMPA 5 mg/MET 850 mg EMPA 5 mg/MET 1,000 mg EMPA 12.5 mg/MET 500 mg EMPA 12.5 mg/MET 850 mg EMPA 12.5 mg/MET 1,000 mg Maximum daily dose: EMPA 25 mg/MET 2,000 mg twice daily.	Available tablet strengths: CANA 50 mg/MET 500 mg CANA 50 mg/MET 850 mg CANA 50 mg/MET 1,000 mg CANA 150 mg/MET 500 mg CANA 150 mg/MET 850 mg CANA 150 mg/MET 1,000 mg Maximum daily dose: CANA 150 mg/MET 1,000 mg twice daily.	Available tablet strengths: DAPA 5 mg/MET 850 mg DAPA 5 mg/MET 1,000 mg Maximum daily dose: DAPA 10 mg/MET 2,000 mg
Serious Side Effects/Safety Issues	Contraindications: unstable and/or T1DM, acute or chronic metabolic acidosis, renal dysfunction, excessive alcohol intake, severe hepatic dysfunction, CV collapse, and in disease states associated with hypoxemia, stress condition, severe dehydration, known hypersensitivity to any ingredient in the formulation.		

CANA = canagliflozin; CV = cardiovascular; DAPA = dapagliflozin; EMPA = empagliflozin; MET = metformin; SGLT2 = sodium-glucose cotransporter-2; SU = sulfonylurea; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a] Health Canada indication.
Source: Product monographs from e-CPS.[14-16]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of EMPA/MET FDC for the treatment of adults with T2DM who have experienced inadequate glycemic control on MET alone or on combination therapy of MET and other glucose-lowering products, or who are already being treated with EMPA and MET co-administered as separate tablets.

2.2 Methods

All manufacturer-provided pivotal trials will be included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults (≥ 18 years) with T2DM who have experienced inadequate glycemic control on MET alone or on MET in combination with other glucose-lowering products, or who are already being treated with EMPA and MET co-administered as separate tablets. **Subgroups:** baseline A1C, eGFR
Intervention	EMPA + MET FDC at the following doses twice daily, with or without other glucose-lowering products, and as adjunct to diet and exercise: 5 mg/500 mg 5 mg/850 mg 5 mg/1,000 mg 12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg The maximum daily dose: 25 mg/2,000 mg
Comparators	MET in combination with other glucose-lowering products: • SGLT2 inhibitors • DPP-4 inhibitors • GLP-1 analogues • Thiazolidinediones • Meglitinides • Insulin/insulin analogues • SU
Outcomes	**Efficacy outcomes** • Mortality • Diabetes-related morbidity (macrovascular, microvascular) • Glycemic control (A1C, FPG)[a] • HRQoL[a] • Body weight[a] • Blood pressure[a] **Harms outcomes**[a] • AEs, SAEs, WDAEs • Notable harms: hypoglycemia, urogenital AEs, renal AEs, dyslipidemia, heart failure, ketoacidosis

Study Design	Published and unpublished phase III RCTs

A1C = glycated hemoglobin; AE = adverse event; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; FDC = fixed-dose combination; GLP-1 = glucagon-like peptide 1; FPG = fasting plasma glucose; HRQoL = health-related quality of life; MET = metformin; RCT = randomized controlled trial; SAE = serious adverse event; SGLT2 = sodium-glucose cotransporter-2; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; WDAE = withdrawal due to adverse event.
[a] Outcomes identified as important by patient groups.

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 through Ovid; Embase (1974–) through 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 Synjardy (empagliflozin and metformin hydrochloride).

No filters were applied to limit the 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. See Appendix 2 for the detailed search strategies.

The initial search was completed on May 30, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on October 12, 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 *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Devices Regulatory Approvals, Advisories and Warnings, Drug Class Review, Databases (free). 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 4.

3. RESULTS

3.1 Findings from the literature

A total of three studies were provided by the manufacturer as pivotal studies; therefore, they were included in this review. There were no studies identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

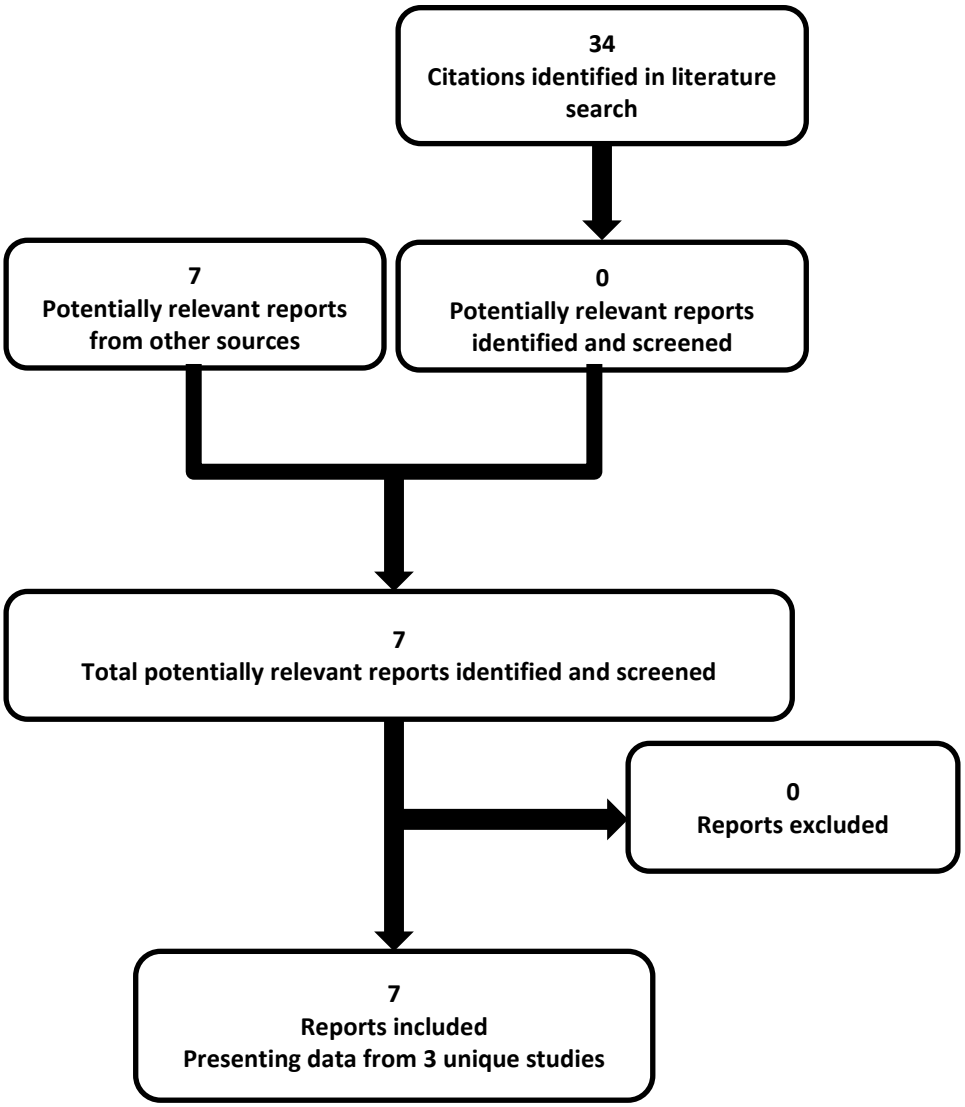


TABLE 4: DETAILS OF INCLUDED STUDIES

		1245.19 (EMPA-REG PIO)	1245.23$_{MET}$ (EMPA-REG MET)	1245.23$_{MET+SU}$ (EMPA-REG MET + SU)
DESIGNS & POPULATIONS	**Study Design**	DB, PL-controlled, RCT, superiority design		
	Locations	69 sites in Canada, China, Greece, India, Philippines, Thailand, Ukraine, and the US	148 sites in Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, and the US	
	Randomized (N)	499	638	669
			Patients with A1C > 10% were treated with OL EMPA 25 mg q.d.	
	Inclusion Criteria	Patients ≥ 18 years (and ≤ 65 years in India), with a diagnosis of T2DM, BMI ≤ 45 kg/m^2, A1C ≥ 7% and ≤ 10% at screening despite a diet and exercise regimen, and a stable dose of PIO monotherapy or PIO + MET ≥ 12 weeks before randomization	Patients ≥ 18 years (and ≤ 65 years in India), with a diagnosis of T2DM, BMI ≤ 45 kg/m^2, A1C ≥ 7% and ≤ 10% at screening despite a diet and exercise regimen, and a stable dose of MET regimen ≥ 12 weeks before randomization	Patients ≥ 18 years (and ≤ 65 years in India), with a diagnosis of T2DM, BMI ≤ 45 kg/m^2, A1C ≥ 7% and ≤ 10% at screening despite a diet and exercise regimen, and a stable dose of MET + SU regimen ≥ 12 weeks before randomization
			Patients with A1C > 10% were eligible in an OL treatment group	
	Exclusion Criteria	Uncontrolled hyperglycemia (> 13.3 mmol/L after overnight fast); severe renal impairment (eGFR < 30 mL/min/1.73 m^2); liver disease before randomization; acute coronary syndrome, stroke or TIA; treatment with anti-obesity drugs within 3 months of consent; GI surgeries that induced chronic malabsorption within 2 years; history of cancer within 5 years; on systemic steroids at the time of consent; had a change in the dose of thyroid hormones within 6 weeks of consent; or had any uncontrolled endocrine disorder except T2DM; investigational drug intake within 30 days of the trial		
		Contraindication to PIO and/or MET	Contraindication to MET	Contraindication to MET or SU
DRUGS	**Intervention**	EMPA 10 mg q.d. PO EMPA 25 mg q.d. PO Add-on to PIO alone (≥ 30 mg/day or the maximum tolerated dose or maximum dose according to the local label) or PIO + MET (MET: ≥ 1,500 mg/day or maximum tolerated dose or maximum dose according to local label)	EMPA 10 mg q.d PO EMPA 25 mg q.d. PO Add-on to MET (≥ 1,500 mg/day or maximum tolerated dose or maximum dose according to local label)	EMPA 10 mg q.d. PO EMPA 25 mg q.d. PO Add-on to MET + SU (MET: ≥ 1,500 mg/day or maximum tolerated dose or maximum dose according to local label; SU: ≥ half the maximum recommended dose, or the maximum tolerated dose or the maximum dose according to local label)
	Comparator(s)	PL q.d. PO	PL q.d. PO	PL q.d. PO

		1245.19 (EMPA-REG PIO)	1245.23$_{MET}$ (EMPA-REG MET)	1245.23$_{MET+SU}$ (EMPA-REG MET + SU)
DURATION	**Phase**			
	Run-in	2 weeks	2 weeks except for patients allocated to the OL group	
	Double-blind	24 weeks		
	Follow-up	1 week if patients did not immediately enter the extension trial		
OUTCOMES	**Primary End Point**	Change from baseline in A1C at week 24		
	Other End Points	Change from baseline in FPG at Week 24 Change from baseline in body weight at Week 24 Mean EQ-5D VAS and health state index score (exploratory end point in the study) Change from baseline in SBP and DBP at Week 24 (exploratory end points in study) Safety: AEs, SAEs, AEs of special interest including hypoglycemic events, protocol-specific significant AEs, CV events, changes from baseline in clinical lab values	Change from baseline in body weight at week 24 Change from baseline in mean daily glucose at week 24 Change from baseline in FPG at week 24 (exploratory end point in the study) Mean EQ-5D VAS and health state index score (exploratory end point in the study) Change from baseline in SBP and DBP at week 24 (exploratory end points in study) Safety: AEs, SAEs, AEs of special interest including hypoglycemic events, protocol-specific significant AEs, CV events, changes from baseline in clinical lab values	
NOTES	**Publications**	Kovacs et al. 2014[17]	Haring et al. 2014[18]	Haring et al. 2013[19]

A1C = glycated hemoglobin; AE = adverse event; BMI = body mass index; CV = cardiovascular; DB = double-blind; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; EQ-5D = EuroQol 5-Dimension Questionnaire; FPG = fasting plasma glucose ; GI = gastrointestinal; MET = metformin; OL = open-label; PIO = pioglitazone; PL = placebo; PO = oral; q.d. = once daily; RCT = randomized controlled trial; SAE = serious adverse event; SBP = systolic blood pressure; SU = sulfonylurea; TIA = transient ischemic attack; T2DM = type 2 diabetes mellitus; VAS = visual analogue scale.
Note: Two additional reports were included (manufacturer's submission,[20] European Medicines Agency [EMA] report[21]).
Source: Clinical Study Reports of 1245.19, 1245.23$_{MET}$ and 1245.23$_{MET+SU,}$[22,23] Kovacs et al. 2014,[17] Haring et al. 2014,[18] Haring et al. 2013.[19]

3.2 Included studies

3.2.1 Description of studies

Three phase III, multi-centre, double-blind (DB), placebo-controlled, randomized controlled trials (RCTs) met the inclusion criteria for this systematic review.[22,23]

The study design of Studies 1245.19, 1245.23$_{MET}$, and 1245.23$_{MET+SU}$ are shown in Figure 2.

All three studies are three-arm superiority studies and evaluated the efficacy and safety of EMPA administered 10 mg once daily or 25 mg once daily as add-on therapy to background therapy compared with placebo for 24 weeks in patients with T2DM with insufficient glycemic control. The background

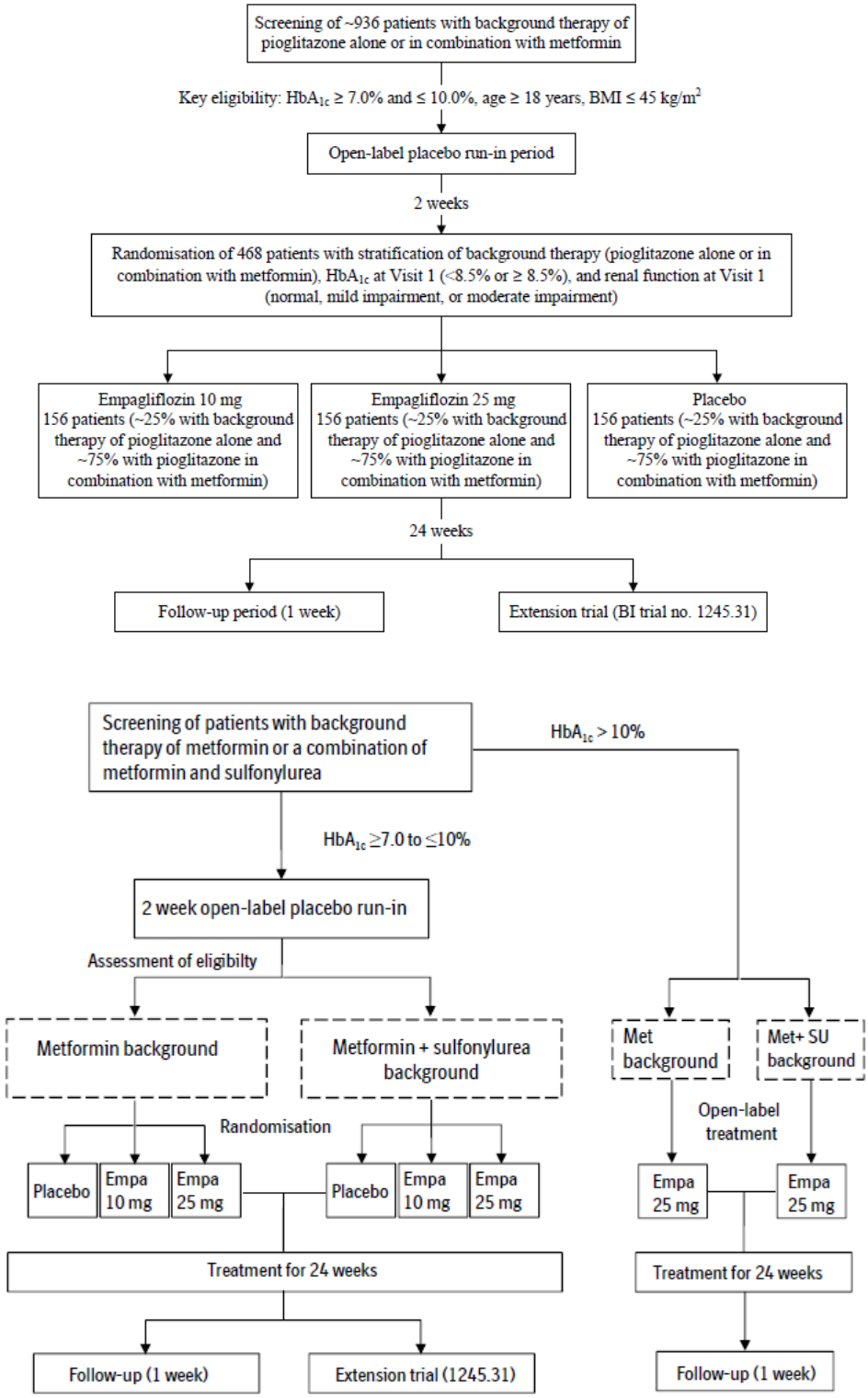
therapy was PIO alone or PIO + MET in Study 1245.19 (N = 499), MET alone in Study 1245.23$_{MET}$ (N = 638), and MET + SU in Study 1245.23$_{MET+SU}$ (N = 669). After screening, there was a two-week placebo run-in period in all three studies. The background medications were continued during the run-in period. After the run-in period, eligible participants were randomized in a ratio of 1:1:1 to receive one of the EMPA + background therapy or placebo + background therapy in a DB manner for 24 weeks. Randomization was carried out using a validated system. From the time of randomization, the patients, the investigators, and persons performing data analysis remained blinded to the treatment allocation.

In Studies 1245.23$_{MET}$ and 1245.23$_{MET+SU}$, patients with A1C ≥ 10% were entered into an open-label (OL) EMPA treatment group. The objective of the OL treatment group of the study was to estimate the efficacy, safety, and tolerability of EMPA 25 mg once daily for 24 weeks in patients with T2DM with very poor glycemic control. There was no run-in period for this treatment group. OL treatment was not allowed in Germany.

In Study 1245.19, randomization was stratified by A1C at screening, background medication, and renal function at screening. In Studies 1245.23$_{MET}$ and 1245.23$_{MET+SU}$, randomization was stratified by A1C at screening, renal function at screening, and geographical region.

In all three trials, patients who completed the 24-week treatment were eligible to continue their randomized treatment by enrolling in an extension trial (Boehringer Ingelheim [BI] trial 1245.31). Patients who did not enter the extension trial were to be followed up for one week.

FIGURE 2: STUDY DESIGN FOR STUDIES 1245.19 (TOP), 1245.23$_{MET}$, AND 1245.23$_{MET+SU}$ (BOTTOM)



BMI = body mass index; Empa = empagliflozin; HbA$_{1C}$ = glycated hemoglobin; Met = metformin; SU = sulfonylurea.
Sources: Clinical Study Reports of 1245.19,[22] 1245.23$_{MET}$, and 1245.23$_{MET+SU}$.[23]

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 background medication (at least 30 mg once daily PIO, at least 1,500 mg once daily MET, and a maximum tolerated dose at least half the maximum dose of an SU [according to local label]) for at least 12 weeks before enrolment. Patients had to have an A1C value between 7.0% and 10.0% at screening. In study 1245.23_{MET+SU}, patients with A1C greater than 10% were eligible to enter an OL treatment group. Patients were excluded if they had uncontrolled hyperglycemia, severe renal impairment, liver disease before randomization, CV events (acute coronary syndrome, stroke or transient ischemic attack) within three months before consent, treatment with anti-obesity drugs within three months of consent, gastrointestinal surgeries that induced chronic malabsorption within two years, history of cancer within five years, on systemic steroids at the time of consent, had a change in the dose of thyroid hormones within six weeks of consent, or had any uncontrolled endocrine disorder except T2DM, or investigational drug intake within 30 days of the study.

b) Baseline characteristics

The mean age of patients ranged between 54 and 57 years across the three studies. The proportions of males and females were comparable in Studies 1245.19 and 1245.23MET+SU. In Study 1245.23MET, there were more males (56% to 58%) than females (42% to 44%). In Studies 1245.19 and 1245.23MET+SU, more than 50% of patients were Asian, while in Study 1245.23MET, the proportion of white patients was slightly greater than Asian patients (Table 5). Physical and disease characteristics such as weight, body mass index (BMI), level of A1C, fasting plasma glucose (FPG), and blood pressure were similar between treatment groups. The majority of patients in the three studies had normal renal function or mild renal function impairment. In Study 1245.19, between 75% and 76% of patients received PIO + MET as background therapy. The background therapy in Studies 1245.23MET and 1245.23MET+SU was MET alone and MET + SU, respectively. With regard to time since diagnosis, the proportion of patients with a diagnosis of T2DM longer than 10 years was higher in Study 1245.23MET+SU, compared with the other two studies.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS – FULL ANALYSIS SET

	1245.19 PIO			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d (N = 217)**	**EMPA 25 mg q.d. (N = 213)**	**PL (N = 207)**	**EMPA 10 mg q.d. (N = 225)**	**EMPA 25 mg q.d. (N = 216)**	**PL (N = 225)**
Age, mean (SD)									
	54.7 (9.9)	54.2 (8.9)	54.6 (10.5)	55.5 (9.9)	55.6 (10.2)	56.0 (9.7)	57.0 (9.2)	57.4 (9.3)	56.9 (9.2)
Sex, n (%)									
Male	83 (50.3)	85 (50.6)	73 (44.2)	125 (57.6)	120 (56.3)	116 (56.0)	113 (50.2)	114 (52.8)	112 (49.8)
Female	82 (49.7)	83 (49.4)	92 (55.8)	92 (42.4)	93 (43.7)	91 (44.0)	112 (49.8)	102 (47.2)	113 (50.2)
Race									
American Indian/ Alaska Native	1 (0.6)	0	1 (0.6)	2 (0.9)	2 (0.9)	0	4 (1.8)	3 (1.4)	3 (1.3)
Asian	91 (55.2)	94 (56.0)	103 (62.4)	99 (45.6)	98 (46.0)	92 (44.4)	129 (57.3)	125 (57.9)	127 (56.4)
Black/ African-American	4 (2.4)	6 (3.6)	1 (0.6)	4 (1.8)	0	2 (1.0)	3 (1.3)	3 (1.4)	7 (3.1)
White	69 (41.8)	68 (40.5)	60 (36.4)	112 (51.6)	113 (53.1)	113 (54.6)	89 (39.6)	85 (39.4)	88 (39.1)
Body weight, kg, mean (SD)									
	78.0 (19.1)	78.9 (19.9)	78.1 (20.1)	81.6 (18.5)	82.2 (19.3)	79.7 (18.6)	77.1 (18.3)	77.5 (18.8)	76.2 (16.9)
BMI, mean (SD), kg/m^2									
	29.2 (5.6)	29.1 (5.5)	29.3 (5.4)	29.1 (5.5)	29.7 (5.7)	28.7 (5.2)	28.3 (5.4)	28.3 (5.5)	27.9 (4.9)
A1C, mean (SD), %									
	8.1 (0.9)	8.1 (0.8)	8.2 (0.9)	7.9 (0.8)	7.9 (0.9)	7.9 (0.9)	8.1 (0.8)	8.1 (0.8)	8.2 (0.8)
< 8.0%, n (%)	82 (49.7)	88 (52.4)	76 (46.1)	122 (56.2)	124 (58.2)	121 (58.5)	110 (48.9)	105 (48.6)	112 (49.8)
8.0% to < 9.0%	57 (34.5)	54 (32.1)	57 (34.5)	67 (30.9)	66 (31.0)	60 (29.0)	81 (36.0)	78 (36.1)	71 (31.6)
≥ 9.0%, n (%)	26 (15.8)	26 (15.5)	32 (19.4)	28 (12.9)	23 (10.8)	26 (12.6)	34 (15.1)	33 (15.3)	42 (18.7)

	1245.19 PIO			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d (N = 217)**	**EMPA 25 mg q.d. (N = 213)**	**PL (N = 207)**	**EMPA 10 mg q.d. (N = 225)**	**EMPA 25 mg q.d. (N = 216)**	**PL (N = 225)**
FPG, mean (SD), mmol/L[a]									
	8.4 (2.1)	8.4 (2.1)	8.4 (2.2)	8.6 (2.0)	8.3 (1.7)	8.7 (1.8)	8.7 (1.8)	8.7 (1.9)	8.4 (2.0)
Blood pressure, mean (SD), mm Hg									
SBP	126.5 (13.7)	125.9 (13.9)	125.7 (12.1)	129.6 (14.1)	130.0 (15.1)	128.6 (14.7)	128.7 (13.9)	129.3 (14.2)	128.8 (14.3)
DBP	77.2 (8.7)	77.2 (8.0)	76.3 (8.7)	79.6 (8.0)	78.4 (8.4)	78.1 (7.9)	78.4 (9.6)	79.0 (8.4)	78.3 (8.6)
eGFR, mean (SD), mL/min/1.73 m^2									
	84.3 (20.9)	87.4 (24.4)	85.5 (20.1)	89.5 (19.6)	87.7 (19.3)	89.7 (21.4)	86.5 (21.8)	88.3 (22.6)	86.9 (20.1)
≥ 90, n (%)	60 (36.4)	67 (39.9)	63 (38.2)	96 (44.2)	91 (42.7)	95 (45.9)	92 (40.9)	94 (43.5)	94 (41.8)
60 to < 90, n (%)	85 (51.5)	85 (50.6)	84 (50.9)	112 (51.6)	108 (50.7)	100 (48.3)	114 (50.7)	105 (48.6)	109 (48.4)
30 to < 60, n (%)	20 (12.1)	16 (9.5)	18 (10.9)	9 (4.1)	14 (6.6)	12 (5.8)	19 (8.4)	17 (7.9)	22 (9.8)
History of hypertension, n (%)									
	94 (57.0)	98 (58.3)	98 (59.4)	124 (57.1)	124 (58.2)	107 (51.7)	143 (63.6)	129 (59.7)	125 (55.6)
Background medication, n (%)									
PIO + Insulin	0	1 (0.6)	0	NA			NA		
PIO only	40 (24.2)	40 (23.8)	41 (24.8)						
MET + PIO	125 (75.8)	127 (75.6)	124 (75.2)						
MET only	NA			212 (97.7)	212 (99.5)	204 (98.6)	2 (0.9)	1 (0.5)	1 (0.4)
MET + SU				5 (2.3)	1 (0.5)	3 (1.4)	222 (98.7)	215 (99.5)	224 (99.6)
MET + SU + Insulin				NR	NR	NR	1 (0.4)	0	0
Time since diagnosis of T2DM, n (%)									
≤ 1 years	29 (17.6)	17 (10.1)	19 (11.5)	20 (9.2)	19 (8.9)	19 (9.2)	3 (1.3)	7 (3.2)	2 (0.9)

	1245.19 PIO			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d (N = 217)**	**EMPA 25 mg q.d. (N = 213)**	**PL (N = 207)**	**EMPA 10 mg q.d. (N = 225)**	**EMPA 25 mg q.d. (N = 216)**	**PL (N = 225)**
> 1 to 5 years	60 (36.4)	76 (45.2)	78 (47.3)	78 (35.9)	69 (32.4)	83 (40.1)	59 (26.2)	43 (19.9)	36 (16.0)
> 5 to 10 years	45 (27.3)	48 (28.6)	42 (25.5)	68 (31.3)	74 (34.7)	65 (31.4)	74 (32.9)	79 (36.6)	94 (41.8)
> 10 years	31 (18.8)	27 (16.1)	26 (15.8)	51 (23.5)	51 (23.9)	40 (19.3)	89 (39.6)	87 (40.3)	93 (41.3)

A1C = glycated hemoglobin; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; FPG = fasting plasma glucose; MET = metformin; NA = not applicable; NR = not reported; PIO = pioglitazone; PL = placebo; q.d. = once daily; SBP = systolic blood pressure; SD = standard deviation; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

[a] The measurement unit of FPG was converted from "mg/dL."

Source: Clinical Study Reports of 1245.19, 1245.23$_{met}$, and 1245.23 $_{MET+SU.}$[22,23]

c) Interventions

In all three studies, patients were randomized 1:1:1 to EMPA 10 mg, EMPA 25 mg, or placebo, administered orally once daily. The treatment groups had a background combination therapy regimen of PIO alone, PIO + MET, MET alone, or MET + SU. Patients were to be on a stable dose of background combination therapy for at least 12 weeks before enrolment. The doses of background medications were required to be at least 30 mg per day for PIO, at least 1,500 mg per day for MET, at least half the maximum recommended dose for SU, or the maximum tolerated dose or maximum dose according to local label for each of them. A two-week placebo lead-in period was implemented before randomization to EMPA and placebo.

During the first 12 weeks of randomized treatment, rescue therapy was to be initiated only if a patient had a confirmed glucose level of greater than 13.3 mmol/L after an overnight fast. During the subsequent 12 weeks, rescue therapy was to be initiated only if a patient had a confirmed glucose level of greater than 11.1 mmol/L after an overnight fast. The decision to initiate rescue therapy, the choice of rescue therapy, and its dosage were at the investigator's discretion; however, SGLT2 inhibitors other than EMPA were not to be used. In case of hypoglycemia, appropriate adjustment of the antidiabetic therapy was to be initiated, such as dose reduction or discontinuation of ongoing rescue therapy or of existing background medication. If the patient's hyperglycemia or hypoglycemia could not be controlled and the investigator anticipated no further effect from the rescue therapy, the patient was to be discontinued from the trial. Other than as rescue therapy or background medication, the use of other antidiabetic drugs was not allowed during the studies.

3.2.4 Outcomes

This outcome was reported in the safety analysis in the included studies.

a) Mortality

Diabetes-related morbidity (macrovascular, microvascular)

The occurrences of diabetes-related morbidity were not evaluated in the included studies.

Glycemic control (glycated hemoglobin, fasting plasma glucose)

Change from baseline in A1C at week 24 was the primary efficacy end point in all three studies. Change from baseline in FPG at week 24 was a key secondary end point in Study 1245.19, but an exploratory end point in Studies 1245.23_{MET} and 1245.23_{MET+SU}. After randomization, blood samples were drawn before breakfast and before administration of study medication. Blood samples for the determination of A1C and FPG were analyzed at the central laboratory. A reduction of 0.3% in A1C is considered a clinically important change.[24] According to the clinical expert consulted for this review, a change of less than 1 mmol/L (approximately 18 mg/dL) in FPG would not be considered clinically important. A change of at least 1.67 mmol/L (30 mg/dL) in FPG from baseline was considered glycemic response in some clinical trials.[25]

Health-Related Quality of Life (EuroQol 5-Dimension Questionnaire)

Health-related quality of life (HRQoL) was assessed using the EuroQol 5-Dimension Questionnaire (EQ-5D) self-report questionnaire. The descriptive system of the EQ-5D consists of five questions assessing the following dimensions: mobility, self-care, usual activities, pain and/or discomfort, and anxiety and/or 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.[26] A minimal clinically important difference (MCID) for EQ-5D

health index score in patients with diabetes was not identified; however, in other conditions, it typically ranges from 0.033 to 0.074.[27] The second component of the EQ-5D is a visual analogue scale (VAS), asking patients to rate their health from 0 to 100 (0 represents worst imaginable health state and 100 represents best imaginable health). The MCID for EQ-5D VAS score has not been identified. Mean EQ-5D VAS and health state index scores by visit over time were measured in the included studies.

Body weight

The change from baseline in body weight after 24 weeks of treatment was a key secondary efficacy end point. Body weight was to be measured on the same scale for each patient. Scales were centrally provided by the sponsor. A 5% to 10% change in body weight was considered clinically important for this outcome.[28,29]

Blood pressure

Changes from baseline in systolic blood pressure (SBP) or diastolic blood pressure (DBP) to week 24 were exploratory end points in the included studies. SBP and DBP were measured after five minutes of rest in the seated position. Previous studies suggested that a reduction of at least 5 mm Hg in SBP and DBP is associated with between 20% and 40% fewer CV complications.[30,31]

Safety

AEs, serious adverse events (SAEs), as well as withdrawals due to adverse events (WDAEs) and notable harms were evaluated in the included studies. An AE is defined as any untoward medical occurrence in a patient who was administered a pharmaceutical product in a clinical investigation, irrespective of causal relationship with this treatment. An SAE is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability and/or incapacity, requires or prolongs patient hospitalization, is a congenital anomaly and/or birth defect, or is deemed serious for any other reason based on appropriate medical judgment.

3.2.5 Statistical analysis

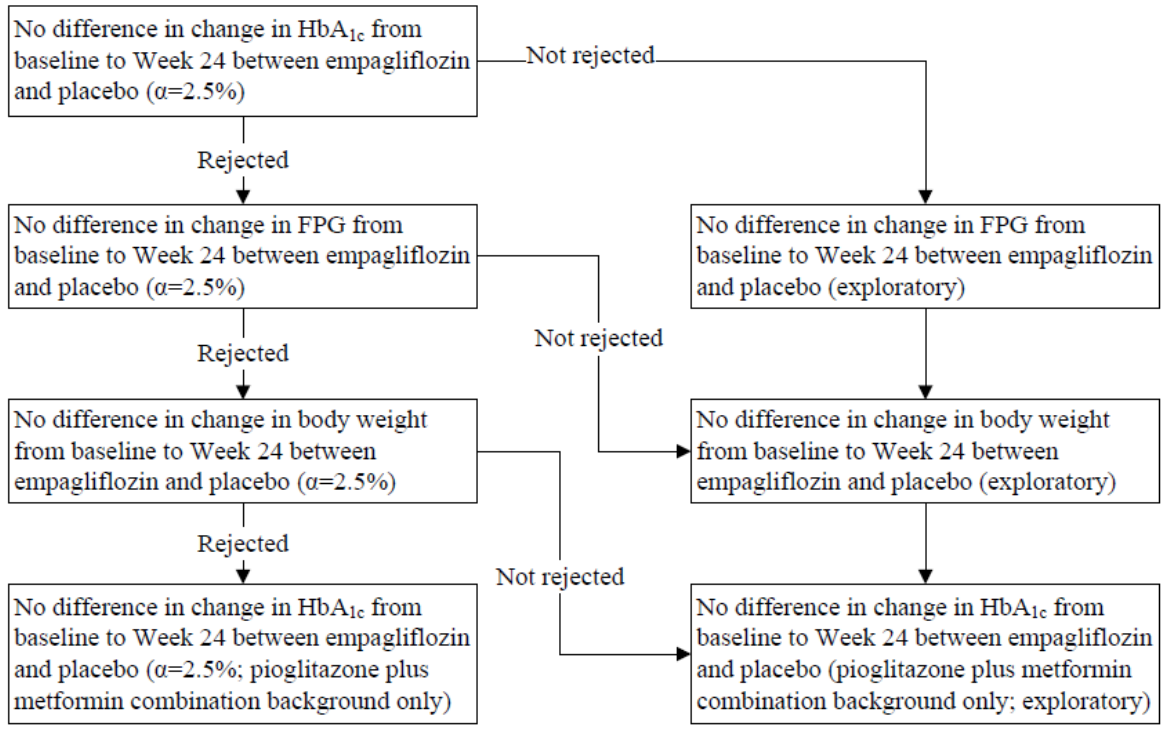
In Study 1245.19, a sample size of 468 patients (156 patients for each randomized treatment group, three arms in total) was planned in order to provide 90% power at a two-sided significance level of 0.025 to detect a difference of 0.5% between EMPA versus placebo for mean change in A1C from baseline to week 24, assuming a 5% dropout rate in the full analysis set (FAS). A standard deviation of 1.1% was selected based on previous experience with EMPA. Randomization was stratified by A1C at screening (< 8.5% or ≥ 8.5%), renal function at screening (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m^2, 60 to 89 mL/min/1.73 m^2, or 30 to 59 mL/min/1.73 m^2), and background medication (PIO alone or with MET). Each dose of EMPA (10 mg or 25 mg) was independently compared with placebo. The hypotheses were tested in a pre-specified hierarchical sequence (primary end point, first key secondary end point, second key secondary end point, and primary end point for patients with PIO in combination with MET background therapy; Figure 3). In this study, the primary end point was the mean change in A1C from baseline to week 24. The statistical model used for the primary analysis was an analysis of covariance (ANCOVA) including "treatment," "background antidiabetic medication," and "renal function at baseline" as fixed effects**,** and baseline A1C as a linear covariate. The analysis of the primary end point for patients with PIO alone as background therapy was removed from the hierarchical sequence and only performed as an exploratory analysis because of the reduction in the number of patients after the implementation of a protocol amendment. The overall significance level for the trial is alpha = 5% (two-sided); alpha was spent equally between the two test sequences for the two doses (i.e., 2.5% on each test). Each step in either test sequence was only regarded as "confirmatory" if the null hypothesis tested before was rejected for that specific dose level. If, at any step, the null hypothesis was

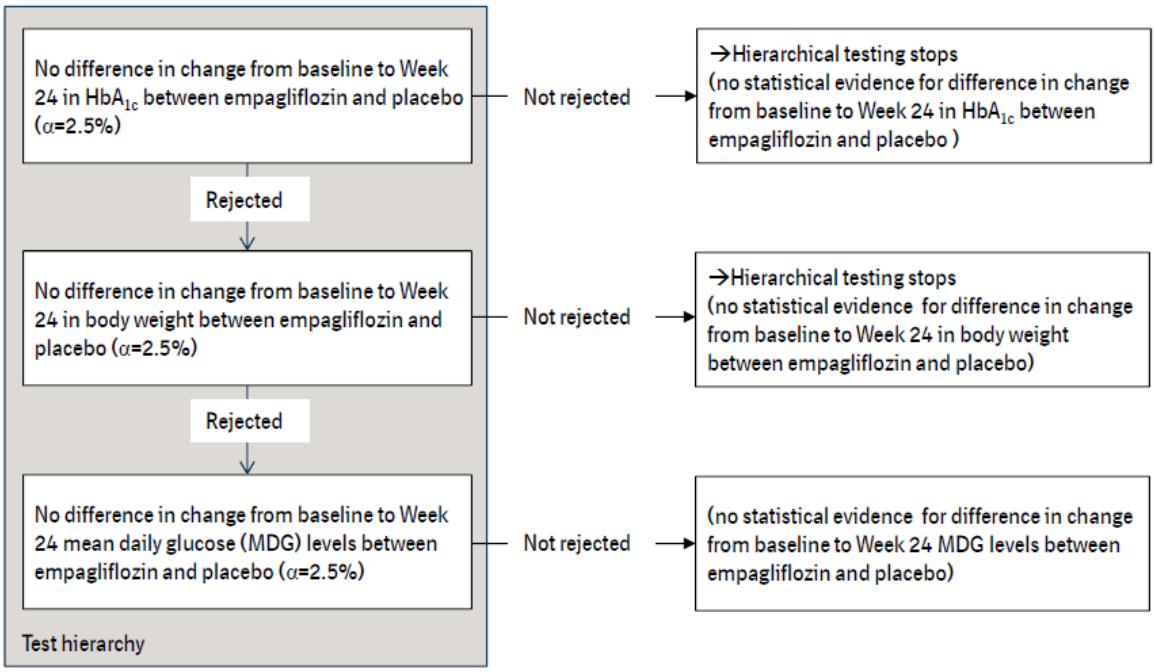
not rejected, the subsequent step(s) of that dose level were regarded as "exploratory." Sensitivity analyses of the primary outcome were carried out using ANCOVA based on different analysis sets and imputation methods; in addition, a restricted maximum likelihood-based mixed model repeated measures (MMRM) approach was used to analyze changes over time for efficacy variables. Continuous exploratory end points were analyzed using a similar model as for the primary analysis. Categorical exploratory end points were tabulated. Binary exploratory end points were analyzed using logistic regression. Subgroup analyses for the primary efficacy end point (change from baseline to week 24 in A1C) were conducted for the following: baseline age, baseline A1C, baseline BMI, baseline body weight, geographical region, race, sex, ethnicity, time since diagnosis of diabetes at baseline, baseline renal function, baseline blood pressure, and history of hypertension. Multiplicity was not addressed in the subgroup analyses.

In Studies 1245.23$_{MET}$ and 1245.23$_{MET+SU}$, a sample size of 615 patients (205 patients for each randomized DB treatment group, three groups in total) for each study was planned in order to provide 90% power at a two-sided significance level of 0.025 to detect a difference of 0.5% between EMPA versus placebo, for each dosing group, for mean change in A1C from baseline to week 24, assuming a 15% dropout rate in the FAS. A standard deviation of 1.2% was selected based on previous experience with EMPA. Randomization was stratified by A1C at screening, renal function at screening, and geographical region. In this study, the primary end point was the mean change in A1C from baseline to week 24. The statistical model used for the primary analysis was ANCOVA, including "treatment," "geographical region," and "renal function at baseline" as fixed effects**,** and baseline A1C as a linear covariate. The primary analysis was performed on the FAS. The analysis of the key secondary end points was carried out using a hierarchical testing approach (Figure 3). If, for a specific dose, the null hypothesis was rejected for the primary end point at 0.025 (two-sided), the same dose was tested against placebo at 0.025 (two-sided) for the first key secondary end point (change from baseline in body weight). Only if superiority over placebo was shown at this gate level did the testing proceed to the second key secondary end point (change from baseline in mean daily glucose, to be measured by patients at eight time points over a single 24-hour period within one week before the scheduled visits) with the same dose, tested at a significance level of 0.025 (two-sided). At any step of the testing procedure, if the null hypothesis was not rejected, the testing was to stop for that dose group. Each hypothesis was to be tested at the significance level of 0.025 to maintain the overall type I error at 5%. The OL group was not included in this analysis. Sensitivity analysis of the primary end point was performed by ANCOVA modelling, using a restricted maximum likelihood (REML)-based MMRM approach and a multiple imputation approach. Key categories used for subgroup analyses of primary and key secondary end points were age, race, baseline A1C, gender, and time since diagnosis of diabetes. Multiplicity was not addressed in the subgroup analyses.

In all three studies in the FAS for the primary analyses of the efficacy end points, missing data were handled using various methods, such as the last observation carried forward (LOCF) approach, "original-results" analyses or "observed-cases" analyses. Values after the patient started rescue medication were excluded from analysis and imputed with an LOCF procedure.

FIGURE 3: FLOW CHART OF HYPOTHESIS TESTING FOR EMPAGLIFLOZIN 10 MG OR 25 MG — STUDY 1245.19 (TOP), STUDY 1245.23$_{MET}$, AND STUDY 1245.23$_{MET+SU}$ (BOTTOM)





FPG = fasting plasma glucose; HbA_{1C} = glycated hemoglobin; MDG = mean daily glucose.
Sources: Clinical Study Reports of 1245.19, 1245.23$_{MET}$ and 1245.23 $_{MET+SU}$.[22,23]

a) Analysis populations

In all three trials, the analysis set was defined as

- Treated set (TS): including all patients treated with at least one dose of randomized study medication
- FAS: including all randomized and treated patients who had a baseline A1C value
- Per-protocol set: including all patients in the FAS without important protocol violations leading to exclusion
- Safety set: consisted of all patients who took at least one dose of randomized study medication. This is as same as the TS.

In addition, in the two 1245.23 studies, an OL set included all patients entered in the EMPA 25 mg OL treatment group.

In the three trials, efficacy analyses were mainly based on the FAS, using the intention-to-treat (ITT) principle. Standard safety analyses were performed based on the TS.

3.3 Patient disposition

Discontinuations between the EMPA and placebo groups varied across the treatment arms. Patients in the placebo arms were more likely to withdraw the study earlier. The most common reason for discontinuation was AE (Table 6).

TABLE 6: PATIENT DISPOSITION

	1245.19			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d.	**EMPA 25 mg q.d.**	**PL**	**EMPA 10 mg q.d.**	**EMPA 25 mg q.d.**	**PL**	**EMPA 10 mg q.d.**	**EMPA 25 mg q.d.**	**PL**
Screened, N	762			970[a]			1010[b]		
Randomized, N	165	168	166	217	214	207	226	218	225
Discontinued, N (%)	11 (6.7)	12 (7.1)	18 (10.9)	8 (3.7)	17 (8.0)	21 (10.1)	17 (7.6)	17 (7.9)	24 (10.7)
AE	2 (1.2)	5 (3.0)	4 (2.4)	2 (0.9)	5 (2.3)	7 (3.4)	6 (2.7)	7 (3.2)	8 (3.6)
Lack of efficacy	0	0	0	0	0	0	0	0	2 (0.9)
Non-compliant to protocol	2 (1.2)	3 (1.8)	2 (1.2)	1 (0.5)	0	2 (1.0)	0	2 (0.9)	2 (0.9)
Lost to follow-up	3 (1.8)	2 (1.2)	4 (2.4)	3 (1.4)	4 (1.9)	2 (1.0)	0	3 (1.4)	3 (1.3)
Patient refusal to continue, not due to AE	2 (1.2)	1 (0.6)	6 (3.6)	2 (0.9)	4 (1.9)	7 (3.4)	4 (1.8)	2 (0.9)	4 (1.8)
Other	2 (1.2)	1 (0.6)	2 (1.2)	0	4 (1.9)	3 (1.4)	7 (3.1)	3 (1.4)	5 (2.2)
FAS, N (%)	165 (100)	168 (100)	165 (99.4)	217 (100)	213 (99.5)	207 (100)	225 (99.6)	216 (99.1)	225 (100)
PPS, N (%)	153 (92.7)	155 (92.3)	152 (92.1)	202 (93.1)	197 (92.5)	181 (87.4)	203 (90.2)	191 (88.4)	196 (87.1)
Safety, N (%)[c]	165 (100)	168 (100)	165 (99.4)	217 (100)	214 (100)	206 (99.5)	224 (99.1)	217 (99.5)	225 (100)

AE = adverse event; EMPA = empagliflozin; FAS = full analysis set; MET = metformin; OL = open-label; PL = placebo; PPS = per-protocol set; q.d = once daily; SU = sulfonylurea.

[a] 69 patients were assigned to OL EMPA 25 mg q.d. treatment group.

[b] 103 patients were assigned to OL EMPA 25 mg q.d. treatment group.

[c] Safety analysis was performed based on the treated set.

Source: Clinical Study Reports of 1245.19, 1245.23$_{MET}$, and 1245.23$_{MET+SU}$, [22,23] Kovacs et al. 2014,[17] Haring et al. 2014,[18] Haring et al. 2013.[19]

3.4 Exposure to study treatments

In all studies, treatment compliance was assessed at each visit, based on tablet count of dispensed and returned medication. Non-compliance was defined as being outside the range of 80% to 120% of tablets consumed. The extent of exposure was similar between groups in the 24-week DB phase and was consistent with the length of treatment.

In Study 1245.19, most patients (86.7% in the placebo group, 93.9% in the EMPA 10 mg group, and 88.7% in the EMPA 25 mg group) were exposed to treatment for 20 to 26 weeks, with mean exposures (standard deviation [SD]) of 164.6 (30.2) days in the placebo group, 165.2 (30.5) days in the EMPA 10 mg group, and 165.0 (28.6) days in the EMPA 25 mg group.

In Study 1245.23$_{MET}$, the mean (SD) exposure to randomized study medication was 170.0 (12.2) days in the EMPA 10 mg group, 164.0 (28.2) days in the EMPA 25 mg group, and 161.4 (35.4) days in the placebo group. The majority of patients were treated with study medication for 20 to 26 weeks: 94.0% in the EMPA 10 mg group, 80.7% in the EMPA 25 mg group, and 87.4% in the placebo group.

In Study 1245.23$_{MET+SU}$, the mean (SD) exposure to randomized study medication was 164.8 (27.7) days in the EMPA 10 mg group, 161.1 (37.0) days in the EMPA 25 mg group, and 162.0 (33.3) days in the placebo group. The majority of patients were treated with study medication for 20 to 26 weeks: 90.6% in the EMPA 10 mg group, 89.9% in the EMPA 25 mg group, and 87.6% in the placebo group.

3.5 Critical appraisal

3.5.1 Internal validity

In the included studies, the randomization list was generated using a validated system, which involved a pseudo-random number generator and a supplied seed number so that the resulting allocation of medication numbers to treatment was both reproducible and non-predictable. Access to the randomization codes was restricted to dedicated randomization personnel. After randomization, all relevant parties were appropriately blinded to treatment-group assignments. The trial was unblinded only after all case-report forms and other electronic data had been entered into the trial database, after all queries had been resolved, and after the database had been locked. The treatment code was only to be broken in emergency situations in order to provide appropriate medical treatment or if required to ensure patient safety. According to the protocols, patients and investigators could review and discuss changes in glycemic parameters, body weight, blood pressure, and AEs during the studies. Some specific drug effects, such as weight loss or urogenital AEs, are known to be associated with the administration of SGLT2 inhibitor class drugs. This may have allowed certain patients (and/or investigators) to surmise that the patients were randomized to receive the active treatment. However, the primary outcome variable in all of the studies, change in A1C, is an objective (hard) outcome measure, which was determined by central laboratories; therefore, if unblinding occurred, it is unlikely that it had an important impact on the study results for the primary analysis.

Randomization was stratified by key baseline characteristics, such as A1C level, renal impairment, and background medication. The overall loss to follow-up was low and similar (between 1% and 2%) across the treatment arms and studies. Despite randomization, numerical differences in baseline characteristics were noted between the EMPA groups and the placebo groups. In Study 1245.19, there was a greater proportion of males in the two EMPA groups compared with the placebo group (50.3% versus 50.6% versus 44.2%), and in Studies 1245.23$_{MET}$ and 1245.23$_{MET+SU}$, the proportions of patients with a history of hypertension varied across the treatment arms. In addition, there were imbalanced proportions of patients in the time since diagnosis of T2DM of one to five years and five to 10 years.

Other diabetes-related baseline characteristics, such as body weight, BMI, level of A1C, level of FPG levels at baseline, were similar between treatment groups. Although imbalances in the baseline characteristics of the EMPA and placebo groups were noted, there was no apparent evidence or strong clinical reason for these imbalances to have a clinically relevant impact on the primary study results.

In terms of the methods of statistical analysis, various approaches (i.e., LOCF) were used to handle missing data in the included studies. Efficacy analyses were performed in FAS. Although a true ITT population was not used (only patients with baseline A1C were included in analysis), it is less likely that this would have an impact on the study results, due to the small number of patients who were excluded from the FAS. A hierarchical testing procedure was used to account for multiple comparisons among the primary end point and the key secondary end points. This is a common strategy to account for multiplicity. The hierarchical sequence in the included studies was pre-specified and included the most clinically relevant outcomes. If at any step the null hypothesis was not rejected, the subsequent steps were regarded as "exploratory" (Study 1245.19) or the testing was to stop for that dose level (Studies 1245.23_{MET} and 1245.23_{MET+SU}). In addition, splitting the alpha to 0.025 and using a 97.5% confidence interval (CI) (two-sided) was also appropriate to control for multiplicity of testing of the primary and secondary end points for the two dosing arms. The manufacturer adhered to its stated hierarchical testing procedure. Outcomes outside of the testing hierarchy, such as change in blood pressure and patient-reported outcomes, need to be interpreted with caution owing to the possibility of inflated type I error.

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

Subgroup analyses were conducted based on a number of factors, and analyses of results versus placebo were presented; however, there was no adjustment made for multiple comparisons. Therefore, no solid conclusions should be drawn from such analyses, as they are prone to type I error; they may be considered as hypothesis-generating only. In addition, although the three studies were adequately powered to evaluate the primary outcome, there were a relatively small number of patients included in the subgroup analyses; therefore, the subgroup analyses may not have sufficient power to detect statistically significant differences in the key efficacy outcomes between treatment arms.

In Study 1245.19, the outcome of change in blood pressure was assessed in a population with mixed background therapy (PIO alone [approximately 24%] and a combination therapy of PIO + MET [approximately 76%]); therefore, the treatment effect of the study drug on the change in blood pressure in the target population (patients with a background therapy of PIO + MET) was uncertain.

In the three studies, efficacy and safety of co-administration of EMPA and MET were assessed up to week 24 after the randomization. There was a lack of longer-term efficacy and safety data available for the combination of EMPA + MET in patients with inadequate glycemic control with previous antidiabetic therapy. In addition, important clinical outcomes such as diabetes-related comorbidity (microvascular and macrovascular events) and diabetes-specific quality of life (QoL) were not assessed, probably because of the short duration of the included studies. CDR is not allowed to assess the clinical benefits and harms in this regard.

3.5.2 External validity

The manufacturer requested reimbursement for EMPA + MET FDC administered twice daily in the study population; however, there were no RCTs available to evaluate the clinical efficacy and safety of this

particular product. Instead, results from bioequivalent studies and a bridging study are examined (Appendices 5 and 8). One non-pivotal study was identified that compared EMPA (25 mg daily) against glimepiride (GLIM; 1 mg to 4 mg daily) for patients with inadequate glycemic control with MET monotherapy (Study 1245.28; see Appendix 6: Summary of Other Phase III Studies); however, no other studies were identified that directly compared EMPA with any other active comparator — in particular other SGLT2 inhibitors — in combination with MET, making it difficult to fully assess the comparative efficacy and harms of EMPA.

Baseline characteristics were somewhat different from a typical Canadian population with diabetes. There were study centres from Canada, with the remaining centres from Asian countries, European countries, and the US. The proportion of Asian patients was higher in the study population. According the clinical expert consulted for this review, this discrepancy may not have an impact on the generalizability of the study results to the Canadian population. On the other hand, because of the restricted inclusion criteria and extensive exclusion criteria, patients with uncontrolled hyperglycemia, severe renal impairment, recent CV events, and those taking concomitant anti-obesity medications, were excluded. This can limit the generalizability of study results to a broader T2DM population.

Generalizability of the results is limited for patients with more severe T2DM and poorer glycemic control, or impaired renal function, as well as for patients at increased risk of AEs associated with antidiabetic drugs.

Furthermore, the three pivotal studies and two non-pivotal studies comparing EMPA with GLIM with add-on MET therapy (Study 1245.28) or comparing EMPA with placebo with add-on therapy of multiple-daily-injection insulin alone or in combination with MET (Study 1245.49) included an OL two-week run-in period to ensure compliance with the study protocol and dosage regimen. This is not reflective of the routine clinical practice in Canada and may, therefore, reduce generalizability of results to the general population with T2DM.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in section 2.2, Table 3. See 0 for detailed efficacy data.

For both EMPA doses, the null hypothesis was rejected for each step of the hierarchical sequence. All sensitivity analyses (based on different analysis sets, imputation methods, or models) for all primary and key secondary end points showed results consistent with the main analysis for the respective end point, with regard to placebo-adjusted mean difference and corresponding 95% CI. This CDR review focuses on the results directly applicable to the Health Canada–approved indication, for example, arms of the included studies with EMPA add-on therapy to MET alone or with other approved antidiabetic drugs, per the review protocol.

3.6.1 Mortality

In Study 1245.19, one death in the placebo group and two deaths in the EMPA 25 mg group (one due to cardio-respiratory arrest and the other due to esophageal rupture, neither of which was considered by the investigator to be related to study drug) were reported.

No deaths were reported in Study 1245.23_{MET} during the treatment period.

In Study 1245.23$_{MET+SU}$, one patient in the EMPA group died during the treatment period. The death was not considered by the investigator or the sponsor to be related to the study drug.

3.6.2 Diabetes-related morbidity

None of the included studies assessed the outcomes related to macrovascular or microvascular complications of T2DM.

3.6.3 Glycemic control

a) Change in glycated hemoglobin

The primary analysis was conducted on the FAS using ANCOVA. Details of the results of change in A1C from baseline are presented in Table 7.

In Study 1245.19, at week 24, the between-group difference in adjusted mean change from baseline in A1C was statistically significant (EMPA 10 mg versus placebo: –0.48%; 97.5% CI, –0.69 to –0.27; $P <$ 0.0001; EMPA 25 mg versus placebo: –0.61%; 97.5% CI, –0.82 to –0.40; $P < 0.0001$) in patients with background therapy of PIO + MET. This difference was also considered clinically important. Similar results for change in A1C from baseline were observed in the overall population, which also included patients with background therapy of PIO alone.

In Study 1245.23$_{MET}$, at week 24, the between-group difference in adjusted mean change from baseline in A1C was statistically significant (EMPA 10 mg versus placebo: –0.57%; 97.5% CI, –0.72 to –0.42; $P <$ 0.0001; EMPA 25 mg versus placebo: –0.64; 97.5% CI, –0.79 to –0.48; $P < 0.0001$) in patients with background therapy of MET alone. This difference was also considered clinically important.

In Study 1245.23$_{MET+SU}$, at week 24, the between-group difference in adjusted mean change from baseline in A1C was statistically significant (EMPA 10 mg versus placebo: –0.64%; 97.5% CI, –0.79 to –0.49; $P < 0.0001$; EMPA 25 mg versus placebo: –0.59; 97.5% CI, –0.74 to –0.44; $P < 0.0001$) in patients with background therapy of MET + SU. This difference was also considered clinically important.

Subgroup analyses based on baseline A1C and baseline renal function were performed to investigate the effect of the study drugs on A1C in these subgroups (Table 13 and Table 14 in Appendix 4). The results were consistent with those observed in patients with background therapy of PIO + MET, MET alone, or a combination of MET + SU. Patients who received either EMPA therapy reported greater reductions in A1C compared with placebo. Larger between-group differences were observed in patients with higher baseline A1C levels (A1C 8.0% to less than 9.0%, or greater than 9.0%), but also in patients with better renal function at baseline (eGFR greater than or equal to 90 mL/min/1.73 m^2 or 60 to less than 90 mL/min/1.73 m^2). The between-group differences were all statistically significant, except for the comparison of EMPA 10 mg versus placebo in the subgroup of baseline A1C less than 8.0% in Study 1245.19, and EMPA 10 mg versus placebo or EMPA 25 mg versus placebo in the subgroups of baseline eGFR 30 to less than 90 mL/min/1.73m^2 in Studies 1245.19 and 1245.23$_{MET}$.

TABLE 7: CHANGE FROM BASELINE IN A1C (%) AT WEEK 24 IN THE INCLUDED STUDIES (FULL ANALYSIS SET)

Parameter	1245.19			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d. (N = 165)	EMPA 25 mg q.d. (N = 168)	PL (N = 165)	EMPA 10 mg q.d. (N = 217)	EMPA 25 mg q.d. (N = 213)	PL (N = 207)	EMPA 10 mg q.d. (N = 225)	EMPA 25 mg q.d. (N = 216)	PL (N = 225)
Overall population [a]									
Baseline, mean (SE)	8.1 (0.1)	8.1 (0.1)	8.2 (0.1)	NR			NR		
Week 24, mean (SE)	7.5 (0.1)	7.4 (0.1)	8.0 (0.1)						
Change from baseline, adjusted mean (SE)	–0.6 (0.1)	–0.7 (0.1)	–0.1 (0.1)						
Comparison vs. PL, adjusted mean (97.5% CI), *P* value	–0.48 (–0.69 to –0.27) < 0.0001	–0.61 (–0.82 to –0.40) < 0.0001	NA						
Background therapy: MET alone or MET + other glucose-lowering drugs:									
	MET + PIO[b]			*MET alone*[c]			*MET + SU*[c]		
	N = 125	N = 127	N = 124	N = 217	N = 213	N = 207	N = 225	N = 216	N = 225
Baseline, mean (SE)	8.1 (0.1)	8.1 (0.1)	8.2 (0.1)	7.9 (0.1)	7.9 (0.1)	7.9 (0.1)	8.1 (0.1)	8.1 (0.1)	8.2 (0.1)
Week 24, mean (SE)	7.5 (0.1)	7.4 (0.1)	8.0 (0.1)	7.2 (0.1)	7.1 (0.1)	7.8 (0.1)	7.3 (0.1)	7.3 (0.1)	8.0 (0.1)
Change from baseline, adjusted mean (SE)	–0.59 (0.1)	–0.72 (0.1)	–0.11 (0.1)	–0.70 (0.1)	–0.77 (0.1)	–0.13 (0.1)	–0.82 (0.05)	–0.77 (0.05)	–0.17 (0.05)
Comparison vs. PL, adjusted mean (97.5% CI), *P* value	–0.48 (–0.69 to –0.27) < 0.0001	–0.61 (–0.82 to –0.40) < 0.0001	NA	–0.57 (–0.72 to –0.42) < 0.0001	–0.64 (–0.79 to –0.48) < 0.0001	NA	–0.64(–0.79 to –0.49) < 0.0001	–0.59 (–0.74 to –0.44) < 0.0001	NA

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; EMPA = empagliflozin; MET = metformin; NA = not applicable; NR = not reported; PIO = pioglitazone; PL = placebo; q.d. = once daily; SE = standard error; SU = sulfonylurea; vs. = versus.

[a] ANCOVA model included treatment, renal function, background medication, and baseline A1C.

[b] ANCOVA model included treatment, renal function, and baseline A1C.

[c] ANCOVA model included treatment, renal function, region, and baseline A1C.

Sources: Clinical Study Reports of 1245.19, 1245.23_{MET}, and 1245.23_{MET+SU}.[22,23]

b) Change in fasting plasma glucose

This was a secondary efficacy outcome in Study 1245.19, but an exploratory outcome in Studies 1245.23_{MET} and 1245.23_{MET+SU}. The analyses were conducted on the FAS using ANCOVA. Details of the results of change in FPG from baseline are presented in Table 8. The measurement unit of FPG was reported as mg/dL in the submission, and it has been converted to mmol/L in this CDR review.

In Study 1245.19, at week 24, the between-group difference in adjusted mean change from baseline in FPG was statistically significant (EMPA 10 mg versus placebo: –1.46 mmol/L; 97.5% CI, –1.93 to –1.00; *P* < 0.0001; EMPA 25 mg versus placebo: –1.80 mmol/L; 97.5% CI, –2.26 to –1.33; *P* < 0.0001) in patients with background therapy of PIO + MET. This difference was also considered clinically important. Similar results on change in FPG from baseline were observed in the overall population, which also included patients with background therapy of PIO alone.

In Study 1245.23_{MET}, at week 24, the between-group difference in adjusted mean change from baseline in FPG was statistically significant (EMPA 10 mg versus placebo: –1.47 mmol/L; 97.5% CI, –1.74 to –1.20; *P* < 0.0001; EMPA 25 mg versus placebo: –1.59 mmol/L; 97.5% CI, –1.86 to –1.32; *P* < 0.0001) in patients with background therapy of MET alone. This difference was also considered clinically important.

In Study 1245.23_{MET+SU}, at week 24, the between-group difference in adjusted mean change from baseline in A1C was statistically significant (EMPA 10 mg versus placebo: –1.60 mmol/L; 97.5% CI, –1.90 to –1.30; *P* < 0.0001; EMPA 25 mg versus placebo: –1.60 mmol/L; 97.5% CI, –1.91 to –1.29; *P* < 0.0001) in patients with background therapy of MET + SU. This difference was also considered clinically important.

In Study 1245.19, subgroup analyses based on baseline A1C and baseline renal function were performed to investigate the effect of the study drugs on FPG in these subgroups (Table 15 and Table 16 in Appendix 4). The results were consistent with those observed in patients with background therapy of PIO + MET. Patients who received either EMPA therapy reported greater reductions in FPG compared with placebo. Larger between-group differences were observed in patients with higher baseline A1C levels (A1C 8.0% to < 9.0%, or > 9.0%), but also in patients with better renal function at baseline (eGFR ≥ 90 mL/min/1.73 m2). The between-group differences were all statistically significant, except for the comparison of EMPA 10 mg versus placebo or EMPA 25 mg versus placebo in the subgroups of baseline eGFR ≥ 90 mL/min/1.73 m2.

TABLE 8: CHANGE FROM BASELINE IN FASTING PLASMA GLUCOSE (MMOL/L) AT WEEK 24 IN THE INCLUDED STUDIES (FULL ANALYSIS SET, LAST OBSERVATION CARRIED FORWARD)

Parameter	1245.19			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d. (N = 217)**	**EMPA 25 mg q.d. (N = 213)**	**PL (N = 207)**	**EMPA 10 mg q.d. (N = 225)**	**EMPA 25 mg q.d. (N = 216)**	**PL (N = 225)**
Overall population [a]									
Baseline, mean (SE)	8.4 (0.2)	8.4 (0.2)	8.4 (0.2)	NR			NR		
Week 24, mean (SE)	7.5 (0.2)	7.2 (0.1)	8.8 (0.2)						
Change from baseline, adjusted mean (SE)	–0.94 (0.14)	–1.22 (0.14)	0.36 (0.14)						
Comparison vs. PL, adjusted mean (97.5% CI), *P* value	–1.30 (–1.77 to –0.84) < 0.0001	–1.58 (–2.04 to –1.12) < 0.0001	NA						
Background therapy: MET alone or MET + other glucose-lowering drugs:									
	MET + PIO[b]			*MET alone*[c]			*MET + SU*[c]		
	N = 123	N = 127	N = 124	N = 216	N = 213	N = 207	N = 225	N = 215	N = 224
Baseline, mean	8.3 (SD 2.1)	8.6 (SD 2.1)	8.3 (SD 2.1)	8.6 (SE 0.1)	8.3 (SE 0.1)	8.7 (SE 0.2)	8.4 (SE 0.1)	8.7 (SE 0.1)	8.4 (SE 0.1)
Week 24, mean	7.5 (SD 2.1)	7.3 (SD 1.6)	9.0 (SD 2.6)	7.4 (SE 0.1)	7.2 (SE 0.1)	8.9 (SE 0.1)	7.1 (SE 2.1)	7.3 (SE 0.1)	8.8 (SE 0.2)
Change from baseline, adjusted mean (SE)	–0.89 (0.17)	–1.23 (0.17)	0.57 (0.17)	–1.11 (0.09)	–1.24 (0.10)	0.35 (0.10)	–1.29 (0.11)	–1.29 (0.11)	0.31 (0.11)

Parameter	1245.19			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d. (N = 217)**	**EMPA 25 mg q.d. (N = 213)**	**PL (N = 207)**	**EMPA 10 mg q.d. (N = 225)**	**EMPA 25 mg q.d. (N = 216)**	**PL (N = 225)**
Comparison vs. PL, adjusted mean (97.5% CI), *P* value	–1.46 (–1.93 to –1.00) < 0.0001	–1.80 (–2.26 to –1.33) < 0.0001	NA	–1.47 (–1.74 to –1.20) < 0.0001	–1.59 (–1.86 to –1.32) < 0.0001	NA	–1.60 (–1.90 to –1.30) < 0.0001	–1.60 (–1.91 to –1.29) < 0.0001	NA

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; EMPA = empagliflozin; FPG = fasting plasma glucose; MET = metformin; NA = not applicable; NR = not reported; PIO = pioglitazone; PL = placebo; q.d. = once daily; SD = standard deviation; SE = standard error; SU = sulfonylurea, vs. = versus.

[a] ANCOVA model included treatment, renal function, background medication, baseline A1C, and baseline FPG.

[b] ANCOVA model included baseline FPG, baseline A1C as linear covariates and baseline estimated glomerular filtration rate, treatment, baseline background medication, and treatment by baseline background medication interaction as fixed effects.

[c] ANCOVA model included treatment, renal function, region, baseline A1C, and baseline FPG.

Sources: Clinical Study Reports of 1245.19, 1245.23_{MET}, and 1245.23_{MET+SU}.[22,23]

3.6.4 Health-Related Quality of Life

a) EuroQol 5-Dimensions Questionnaire

This was not a key efficacy outcome in the included studies. HRQoL was assessed using the EQ-5D and was analyzed descriptively in all three studies. The data on change in EQ-5D in Studies 1245.23$_{MET}$ and 1245.23$_{MET+SU}$ were evaluated on a FAS population. It is unclear whether the data in Study 1245.19 were analyzed on FAS. Statistical comparisons were not performed for the EQ-5D data. Detailed data were not reported in the Clinical Study Reports of the three studies.

In Study 1245.19, the EQ-5D data showed that, at baseline, patients' responses to all five questions (mobility, self-care, usual activities, the presence of pain and/or discomfort, and anxiety and/or depression) were similar in the three treatment groups. At the end of the 24-week treatment period, the data were similar to baseline and similar across the three treatment groups. The baseline of the EQ-5D VAS on the state of health was also similar among the three treatment groups; the mean change from baseline at any trial visit was small and similar for the three groups.

In Study 1245.23$_{MET}$, very few changes were observed from baseline to week 24 in patients' responses to four of the five questions (mobility, pain and discomfort, usual activities, and self-care) for patients in the randomized treatment groups. The frequency of patients who reported moderate or extreme anxiety and depression decreased over the treatment period, and the effect was consistent in all treatment groups. Overall, a positive mean change from baseline in the state of health after 24 weeks of treatment was noted in all randomized treatment groups.

In Study 1245.23$_{MET+SU}$, very few changes were noted from baseline to week 24 in patients' responses to all five questions in EQ-5D for patients in the randomized treatment groups. Overall, a positive mean change from baseline in the state of health after 24 weeks of treatment was noted in all randomized treatment groups.

3.6.5 Change in body weight

This was a secondary efficacy outcome in all three studies. The analyses were conducted on the FAS using ANCOVA. Details of the results of change in body weight from baseline are presented in Table 9.

In Study 1245.19, at week 24, the between-group difference in adjusted mean change from baseline in body weight was statistically significant (EMPA 10 mg versus placebo: –2.16 kg; 97.5% CI, –2.84 to –1.47, $P < 0.0001$; EMPA 25 mg versus placebo: –2.00 kg; 97.5% CI, –2.68 to –1.31; $P < 0.0001$) in patients with background therapy of PIO + MET. The difference was translated to approximately 2.5% change in body weight from baseline, which is not considered clinically important. Similar results on change in body weight from baseline were observed in the overall population, which also included patients with background therapy of PIO alone.

In Study 1245.23$_{MET}$, at week 24, the between-group difference in adjusted mean change from baseline in body weight was statistically significant (EMPA 10 mg versus placebo: –1.63 kg; 97.5% CI, –2.17 to –1.08; $P < 0.0001$; EMPA 25 mg versus placebo: –2.01 kg; 97.5% CI, –2.56 to –1.46; $P < 0.0001$) in patients with background therapy of MET alone. This difference is not considered clinically important.

In Study 1245.23$_{MET+SU}$, at week 24, the between-group difference in adjusted mean change from baseline in body weight was statistically significant (EMPA 10 mg versus placebo: –1.76 kg; 97.5% CI, –2.25 to –1.28; $P < 0.0001$; EMPA 25 mg versus placebo: –1.99 kg; 97.5% CI, –2.48 to –1.50; $P < 0.0001$) in patients with background therapy of MET + SU. This difference is not considered clinically important.

Subgroup analyses based on baseline A1C and baseline renal function were performed to investigate the effect of the study drugs on body weight in these subgroups (Table 17 and Table 18 in Appendix 4). The results were consistent with those observed in patients with background therapy of PIO + MET, MET alone, or combination of MET + SU. Patients who received either EMPA therapy reported greater reductions in body weight from baseline compared with placebo. The between-group differences were all statistically significant, except for EMPA 10 mg versus placebo in the subgroup of baseline A1C 8.0% to less than 9.0% in Study 1245.19, and EMPA 10 mg versus placebo in the subgroups of baseline A1C greater than 9.0% in Study 1245.23_{MET}. This difference is not considered clinically important.

TABLE 9: CHANGE FROM BASELINE IN BODY WEIGHT (KG) AT WEEK 24 IN THE INCLUDED STUDIES (FULL ANALYSIS SET, LAST OBSERVATION CARRIED FORWARD)

Parameter	1245.19			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d. (N = 165)	EMPA 25 mg q.d. (N = 168)	PL (N = 165)	EMPA 10 mg q.d. (N = 217)	EMPA 25 mg q.d. (N = 214)	PL (N = 207)	EMPA 10 mg q.d. (N = 225)	EMPA 25 mg q.d. (N = 216)	PL (N = 225)
Overall population [a]									
Baseline, mean (SE)	78.0 (1.5)	78.9 (1.5)	78.1 (1.6)	NR			NR		
Week 24, mean (SE)	76.4 (1.5)	77.4 (1.5)	78.5 (1.5)						
Change from baseline, adjusted mean (SE)	–1.62 (0.21)	–1.47 (0.21)	0.34 (0.21)						
Comparison vs. PL, adjusted mean (97.5% CI), *P* value	–1.95 (–2.64 to –1.27) < 0.0001	–1.81 (–2.49 to –1.13) < 0.0001	NA						
Background therapy: MET alone or MET + other glucose-lowering drugs									
	MET + PIO[b]			*MET alone*[c]			*MET + SU*[c]		
	N = 125	N = 127	N = 124	N = 217	N = 213	N = 207	N = 225	N = 216	N = 225
Baseline, mean (SE)	79.4 (SD 19.6)	81.0 (SD 20.3)	79.5 (SD 21.2)	81.6 (1.3)	82.2 (1.3)	79.7 (1.3)	77.1 (1.2)	77.5 (1.3)	76.2 (1.1)
Week 24, mean (SE)	77.7 (SD 19.2)	79.4 (SD 20.0)	79.9 (SD 20.9)	79.5 (1.2)	79.7 (1.3)	79.3 (1.3)	74.9 (1.2)	75.1 (1.3)	75.9 (1.1)
Change from baseline, adjusted mean (SE)	–1.71 (0.25)	–1.55 (0.25)	0.45 (0.25)	–2.08 (0.17)	–2.46 (0.17)	–0.45 (0.17)	–2.16 (0.15)	–2.39 (0.16)	–0.39 (0.15)

Parameter	1245.19			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d. (N = 217)**	**EMPA 25 mg q.d. (N = 214)**	**PL (N = 207)**	**EMPA 10 mg q.d. (N = 225)**	**EMPA 25 mg q.d. (N = 216)**	**PL (N = 225)**
Comparison vs. PL, adjusted mean (95% CI), *P* value	–2.16 (–2.84 to –1.47) < 0.0001	–2.00 (–2.68 to –1.31) < 0.0001	NA	–1.63 (–2.17 to –1.08) < 0.0001	–2.01 (–2.56 to –1.46) < 0.0001	NA	–1.76 (–2.25 to –1.28) < 0.0001	–1.99 (–2.48 to –1.50) < 0.0001	NA

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; EMPA = empagliflozin; MET = metformin; NA = not applicable; NR = not reported; PIO = pioglitazone; PL = placebo; q.d = once daily; SD = standard deviation; SE = standard error; SU = sulfonylurea, vs. = versus.

[a] ANCOVA model included treatment, renal function, background medication, baseline A1C, and baseline body weight.

[b] ANCOVA model included baseline weight, baseline A1C as linear covariates, and baseline estimated glomerular filtration rate, treatment by baseline background medication interaction as fixed effects.

[c] ANCOVA model included treatment, renal function, region, baseline A1C, and baseline body weight.

Sources: Clinical Study Reports of 1245.19, 1245.23_{MET}, and 1245.23_{MET+SU}.[22,23]

3.6.6 Change in blood pressure

The change in SBP or DBP from baseline to week 24 was an exploratory end point in the included studies, and therefore was not included in the testing hierarchy.

In Study 1245.19 at week 24, there were statistically significantly greater reductions in SBP from baseline in the EMPA groups compared with placebo (adjusted mean change for EMPA 10 mg versus placebo: –3.86 mm Hg; 95% CI, –6.23 to –1.50; *P* = 0.0014; EMPA 25 mg versus placebo: –4.73 mm Hg; 95% CI, –7.08 to –2.37; *P* < 0.0001; Table 10). These differences are not considered clinically important, based on an MCID of 5 mm Hg for SBP. The end point was reported for the overall population, which included patients with background therapy of PIO alone and of a combination of PIO + MET.

In Study 1245.23$_{MET}$, statistically significantly greater reductions in SBP from baseline in the EMPA groups compared with placebo were observed (adjusted mean change for EMPA 10 mg versus placebo: –4.1 mm Hg; 95% CI, –6.2 to –2.1; *P* < 0.0001; EMPA 25 mg versus placebo: –4.8 mm Hg; 95% CI, –6.9 to –2.7; *P* < 0.0001). These differences are not considered clinically important based on an MCID of 5 mm Hg for SBP.

In Study 1245.23$_{MET+SU}$, statistically significantly greater reductions in SBP from baseline in the EMPA groups compared with placebo were observed (adjusted mean change for EMPA 10 mg versus placebo: –2.7 mm Hg; 95% CI, –4.6 to –0.8; *P* = 0.0049; EMPA 25 mg versus placebo: –2.1 mm Hg; 95% CI, –4.0 to –0.2; *P* = 0.0321). These differences are not considered clinically important based on an MCID of 5 mm Hg for SBP.

In Study 1245.19, the change from baseline in DBP at week 24 was statistically significantly greater in the EMPA groups compared with the placebo group (adjusted mean change for EMPA 10 mg versus placebo: –1.78 mm Hg; 95% CI, –3.20 to –0.36; *P* = 0.0144; EMPA 25 mg versus placebo: –2.50 mm Hg; 95% CI, –3.92 to –1.08; *P* = 0.0006; Table 11). These differences are not considered clinically important, based on an MCID of 5 mm Hg for DBP. The end point was reported for the overall population, which included patients with background therapy of PIO alone and of a combination of PIO + MET.

In Study 1245.23$_{MET}$, statistically significantly greater reductions in DBP from baseline in the EMPA groups compared with placebo were observed (adjusted mean change for EMPA 10 mg versus placebo: –1.9 mm Hg; 95% CI, –3.3 to –0.6; *P* = 0.0057; EMPA 25 mg versus placebo: –1.6 mm Hg; 95% CI, –2.9 to –0.2; *P* = 0.0258). These differences are not considered clinically important, based on an MCID of 5 mm Hg for DBP.

In Study 1245.23$_{MET+SU}$, greater reductions in DBP from baseline in the EMPA groups compared with placebo were observed (adjusted mean change for EMPA 10 mg versus placebo: –0.4 mm Hg; 95% CI, –1.6 to 0.9; *P* = 0.5566; EMPA 25 mg versus placebo: –0.4 mm Hg; 95% CI, –1.6 to 0.8; *P* = 0.5343). These between-group differences were not statistically or clinically significant.

TABLE 10: CHANGE FROM BASELINE IN SYSTOLIC BLOOD PRESSURE (MM HG) AT WEEK 24 IN THE INCLUDED STUDIES (FULL ANALYSIS SET, LAST OBSERVATION CARRIED FORWARD)

Parameter	1245.19			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d. (N = 165)	EMPA 25 mg q.d. (N = 168)	PL (N = 165)	EMPA 10 mg q.d. (N = 217)	EMPA 25 mg q.d. (N = 213)	PL (N = 207)	EMPA 10 mg q.d. (N = 225)	EMPA 25 mg q.d. (N = 216)	PL (N = 225)
Overall population[a]									
Baseline, mean (SE)	126.5 (1.1)	126.0 (1.1)	125.7 (0.9)	NR			NR		
Week 24, mean (SE)	123.3 (1.0)	121.9 (1.0)	126.6 (1.2)						
Change from baseline, adjusted mean (SE)	–3.14 (0.85)	–4.00 (0.84)	0.72 (0.85)						
Comparison vs. PL, adjusted mean (97.5% CI), *P* value	–3.86 (–6.23 to –1.50) = 0.0014	–4.73 (–7.08 to –2.37) < 0.0001	NA						
Background therapy: MET alone or MET + other glucose-lowering drugs									
	MET + PIO			*MET alone*[b]			*MET + SU*[b]		
	NR			N = 217	N = 213	N = 207	N = 225	N = 216	N = 225
Baseline, mean (SE)				129.6 (1.0)	130.0 (1.0)	128.6 (1.0)	128.7 (0.9)	129.3 (1.0)	128.8 (1.0)
Week 24, mean (SE)				125.0 (0.9)	124.6 (1.0)	128.5 (1.0)	124.7 (1.0)	125.7 (0.8)	127.4 (0.9)
Change from baseline, adjusted mean (SE)				–4.5 (0.7)	–5.2 (0.7)	–0.4 (0.7)	–4.1 (0.7)	–3.5 (0.7)	–1.4 (0.7)
Comparison vs. PL, adjusted mean (95% CI), *P* value				–4.1 (–6.2 to –2.1) < 0.0001	–4.8 (–6.9 to –2.7) < 0.0001	NA	–2.7 (–4.6 to –0.8) = 0.0049	–2.1 (–4.0 to –0.2) = 0.0321	NA

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; EMPA = empagliflozin; MET = metformin; NA = not applicable; NR = not reported; PIO = pioglitazone; PL = placebo; q.d. = once daily; SBP = systolic blood pressure; SE = standard error; SU = sulfonylurea, vs. = versus.

[a] ANCOVA model included treatment, renal function, background medication, baseline A1C, and baseline SBP.

[b] ANCOVA model included treatment, renal function, region, baseline A1C, and baseline SBP.

Sources: Clinical Study Reports of 1245.19, 1245.23_{MET}, and 1245.23_{MET+SU}.[22,23]

TABLE 11: CHANGE FROM BASELINE IN DIASTOLIC BLOOD PRESSURE (MM HG) AT WEEK 24 IN THE INCLUDED STUDIES (FULL ANALYSIS SET, LAST OBSERVATION CARRIED FORWARD)

Parameter	1245.19			1245.23 MET			1245.23 MET + SU		
	EMPA 10 mg q.d. (N = 165)	EMPA 25 mg q.d. (N = 168)	PL (N = 165)	EMPA 10 mg q.d. (N = 217)	EMPA 25 mg q.d. (N = 213)	PL (N = 207)	EMPA 10 mg q.d. (N = 225)	EMPA 25 mg q.d. (N = 216)	PL (N = 225)
Overall population[a]									
Baseline, mean (SE)	77.2 (0.7)	77.2 (0.6)	76.3 (0.7)	NR			NR		
Week 24, mean (SE)	75.6 (0.6)	74.8 (0.7)	76.8 (0.7)						
Change from baseline, adjusted mean (SE)	–1.49 (0.51)	–2.21 (0.51)	0.29 (0.51)						
Comparison vs. PL, adjusted mean (97.5% CI), *P* value	–1.78 (–3.20 to –0.36) = 0.0144	–2.50 (–3.92 to –1.08) = 0.0006	NA						
Background therapy: MET alone or MET + other glucose-lowering drugs									
	MET + PIO			*MET alone*[b]			*MET + SU*[b]		
	NR			N = 217	N = 213	N = 207	N = 225	N = 216	N = 225
Baseline, mean (SE)				79.6 (0.5)	78.4 (0.6)	78.1 (0.6)	78.4 (0.6)	79.0 (0.6)	78.3 (0.6)
Week 24, mean (SE)				77.3 (0.5)	76.9 (0.6)	78.4 (0.6)	76.3 (0.6)	76.7 (0.5)	76.6 (0.6)
Change from baseline, adjusted mean (SE)				–2.0 (0.5)	–1.6 (0.5)	0 (0.5)	–2.1 (0.4)	–2.2 (0.4)	–1.8 (0.4)
Comparison vs. PL, adjusted mean (95% CI), *P* value				–1.9 (–3.3 to –0.6) = 0.0057	–1.6 (–2.9 to –0.2) = 0.0258	NA	–0.4 (–1.6 to 0.9) = 0.5566	–0.4 (–1.6 to 0.8) = 0.5343	NA

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; DBP = diastolic blood pressure; EMPA = empagliflozin; MET = metformin; NA = not applicable; NR = not reported; PIO = pioglitazone; PL = placebo; q.d. = once daily; SE = standard error; SU = sulfonylurea, vs. = versus.

[a] ANCOVA model included treatment, renal function, background medication, baseline A1C, and baseline DBP.

[b] ANCOVA model included treatment, renal function, region, baseline A1C, and baseline DBP.

Sources: Clinical Study Reports of 1245.19, 1245.23_{MET}, and 1245.23_{MET+SU}.[22,23]

3.7 Harms

Only those harms identified in the review protocol are reported below (see section 2.2.1, Protocol).

3.7.1 Adverse events

In two studies (1245.19 and 1245.23$_{MET}$), patients in the placebo groups reported higher rates of AEs (58.7% to 72.7%) compared with those in the EMPA groups (49.5% to 71.4%) during the 24-week DB treatment period. In Study 1245.23$_{MET+SU}$, patients treated with EMPA 10 mg or 25 mg (64.1% and 67.9%) were more likely to experience at least one AE during the treatment compared with the placebo group (62.7%; Table 12). The majority of patients reported AEs of mild or moderate intensity. Commonly reported AEs were urinary tract infection, nasopharyngitis, upper respiratory tract infection, and dyslipidemia. Patients in the placebo group reported higher risks of hyperglycemia in all three studies.

3.7.2 Serious adverse events

In general during the 24-week DB period, the proportions of patients who reported an SAE were low (less than 5%) in all treatment arms, except that in Study 1245.23$_{MET+SU}$, patients in the placebo group reported higher risks of SAEs (6.2%; Table 12). There was no clear pattern of specific SAEs occurring more frequently in any of the groups.

3.7.3 Withdrawal due to adverse events

During the 24-week DB period, the proportions of patients discontinuing study treatment due to an AE were low in all treatment arms (Table 12). There was no clear pattern of reason for discontinuing due to an AE in any group.

3.7.4 Mortality

Mortality is reported as an efficacy outcome in this review. See section 3.6.1 for details.

3.7.5 Notable harms

During the 24-week DB period, in Studies 1245.19 and 1245.23$_{MET}$, the proportion of patients with a confirmed AE of hypoglycemia was relatively low (1.2%, 2.4%, and 1.8% in Study 1245.19 for EMPA 10 mg, EMPA 25 mg and placebo, respectively; 1.8%, 1.4%, and 0.5% in Study 1245.23$_{MET}$ for EMPA 10 mg, EMPA 25 mg and placebo, respectively). The risk of hypoglycemia became higher in Study 1245.23$_{MET+SU}$, in which the background medication was a combination of MET + SU (11.5% to 16.1% with EMPA versus 8.4% with placebo). Genital infections were more common with EMPA than placebo (2.3% to 8.5% versus 0% to 2.4%) in all three studies. Cardiac failure congestive and renal AEs were rare. Ketoacidosis was not reported in any of the studies.

TABLE 12: HARMS AT 24 WEEKS (SAFETY ANALYSIS SET)

Parameter	1245.19			1245.23$_{MET}$			1245.23$_{MET+SU}$		
	EMPA 10 mg q.d. (N = 165)	EMPA 25 mg q.d. (N = 168)	PL (N = 165)	EMPA 10 mg q.d. (N = 217)	EMPA 25 mg q.d. (N = 214)	PL (N = 206)	EMPA 10 mg q.d. (N = 224)	EMPA 25 mg q.d. (N = 217)	PL (N = 225)
TEAEs, n (%)									
≥ 1 TEAE	111 (67.3)	120 (71.4)	120 (72.7)	124 (57.1)	106 (49.5)	121 (58.7)	152 (67.9)	139 (64.1)	141 (62.7)
Most common:									
Urinary tract infection	24 (14.5)	18 (10.7)	18 (10.9)	9 (4.1)	9 (4.2)	8 (3.9)	21 (9.4)	15 (6.9)	15 (6.7)
Hyperglycemia	8 (4.8)	4 (2.4)	26 (15.8)	5 (2.3)	2 (0.9)	23 (11.2)	6 (2.7)	5 (2.3)	28 (12.4)
Dyslipidemia	18 (10.9)	12 (7.1)	17(10.3)	5 (2.3)	3 (1.4)	4 (1.9)	1 (0.4)	1 (0.5)	3 (1.3)
Hypertension	3 (1.8)	2 (1.2)	9 (5.5)	2 (0.9)	2 (0.9)	2 (1.0)	3 (1.3)	1 (0.5)	1 (0.4)
Nasopharyngitis	6 (3.6)	4 (2.4)	6 (3.6)	12 (5.5)	15 (7.0)	16 (7.8)	18 (8.0)	13 (6.0)	11 (4.9)
Upper respiratory tract infection	6 (3.6)	7 (4.2)	5 (3.0)	2 (0.9)	9 (4.2)	9 (4.4)	7 (3.1)	11 (5.1)	12 (5.3)
Diarrhea	2 (1.2)	3 (1.8)	5 (3.0)	4 (1.8)	3 (1.4)	7 (3.4)	6 (2.7)	4 (1.8)	5 (2.2)
SAEs, n (%)									
≥ 1 SAE	7 (4.2)	6 (3.6)	7 (4.2)	7 (3.2)	5 (2.3)	7 (3.4)	11 (4.9)	1 (0.5)	14 (6.2)
	Amoebic colitis, cellulitis, urosepsis, diabetic retinopathy, cholecystitis, arthralgia/ joint swelling, musculoskeletal chest pain	Dengue fever/septic shock/atrial fibrillation/ atrial flutter/ cardio-respiratory arrest, brain stem infarction, breast cancer, esophageal rupture, hemoglobin decreased	Acute pyelonephritis, skin ulcer/ myocardial ischemia/ hemoglobin decreased, anal fissure, constipation, cholecystitis acute, hand fracture/ humerus fracture/road traffic accident, traumatic	Lacunar infarction, trigeminal neuralgia, unstable angina, arteriosclerosis coronary artery, benign prostatic hyperplasia, comminuted fracture, facial bones fracture/fall	Breast cancer, prostatic adenoma, peripheral arterial occlusive disease, diabetic nephropathy, ligament rupture/ tendon rupture	Anal abscess/ cellulitis/sepsis, hypersensitivity, congestive cardiac failure, myocardial infarction, toxic hepatitis, foot deformity, non-cardiac chest pain	Stress, dizziness, syringomyelia, acute myocardial infarction, peripheral arterial occlusive disease, gastritis, abdominal hernia, duodenal ulcer, faecaloma, phimosis, fall, femoral neck fracture, neck injury, post-traumatic neck syndrome	Cerebrovascular accident	Herpes zoster, listeria sepsis, pneumonia, pneumonia primary atypical, colon cancer, goitre, intercostal neuralgia, aortic valve stenosis, myocardial infarction, osteoarthritis, cystitis hemorrhagic, hydrocele, chest pain, blood creatinine increased

Parameter	1245.19			1245.23$_{MET}$			1245.23$_{MET+SU}$		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d. (N = 217)**	**EMPA 25 mg q.d. (N = 214)**	**PL (N = 206)**	**EMPA 10 mg q.d. (N = 224)**	**EMPA 25 mg q.d. (N = 217)**	**PL (N = 225)**
			fracture						
WDAEs, n (%)									
Any events	2 (1.2)	5 (3.0)	4 (2.4)	2 (0.9)	5 (2.3)	7 (3.4)	6 (2.7)	7 (3.2)	8 (3.6)
Most common	Urosepsis, polyuria	Dengue fever/septic shock, myocardial ischemia, dyspepsia, esophageal rupture, weight decreased	Acute pyelonephritis, abdominal discomfort, skin ulcer, traumatic fracture	Vulvovaginal mycotic infection, comminuted fracture	Fungal infection, balanitis, beta-*N*-acetyl-d-glucosaminidase increased, weight decreased	Hypersensitivity, memory impairment, congestive cardiac failure, myocardial infarction, toxic hepatitis, allergic dermatitis, pruritus	Urinary tract infection, insomnia, headache, acute myocardial infarction, gastritis, alopecia, renal impairment, vulvovaginal pruritus, blood creatinine increased	Hepatitis B, hypersensitivity, headache, dizziness, ventricular extrasystoles, epigastric discomfort, hyperhidrosis, myalgia, chills, pyrexia, hepatic enzyme increased, transaminases increased, weight decreased	Hyperglycemia, syncope, dizziness, myocardial infarction, palpitations, nausea, constipation, abdominal pain, diarrhea, dyspepsia, muscular weakness, myalgia, arthralgia, pruritus genital, mucosal ulceration, increased blood creatinine
Deaths, n (%)	0	2	1	0	0	0	1	0	0
		Cardio-respiratory arrest, esophageal rupture	Skin ulcer/ myocardial ischemia/ hemoglobin decreased				Acute myocardial infarction		
Notable harms, n (%)									
Hypoglycemia									
Investigator-defined	2 (1.2)	6 (3.6)	4 (2.4)	7 (3.2)	8 (3.7)	1 (0.5)	40 (17.9)	29 (13.4)	22 (9.8)
Confirmed	2 (1.2)	4 (2.4)	3 (1.8)	4 (1.8)	3 (1.4)	1 (0.5)	36 (16.1)	25 (11.5)	19 (8.4)
Genital infections	14 (8.5)	6 (3.6)	4 (2.4)	8 (3.7)	10 (4.7)	0	6 (2.7)	5 (2.3)	2 (0.9)
Cardiac failure	1 (0.6)	0	0	0	0	1 (0.5)	NR	NR	NR

Parameter	1245.19			1245.23$_{MET}$			1245.23$_{MET+SU}$		
	EMPA 10 mg q.d. (N = 165)	**EMPA 25 mg q.d. (N = 168)**	**PL (N = 165)**	**EMPA 10 mg q.d. (N = 217)**	**EMPA 25 mg q.d. (N = 214)**	**PL (N = 206)**	**EMPA 10 mg q.d. (N = 224)**	**EMPA 25 mg q.d. (N = 217)**	**PL (N = 225)**
congestive									
Renal AEs	1 (0.6)	2 (1.2)	1 (0.6)	0	1 (0.5)	0	3 (1.3)	0	1 (0.4)
Ketoacidosis	NR	NR	NR	NR	NR	NR	NR	NR	NR

AE = adverse events; EMPA = empagliflozin; MET = metformin; NR = not reported; PL = placebo; q.d. = once daily; SAE = serious adverse event; SU = sulfonylurea, TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

Sources: Clinical Study Reports of 1245.19, 1245.23$_{MET}$, and 1245.23$_{MET+SU}$.[22,23]

4. DISCUSSION

4.1 Summary of available evidence

No RCTs of EMPA/MET FDC were identified from the literature search. Three international, multi-centre, placebo-controlled, DB RCTs were submitted by the manufacturer and included in this review. All three studies had a 24-week treatment period that evaluated the efficacy and safety of EMPA 10 mg or 25 mg once daily in patients with T2DM who had inadequate glycemic control (A1C greater than or equal to 7.0% and less than or equal to 10%) on a background therapy of MET alone (Study 1245.23$_{MET}$, N = 638), MET + SU (Study 1245.23$_{MET+SU}$, N = 669), or MET + PIO (Study 1245.19, N = 499). The doses of the background medications were greater than or equal to 30 mg per day for PIO, greater than or equal to 1,500 mg per day for MET, greater than or equal to 50% the maximum dose of SU, or the maximum tolerated dose or maximum dose according to local label for each of these medications. Patients were randomized in a 1:1:1 ratio to EMPA 10 mg per day, EMPA 25 mg per day or placebo add-on to the background therapy after a two-week OL, placebo lead-in period. The primary outcome was the change from baseline in level of A1C at week 24. Key secondary outcomes included the change in FPG and body weight from baseline at week 24. Other efficacy outcomes included the change in blood pressure from baseline at week 24, HRQoL measured with the EQ-5D, and safety outcomes outside of a testing hierarchy.

The main limitation of these studies was the lack of data regarding diabetes-related morbidity (microvascular or macrovascular). CADTH also noted imbalanced baseline patient characteristics between the EMPA groups and the placebo group (such as gender, the proportion of patients with a history of hypertension, and the distribution of time since initial diagnosis of T2DM); however, there was no apparent evidence or strong clinical reason for these imbalances to have a clinically relevant impact on the primary study results.

Results of the outcomes measures outside of the testing hierarchy, such as change in blood pressure and patient-reported outcomes, should be interpreted with caution. There was a lack of adjustment in multiple comparisons in the subgroup analyses; in addition, because there were fewer patients in the subgroups, the results of subgroup analyses should be interpreted with caution.

Generalizability to the Canadian population is limited because of the restricted inclusion criteria of the studies. Based on the eligibility criteria of the included studies, patients with uncontrolled hyperglycemia, recent occurrence of CV events, severe renal impairment, or a number of other conditions were excluded. The recruited patient population had milder disease (close to normal level of A1C, normal renal function or mild renal impairment, and well-controlled blood pressure); therefore, the generalizability of the study results to a broader diabetic population is uncertain. A lack of longer-term efficacy and safety data (beyond six months) was another limitation.

4.2 Interpretation of results

4.2.1 Efficacy

Results from the included studies suggest that EMPA 10 mg or 25 mg once daily is associated with a greater reduction in A1C compared with placebo after 24 weeks. The differences between EMPA of either dose and placebo were considered statistically and clinically significant. EMPA as add-on therapy to the background therapy was also related to weight loss (statistically significant), decreased levels of FPG (statistically and clinically significant), and reduced blood pressure (statistically significant). Its effect on patient-reported outcomes was not remarkable. These results suggest that 24-week treatment with

EMPA can provide additional glycemic control and weight benefit when added to a background of MET monotherapy or combination therapy of MET + PIO or MET + SU in patients with T2DM.

The change in A1C and change in FPG did not seem congruent in the included studies. Results indicated that, after 24 weeks of treatment, placebo-treated patients had a decreased level of A1C but increased FPG (Table 7 and Table 8). Previous research suggested that postprandial glucose (PPG) plays an important role in fairly controlled diabetic patients (suffering from mild to moderate hyperglycemia), while FPG becomes a main contributor to the overall hyperglycemia when the A1C level rises above 8.4% (indicating poorly controlled diabetes).[32] In the included studies of this review, although the study participants had inadequate response to previous antidiabetic drugs before entering the study, their mean A1C at baseline (approximately 8%) approached the glycemic target value of ≤ 7%. Change in FPG from baseline at week 24 does not seem to be well correlated to the change in A1C at this level. PPG may be a more appropriate outcome measure to reflect the treatment effect of the study drug compared with FPG in patients with milder disease.

The relatively short duration of the included studies, including the extension period, limits the ability to assess key clinical outcomes, such as mortality and diabetic-related morbidity. A continuous relationship between A1C and diabetes complications, with no apparent threshold of benefit, was demonstrated in previous studies. Previous studies indicated that a 10% reduction in A1C was associated with a 40% to 50% lower risk of retinopathy progression, although the absolute reduction in risk was substantially less at lower A1C levels. In the United Kingdom Prospective Diabetes Study (UKPDS), this relationship was directly linear, with each 1.0% (absolute) reduction in mean A1C associated with a 37% decline in the risk of microvascular complications, a 14% lower rate of myocardial infarction, and a 21% reduction in deaths from diabetes. The UKPDS also showed that for every 10 mm Hg decrease in SBP, there is a 15% decrease in diabetes-related deaths.[12] Both FPG and PPG are directly correlated to the risk of complications, with some evidence that PPG might constitute a stronger risk factor for CV complications.[10]

One non-pivotal study was identified that compared EMPA (25 mg daily) against GLIM (1 mg to 4 mg daily) for patients with inadequate glycemic control with MET monotherapy (Study 1245.28; Appendix 6); however, no other studies were identified that directly compared EMPA with any other active comparator — in particular other SGLT2 inhibitors — in combination with MET, making it difficult to fully assess the comparative efficacy and harms of EMPA.

The manufacturer requested reimbursement for EMPA/MET FDC (Synjardy); however, there have been no clinical efficacy studies conducted with Synjardy. The bioequivalence of Synjardy to EMPA and MET co-administered as individual tablets was demonstrated in healthy individuals. The bioequivalence between Synjardy and the individual components administered separately has been demonstrated in bioequivalence studies, which were phase I, OL, single-dose RCTs investigating the bioequivalence of EMPA/MET FDC tablet compared with administration of the individual components in healthy patients (0). Non-pivotal phase III RCTs investigated the use of EMPA in combination with MET in: 1) one DB RCT (Study 1245.28) comparing EMPA 25 mg per day against GLIM 1 mg to 4 mg per day for patients with inadequate glycemic control with MET monotherapy, and 2) one DB placebo-controlled RCT (Study 1245.49) comparing the addition of EMPA 10 mg or 25 mg per day against placebo for patients with inadequate glycemic control on existing multiple-daily-injection insulin, with or without MET. Study findings suggested that, after 104 weeks of treatment, EMPA 25 mg once daily was statistically significantly superior to GLIM in improving A1C, FPG, SBP, DBP, and body weight, although the glycemic control outcomes might have been biased as a result of the inconsistency in titration scheme for GLIM

between that adopted in Study 1245.28 and routine clinical practice. Results of subgroup analyses in Study 1245.49 indicated that treatment with EMPA 10 mg or 25 mg per day was associated with statistically significant reductions in A1C, body weight, and daily insulin dosage, compared with placebo, when MET in combination with insulin was the background therapy in the study population (0). The efficacy of EMPA administered twice daily was compared with EMPA administered once daily in a bridging study enrolling patients with T2DM and inadequate glycemic control with MET monotherapy (Study 1276.10; 0). The results suggested that EMPA administered twice daily at a dose of 5 mg or 12.5 mg was noninferior to once-daily administration of 10 mg or 25 mg for improving glycemic control.

The mechanism of EMPA depends on filtration of glucose at the glomerulus; therefore, EMPA is expected to be less effective with reduced renal function. Subgroup analysis of the primary end point based on renal impairment found that patients with moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m^2) had a smaller reduction in A1C and FPG with EMPA compared with placebo when compared with patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2); however, such trend was not observed in the change in body weight. In the included studies, more than 50% of the study participants had a history of hypertension. SGLT2 inhibitors increase glucose excretion in the urine, cause osmotic diuresis, and contribute to a modest antihypertensive effect. This was observed in the three studies through a greater decrease in SBP with EMPA than with placebo at week 24 (outside of testing hierarchy), and a smaller decrease in DBP (outside of testing hierarchy); however, the between-group differences were not considered clinically important. It is unclear whether the decrease in SBP seen with EMPA will have an effect on CV outcomes. A study published in 2015 (EMPA-REG OUTCOME; N = 7,020) reported that patients who received add-on therapy with EMPA did not have increased risk of major CV AEs compared with standard of care. At the time of this review, EMPA is undergoing review by CDR for CV outcomes.

4.2.2 Harms

Overall, the proportion of patients reporting an AE was balanced between the EMPA and the placebo groups. Isolated cases of SAEs and withdrawal due to AEs were reported across the studies and treatment groups; therefore, there were no clear patterns of specific SAEs occurring more frequently in any of the groups, or no clear pattern of reasons for discontinuing due to an AE in any group. Some AEs were more likely to be reported in patients treated with placebo. This could be partially explained by chance, due to the small number of events being reported.

As EMPA is used in combination with an SU and MET, and given its mechanism in inhibiting glucose reabsorption, it is expected that there may be an increase in hypoglycemia with EMPA. In the included studies, a higher proportion of patients in the EMPA group had a confirmed AE of hypoglycemia than in the placebo group at 24 weeks.

The (draft) product monograph for Synjardy states that renal function abnormalities can occur after initiating EMPA, and that increases in serum creatinine and decreases in eGFR may also be observed. In the included studies, renal impairment was rarely reported across the treatment groups.

SGLT2 inhibitors increase urinary glucose concentration, which may provide a favourable environment for the development of urogenital infections. In the included studies, more patients in the EMPA groups than receiving placebo reported developing a genital infection during the 24-week period. This is consistent with the findings from an indirect treatment comparison, which indicating that SGLT2 inhibitors were associated with an increased risk of genital tract infection.[24]

Ketoacidosis was not reported in any study; this may be because the patient population had a low risk of developing this AE, with the relatively mild conditions.

Longer-term safety was explored in an extension study (1245.31; Appendix 7). The extension study included patients from four separate DB RCTs with different background therapies. Patients in this extension study continued to receive DB treatment in accordance with their original treatment allocation in the core study. Data at week 76 (24 weeks of core studies and 52 weeks of extension) were presented. Safety was the main objective of this study. The findings suggested that the overall frequency of AEs was generally similar across the treatment groups. The frequency and severity of the AEs reported during the extension phase were similar to those reported during the core studies.

4.3 Potential place in therapy

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

Patients with T2DM have an increasing choice of drugs with low risk of hypoglycemia and low or reduced risk of weight gain. SGLT2 inhibitors add to this choice, with additional benefits for blood pressure reduction. Like other members of this drug class, EMPA is a good choice for people who have hypertension and wish to avoid weight gain and hypoglycemia. EMPA is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM for whom MET is inappropriate because of contraindications or intolerance, and as an add-on combination when MET used alone does not provide adequate glycemic control, in combination with MET, MET + SU, PIO (alone or with MET), or basal or prandial insulin (alone or with MET). The revised Canadian Diabetes Association guidelines also suggest it as first choice for the prevention of CV events as an adjunct to standard care therapy in patients with T2DM at high CV risk.[33] However, MET remains the cornerstone of treatment, and it is expected that 60% of people prescribed EMPA will also be on MET.[34]

Combining the two in one pill is likely to reduce pill burden for patients and facilitate adherence to prescribed therapy.[35] As other SGLT2 inhibitors are available in combination with MET, there will also be patient expectation that EMPA will also be available in this way.

5. CONCLUSIONS

No phase III RCTs evaluating the efficacy and safety of EMPA/MET FDC (Synjardy) were available. Instead, three international, multi-centre, placebo-controlled, DB RCTs with a 24-week treatment period met inclusion criteria for this review. The efficacy and safety of EMPA 10 mg or 25 mg once daily was evaluated in patients with T2DM who had inadequate glycemic control on MET monotherapy, or on a combination therapy of MET and an SU, or MET and PIO.

Results from the three studies suggest that EMPA 10 mg or 25 mg once daily is associated with a statistically and clinically significant reduction in A1C and FPG compared with placebo after 24 weeks. Diabetes-related morbidity was not assessed in any of the studies. The use of EMPA was also related to non–clinically significant reductions in body weight and blood pressure, but its effect on patient-reported QoL (measured with EQ-5D) was minimal. Longer-term efficacy and safety data suggested that, by week 76, the treatment effect of EMPA on A1C, FPG, body weight, and blood pressure was maintained. The safety profile at week 76 was similar to that reported in the core studies. Several important limitations introduce a high risk of bias to the studies: imbalanced patient demographic characteristics and disease characteristics suggesting a potential failure of the randomization methods, lack of long-term comparative efficacy and safety data, and limited generalizability of the study results to a typical Canadian T2DM patient population. Statistical methodology for some secondary outcomes is of questionable validity.

Findings from bioequivalence studies demonstrated that Synjardy is bioequivalent to the individual components administered separately. Data from other non-pivotal phase III DB RCTs suggested that EMPA was superior to GLIM for improving glycemic control outcomes, decreasing blood pressure, and reducing weight. EMPA was also superior to placebo in glycemic control, body weight reduction, and insulin usage reduction in patients with a background therapy of MET combined with insulin.

AE data were generally similar between groups. Isolated cases of SAEs and WDAEs were reported in the included studies. A greater proportion of patients in the EMPA group reported hypoglycemia episode and genital infections. Ketoacidosis was not reported in any studies.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups.

1. Brief description of patient group(s) supplying input

One patient group provided feedback. The Canadian Diabetes Association (CDA) helps people with diabetes live healthy lives while work continues toward finding a cure. The CDA is supported in its efforts by a network of volunteers, employees, health care professionals, researchers, and partners. It provides education and services, advocates on behalf of people with diabetes, supports research, and translates research into practical applications. The CDA solicits and receives unrestricted educational grants from multiple manufacturers and vendors of pharmaceuticals, supplies, and devices for diabetes. 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 reported no conflicts of interest in the preparation of this submission.

2. Condition-related information

The CDA solicited patient input through surveys distributed via social media and email blasts. Content of this submission is derived from three surveys. Two surveys, conducted in August 2014 and October 2015, gathered information from Canadians with type 2 diabetes mellitus (T2DM) and their caregivers about the impacts of diabetes and aspects of diabetes they want medications to address; the surveys were answered by 376 and 212 individuals, respectively. The third survey, conducted in April 2015 during three weeks, provided information from Canadians with T2DM (n = 349) and their caregivers (n = 75) about current drug therapies and experience with Jardiance (empagliflozin [EMPA]), and the most important aspects of diabetes they would like medications to address.

T2DM 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. The goal of diabetes management is to keep glucose levels within the target range to minimize symptoms and avoid or delay complications. Common symptoms of diabetes include fatigue, thirst, and weight change. Diabetes requires considerable self-management, including healthy eating, regular physical activity, healthy body weight, adherence to diabetes medications (oral and/or injection) as prescribed, blood glucose monitoring, and stress management. Poor glucose control can result in serious complications, such as heart disease, stroke, blindness, kidney problems, nerve damage, and erectile dysfunction. Patients also noted that diabetes has a psychological and emotional impact on their lives (through stress; anxiety; adjustment to changes in diet, lifestyle, medication, and treatment management; as well as effects on relationships with family).

Surveyed patients were asked which aspects of diabetes were the most important. The majority of patients indicated that daily fluctuations in blood sugar and weight gain were the most important aspects of diabetes to control. The blood sugar fluctuations affect the ability to work, interactions with friends and family, and participation in normal activities of daily living, and cause stress and worry. Weight gain and the stigma associated with the disease can result in reduced quality of life (QoL). Maintaining control of diabetes can reduce anxiety and avoid or delay complications, as well as improve overall QoL.

3. Current therapy-related information

A large proportion of people with T2DM fail to achieve optimal glycemic control, which places patients at risk for both acute and chronic diabetes complications. The initial therapy is most often metformin (MET), but, over time, most patients will require the addition of a second or third drug to reach glycemic targets. Many of the currently available therapies cause significant weight gain, while their ability to achieve optimal glycemic control may be limited by hypoglycemia. Weight gain adds to the sense of failure and anxiety in this patient population, who frequently blame themselves for their health status.

The CDA surveyed patients and asked them to rate the importance of the following benefits and/or side effects when choosing diabetes medications, using a five-point scale from "not at all important" to "very important." More than 90% of respondents indicated "quite important" or "very important" regarding the following benefits of therapy:

- Blood sugars kept at satisfactory levels in the morning and/or after fasting (96%)
- Blood sugars kept at satisfactory levels during the day and/or after meals (95%)
- Avoiding low blood sugar during the day and/or overnight (90%).

The following aspects were also considered important by the vast majority:

- Avoiding weight gain (89%)
- Avoiding gastrointestinal effects (84%)
- Reducing high blood pressure (83%)
- Avoiding fluid retention (82%)
- Avoiding urinary tract infection (81%).

Other aspects deemed important when choosing medications included "avoiding kidney strain and heart problems" and "depression." Some respondents simply wanted drugs to "allow them to lead as normal a life as possible" and provide a "life without concerns about complications because of diabetes."

4. Expectations about the drug being reviewed

Patients reported that the following would be important benefits of new drugs for T2DM:

- Maintain or improve blood glucose levels
- Minimal side effects, including fewer events of hypoglycemia
- Result in weight loss or no weight gain
- Slow the progression of disease and/or complications
- Improve blood pressure
- Reduce the need for other diabetes medications, including insulin
- Lower cost and/or coverage provided by public drug plans.

Patients also indicated that current treatments can require a significant number of pills and/or injections. They noted that fixed-dose combination products, such as EMPA/metformin, can be associated with a reduced pill burden, which may promote greater adherence and improved QoL.

The CDA reported that 14 respondents to their survey had taken EMPA as part of a clinical trial. Patients who had taken EMPA noted its effectiveness in keeping blood sugar levels at target and minimizing sides effects (e.g., diarrhea, stomach ache, weight gain), and in providing "better quality of life" from their perspective. A patient who has used EMPA in a past trial and is now on another class of drugs expressed a wish that he could access it because "it worked…[other drugs] cause weight gain and do not work as well as empagliflozin."

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 30, 2016
Alerts:	Bi-weekly search updates until October 12, 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
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.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	
1	*empagliflozin plus metformin/
2	((empagliflozin adj3 metformin) or synjardy* or jardiamet* or jardiancemet*).ti,ab,kw.
3	1 or 2
4	3 use oemezd
5	((empagliflozin adj3 metformin) or synjardy* or jardiamet* or jardiancemet* or S900006750).ti,ab,ot,hw,kf,rn,nm.
6	5 use pmez
7	3 or 6
8	conference abstract.pt.
9	7 not 8
10	remove duplicates from 9

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. 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:	May 25, 2016
Keywords:	Synjardy (empagliflozin / metformin) OR jardiamet OR jardiancement
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 searching health-related grey literature" (https://www.cadth.ca/grey-matters) were searched:

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

APPENDIX 3: EXCLUDED STUDIES

There were no studies excluded from the study selection.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 13: CHANGE FROM BASELINE IN GLYCATED HEMOGLOBIN (%) AT WEEK 24 – SUBGROUP ANALYSIS BY BASELINE GLYCATED HEMOGLOBIN (%) (FULL ANALYSIS SET, LAST OBSERVATION CARRIED FORWARD)

Parameter	1245.19[a]			1245.23$_{MET}$[b]			1245.23$_{MET+SU}$[b]		
	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL
Baseline A1C < 8.0%									
N	82	88	76	122	124	121	110	105	112
Baseline, mean (SD)	7.37 (0.43)	7.42 (0.34)	7.38 (0.41)	7.36 (0.36)	7.26 (0.32)	7.30 (0.38)	7.40 (0.40)	7.43 (0.37)	7.46 (0.33)
Week 24, mean (SD)	7.11 (0.75)	7.00 (0.68)	7.36 (0.85)	6.93 (0.46)	6.82 (0.50)	7.30 (0.70)	6.94 (0.66)	6.98 (0.63)	7.40 (0.74)
Change from baseline, adjusted mean (SE)	–0.27 (0.10)	–0.42 (0.09)	–0.03 (0.10)	–0.44 (0.07)	–0.44 (0.06)	–0.01 (0.07)	–0.46 (0.07)	–0.46 (0.07)	–0.08 (0.07)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–0.24 (–0.51 to 0.04 = 0.0897	–0.39 (–0.66 to –0.12) = 0.0048	NA	–0.43 (–0.61 to –0.25) < 0.0001	–0.44 (–0.62 to –0.25) < 0.0001	NA	–0.38 (–0.57 to –0.20) < 0.0001	–0.38 (–0.58 to –0.19) < 0.0001	NA
Baseline A1C 8.0% to < 9.0%									
N	57	54	57	67	66	60	81	78	71
Baseline, mean (SD)	8.39 (0.29)	8.43 (0.29)	8.43 (0.27)	8.41 (0.29)	8.38 (0.27)	8.39 (0.26)	8.40 (0.26)	8.38 (0.27)	8.46 (0.26)
Week 24, mean (SD)	7.71 (0.86)	7.71 (0.73)	8.31 (1.02)	7.44 (0.71)	7.36 (0.98)	8.18 (0.73)	7.41 (0.67)	7.42 (0.73)	8.25 (0.92)
Change from baseline, adjusted mean (SE)	–0.67 (0.12)	–0.71 (0.12)	–0.11 (0.12)	–0.95 (0.09)	–1.01 (0.09)	–0.19 (0.09)	–0.98 (0.08)	–0.93 (0.08)	–0.22 (0.08)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–0.57 (–0.89 to –0.24) = 0.0006	–0.60 (–0.93 to –0.27) = 0.0004	NA	–0.76 (–1.02 to –0.51) < 0.0001	–0.83 (–1.08 to –0.57) < 0.0001	NA	–0.76 (–0.99 to –0.54) < 0.0001	–0.72 (–0.95 to –0.48) < 0.0001	NA

	1245.19[a]			1245.23$_{MET}$[b]			1245.23$_{MET+SU}$[b]		
	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL
Baseline A1C ≥ 9.0%									
N	26	26	32	28	23	26	34	33	42
Baseline, mean (SD)	9.60 (0.43)	9.46 (0.38)	9.51 (0.65)	9.34 (0.33)	9.58 (0.73)	9.59 (0.53)	9.43 (0.36)	9.55 (0.47)	9.47 (0.30)
Week 24, mean (SD)	8.24 (0.98)	7.83 (1.03)	9.07 (1.07)	7.99 (1.09)	7.93 (0.81)	9.03 (0.98)	7.94 (0.98)	8.21 (0.91)	9.00 (0.90)
Change from baseline, adjusted mean (SE)	–1.34 (0.17)	–1.63 (0.17)	–0.44 (0.16)	–1.38 (0.14)	–1.64 (0.15)	–0.59 (0.14)	–1.48 (0.12)	–1.31 (0.12)	–0.44 (0.11)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–0.91 (–1.36 to –0.45) = 0.0001	–1.19 (–1.65 to –0.73) < 0.0001	NA	–0.78 (–1.17 to –0.40) < 0.0001	–1.05 (–1.45 to –0.64) < 0.0001	NA	–1.04 (–1.36 to –0.71) < 0.0001	–0.87 (–1.20 to –0.54) < 0.0001	NA

A1C = glycated hemoglobin; CI = confidence interval; EMPA = empagliflozin; MET = metformin; NA = not applicable; PL = placebo; q.d. = once daily; SD = standard deviation; SE = standard error, SU = sulfonylurea; vs. = versus.

[a] Analysis of covariance (ANCOVA) model includes baseline estimated glomerular filtration rate (eGFR), baseline background medication, treatment, baseline A1C, and treatment by baseline A1C interaction as fixed effect(s).

[b] ANCOVA model includes baseline eGFR, geographical region, treatment, baseline A1C, and treatment by baseline A1C interaction as fixed effects.

Sources: Clinical Study Reports of 1245.19, 1245.23$_{MET}$, and 1245.23$_{MET+SU}$.[22,23]

TABLE 14: CHANGE FROM BASELINE IN GLYCATED HEMOGLOBIN (%) AT WEEK 24 – SUBGROUP ANALYSIS BY BASELINE RENAL IMPAIRMENT (FULL ANALYSIS SET, LAST OBSERVATION CARRIED FORWARD)

Parameter	1245.19[a]			1245.23$_{MET}$[b]			1245.23$_{MET+SU}$[b]		
	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL
Baseline eGFR ≥ 90 mL/min/1.73 m^2									
N	60	67	63	96	91	95	92	94	94
Baseline, mean (SD)	8.2 (1.0)	8.1 (0.8)	8.3 (1.1)	7.9 (0.7)	7.9 (1.0)	7.9 (0.9)	8.05 (0.82)	8.11 (0.86)	8.22 (0.84)
Week 24, mean (SD)	7.5 (0.8)	7.2 (0.8)	8.2 (1.2)	7.3 (0.9)	7.0 (0.7)	7.8 (0.9)	7.15 (0.79)	7.17 (0.79)	7.98 (1.11)

Parameter	1245.19[a]			1245.23$_{MET}$[b]			1245.23$_{MET+SU}$[b]		
	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL
Change from baseline, adjusted mean (SE)	–0.68 (0.11)	–0.90 (0.10)	0.02 (0.11)	–0.64 (0.07)	–0.90 (0.07)	–0.10 (0.07)	–0.90 (0.07)	–0.92 (0.07)	–0.17 (0.07)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–0.70 (–1.00 to –0.40) < 0.0001	–0.92 (–1.21 to –0.62) < 0.0001	NA	–0.54 (–0.74 to –0.34) < 0.0001	–0.80 (–1.00 to –0.60) < 0.0001	NA	–0.73 (–0.94 to –0.53) < 0.0001	–0.75 (–0.96 to –0.55) < 0.0001	NA
Baseline eGFR 60 to < 90 mL/min/1.73 m^2									
N	85	85	84	112	108	100	114	105	109
Baseline, mean (SD)	8.0 (0.8)	8.0 (0.8)	8.1 (0.8)	8.0 (0.8)	7.8 (0.8)	7.9 (0.9)	8.08 (0.84)	8.14 (0.83)	8.11 (0.85)
Week 24, mean (SD)	7.6 (1.0)	7.4 (0.9)	8.0 (1.2)	7.2 (0.6)	7.2 (0.8)	7.8 (1.0)	7.29 (0.78)	7.46 (0.86)	7.89 (0.96)
Change from baseline, adjusted mean (SE)	–0.50 (0.09)	–0.66 (0.09)	–0.13 (0.09)	–0.78 (0.07)	–0.71 (0.07)	–0.13 (0.07)	–0.81 (0.07)	–0.68 (0.07)	–0.23 (0.07)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–0.37 (–0.63 to –0.11) = 0.0048	–0.52 (–0.78 to –0.27) < 0.0001	NA	–0.64 (–0.83 to –0.46) < 0.0001	–0.57 (–0.76 to –0.38) < 0.0001	NA	–0.58 (–0.76 to –0.39) < 0.0001	–0.45 (–0.64 to –0.26) < 0.0001	NA
Baseline eGFR 30 to < 60 mL/min/1.73 m^2									
N	20	16	18	9	14	12	19	17	22
Baseline, mean (SD)	7.9 (0.9)	7.9 (0.9)	7.9 (0.5)	7.5 (0.8)	7.9 (0.8)	8.0 (1.0)	8.03 (0.63)	7.74 (0.60)	8.03 (0.63)
Week 24, mean (SD)	7.3 (0.8)	7.7 (0.9)	7.6 (0.8)	7.2 (0.6)	7.6 (1.1)	7.6 (0.8)	7.63 (0.900)	7.42 (0.77)	8.28 (1.04)
Change from baseline, adjusted mean (SE)	–0.64 (0.19)	–0.28 (0.21)	–0.42 (0.20)	–0.46 (0.23)	–0.40 (0.19)	–0.41 (0.20)	–0.44 (0.16)	–0.48 (0.17)	0.15 (0.15)

Parameter	1245.19[a]			1245.23$_{MET}$[b]			1245.23$_{MET+SU}$[b]		
	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL
Comparison vs. PL, adjusted mean (95% CI), *P* value	–0.21 (–0.76 to 0.33) = 0.4406	0.15 (–0.43 to 0.72) = 0.6187	NA	–0.05 (–0.65 to 0.55) = 0.8689	0.01 (–0.53 to 0.54) = 0.9822	NA	–0.58 (–1.02 to –0.14) = 0.0093	–0.63 (–1.08 to –0.18) = 0.0063	NA

CI = confidence interval; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; MET = metformin; NA = not applicable; PL = placebo; q.d. = once daily; SD = standard deviation; SE = standard error, SU = sulfonylurea; vs. = versus.

[a] Analysis of covariance (ANCOVA) model includes baseline glycated hemoglobin (A1C) as a linear covariate and baseline background medication, treatment, baseline eGFR, and treatment by baseline eGFR interaction as fixed effects.

[b] ANCOVA model includes baseline A1C as a linear covariate, and geographical region, treatment, baseline eGFR, and treatment by baseline eGFR interaction as fixed effects.

Sources: Clinical Study Reports of 1245.19, 1245.23$_{MET}$, and 1245.23$_{MET+SU}$.[22,23]

TABLE 15: CHANGE FROM BASELINE IN FASTING PLASMA GLUCOSE (MMOL/L) AT WEEK 24 — SUBGROUP ANALYSIS BY BASELINE GLYCATED HEMOGLOBIN (%) (FULL ANALYSIS SET, LAST OBSERVATION CARRIED FORWARD)

Parameter	1245.19[a]			1245.23$_{MET}$			1245.23$_{MET+SU}$		
	EMPA 10 mg q.d.	**EMPA 25 mg q.d.**	**PL**	**EMPA 10 mg q.d.**	**EMPA 25 mg q.d.**	**PL**	**EMPA 10 mg q.d.**	**EMPA 25 mg q.d.**	**PL**
Baseline A1C < 8.0%									
N	82	88	76	NR			NR		
Baseline, mean (SD)	7.61 (1.67)	7.71 (1.59)	7.38 (1.71)						
Week 24, mean (SD)	6.96 (1.78)	6.85 (1.46)	7.70 (2.01)						
Change from baseline, adjusted mean (SE)	–1.07 (0.21)	–1.22 (0.20)	–0.22 (0.22)						
Comparison vs. PL, adjusted mean (95% CI), *P* value	–0.86 (–1.43 to –0.28) = 0.0034	–1.01 (–1.57 to –0.44) = 0.0005	NA						
Baseline A1C 8.0% to < 9.0%									
N	56	54	57	NR			NR		
Baseline, mean (SD)	8.95 (1.91)	8.87 (2.25)	8.85 (2.09)						

Parameter	1245.19[a]			1245.23$_{MET}$			1245.23$_{MET+SU}$		
	EMPA 10 mg q.d.	**EMPA 25 mg q.d.**	**PL**	**EMPA 10 mg q.d.**	**EMPA 25 mg q.d.**	**PL**	**EMPA 10 mg q.d.**	**EMPA 25 mg q.d.**	**PL**
Week 24, mean (SD)	7.95 (2.36)	7.61 (1.50)	9.01 (2.25)	NR			NR		
Change from baseline, adjusted mean (SE)	–0.75 (0.25)	–1.06 (0.25)	0.39 (0.24)						
Comparison vs. PL, adjusted mean (95% CI), *P* value	–1.14 (–1.82 to –0.46) = 0.0010	–1.45 (–2.13 to –0.76) < 0.0001	NA						
Baseline A1C ≥ 9.0%									
N	25	26	32	NR			NR		
Baseline, mean (SD)	10.07 (2.65)	10.00 (1.99)	10.22 (2.30)						
Week 24, mean (SD)	8.39 (3.62)	7.63 (1.70)	11.07 (2.73)						
Change from baseline, adjusted mean (SE)	–0.99 (0.37)	–1.58 (0.36)	1.73 (0.33)						
Comparison vs. PL, adjusted mean (95% CI), *P* value	–2.73 (–3.69 to –1.76) < 0.0001	–3.31 (–4.26 to –2.36) < 0.0001	NA						

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; EMPA = empagliflozin; MET = metformin; NA = not applicable; NR = not reported; PL = placebo; q.d. = once daily; SD = standard deviation; SE = standard error, SU = sulfonylurea; vs. = versus.

[a] ANCOVA model includes baseline fasting plasma glucose as linear covariate(s), and baseline estimated glomerular filtration rate, baseline background medication, treatment, baseline A1C, and treatment by baseline A1C interaction as fixed effect(s).

Sources: Clinical Study Report of 1245.19.[22]

TABLE 16: CHANGE FROM BASELINE IN FASTING PLASMA GLUCOSE (MMOL/L) AT WEEK 24 –SUBGROUP ANALYSIS BY BASELINE RENAL IMPAIRMENT (FULL ANALYSIS SET, LAST OBSERVATION CARRIED FORWARD)

Parameter	1245.19[a]			1245.23$_{MET}$			1245.23$_{MET+SU}$		
	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL
Baseline eGFR ≥ 90 mL/min/1.73 m^2									
N	60	67	63	NR			NR		
Baseline, mean (SD)	8.15 (2.16)	8.32 (1.97)	8.46 (2.39)						
Week 24, mean (SD)	7.14 (1.78)	6.93 (1.40)	9.02 (2.76)						
Change from baseline, adjusted mean (SE)	–1.18 (0.24)	–1.47 (0.23)	0.53 (0.24)						
Comparison vs. PL, adjusted mean (95% CI), *P* value	–1.71 (–2.37 to –1.05) < 0.0001	–1.99 (–2.63 to –1.35) < 0.0001	NA						
Baseline eGFR 60 to < 90 mL/min/1.73 m^2									
N	83	85	84	NR			NR		
Baseline, mean (SD)	8.67 (2.17)	8.49 (2.10)	8.38 (2.09)						
Week 24, mean (SD)	7.93 (2.87)	7.34 (1.65)	8.79 (2.51)						
Change from baseline, adjusted mean (SE)	–0.68 (0.20)	–1.11 (0.20)	0.39 (0.20)						
Comparison vs. PL, adjusted mean (95% CI), *P* value	–1.06 (–1.63 to –0.50) = 0.0003	–1.50 (–2.06 to –0.93) < 0.0001	NA						
Baseline eGFR 30 to < 60 mL/min/1.73 m^2									
N	20	16	18	NR			NR		
Baseline, mean (SD)	8.37 (1.77)	8..63 (2.31)	8.62 (2.53)						
Week 24, mean (SD)	6.99 (1.52)	7.75 (1.48)	8.16 (2.03)						

Parameter	1245.19[a]			1245.23$_{MET}$			1245.23$_{MET+SU}$		
	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL
Change from baseline, adjusted mean (SE)	–1.36 (0.42)	–0.78 (0.47)	–0.35 (0.46)	NR			NR		
Comparison vs. PL, adjusted mean (95% CI), *P* value	–1.01 (–2.20 to 0.17) = 0.0940	–0.43 (–1.68 to 0.82) = 0.5008	NA						

A1C = glycated hemoglobin; CI = confidence interval; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; MET = metformin; NA = not applicable; NR = not reported; PL = placebo; q.d. = once daily; SD = standard deviation; SE = standard error, SU = sulfonylurea; vs. = versus.
[a] Analysis of covariance (ANCOVA) model includes baseline fasting plasma glucose, baseline A1C as linear covariate(s), and baseline background medication, treatment, baseline eGFR, and treatment by baseline eGFR interaction as fixed effect(s).
Sources: Clinical Study Report of 1245.19.[22]

TABLE 17: CHANGE FROM BASELINE IN BODY WEIGHT (KG) AT WEEK 24 — SUBGROUP ANALYSIS BY BASELINE GLYCATED HEMOGLOBIN (%) (FULL ANALYSIS SET, LAST OBSERVATION CARRIED FORWARD)

Parameter	1245.19[a]			1245.23$_{MET}$[b]			1245.23$_{MET+SU}$[b]		
	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL
Baseline A1C < 8.0%									
N	82	88	76	122	124	121	110	105	112
Baseline, mean (SD)	77.4 (17.6)	81.1 (22.1)	78.2 (21.6)	80.54 (18.22)	84.04 (19.60)	80.52 (17.99)	75.92 (18.30)	78.55 (20.05)	76.90 (17.54)
Week 24, mean (SD)	75.5 (16.2)	80.0 (21.9)	79.0 (21.3)	78.40 (17.88)	81.48 (19.07)	79.96 (17.96)	73.50 (18.43)	76.14 (19.63)	76.63 (17.47)
Change from baseline, adjusted mean (SE)	–1.96 (0.30)	–1.44 (0.29)	0.85 (0.32)	–2.18 (0.23)	–2.49 (0.23)	–0.56 (0.23)	–2.39 (0.22)	–2.41 (0.22)	–0.25 (0.22)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–2.81 (–3.67 to –1.95) < 0.0001	–2.28 (–3.13 to –1.44) < 0.0001	NA	–1.62 (–2.25 to –0.99) < 0.0001	–1.92 (–2.55 to –1.29) < 0.0001	NA	–2.15 (–2.75 to –1.54) < 0.0001	–2.16 (–2.77 to –1.54) < 0.0001	NA

Parameter	1245.19[a]			1245.23$_{MET}$[b]			1245.23$_{MET+SU}$[b]		
	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL
Baseline A1C 8.0% to < 9.0%									
N	57	54	57	67	66	60	81	78	71
Baseline, mean (SD)	82.0 (21.8)	77.5 (16.2)	78.7 (19.2)	80.86 (16.58)	80.00 (17.50)	76.42 (18.42)	78.23 (18.32)	75.41 (16.25)	76.28 (15.77)
Week 24, mean (SD)	80.7 (22.4)	76.0 (15.9)	78.3 (18.8)	78.60 (15.64)	77.61 (16.65)	76.33 (18.33)	76.50 (18.51)	72.80 (16.28)	75.74 (15.78)
Change from baseline, adjusted mean (SE)	–1.17 (0.37)	–1.49 (0.37)	–0.37 (0.36)	–2.26 (0.31)	–2.39 (0.31)	–0.33 (0.33)	–1.74 (0.26)	–2.59 (0.26)	–0.56 (0.27)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–0.80 (–1.82 to 0.21) = 0.1202	–1.12 (–2.15 to –0.09) = 0.0324	NA	–1.93 (–2.81 to –1.05) < 0.0001	–2.06 (–2.94 to –1.17) < 0.0001	NA	–1.18 (–1.91 to –0.44) = 0.0017	–2.03 (–2.77 to –1.29) < 0.0001	NA
Baseline A1C ≥ 9.0%									
N	26	26	32	28	23	26	34	33	42
Baseline, mean (SD)	70.9 (15.8)	74.8 (18.8)	76.9 (18.6)	87.91 (23.14)	78.67 (21.99)	83.70 (20.99)	78.06 (18.86)	79.09 (20.50)	74.38 (17.15)
Week 24, mean (SD)	69.6 (15.7)	73.3 (17.9)	77.3 (18.5)	86.50 (22.69)	76.22 (20.75)	83.28 (20.62)	75.70 (17.92)	77.21 (20.22)	74.00 (17.24)
Change from baseline, adjusted mean (SE)	–1.51 (0.54)	–1.56 (0.54)	0.40 (0.49)	–1.15 (0.48)	–2.54 (0.52)	–0.21 (0.49)	–2.39 (0.39)	–1.84 (0.40)	–0.51 (0.36)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–1.90 (–3.34 to –0.47) = 0.0092	–1.95 (–3.38 to –0.52) = 0.0075	NA	–0.94 (–2.29 to 0.40) = 0.1673	–2.33 (–3.74 to –0.92) = 0.0012	NA	–1.89 (–2.93 to –0.84) = 0.0004	-1.33 (–2.38 to –0.28) = 0.0134	NA

A1C = glycated hemoglobin; CI = confidence interval; EMPA = empagliflozin; MET = metformin; NA = not applicable; PL = placebo; q.d. = once daily; SD = standard deviation; SE = standard error, SU = sulfonylurea; vs. = versus.

[a] Analysis of covariance (ANCOVA) model includes baseline weight as linear covariate(s) and baseline estimated glomerular filtration rate (eGFR), baseline background medication, treatment, baseline A1C, and treatment by baseline A1C interaction as fixed effect(s).

[b] ANCOVA model includes baseline weight as a linear covariate, and baseline eGFR, geographical region, treatment, baseline A1C, and treatment by baseline A1C interaction as fixed effects.

Sources: Clinical Study Reports of 1245.19, 1245.23$_{MET}$, and 1245.23$_{METt+SU}$.[22,23]

TABLE 18: CHANGE FROM BASELINE IN BODY WEIGHT (KG) AT WEEK 24 — SUBGROUP ANALYSIS BY BASELINE RENAL IMPAIRMENT (FULL ANALYSIS SET, LAST OBSERVATION CARRIED FORWARD)

Parameter	1245.19[a]			1245.23$_{MET}$[b]			1245.23$_{MET+SU}$[b]		
	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL	EMPA 10 mg q.d.	EMPA 25 mg q.d.	PL
Baseline eGFR ≥ 90 mL/min/1.73 m^2									
N	60	67	63	96	91	95	92	94	94
Baseline, mean (SD)	74.5 (17.6)	73.6 (19.0)	73.8 (17.9)	78.36 (17.39)	78.85 (19.94)	74.97 (16.35)	76.54 (19.94)	75.45 (18.09)	72.38 (14.87)
Week 24, mean (SD)	73.0 (17.6)	72.2 (18.8)	74.3 (17.4)	76.57 (17.00)	76.92 (19.40)	74.77 (16.00)	74.66 (20.21)	72.88 (17.93)	71.90 (14.88)
Change from baseline, adjusted mean (SE)	–1.52 (0.36)	–1.52 (0.34)	0.46 (0.35)	–1.92 (0.26)	–2.03 (0.26)	–0.41 (0.26)	–1.81 (0.24)	–2.55 (0.24)	–0.54 (0.24)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–1.98 (–2.96 to –1.00) < 0.0001	–1.98 (–2.93 to –1.02 < 0.0001	NA	–1.51 (–2.22 to –0.80) < 0.0001	–1.63 (–2.35 to –0.91) < 0.0001	NA	–1.27 (–1.94 to –0.60) = 0.0002	–2.01 (–2.67 to –1.35) < 0.0001	NA
Baseline eGFR 60 to < 90 mL/min/1.73 m^2									
N	85	85	84	112	108	100	114	105	109
Baseline, mean (SD)	79.8 (20.6)	81.6 (19.2)	80.2 (20.9)	84.03 (19.32)	84.14 (17.19)	83.12 (19.12)	76.78 (16.86)	78.38 (18.94)	77.85 (17.35)
Week 24, mean (SD)	77.9 (20.2)	80.1 (18.7)	80.3 (20.9)	81.76 (18.84)	81.36 (16.63)	82.53 (19.30)	74.38 (16.68)	76.04 (18.71)	77.54 (17.26)
Change from baseline, adjusted mean (SE)	–1.79 (0.30)	–1.44 (0.30)	0.15 (0.30)	–2.17 (0.24)	–2.66 (0.24)	–0.51 (0.25)	–2.43 (0.22)	–2.34 (0.22)	–0.32 (0.22)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–1.95 (–2.78 to –1.11) < 0.0001	–1.60 (–2.43 to –0.76) = 0.0002	NA	–1.66 (–2.34 to –0.98) < 0.0001	–2.15 (–2.83 to –1.47) < 0.0001	NA	–2.11 (–2.72 to –1.51) < 0.0001	–2.03 (–2.64 to –1.41) < 0.0001	NA

Parameter	1245.19[a]			1245.23$_{MET}$[b]			1245.23$_{MET+SU}$[b]		
Baseline eGFR 30 to < 60 mL/min/1.73 m^2									
N	20	16	18	9	14	12	19	17	22
Baseline, mean (SD)	81.0 (16.5)	87.1 (23.0)	83.6 (22.0)	85.64 (16.11)	89.21 (26.79)	89.22 (21.99)	81.44 (19.25)	83.37 (21.34)	84.66 (18.88)
Week 24, mean (SD)	79.8 (15.1)	85.4 (22.9)	84.2 (21.3)	82.87 (15.57)	85.06 (25.29)	88.63 (21.66)	79.28 (19.01)	81.55 (20.46)	84.44 (18.96)
Change from baseline, adjusted mean (SE)	–1.12 (0.62)	–1.47 (0.69)	0.78 (0.65)	–2.52 (0.84)	–3.79 (0.67)	–0.24 (0.73)	–2.23 (0.53)	–1.75 (0.56)	–0.14 (0.49)
Comparison vs. PL, adjusted mean (95% CI), *P* value	–1.90 (–3.67 to –0.14) = 0.0348	–2.25 (–4.11 to –0.38) = 0.0186	NA	–2.28 (–4.45 to –0.11) = 0.0395	–3.55 (–5.48 to –1.61) = 0.0003	NA	–2.09 (–3.51 to –0.67) = 0.0039	–1.61 (–3.07 to –0.15) = 0.0308	NA

ANCOVA = analysis of covariance; CI = confidence interval; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; MET = metformin; NA = not applicable; PL = placebo; q.d. = once daily; SD = standard deviation; SE = standard error, SU = sulfonylurea; vs. = versus.

[a] ANCOVA model includes baseline weight, baseline glycated hemoglobin (A1C) as linear covariate(s), and baseline background medication, treatment, baseline eGFR, and treatment by baseline eGFR interaction as fixed effect(s).

[b] ANCOVA model includes baseline weight, baseline A1C as a linear covariate, and geographical region, treatment, baseline eGFR, and treatment by baseline eGFR interaction as fixed effects.

Sources: Clinical Study Reports of 1245.19, 1245.23$_{MET}$, and 1245.23$_{MET+SU}$.[22,23]

APPENDIX 5: SUMMARY OF BIOEQUIVALENCE STUDIES

Objective

To summarize the results of four phase I, randomized, open-label (OL), single-dose, crossover studies that evaluated the bioequivalence of empagliflozin (EMPA) and metformin (MET) administered as a fixed-dose combination (FDC) tablet compared with administration of the individual components.

Bioequivalence studies

Study characteristics

The manufacturer conducted four phase I studies to evaluate the bioequivalence of the EMPA/MET FDC and the free-dose combination of the two components in both the fed and fasting state. All four studies were OL, single-dose, crossover studies conducted in healthy volunteers (Table 19). Three studies were designed as bioequivalence trials (1276.6, 1276.7, and 1276.8) and one study was designed as a bioavailability study (1276.5).

TABLE 19: STUDY CHARACTERISTICS OF BIOEQUIVALENCE AND BIOAVAILABILITY STUDIES

Description	Study ID			
	1276.5	1276.6	1276.7	1276.8
Study design	Phase I, OL, randomized, three-way crossover, bioavailability	Phase I, OL, randomized, four-way crossover, bioequivalence	Phase I, OL, randomized, four-way crossover, bioequivalence	Phase I, OL, randomized, crossover, bioequivalence
Test therapies (FDC)	• EMPA 12.5 mg/MET 1,000 mg (fasted) • EMPA 12.5 mg/MET 1,000 mg (fed)	• EMPA 12.5 mg/MET 500 mg (fed) • EMPA 5 mg/MET 500 mg (fed)	• EMPA 12.5 mg/MET 850 mg (fed) • EMPA 5 mg/MET 850 mg (fed)	• Part 1: ○ EMPA 12.5 mg/MET 1,000 mg (fed) ○ EMPA 12.5 mg/MET 1,000 mg (fasted) • Part 2: ○ EMPA 5 mg/MET 1,000 mg (fed)
Reference therapies (individual components)	• EMPA 10 mg + EMPA 2.5 mg + MET 1,000 mg (fasted)	• EMPA 10 mg + EMPA 2.5 mg + MET 500 mg (fed) • EMPA 5 mg + MET 500 mg (fed)	• EMPA 10 mg + EMPA 2.5 mg + MET 850 mg (fed) • EMPA 5 mg + MET 850 mg (fed)	• Part 1: ○ EMPA 12.5 mg + MET 1,000 mg (fed) ○ EMPA 12.5 mg + MET 1,000 mg (fasted) • Part 2: ○ EMPA 5 mg + MET 1,000 mg (fed)

EMPA = empagliflozin; FDC = fixed-dose combination; MET = metformin; OL = open-label.
Source: Manufacturer's Clinical Summary[36] and Common Technical Document Section 2.7.1.[37]

Treatments and references

As shown in Table 19, bioequivalence of the FDC with the individual components was investigated using the following five FDC tablets (EMPA/MET, respectively): 5 mg/850 mg, 5 mg/1,000 mg, 12.5 mg/500 mg, 12.5 mg/850 mg, and 12.5 mg/1,000 mg. The reference treatments consisted of the separate tablets

containing the individual components (i.e., 2.5 mg, 5 mg, or 12.5 mg of EMPA and 500 mg, 850 mg, or 1,000 mg of MET).

End points

The primary end points in all four studies were area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity ($AUC_{0-\infty}$) and maximum measured concentration of the analyte in plasma (C_{max}) for both EMPA and MET (Table 20). The analyses were conducted using an analysis of variance (ANOVA) on the logarithmic scale including effects for "sequence," "patients within sequences," "period," and "treatment." Two-sided 90% confidence intervals (CIs) were calculated for the ratios of the geometric means (test and/or reference) for the primary end points. The pre-specified acceptance range for bioequivalence was 80.00% to 125.00% for the 90% CI.

TABLE 20: END POINTS EVALUATED IN THE BIOEQUIVALENCE AND BIOAVAILABILITY STUDIES

End point	Description
Primary end points	
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
C_{max}	Maximum measured concentration of the analyte in plasma
Secondary and other end points	
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the time of the last quantifiable data point
t_{max}	Time from dosing to the maximum concentration of the analyte in plasma
λ_z	Terminal elimination rate constant in plasma
$t_{1/2}$	Terminal half-life of the analyte in plasma
MRT_{po}	Mean residence time of the analyte in the body after oral administration
CL/F	Apparent clearance of the analyte in the plasma after extravascular administration
V_z/F	Apparent volume of distribution during the terminal phase λ_z

Source: Clinical Study Reports for 1276.5, 1276.6, 1276.7, and 1276.8.[38–41]

Study populations

Sample sizes ranged from between 16 and 48 healthy patients. The characteristics of the study populations were generally consistent across the four studies (Table 21). All patients were white, with mean ages ranging from between 31.5 and 35.8 years. Reviewers for the European Medicines Agency (EMA) noted that total exposure to EMPA (AUC) is slightly greater in patients with type 2 diabetes mellitus (T2DM) compared with healthy volunteers; however, the difference is not considered to be clinically significant.[21] Therefore, healthy volunteers were considered to be an acceptable population for the bioequivalence studies.[21] Reduced renal function in patients with T2DM is believed to contribute to the increased exposure compared with healthy volunteers.

TABLE 21: POPULATION CHARACTERISTICS OF BIOEQUIVALENCE AND BIOAVAILABILITY STUDIES

Description	Study ID			
	1276.5	1276.6	1276.7	1276.8
N	16	24	36	48
Male, n (%)	7 (44)	9 (38)	22 (61)	23 (48)
Female, n (%)	9 (56)	15 (62)	14 (39)	25 (52)
White, n (%)	16 (100)	24 (100)	36 (100)	48 (100)
Age (years), mean (range)	35.8 (24, 51)	35.6 (20, 48)	33.6 (21, 50)	31.5 (20, 48)
BMI (kg/m^2), mean (range)	24.2 (19.4, 29.7)	23.7 (18.8, 29.1)	23.9 (19.7, 28.0)	23.0 (18.7, 29.4)

BMI = body mass index.
Source: Manufacturer's Clinical Summary[36] and Common Technical Document Section 2.7.1.[37]

Pharmacokinetic results

Table 22 summarizes the key results from the bioequivalence studies. Across all the three bioequivalence trials (1276.6, 1276.7, and 1276.8) and the bioavailability study (1276.5), the geometric means and corresponding 90% CIs for the EMPA/MET FDC were contained within the 80% to 125% boundary criteria pre-specified for bioequivalence. Reviewers for the EMA and Health Canada concluded that the EMPA/MET FDC is bioequivalent compared with both of the individual compounds.[21,42]

TABLE 22: KEY RESULTS FROM BIOEQUIVALENCE AND BIOAVAILABILITY STUDIES

Study	Treatment	Reference	Geometric Mean Ratios (%; 90% CI)	
			EMPA	MET
$AUC_{0-\infty}$				
1276.5	EMPA 12.5/MET 1,000 (fasted)	EMPA 10 + EMPA 2.5 + MET 1,000 (fasted)	100.59 (95.75 to 105.67)	102.15 (93.87 to 111.15)
	EMPA 12.5/MET 1,000 (fed)		94.94 (89.85 to 100.33)	100.67 (91.70 to 110.51)
1276.6	EMPA 12.5/MET 500 (fed)	EMPA 10 + EMPA 2.5 + MET 500 (fed)	97.92 (93.53 to 102.52)	96.25 (88.54 to 104.63)
	EMPA 5/MET 500 (fed)	EMPA 5 + MET 500 (fed)	102.79 (99.08 to 106.63)	96.79 (91.77 to 102.09)
1276.7	EMPA 12.5/MET 850 (fed)	EMPA 10 + EMPA 2.5 + MET 850 (fed)	101.31 (96.89 to 105.93)	101.61 (97.94 to 105.41)
	EMPA 5/MET 850 (fed)	EMPA 5 + MET 850 (fed)	100.30 (97.40 to 103.29)	98.6 (94.24 to 103.08)
1276.8	EMPA 12.5/MET 1,000 (fed)	EMPA 12.5 + MET 1,000 (fed)	98.88 (94.88 to 103.06)	99.34 (92.56 to 106.62)
	EMPA 12.5/MET 1,000 (fasted)	EMPA 12.5 + MET 1,000 (fasted)	102.55 (99.53 to 105.65)	96.13 (91.25 to 101.26)
	EMPA 5/MET 1,000 (fed)	EMPA 5 + MET 1,000 (fed)	106.00 (102.73 to 109.39)	100.81 (95.74 to 106.14)
C_{max}				
1276.5	EMPA 12.5/MET 1,000 (fasted)	EMPA 10 + EMPA 2.5 + MET 1,000 (fasted)	99.31 (91.76 to 107.49)	103.49 (95.30 to 112.39)
	EMPA 12.5/MET 1,000 (fed)		64.30 (55.97 to 73.87)	75.13 (63.68 to 88.64)

Study	Treatment	Reference	Geometric Mean Ratios (%; 90% CI)	
			EMPA	MET
1276.6	EMPA 12.5/MET 500 (fed)	EMPA 10 + EMPA 2.5 + MET 500 (fed)	104.61 (99.88 to 109.56)	94.76 (89.06 to 100.82)
	EMPA 5/MET 500 (fed)	EMPA 5 + MET 500 (fed)	102.96 (97.92 to 108.26)	93.83 (88.01 to 100.03)
1276.7	EMPA 12.5/MET 850 (fed)	EMPA 10 + EMPA 2.5 + MET 850 (fed)	102.70 (98.75 to 106.81)	99.64 (95.39 to 104.09)
	EMPA 5/MET 850 (fed)	EMPA 5 + MET 850 (fed)	100.97 (95.94 to 106.27)	97.89 (93.81 to 102.15)
1276.8	EMPA 12.5/MET 1,000 (fed)	EMPA 12.5 + MET 1,000 (fed)	106.52 (95.86 to 118.35)	97.97 (92.34 to 103.94)
	EMPA 12.5/MET 1,000 (fasted)	EMPA 12.5 + MET 1,000 (fasted)	102.12 (96.26 to 108.35)	94.87 (88.93 to 101.21)
	EMPA 5/MET 1,000 (fed)	EMPA 5 + MET 1,000 (fed)	104.54 (99.15 to 110.22)	102.95 (97.17 to 109.08)
AUC_{0-tz}				
1276.5	EMPA 12.5/MET 1,000 (fasted)	EMPA 10 + EMPA 2.5 + MET 1,000 (fasted)	100.94 (96.03 to 106.11)	103.13 (95.59 to 111.25)
	EMPA 12.5/MET 1,000 (fed)		94.39 (89.22 to 99.87)	96.96 (87.23 to 107.78)
1276.6	EMPA 12.5/MET 500 (fed)	EMPA 10 + EMPA 2.5 + MET 500 (fed)	98.00 (93.53 to 102.69)	95.78 (88.00 to 104.26)
	EMPA 5/MET 500 (fed)	EMPA 5 + MET 500 (fed)	102.77 (99.15 to 106.52)	95.94 (91.20 to 100.93)
1276.7	EMPA 12.5/MET 850 (fed)	EMPA 10 + EMPA 2.5 + MET 850 (fed)	101.20 (96.9 to 105.7)	101.51 (97.95 to 105.21)
	EMPA 5/MET 850 (fed)	EMPA 5 + MET 850 (fed)	100.31 (97.41 to 103.29)	98.57 (94.50 to 102.81)
1276.8	EMPA 12.5/MET 1,000 (fed)	EMPA 12.5 + MET 1,000 (fed)	98.82 (94.78 to 103.04)	99.31 (92.14 to 107.03)
	EMPA 12.5/MET 1,000 (fasted)	EMPA 12.5 + MET 1,000 (fasted)	102.33 (99.32 to 105.43)	94.89 (89.80 to 100.26)
	EMPA 5/MET 1,000 (fed)	EMPA 5 + MET 1,000 (fed)	105.98 (102.73 to 109.33)	100.74 (95.77 to 105.96)

$AUC_{0-\infty}$ = area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum concentration of the analyte; EMPA = empagliflozin; MET = metformin.
Source: Adopted from Manufacturer's Clinical Summary[36] and Common Technical Document Section 2.7.1.[37]

Conclusions

Four phase I, single-administration studies demonstrated that the EMPA/MET FDC is bioequivalent to the individual components administered separately, based on commonly accepted criteria.

APPENDIX 6: SUMMARY OF OTHER Phase III STUDIES

Aim

To summarize the key findings of the following non-pivotal phase III studies that investigated the use of empagliflozin (EMPA) in combination with the metformin (MET).

- Study 1245.28: a double-blind (DB) randomized controlled trial (RCT) comparing EMPA (25 mg per day) against glimepiride (GLIM; 1 mg to 4 mg per day) for patients with inadequate glycemic control with MET monotherapy.
- Study 1245.49: a DB, placebo-controlled RCT comparing the addition of EMPA (10 mg or 25 mg once daily) against placebo for patients with inadequate glycemic control on their existing multiple-daily-injection (MDI) insulin, with or without MET.

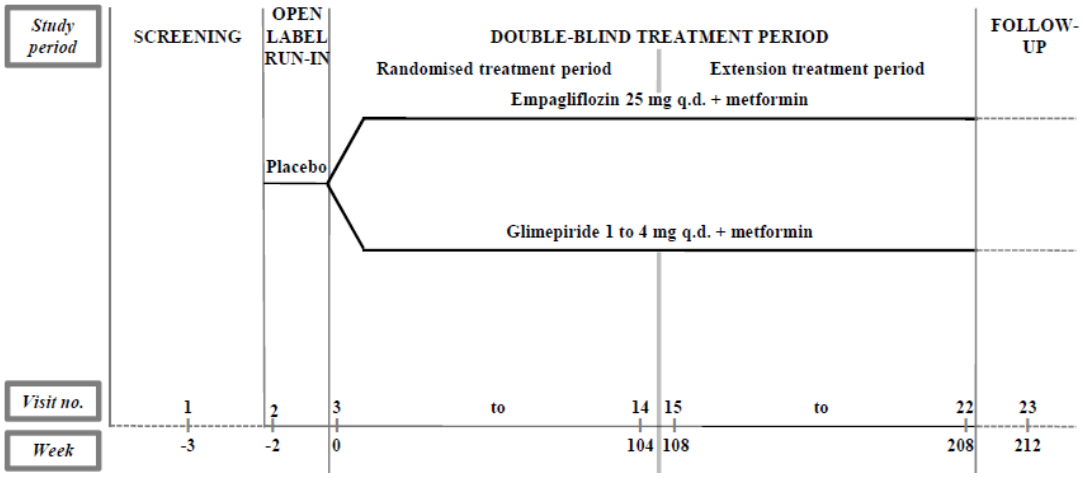
To be eligible for inclusion in this supplemental issue, the study must have been a non-pivotal phase III RCT that reported efficacy for patients using EMPA in combination with MET (as the full study population or in a separate subgroup analysis).

Empagliflozin versus glimepiride (add-on to metformin)

Study design

Study 1245.28 was a randomized, DB, double-dummy, active-controlled, parallel-group noninferiority trial evaluating the efficacy and safety of EMPA (25 mg per day) versus GLIM (1 mg to 4 mg per day) as add-on therapy to immediate release MET in patients with type 2 diabetes mellitus (T2DM) and insufficient glycemic control. As shown in Figure 4, Study 1245.28 consisted of a two-week, open-label (OL), placebo run-in period, a DB study period of 104 weeks, a 104-week DB extension phase, and a four-week follow-up phase following discontinuation of the study treatment. The study was designed to investigate noninferiority of EMPA to GLIM with an option to test for superiority if the noninferiority criterion was met.[43]

FIGURE 4: STUDY DESIGN OF 1245.28



q.d. = once daily.
Source: Clinical Study Report for 1245.28.[43]

Eligibility criteria

Adults with T2DM and inadequate glycemic control (i.e., A1C 7% to 10%) and a BMI (body mass index) less than 45 kg/m² were eligible provided than had been receiving a stable dose of MET immediate release (≥ 1,500 mg per day, maximum tolerated dose, or maximum dose) for at least 12 weeks. Key exclusion criteria included any of the following: eGFR (estimated glomerular filtration rate) less than 60 mL per min per 1.73 m²; fasting plasma glucose (FPG) greater than 13.3 mmol/L; or the use of any antihyperglycemic drugs other than MET immediate release (IR) during the 12 weeks before randomization.[43]

Intervention and comparators

The dose of EMPA was fixed at 25 mg once daily, whereas the dose of GLIM could be titrated between 1 mg and 4 mg daily. The dosage of GLIM could be increased if fasting glucose values were > 6.1 mmol/L up to 4 mg per day at four weekly intervals up to week 12. After 12 weeks, only maintenance or down titration of the GLIM dose was to occur.[43] The dose of GLIM could be uptitrated during the first 12 weeks of the treatment period. The highest dose of GLIM (i.e., 4 mg per day) was reached for 40.1% of patients on GLIM. The mean (standard deviation [SD]) highest daily dose of GLIM was 2.71 mg (1.24 mg).[43]

All study participants were to receive two placebo tablets once daily during the two-week, OL, run-in period. During the DB, double-dummy phase, study participants were instructed to take one tablet and one capsule daily. Patients in the EMPA group were to take one active drug tablet of EMPA (25 mg) and one placebo capsule matching the GLIM dose. Patients in the GLIM treatment group were to take one placebo tablet matching the EMPA dose and one capsule containing active GLIM dose. Patients were asked to continue their background therapy of MET IR in an unchanged dose and dosing regimen throughout the trial.[43]

Outcomes

The primary end point of Study 1245.28 was change from baseline in A1C after 104 weeks of treatment. The noninferiority margin for the primary end point was defined as an A1C level of 0.3%. The following key secondary end points were evaluated in the following hierarchical order: body weight, confirmed hypoglycemia, A1C (superiority), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Patient-reported outcomes included the EuroQol 5-Dimension Questionnaire (EQ-5D) and Diabetes Treatment Satisfaction Questionnaire.[43]

TABLE 23: DETAILS

		1245.28
DESIGNS & POPULATIONS	**Study Design**	104-week, phase III, DB, multi-centre, active-controlled, parallel-group RCT
	Locations	181 sites in 23 countries (North America, South America, Europe, Asia)
	Enrolled (N)	1549
	Inclusion Criteria	• Adults with T2DM • BMI ≤ 45 kg/m² • A1C 7% to 10% • Stable dose of metformin IR (≥ 1500 mg/day, maximum tolerated dose, or maximum dose) for ≥ 12 weeks
	Exclusion Criteria	• eGFR < 60 mL/min per 1.73 m² during screening or placebo run-in • FPG > 13.3 mmol/L • Use of antidiabetes drugs other than metformin IR during the 12 weeks before randomization
DRUGS	**Intervention**	• EMPA 25 mg q.d.
	Comparator(s)	• GLIM 1 mg to 4 mg q.d.
DURATION	**Phase**	
	Run-in period	2-week, OL, placebo run-in
	Core phase	104 weeks
	Extension	104 weeks
	Follow-up	4 weeks
OUTCOMES	**Primary End Point**	• A1C at 104 weeks
	Other End Points	• Body weight at 104 weeks • Confirmed hypoglycemia over 104 weeks • SBP at 104 weeks • DBP at 104 weeks • FPG at 104 weeks • EQ-5D and DTSQ • AEs, SAEs, WDAEs
NOTES	**Publications**	• Ridderstrale et al., 2014[44] • Ridderstrale et al., 2014[45]

A1C = glycated hemoglobin; AE = adverse event; BMI = body mass index; DB = double-blind; DBP = diastolic blood pressure; DTSQ = Diabetes Treatment Satisfaction Questionnaire; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; EQ-5D = EuroQol 5-Dimensions Questionnaire; FPG = fasting plasma glucose; GLIM = glimepiride; IR = immediate release; OL = open-label; q.d. = once daily; RCT = randomized controlled trial; SAE = serious adverse event; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for 1245.28.[43]

Patient disposition

Patient disposition for the extension study is summarized in Table 24. A total of 2,637 patients were screened for inclusion in Study 1245.28 and 1,678 were enrolled in the OL, placebo run-in period. Of those, 1,549 patients were randomized to DB treatment with EMPA (n = 769) or GLIM (n = 780). Nearly all randomized patients (n = 1,545) received at least dose of the study treatments. After 104 weeks, 1,197 (77.5%) patients were still in the trial. Of the patients no longer in the trial, 165 patients (10.7%) elected not to continue into the extension phase and 183 (11.8%) had discontinued from the trial.

TABLE 24: PATIENT DISPOSITION IN STUDY 1245.28

Disposition, n (%)	EMPA 25 mg	GLIM (1 mg to 4 mg)
Screened	2637	
Randomized	769	780
Treated	765 (99.5%)	780 (100%)
Still on treatment	555 (72.2%)	521 (67%)
Discontinued	117 (15.2%)	132 (17%)
AEs	35 (4.6%)	32 (4%)
Lack of efficacy	3 (0.4%)	3 (0%)
Protocol violation	6 (0.8%)	12 (2%)
Lost to follow-up	15 (2.0%)	14 (2%)
Refused to continue trial medication	36 (4.7%)	30 (4%)
Other	22 (2.9%)	41 (5%)
Still in trial	602 (78.3%)	595 (76%)

AE = adverse event; EMPA = empagliflozin; GLIM = glimepiride.
Sources: CADTH Common Drug Review submission for Synjardy.[20]

Baseline characteristics

Key baseline characteristics for the patients enrolled in the study are summarized in Table 25. The majority of study participants were male (55.2%), white (65.8%), and recruited from Europe (41.4%). North American participants represented a minority of the study population (12.7%). The mean age of patients was 55.9 years. Nearly all study participants had been receiving a daily dose of MET greater than or equal to 1500 mg per day (approximately 96% overall). The overall mean A1C at baseline was 7.9%, with the majority of patients (76%) having A1C less than 8.5%. Mean blood pressure at baseline mean was 133.5 mm Hg for SBP and 79.5 mm Hg for DBP.

TABLE 25: BASELINE CHARACTERISTICS

Characteristics	EMPA 25 mg (N = 765)	GLIM (1 mg – 4 mg) (N = 780)
Sex, N (%)		
Male	432 (56.5)	421 (54.0)
Female	333 (43.5)	359 (46.0)
Race, N (%)		
White	498 (65.1)	519 (66.5)
Asian	254 (33.2)	253 (32.4)
Black / African-American	12 (1.6)	8 (1.0)
Hawaiian / Pacific Islander	1 (0.1)	0
Age [years], mean (SD)	56.2 (10.3)	55.7 (10.4)
eGFR [mL/min/1.73m^2], mean (SD)	87.94 (16.82)	88.11 (17.85)
A1C [%], mean (SD)	7.92 (0.81)	7.92 (0.86)
FPG [mmol/L], mean (SD)	8.32 (0.06)	8.32 (0.07)
Weight [kg], mean (SD)	82.52 (19.16)	83.03 (19.22)
BMI [kg/m^2], mean (SD)	29.95 (5.28)	30.27 (5.3)
SBP [mm Hg], mean (SD)	133.4 (15.9)	133.5 (16.0)

Characteristics	EMPA 25 mg (N = 765)	GLIM (1 mg – 4 mg) (N = 780)
DBP [mm Hg], mean (SD)	79.5 (9.6)	79.4 (9.2)
History of hypertension, N (%)	479 (62.6)	471 (60.4)

A1C = glycated hemoglobin; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; FPG = fasting plasma glucose; GLIM = glimepiride; SBP = systolic blood pressure; SD = standard deviation.
Source: Clinical Study Report for 1245.28.[43]

Efficacy

As shown in Table 26, after 104 weeks, EMPA was noninferior and superior to GLIM for improving A1C (mean difference −0.11; 95% CI, −0.19 to −0.02). The results of the primary analysis (conducted using the FAS [full analysis set]) were supported by a number of sensitivity analyses, including an analysis using the per-protocol (PP) data set (mean difference −0.13; 95% CI, −0.22 to −0.03). EMPA was also shown to be statistically superior to GLIM for reducing FPG (−0.69 mmol/L), SBP (−5.6 mm Hg), DBP (−2.7 mm Hg), and body weight (−4.46 kg) (all $P < 0.0001$).

TABLE 26: SUMMARY OF EFFICACY END POINTS AT 104 WEEKS

Outcomes	GLIM	EMPA
A1C (%)		
Baseline, mean (SE)	7.92 (0.03)	7.92 (0.03)
Change from baseline, mean (95% CI)	−0.55 (−0.61 to −0.49)	−0.66 (−0.72 to −0.60)
Adjusted mean difference vs. GLIM (95% CI)[a]	−0.11 (95% CI, −0.19 to −0.02)	
P value (noninferiority)	< 0.0001	
P value (superiority)	0.0153	
FPG (mmol/L)		
Baseline, mean (SE)	8.32 (0.06)	8.32 (0.07)
Change from baseline	−0.17 (−0.29 to −0.04)	−0.85 (−0.97 to –0.73)
Adjusted mean difference vs. GLIM (95% CI)[b]	−0.69 (95% CI, −0.86 to −0.51)	
P value	< 0.0001	
SBP (mm Hg)		
Baseline, mean (SE)	133.5 (0.6)	133.4 (0.6)
Change from baseline	2.5 (1.7 to 3.4)	−3.1 (−3.9 to −2.2)
Adjusted mean difference vs. GLIM (95% CI)[b]	−5.6 (95% CI, −6.8 to −4.4)	
P value	< 0.0001	
DBP (mm Hg)		
Baseline, mean (SE)	79.4 (0.3)	79.5 (0.3)
Change from baseline	0.9 (0.4 to 1.4)	−1.8 (−2.3 to −1.2)
Adjusted mean difference vs. GLIM (95% CI)[b]	−2.7 (95% CI, −3.4 to −1.9)	
P value	< 0.0001	
Body weight (kg)		
Baseline, mean (SE)	83.03 (0.69)	82.52 (0.69)
Change from baseline, mean (SE)	1.34 (0.13)	−3.12 (0.13)
Adjusted mean difference vs. GLIM (95% CI)[b]	−4.46 (95% CI, −4.81 to −4.10)	

Outcomes	GLIM	EMPA
P value	< 0.0001	

A1C = glycated hemoglobin; CI = confidence interval; DBP = diastolic blood pressure; EMPA = empagliflozin; FPG = fasting plasma glucose; GLIM = glimepiride; SBP = systolic blood pressure; SE = standard error, vs. = versus.
[a] Analysis of covariance (ANCOVA) including treatment, geographical region, and renal function at baseline as fixed effects, and baseline A1C as a linear covariate.
[b] ANCOVA models included baseline value of the end point, baseline A1C as linear covariate, and baseline estimated glomerular filtration rate (eGFR), geographical region, and treatment as fixed effects.
Source: Ridderstrale and colleagues, 2014[45] and Clinical Study Report for 1245.28.[43]

Harms

Table 27 provides a summary of key adverse event (AE) data from Study 1245.28. The proportion of patients who experienced at least one AE was similar between the two treatment groups (approximately 86% in each group). Serious adverse events (SAEs) were numerically more commonly reported in the EMPA group compared with the GLIM group (16% versus 11%). The proportion of patients who discontinued as a result of AEs was similar between the two groups. Both hypoglycemia and hyperglycemia were more commonly reported in the GLIM group (25% and 22%, respectively) compared with the EMPA group (4% and 14%, respectively).[43]

Confirmed hypoglycemia was a key secondary end point of Study 1245.28. After 104 weeks, statistically significantly fewer EMPA-treated patients had experienced at least one confirmed hypoglycemic event compared with GLIM (2.5% versus 24.2%; *P* < 0.0001). The manufacturer reported an adjusted risk ratio (RR) of 0.102 (97.5% CI, 0.060 to 0.173) for EMPA versus GLIM (the model was adjusted for A1C at baseline [less than 8.5% versus greater than or equal to 8.5%]). There were no EMPA-treated patients and two GLIM-treated patients (0.3%) who had a hypoglycemic event that required assistance.[43]

TABLE 27: SUMMARY OF HARMS AT 104 WEEKS

AEs, N (%)	GLIM	EMPA
At least one AE	673 (86%)	661 (86%)
At least one SAEs	89 (11%)	119 (16%)
WDAEs	34 (4%)	39 (5%)
Deaths	5 (< 1%)	5 (< 1%)
AEs with a frequency of ≥ 5%		
Hypoglycemia	197 (25%)	32 (4%)
Hyperglycemia	168 (22%)	105 (14%)
Urinary tract infection	99 (13%)	95 (12%)
Nasopharyngitis	89 (11%)	76 (10%)
URTI	74 (9%)	79 (10%)
Back pain	64 (8%)	63 (8%)
Hypertension	77 (10%)	41 (5%)
Arthralgia	66 (8%)	44 (6%)
Influenza	51 (7%)	51 (7%)
Headache	55 (7%)	48 (6%)
Dizziness	49 (6%)	49 (6%)
Diarrhea	51 (7%)	39 (5%)
Cough	47 (6%)	42 (5%)
Dyslipidemia	39 (5%)	41 (5%)

AEs, N (%)	GLIM	EMPA
Pain in extremity	32 (4%)	39 (5%)
UTI	102 (13%)	105 (14%)
Men	21 (5%)	31 (7%)
Women	81 (23%)	74 (22%)
Genital infection	17 (2%)	90 (12%)
Men	5 (1%)	41 (9%)
Women	12 (3%)	49 (15%)

AE = adverse event; EMPA = empagliflozin; GLIM = glimepiride; SAE = serious adverse event; UTI = urinary tract infection; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Source: Ridderstrale and colleagues, 2014.[45]

Critical appraisal

Internal validity

Participants in Study 1245.28 were randomized using an interactive voice/Web response system that adequately concealed the allocation of participants. Randomization was stratified by relevant factors, including A1C at screening (less than 8.5% or greater than or equal to 8.5%), renal function at screening (normal renal function eGFR greater than or equal to 90 mL/min/1.73m^2 or impaired renal function eGFR less than 90 mL/min/1.73m^2), and geographical region. Treatment groups were well balanced with respect to key demographic and disease characteristics.

The study treatments were administered in a DB manner using a double-dummy design. It is unclear from the study protocols if changes in glycemic parameters (e.g., A1C or FPG), body weight, or blood pressure were available to investigators and/or discussed with participants during study visits. The AE profile was not likely to have significantly compromised blinding in either study; however, those affected by urogenital AEs could have surmised that the allocated treatment was EMPA, given that these events are known to occur with sodium-glucose cotransporter-2 (SGLT2) inhibitor class drugs. Similarly, patients who experienced treatment-emergent weight gain or hypoglycemic events may have inferred that they were receiving sulfonylurea (SU).

Study end points were appropriately measured and consistent with guidance from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for antihyperglycemic treatments. Consistent with study protocols, the dosage of MET remained relatively constant during the DB treatment phase. The statistical approach used in Study 1245.28 was well described and appropriate. Consistent with guidance from regulatory authorities (e.g., EMA), baseline A1C was included as a covariate in the analysis of the primary end point. A number of sensitivity analyses were conducted to support the findings of the primary analysis. Study 1245.28 used a hierarchal approach to control type I error rate given the multiple statistical analyses performed for the primary and key secondary end points.

The noninferiority margin selected in Study 1245.28 (i.e., 0.3%) is reflective of guidance from the FDA and EMA and is consistent with other trials conducted for antihyperglycemic treatments. Due to the demonstration of the superiority, the selection of the noninferiority margin is not particularly relevant for this review.

The primary analysis of Study 1245.28 (i.e., the FAS) used a modified intention-to-treat (ITT) analysis as opposed to a true ITT analysis; however, only a very small number of patients were excluded (n = 4 in the GLIM group and none from the EMPA group). Early discontinuations were common in both groups over the two-year study period, though the reasons and overall proportion of patients was similar between the two groups.

External validity

The patients enrolled in Study 1245.28 are representative of the target Canadian population in terms of demography, comorbidities, and disease characteristics. The baseline dosage of MET used in Study 1245.49 is reflective of situations where second-line therapy would be considered by physicians in Canada. Twelve weeks of stable doses of background medication is at the upper end of the range recommended by the EMA (i.e., eight to 12 weeks) to ensure the maximal effect of the previous medication has been achieved and that A1C is stabilized at baseline.

The comparative efficacy of EMPA and GLIM was assessed using surrogate end points (e.g., A1C). Study 1245.28 was of inadequate size or duration to evaluate macrovascular or microvascular complications of diabetes, or on mortality. The 104 duration of the trial (208 weeks including the extension of phase), is sufficient to detect differences in the primary end point (i.e., A1C) and the key secondary end points (e.g., body weight, SBP). Although the findings of Study 1245.28 may not be indicative of long-term efficacy and safety, the duration of this trial exceeds the six-month duration that is typically observed in phase III studies for antihyperglycemic groups.

GLIM is an appropriate active comparator, as CADTH's recommendation for sequential therapy of diabetes is that a SU (such as GLIM) be used as second-line therapy for patients whose hyperglycemia is inadequately controlled with MET monotherapy. The Canadian product monograph for GLIM states that the typical maintenance dose is 1 mg to 4 mg once daily, which is consistent with dosage range permitted in Study 1245.28.[46] However, the product monograph states that the maximum recommended dose is 8 mg once daily.[46] In addition, although the trial is planned for a total duration of 208 weeks, the dosage of GLIM could only be uptitrated during the first 12 weeks of Study 1245.28. This is not reflective of routine clinical practice, where the dosage could be adjusted as required to maintain glycemic control. Overall, the fact that patients were not permitted to titrate to the maximum dose of GLIM may bias efficacy results in favour of EMPA; however, increased weight gain and hypoglycemia may have been observed in the GLIM group had titration to 8 mg per day been permitted.

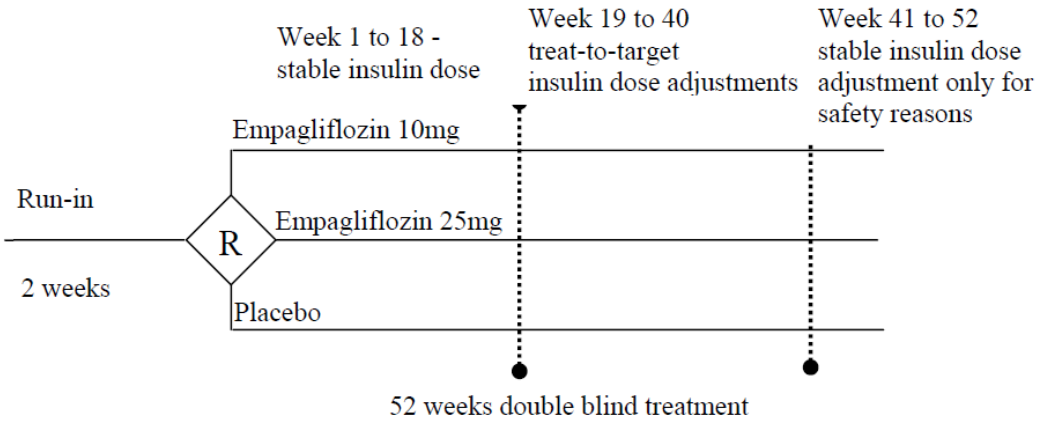
Study 1245.28 involved extensive patient contact with health care professionals (i.e., 14 visits from screening to end point). In addition, the trial included an OL two-week run-in period to ensure compliance with the study protocol and dosage regimen. This is not reflective of routine clinical practice in Canada and may, therefore, reduce generalizability of results to the general population with T2DM.

Empagliflozin versus placebo (add-on to multiple-daily-injection Insulin)

Study design

Study 1245.49 was a three-arm, DB, placebo-controlled RCT. Eligible patients were randomized (1:1:1) to EMPA 10 mg once daily, EMPA 25 mg once daily, or placebo. The study consisted of a two-week OL placebo run-in period to establish compliance, a 52-week DB treatment period, and a four-week follow-up period.

FIGURE 5: STUDY DESIGN OF 1245.49



R = randomization.
Source: Clinical Study Report for 1245.49.[47]

Eligibility criteria

Adult patients with T2DM and inadequate glycemic (i.e., ≥ 7.5 to ≤ 10%) and considered to be obese (i.e., BMI ≥ 30 and ≤ 45 kg/m^2) were eligible for enrolment provided they had been receiving a stable dose of MDI insulin (total daily dose > 60 IU) alone or in combination with a stable dose MET (immediate or extended release; ≥ 1,500 mg per day, maximum tolerated dose, or maximum dose).[47]

Intervention and comparators

All study participants were to receive two placebo tablets once daily during the two-week OL run-in period. The 52-week DB period used a double-dummy design. Patients in the EMPA treatment groups were to take one active drug tablet of their assigned EMPA dose (10 mg or 25 mg) and one placebo tablet. Patients in the placebo treatment group were to take two placebo tablets (one tablet matching each EMPA dose).[47]

Outcomes

Change from baseline in A1C at week 18 was the primary end point of Study 1245.49. Key secondary end points were evaluated at 52 weeks and included: change from baseline in insulin daily dose, body weight, and A1C. Exploratory end points also included changes in FPG, SBP, and DBP.

TABLE 28: DETAILS OF STUDY 1245.49

		1245.49
DESIGNS & POPULATIONS	**Study Design**	52-week, phase III, DB, multi-centre, placebo-controlled RCT
	Locations	104 sites in 14 countries (Europe, North America, South America)
	Enrolled (N)	566
	Inclusion Criteria	• Adults with T2DM • Obese (BMI ≥ 30 and ≤ 45 kg/m^2) • A1C ≥ 7.5 to ≤ 10% • Stable dose of MDI insulin (total daily dose > 60 IU) alone or in combination with a stable dose MET (IR or XR; ≥ 1,500 mg/day, maximum tolerated dose, or maximum dose)
	Exclusion Criteria	• FPG > 13.3 mmol/L • Acute coronary syndrome • Stroke or transient ischemic attack within 3 months • Indication of liver disease • eGFR < 60 mL/min/1.73 m^2
DRUGS	**Intervention**	• EMPA 25 mg q.d. • EMPA 10 mg q.d.
	Comparator(s)	• Placebo
DURATION	**Phase**	
	Run-in period	2-week, OL, placebo run-in
	Core phase	52 weeks
	Extension	NA
	Follow-up	4 weeks
OUTCOMES	**Primary End Point**	• A1C at week 18
	Other End Points	• Insulin dose at 52 weeks • Body weight at 52 weeks • A1C at 52 weeks • FPG at 52 weeks • A1C < 7% at 18 and 52 weeks • EQ-5D and DTSQ • AEs, SAEs, WDAEs
NOTES	**Publications**	• Rosenstock et al., 2014[48]

A1C = glycated hemoglobin; AE = adverse event; BMI = body mass index; DB = double-blind; DTSQ = Diabetes Treatment Satisfaction Questionnaire; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; EQ-5D = EuroQol 5-Dimensions Questionnaire; FPG = fasting plasma glucose; IR = immediate release; IU = international units; MET = metformin; MDI = multiple daily injections; NA = not applicable; OL = open-label; q.d. = twice daily; RCT = randomized controlled trial; SAE = serious adverse event; T2DM = type 2 diabetes mellitus; WDAE = withdrawal due to adverse event; XR = extended release.
Source: Clinical Study Report for 1245.49.[47]

Patient disposition

Patient disposition for Study 1245.49 is summarized in Table 29. A total of 1171 patients were screened for enrolment and 566 patients were randomized. Of those, 563 were treated with at least one dose of the study medications. A similar proportion of patients completed the 52-week trial in each of the three

study groups (83.5% with placebo, 83.3% with EMPA 10 mg, and 86.2% with EMPA 25 mg). Withdrawal of consent was specified as the most common reason for discontinuing the study.[47]

TABLE 29: PATIENT DISPOSITION IN STUDY 1245.49

DISPOSITION, N (%)	PL	EMPA 10 MG	EMPA 25 MG
Screened	1171		
Entered	189	187	190
Treated	188 (100.0)	186 (100.0)	189 (100.0)
Completed trial	161 (85.6)	159 (85.5)	168 (88.9)
Discontinued trial	27 (14.4)	27 (14.5)	21 (11.1)
Lost to follow-up	3 (1.6)	5 (2.7)	4 (2.1)
Consent withdrawn	24 (12.8)	22 (11.8)	16 (8.5)
Death	0	0	1 (0.5)

Abbreviations: EMPA = empagliflozin; PL = placebo.
Source: Clinical Study Report for 1245.49.[47]

Baseline characteristics

Key baseline characteristics for the patients enrolled in the study are summarized in Table 30. Baseline characteristics are only available for the full study population (i.e., they are not restricted to the insulin and MET subgroup that is of interest for the current CADTH Common Drug Review [CDR] review). A majority of study participants were female (64.5%) and 94.3% were white. The mean age at baseline was 56.7 years, mean BMI was 34.79 kg/m^2, and mean A1C was 8.3%. With regard to blood pressure, mean SBP was 133.3 mm Hg and mean DBP was 78.8 mm Hg. A majority of patients (71%) were using insulin in combination with MET at baseline. The mean total daily insulin dose was 92.0 IU and the mean daily MET dose was 2027 mg (Table 31).[47]

TABLE 30: BASELINE CHARACTERISTICS

Characteristic	PL (N = 188)	EMPA 10 mg (N = 186)	EMPA 25 mg (N = 189)
Sex, N (%)			
Male	75 (39.9)	97 (52.2)	84 (44.2)
Female	113 (60.1)	89 (47.8)	105 (55.6)
Race, N (%)			
White	174 (92.6)	175 (94.1)	182 (96.3)
Black/African-American	8 (4.3)	7 (3.8)	4 (2.1)
American Indian/Alaska Native	4 (2.1)	3 (1.6)	2 (1.1)
Asian	2 (1.1)	0	1 (0.5)
Hawaiian/Pacific Islander	0	1 (0.5)	0
Age, mean (SD) [years]	55.3 (10.1)	56.7 (8.7)	58.0 (9.4)
eGFR, mean (SD) [mL/min/1.73m^2]	83.41 (15.40)	84.14 (17.76)	84.35(16.59)
A1C, mean (SD) [%]	8.33 (0.72)	8.39 (0.74)	8.29 (0.72)
FPG, mean (SE) [mmol/L]	8.41 (0.19)	8.83 (0.20)	8.34 (0.20)
Body weight, mean (SD) [kg]	95.5 (17.5)	96.7 (17.9)	95.9 (17.3)
BMI, mean (SD) [kg/m^2]	34.65 (4.30)	34.72 (3.83)	34.99 (4.04)
SBP, mean (SD) [mm Hg]	132.6 (15.8)	134.2 (16.4)	132.9 (14.2)

Characteristic	PL (N = 188)	EMPA 10 mg (N = 186)	EMPA 25 mg (N = 189)
DBP, mean (SD) [mm Hg]	78.2 (8.8)	79.5 (8.5)	78.7 (8.5)
History of hypertension	150 (79.8)	146 (78.5)	143 (75.7)

A1C = glycated hemoglobin; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; FPG = fasting plasma glucose; PL = placebo; SBP = systolic blood pressure; SD = standard deviation.
Source: Clinical Study Report for 1245.49.[47]

TABLE 31: BACKGROUND THERAPY IN STUDY 1245.49

Parameters	PL	EMPA 10 mg	EMPA 25 mg
N (%)	188 (100.0)	186 (100.0)	189 (100.0)
Insulin only, N (%)	53 (28.2)	58 (31.2)	52 (27.5)
Insulin + MET, N (%)	135 (71.8)	128 (68.8)	137 (72.5)
MET daily dose at baseline			
Mean dose (SD), [mg]	2023.0 (585.9)	1977.1 (526.5)	2077.0 (510.5)
Total daily insulin dose at baseline			
Mean dose (SD), N (%) [IU/day]	93.1 (43.6)	89.9 (38.0)	92.9 (45.8)
Basal, mean (SD)	52.74 (31.57)	49.32 (23.16)	50.76 (25.00)
Prandial, mean (SD)	39.58 (29.08)	40.03 (28.57)	41.24 (34.93)

EMPA = empagliflozin; IU = international units; MET = metformin; PL = placebo; SD = standard deviation.
Source: Clinical Study Report for 1245.49[47]

Efficacy

Subgroup analyses for patients who were using background MET in addition to insulin were conducted for the primary end point (A1C) and the key secondary end points (body weight and insulin dosage). In accordance with the CDR review protocol, which is focused on the use of EMPA in combination with MET, only data for these subgroups are summarized in this supplemental issue. As shown in Table 32, both the 10 mg and 25 mg doses of EMPA were associated with statistically significant reductions in A1C (−0.42% and −0.46%, respectively), body weight (−2.9 kg and −2.4 kg, respectively), and daily insulin dosage (−12.3 IU and −14.9 IU, respectively) compared with placebo. Data for the A1C subgroup analysis was analyzed using the FAS data set; whereas, the subgroup analyses for change in body weight and insulin dosage were analyzed using the PP completers set.

TABLE 32: SUMMARY OF EFFICACY END POINTS FOR INSULIN + METFORMIN BACKGROUND

Outcomes	PL	EMPA 10 mg	EMPA 25 mg
A1C (%) at 18 weeks			
N (FAS)	135	128	137
Baseline	NR	NR	NR
Mean change (SE)	−0.57 (0.06)	−0.99 (0.06)	−1.03 (0.06)
Mean difference vs. placebo[a] (95% CI)		−0.42 (−0.60 to −0.25)	−0.46 (−0.64 to −0.29)
P value		< 0.0001	< 0.0001
Body weight (kg)			
N (PPS-completers)	86	84	87
Baseline	NR	NR	NR
Mean change (SE)	0.39 (0.42)	−2.49 (0.43)	−1.98 (0.42)

Outcomes	PL	EMPA 10 mg	EMPA 25 mg
Mean difference vs. placebo[b] (95% CI)		−2.88 (−4.06 to −1.70)	−2.38 (−3.54 to −1.21)
P value		< 0.0001	< 0.0001
Insulin daily dose (IU/day)			
N (PPS-completers)	86	83	86
Baseline	NR	NR	NR
Mean change (SE)	12.36 (2.50)	0.11 (2.54)	−2.47 (2.49)
Mean difference vs. placebo[b] (95% CI)		−12.26 (−19.29 to −5.22)	−14.83 (−21.77 to −7.88)
P value		0.0007	< 0.0001

A1C = glycated hemoglobin; CI = confidence interval; EMPA = empagliflozin; FAS = full analysis set; NR = not reported; PL = placebo; PPS = per-protocol set; SE = standard error, vs = versus.

[a] Model included baseline A1C as linear covariate and baseline estimated glomerular filtration rate (eGFR), geographical region, baseline background medication, and treatment as fixed effects.

[b] Models included treatment, renal function, region, background medication, baseline A1C, and baseline body weight.

Source: Clinical Study Report for 1245.49.[47]

Critical appraisal

Internal validity

Participants in Study 1245.49 were randomized using an interactive voice and/or Web response system that adequately concealed the allocation of participants. Randomization was stratified by relevant factors, including A1C at screening (< 8.5% or ≥ 8.5%), renal function at screening (normal renal function eGFR ≥ 90 mL/min/1.73m^2 or impaired renal function eGFR < 90 mL/min/1.73m^2), geographical region, and background antidiabetic therapy (insulin alone or insulin in combination with MET). Treatment groups were well balanced with respect to key demographic and disease characteristics.

The study treatments were administered in a DB manner using a double-dummy design. It is unclear from the study protocols if changes in glycemic parameters (e.g., A1C or FPG), body weight, or blood pressure were available to investigators and/or discussed with participants during study visits. The AE profile was not likely to have significantly compromised blinding in either study; however, those affected by urogenital AEs could have surmised that the allocated treatment was EMPA.

Study end points were appropriately measured and consistent with guidance from the FDA and EMA for antihyperglycemic treatments. Consistent with study protocols, the dosage of MET remained relatively constant during the DB treatment phase and the dosage of insulin could be reduced (which was captured as a pre-specified efficacy end point). The statistical approach used in Study 1245.49 was well described and appropriate. Consistent with guidance from regulatory authorities (e.g., EMA), baseline A1C was included as a covariate in the analysis of the primary end point. A number of sensitivity analyses were conducted to support the findings of the primary analysis. Study 1245.49 used a hierarchal approach to control type I error rate given the multiple statistical analyses performed for the primary and key secondary end points; however, the subgroup analyses for those using a background regimen of insulin and MET were not adjusted for multiple comparisons. The primary analysis of Study 1245.49 (i.e., the FAS) used a modified ITT analysis as opposed to a true ITT analysis; however, only a small number of patients were excluded (n = 2 in each of the three treatment groups). Subgroup analyses for those on the insulin and MET background were only reported for the PP data set. The proportion of patients who discontinued the study ranged from 11.1% to 14.5% across the treatment groups. Although the reasons for discontinuation were balanced across the groups, these withdrawals

could affect the validity of the study results. Subgroup analyses for those on the insulin and MET background were only reported for the PP data set.

External validity

The patients enrolled in Study 1245.49 are representative of the target Canadian population in terms of demography, comorbidities, and disease characteristics. Twelve weeks of stable doses of background medication is at the upper end of the range recommended by the EMA (i.e., eight to 12 weeks) to ensure the maximal effect of the previous medication has been achieved and that A1C is stabilized at baseline. The study used surrogate end points (e.g., A1C) and was of inadequate size or duration to evaluate macrovascular or microvascular complications of diabetes, or on mortality.

The primary limitation of Study 1245.49 is the use of placebo as the comparator, as opposed to an intensified insulin regimen for patients inadequately controlled on their existing insulin regimen. Study 1245.49 involved extensive patient contact with health care professionals (i.e., 16 visits from screening to end point). In addition, the trial included an OL two-week run-in period to ensure compliance with the study protocol and dosage regimen. This is not reflective of routine clinical practice in Canada and may, therefore, reduce generalizability of results to the general population with T2DM.

Summary

One DB RCT (Study 1245.28) demonstrated that after 104 weeks of treatment, EMPA (25 mg once daily) was superior to GLIM (1 mg to 4 mg once daily) for improving A1C (−0.11%; 95% CI, −0.19 to −0.02), FPG (−0.69 mmol/L; 95% CI, −0.86 to −0.51), SBP (−5.6 mm Hg; 95% CI, −6.8 to −4.4), DBP (−2.7 mm Hg; 95% CI, −3.4 to −1.9), and body weight (−4.46 kg; 95% CI, −4.81 to −4.10). After 104 weeks, statistically significantly fewer EMPA-treated patients had experienced at least one confirmed hypoglycemic event compared with GLIM (2.5% versus 24.2%; $P < 0.0001$). The titration scheme for GLIM was more restrictive than would be expected in routine clinical practice (i.e., only permitted during the first 12 weeks of a 208-week study) and the maximum dosage of 4 mg per day is less than the 8 mg per day maximum dosage recommended in the Canadian product monograph. These restrictions may have biased glycemic control outcomes in favour of EMPA; however, increasing the dosage of GLIM would likely result in additional hypoglycemic events and weight gain for some patients.

One 52-week, three-arm, DB, placebo-controlled, RCT (Study 1245.49) demonstrated that treatment with EMPA (10 mg or 25 mg once daily) was superior to placebo. In the subgroup of patients who were using MET in combination with insulin, both the 10 mg and 25 mg doses of EMPA were associated with statistically significant reductions in A1C (−0.42% and −0.46%, respectively), body weight (−2.9 kg and −2.4 kg, respectively), and daily insulin dosage (−12.3 IU and −14.9 IU, respectively) compared with placebo. The primary limitation of Study 1245.49 is the use of placebo as the comparator, as opposed to an intensified insulin regimen for patients inadequately controlled on their existing insulin regimen.

APPENDIX 7: SUMMARY OF EXTENSION STUDIES

Aim

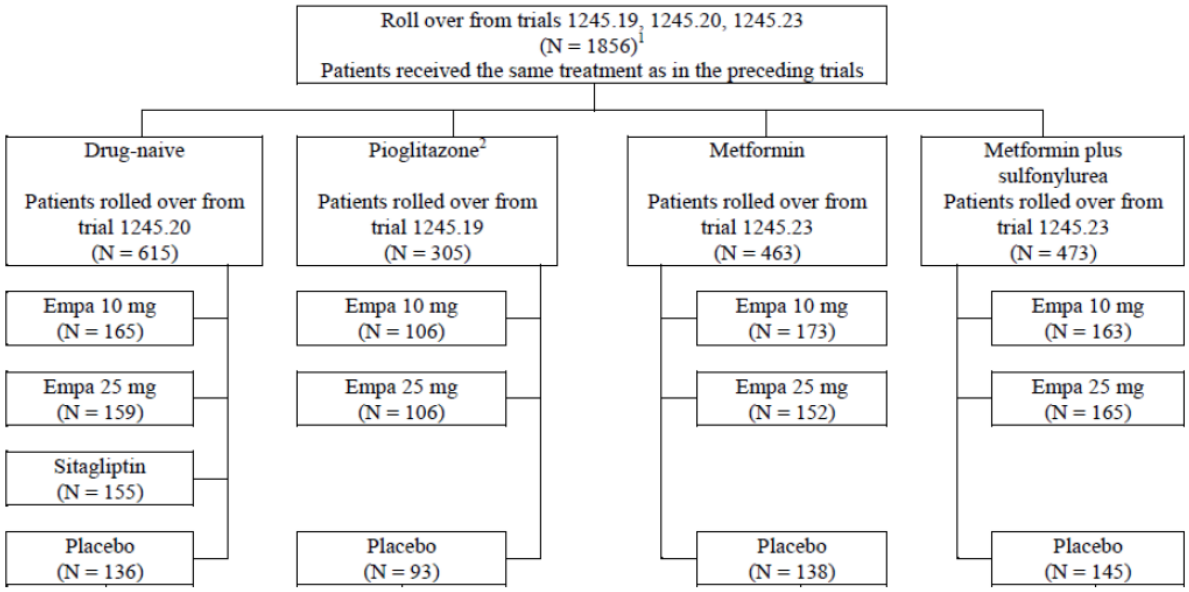
To summarize the key findings of the 1245.31 extension study.

Findings

Study design

As shown in Figure 6, the 1245.31 extension study was designed as four separate studies combined under a single study protocol. The four studies reflect the background therapies that were used in the core studies: no background therapy (Study 1245.20), pioglitazone (PIO) with or without metformin (MET; Study 1245.19), MET (Study 1245.23$_{MET}$), and MET plus a sulfonylurea (SU; Study 1245.23$_{MET+SU}$).[49]

FIGURE 6: DESIGN OF THE 1245.31 EXTENSION STUDIES



Abbreviations: EMPA = empagliflozin.
Source: Reproduced from Clinical Study Report for 1245.31.[49]

Eligibility criteria

Patients were eligible for the 1245.31 extension if they had successfully completed the entire treatment period of one of the following four double-blind (DB) trials: 1245.19, 1245.20, 1245.23$_{MET}$, or 1245.23$_{MET+SU}$, with or without rescue therapy.[49] Key exclusion criteria for the extension included the following items (as determined during last visit of preceding trial): indication of liver disease, defined by serum levels of either alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase of greater than three times the upper limit of normal (ULN); or impaired renal function defined as estimated glomerular filtration rate (eGFR) less than 30 mL per minute.[49]

Assessment

Safety was the main objective of Study 1245.31. The safety analyses were based on the combined data of the preceding trial and the extension trial. There was no primary efficacy end point specified for Study 1245.31. Secondary efficacy end points included change from baseline in A1C, body weight, waist circumference, fast plasma glucose (FPG), systolic blood pressure (SBP), and diastolic blood pressure

(DBP) after 76 weeks of treatment (i.e., 24 weeks in the core study and 52 weeks in the extension study). Baseline values were derived from the core studies (i.e., the last evaluation before any exposure to the study treatments). Exploratory efficacy analyses were conducted primarily using last observation carried forward (LOCF) to impute missing data; however, exploratory sensitivity analyses were conducted with observed cases.

TABLE 33: DETAILS OF THE EXTENSION STUDY

		1245.31 EXTENSION
DESIGNS & POPULATIONS	**Study Design**	76-week, phase III, DB, extension, placebo-controlled parallel-group safety and efficacy trial
	Locations	243 sites in 20 countries (Asia, Europe, North America)
	Enrolled (N)	1870 patients were enrolled from 1245.19, 1245.20, 1245.23$_{MET}$, and 1245.23$_{MET + SU}$
	Inclusion Criteria	• Completed entire treatment period of: 1245.19, 1245.20, 1245.23$_{MET}$, or 1245.23$_{MET + SU}$
	Exclusion Criteria	• Indication of liver disease (i.e., ALT, AST, or ALP ≥ 3x ULN) • Impaired renal function (i.e., eGFR < 30 mL/min)
DRUGS	**Intervention**	• EMPA 10 mg q.d. + background therapy • Empagliflozin 25 mg 10 mg q.d + background therapy
	Comparator(s)	• Placebo + background therapy
DURATION	**Phase**	
	Core study	24 weeks
	Extension study	52 weeks (total of 76 weeks)
	Follow-up	4 weeks
OUTCOMES	**Primary End Point**	• No primary end point
	Other End Points	• change from baseline in A1C and FPG • change from baseline body weight and waist circumference • change from baseline SBP and DBP • AE, SAE, WDAE
NOTES	**Publications**	• Merker et al., 2015[50] • Kovacs et al., 2015[51] • Haering et al., 2015[52]

A1C = glycated hemoglobin; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; DB = double-blind; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; FPG = fasting plasma glucose; q.d. = once daily; SAE = serious adverse event; SBP = systolic blood pressure; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for 1245.31.[49]

Baseline characteristics

Key baseline characteristics for the patients enrolled in the extension study are summarized in Table 34. As noted previously, these values are derived from the baseline measures in the core studies (i.e., the last evaluation prior any to exposure to the study treatments).

TABLE 34: BASELINE CHARACTERISTICS

Parameter	PL	EMPA 10 mg	EMPA 25 mg
MET			
N	207	217	213
Male, n (%)	116 (56.0)	125 (57.6)	120 (56.3)
Age, years	56.0 (9.7)	55.5 (9.9)	55.6 (10.2)
Body weight, kg	79.7 (18.6)	81.6 (18.5)	82.2 (19.3)
BMI, kg/m^2	28.7 (5.2)	29.1 (5.5)	29.7 (5.7)
A1C, %	7.9 (0.9)	7.9 (0.8)	7.9 (0.9)
FPG, mmol/L	8.7 (1.8)	8.6 (2.0)	8.3 (1.7)
SBP, mm Hg	128.6 (14.7)	129.6 (14.1)	130.0 (15.1)
DBP, mm Hg	78.1 (7.9)	79.6 (8.0)	78.4 (8.4)
eGFR, mL/min/1.73 m^2	89.7 (21.4)	89.5 (19.6)	87.7 (19.3)
PIO (with or without MET)			
N	165	165	1658
Male, n (%)	73 (44.2)	83 (50.3)	85 (50.6)
Age, years	54.6 (10.5)	54.7 (9.9)	54.2 (8.9)
Weight, kg	78.1 (20.1)	78.0 (19.2)	78.9 (19.9)
BMI, kg/m^2	29.3 (5.4)	29.2 (5.6)	29.1 (5.5)
A1C, %	8.16 (0.92)	8.07 (0.89)	8.06 (0.82)
FPG, mmol/L	8.4 (2.2)	8.4 (2.1)	8.4 (2.1)
SBP, mm Hg	125.7 (12.1)	126.5 (13.7)	125.9 (13.9)
DBP, mm Hg	76.3 (8.7)	77.2 (8.7)	77.2 (8.0)
eGFR, mL/min/1.73 m^2	85.5 (20.1)	84.3 (20.9)	87.4 (24.4)
MET + SU			
N	225	225	216
Male, n (%)	112 (49.8)	113 (50.2)	114 (52.8)
Age, years	56.9 (9.2)	57.0 (9.2)	57.4 (9.3)
Body weight, kg	76.2 (16.9)	77.1 (18.3)	77.5 (18.8)
BMI, kg/m^2	27.9 (4.9)	28.3 (5.4)	28.3 (5.5)
A1C, %	8.2 (0.8)	8.1 (0.8)	8.1 (0.8)
FPG, mmol/L	8.4 (2.0)	8.4 (1.8)	8.7 (1.9)
SBP, mm Hg	128.8 (14.3)	128.7 (13.9)	129.3 (14.2)
DBP, mm Hg	78.3 (8.6)	78.4 (9.6)	79.0 (8.4)
eGFR, mL/min/1.73 m^2	86.9 (20.1)	86.5 (21.8)	88.3 (22.6)

A1C = glycated hemoglobin; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; FPG = fasting plasma glucose; MET = metformin; PIO = pioglitazone; PL = placebo; SBP = systolic blood pressure; SD = standard deviation; SU = sulfonylurea.
Note: All values are mean SD unless otherwise noted.
Sources: Merker et al., 2015[50]; Kovacs et al., 2015[51]; Haering et al., 2015.[52]

Patient disposition

Patient disposition for the extension study is summarized in Table 35. For the patients who were receiving PIO as background therapy (i.e., those enrolled in Study 1245.19), of the 498 patients who were treated in the core study (1245.19), 305 patients elected to participate in the extension trial. For those using MET as background therapy (i.e., enrolled from 1245.23$_{MET}$), of the 637 patients who were

treated in the core phase, 463 patients elected to participant in extension trial. For those using MET as background therapy (i.e., enrolled from 1245.23$_{MET+SU}$), of the 666 patients who were treated in the core phase a total of 474 patients participated in the 1245.31 extension trial. In all studies, discontinuations were more commonly reported in the placebo groups compared with the empagliflozin (EMPA) groups. For all treatment groups, the most common reason for discontinuation was electing not to enroll in the extension trial (20.1% to 30.5% overall). The proportion of patients who completed both the core and extension phases of the studies was relatively low (i.e., 47.3% to 58.5% with placebo, 56.4% to 74.7% with EMPA 10 mg, and 56.0% to 69.4% with EMPA 25 mg).

TABLE 35: PATIENT DISPOSITION

Disposition, n (%)	PL	EMPA 10 mg	EMPA 25 mg
MET			
Treated in 1245.23	207	217	214
Completed the preceding trial	186 (89.9)	209 (96.3)	196 (92.0)
Continued in extension trial	138 (66.7)	173 (79.7)	152 (71.4)
Discontinued extension trial	17 (8.2)	11 (5.1)	13 (6.1)
Withdrew consent	13 (6.3)	9 (4.1)	12 (5.6)
Lost to follow-up	4 (1.9)	2 (0.9)	1 (0.5)
Completed extension trial	121 (58.5)	162 (74.7)	139 (65.3)
PIO + MET			
Treated in 1245.19	165	165	168
Completed the preceding trial	147 (89.1)	154 (93.3)	156 (92.9)
Continued in extension trial	93 (56.4)	106 (64.2)	106 (63.1)
Discontinued extension trial	15 (9.1)	13 (7.9)	12 (7.1)
Withdrew consent	13 (7.9)	8 (4.8)	7 (4.2)
Lost to follow-up	2 (1.2)	3 (1.8)	4 (2.4)
Death	0 (0.0)	2 (1.2)	1 (0.6)
Completed extension trial	78 (47.3)	93 (56.4)	94 (56.0)
MET + SU			
Treated in 1245.23	225 (100.0)	225 (100.0)	216 (100.0)
Completed the preceding trial	201 (89.3)	209 (92.9)	199 (92.1)
Continued in extension trial	145 (64.4)	164 (72.9)	165 (76.4)
Discontinued extension trial	18 (8.0)	13 (5.8)	15 (6.9)
Withdrew consent	16 (7.1)	11 (4.9)	13 (6.0)
Lost to follow-up	2 (0.9)	2 (0.9)	1 (0.5)
Death	0 (0.0)	0 (0.0)	1 (0.5)
Completed extension trial	127 (56.4)	150 (66.7)	150 (69.4)

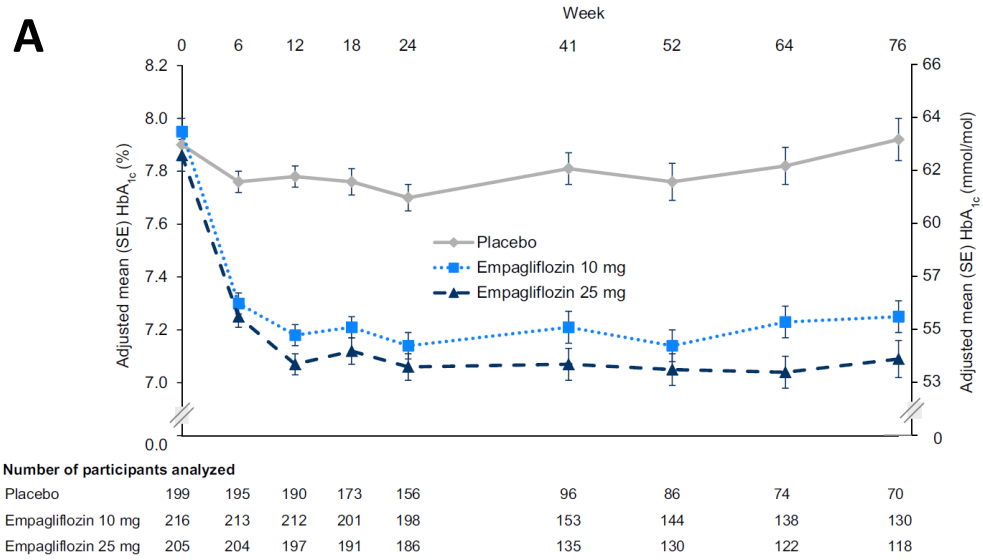
EMPA = empagliflozin; MET = metformin; PIO = pioglitazone; PL = placebo; SU = sulfonylurea.
Sources: Merker et al., 2015[50]; Kovacs et al., 2015[51]; Haering et al., 2015[52]; and Clinical Study Report for 1245.31.[49]

Efficacy

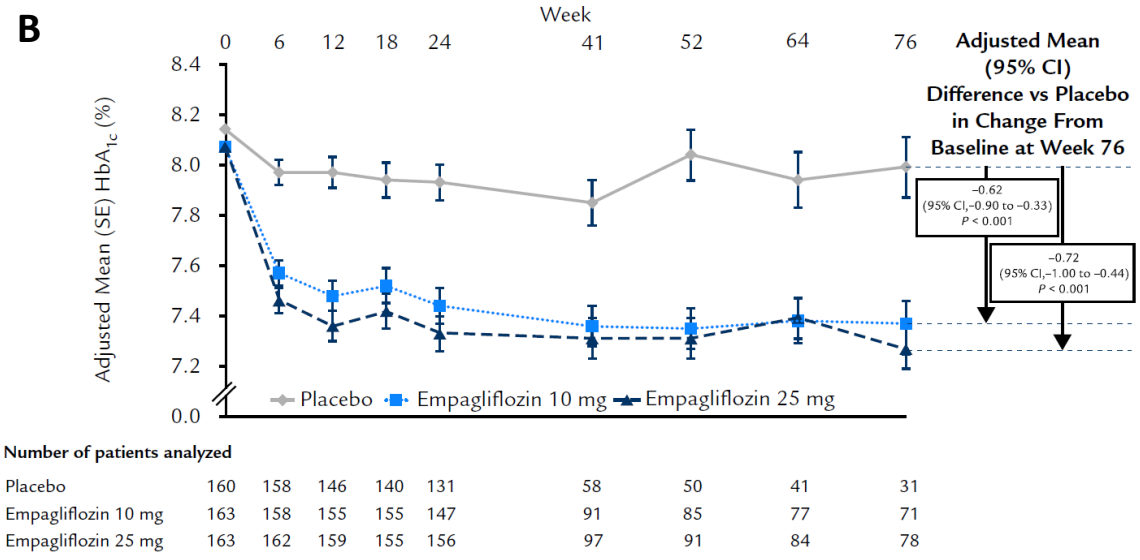
As shown in Figure 7, both doses of EMPA demonstrated consistent reductions in glycated hemoglobin (A1C) compared with placebo up to the 76-week cut-off point. At the conclusion of the extension study, the adjusted mean change in A1C relative to placebo was relative consistent across the different background therapies, ranging from −60.0% to −0.70% for the EMPA 10 mg dose and −0.68% to −0.70% for the EMPA 25 mg dose. As shown in Table 36, both EMPA groups demonstrated improvements in

body weight, SBP, and DBP relative to placebo across the three studies. The magnitude of improvement at the end of the 76-week extension phase was consistent with the magnitude observed in the 24-week core phase.

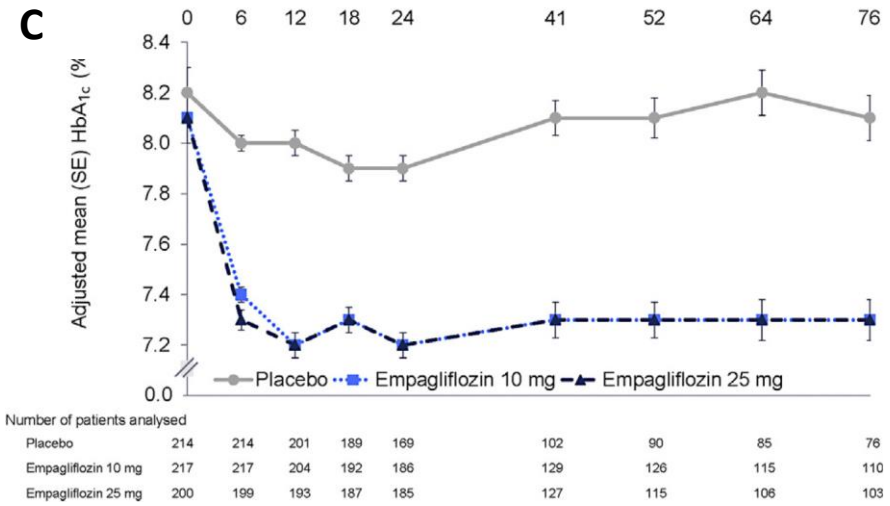
FIGURE 7: MEAN A1C TO 76 WEEKS FOR BACKGROUND METFORMIN (A), BACKGROUND PIOGLITAZONE WITH OR WITHOUT METFORMIN (B), AND METFORMIN AND A SULFONYLUREA (C)



Source: Reproduced from Merker L, Haring HU, Christiansen AV, Roux F, Salsali A, Kim G, et al. Empagliflozin as add-on to metformin in people with Type 2 diabetes. Diabet Med. 2015 Dec;32(12):1555-67. Copyright 2015, with permission of John Wiley and Sons.



Source: Reproduced from Clin. Ther. 37/8, Kovacs CS, Seshiah V, Merker L, Christiansen AV, Roux F, Salsali A, et al.. Empagliflozin as Add-on Therapy to Pioglitazone With or Without Metformin in Patients With Type 2 Diabetes Mellitus. Pages: 1773-88. Copyright 2015, with permission of Elsevier.



A1C = glycated hemoglobin; SE = standard error.
Note: Figure shows adjusted mean (standard error) hemoglobin A1C up to 76 weeks for patients using background metformin (A); background pioglitazone with or without metformin (B); and metformin and a sulfonylurea (C).
Source: Reproduced from Haering HU, Merker L, Christiansen AV, Roux F, Salsali A, Kim G, et al. Empagliflozin as add-on to metformin plus sulphonylurea in patients with type 2 diabetes. Diabetes Res Clin Pract. 2015 Oct;110(1):82-90. Copyright 2015, with permission of John Wiley and Sons.

TABLE 36: KEY FINDINGS FROM STUDY 1245.31

Outcomes	Parameter	PL	EMPA 10 mg	EMPA 25 mg
MET (Week 76)				
A1C (%)	BL (SE)	7.9 (0.1)	7.3 (0.1)	7.2 (0.1)
	Mean change (SE)	–0.0 (0.1)	–0.6 (0.1)	–0.7 (0.1)
	MD (95% CI)[a]	—	–0.6 (–0.8 to –0.5)	–0.7 (–0.9 to –0.6)
	P value	—	< 0.001	< 0.001
Body weight (kg)	BL (SE)	80.7 (0.2)	78.8 (0.2)	78.5 (0.2)
	Mean change (SE)	–0.5 (0.2)	–2.4 (0.2)	–2.7 (0.2)
	MD (95% CI)[b]	—	–1.9 (–2.5 to –1.3)	–2.2 (–2.8 to –1.6)
	P value	—	< 0.001	< 0.001
SBP (mm Hg)	BL (SE)	128.6 (0.8)	124.1 (0.8)	124.8 (0.8)
	Mean change (SE)	–0.8 (0.8)	–5.2 (0.8)	–4.5 (0.8)
	MD (95% CI)[c]	—	–4.4 (–6.6 to –2.3)	–3.7 (–5.9 to –1.5)
	P value	—	< 0.001	< 0.001
DBP (mm Hg)	BL (SE)	78.2 (0.5)	76.2 (0.5)	76.8 (0.5)
	Mean change (SE)	–0.5 (0.5)	–2.5 (0.5)	–1.9 (0.5)
	MD (95% CI)[d]	—	–2.0 (–3.4 to –0.5)	–1.4 (–2.8 to 0.1)
	P value	—	0.008	0.068
PIO + MET (Week 76)				
A1C (%)	BL	NR	NR	NR
	Mean change (SE)	0.01 (0.08)	−0.59 (0.08)	−0.69 (0.08)
	MD (95% CI)[a]	—	−0.61 (−0.83 to −0.38)	−0.70 (−0.92 to −0.48)

Outcomes	Parameter	PL	EMPA 10 mg	EMPA 25 mg
	P value	—	< 0.0001	< 0.0001
Body weight (kg)	BL	NR	NR	NR
	Mean change (SE)	0.77 (0.28)	−1.65 (0.28)	−1.64 (0.28)
	MD (95% CI)[b]	—	−2.42 (−3.19 to −1.64)	−2.41 (−3.19 to −1.64)
	P value	—	< 0.0001	< 0.0001
MET + SU (Week 76)				
A1C (%)	BL (SE)	8.15 (0.06)	8.07 (0.05)	8.10 (0.06)
	Mean change (SE)	–0.03 (0.06)	–0.74 (0.06)	–0.72 (0.06)
	MD (95% CI)[a]	—	–0.72 (–0.87 to –0.56)	–0.69 (–0.85 to –0.53)
	P value	—	< 0.0001	< 0.0001
Body weight (kg)	BL (SE)	76.23 (1.13)	77.08 (1.22)	77.50 (1.28)
	Mean change (SE)	–0.63 (0.19)	–2.44 (0.19)	–2.28 (0.20)
	MD (95% CI)[b]	—	–1.81 (–2.34 to –1.27)	–1.64 (–2.18 to –1.11)
	P value	—	NR	NR
SBP (mm Hg)	BL (SE)	128.8 (1.0)	128.7 (0.9)	129.3 (1.0)
	Mean change (SE)	–1.6 (0.7)	–3.8 (0.7)	–3.7 (0.7)
	MD (95% CI)[c]	—	–2.2 (–4.1 to –0.3)	–2.1 (–4.1 to –0.2)
	P value	—	NR	NR
DBP (mm Hg)	BL (SE)	78.3 (0.6)	78.4 (0.6)	79.0 (0.6)
	Mean change (SE)	–1.4 (0.5)	–2.6 (0.5)	–2.3 (0.5)
	MD (95% CI)[d]	—	–1.1 (–2.4 to 0.1)	–0.9 (–2.2 to 0.4)
	P value	—	NR	NR

A1C = glycated hemoglobin; BL = baseline; CI = confidence interval; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EMPA = empagliflozin; MD = mean difference; MET = metformin; NR = not reported; PIO = pioglitazone; PL = placebo; SBP = systolic blood pressure; SE = standard error; SU = sulfonylurea.

[a] Model included baseline A1C as linear covariate and baseline eGFR, geographical region, and treatment as fixed effects.

[b] Model included baseline weight and baseline A1C as linear covariates, and baseline eGFR, geographical region and treatment as fixed effects.

[c] Model included baseline SBP seated and baseline A1C as linear covariates and baseline eGFR, geographical region and treatment as fixed effects.

[d] Model including baseline DBP seated and baseline A1C as linear covariates, and baseline eGFR, geographical region and treatment as fixed effects.

Source: Clinical Study Report for 1245.31[49] and Merker et al., 2015.[50]

Safety

A summary of key adverse event (AE) data is provided in Table 37. The overall frequency of AEs was generally similar across the treatment groups (77.7% to 82.4% with placebo, 76.4% to 81.7% with EMPA 10 mg, and 72.0% to 82.1% with EMPA 25 mg). The proportion of patients who experienced at least one serious adverse event (SAE) ranged from 6.7% to 13.8% with placebo, 7.9% to 12.9% with 10 mg EMPA, and 7.9% to 11.1% with 25 mg EMPA. The proportion of patients who withdrew as a result of AEs was similar across all studies and treatment groups: 4.2% to 7.1% with placebo; 3.0% to 4.5% with EMPA 10 mg; and 4.8% to 6.9% with EMPA 25 mg.[49-52]

The proportion of patients who experienced one or more hypoglycemic events varied depending on the background therapy being administered. Events were relatively rare in the extension studies for patients who were receiving concomitant treatment with MET and PIO (with or without MET), with the proportion of patients ranging from 3.4% to 4.2% in the placebo groups and 1.8% to 4.0% in the EMPA groups. In contrast, when the study treatments were administered with MET and a SU, hypoglycemic events were more frequently reported. In that extension study, there was a numerical increase in the proportion of the patients with at least one hypoglycemic event in the EMPA groups (23.7% in the 10 mg group and 19.4% in the 25 mg group) compared with the placebo group (15.6%). In all three extension studies, events of severe hypoglycemic (i.e., those requiring assistance) were rare — with no more than one event per group. Hyperglycemia was commonly reported in the placebo groups (26.2% to 27.2%) compared with the EMPA groups (10.4% to 16.4% with 10 mg and 6.5% to 13.7% with 25 mg).

The manufacturer conducted a customized MedDRA search to identify events consisted with genital infections. Across all three studies, these events were more frequently reported in the EMPA groups (4.5% to 10.3% in the 10 mg group and 4.2% to 9.3% in the 25 mg group) compared with the placebo groups (0.5% to 3.0%). As shown in Table 37, genital infections were much more common in female patients compared with male patients.

TABLE 37: KEY ADVERSE EVENT DATA FROM STUDY 1245.31

AEs, n (%)	MET			MET + SU			PIO ± MET		
	PL	EMPA 10 mg	EMPA 25 mg	PL	EMPA 10 mg	EMPA 25 mg	PL	EMPA 10 mg	EMPA 25 mg
≥ 1 AE	160 (77.7)	174 (80.2)	154 (72.0)	183 (81.3)	183 (81.7)	178 (82.0)	136 (82.4)	126 (76.4)	138 (82.1)
≥ 1 WDAE	10 (4.9)	7 (3.2)	12 (5.6)	16 (7.1)	10 (4.5)	15 (6.9)	7 (4.2)	5 (3.0)	8 (4.8)
≥ 1 SAE	24 (11.7)	19 (8.8)	17 (7.9)	31 (13.8)	29 (12.9)	24 (11.1)	11 (6.7)	13 (7.9)	15 (8.9)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.6)	1 (0.6)	3 (1.8)
AEs with frequency of ≥ 5%									
Hypoglycemia	8 (3.9)	15 (6.9)	10 (4.7)	40 (17.8)	53 (23.7)	46 (21.2)	< 5%		
Hyperglycemia	56 (27.2)	25 (11.5)	14 (6.5)	59 (26.2)	24 (10.7)	26 (12.0)	49 (29.7)	27 (16.4)	23 (13.7)
UTI	23 (11.2)	25 (11.5)	18 (8.4)	29 (12.9)	33 (14.7)	33 (15.2)	34 (20.6)	29 (17.6)	33 (19.6)
Nasopharyngitis	39 (18.9)	36 (16.6)	29 (13.6)	24 (10.7)	36 (16.1)	34 (15.7)	7 (4.2)	10 (6.1)	9 (5.4)
URTI	17 (8.3)	7 (3.2)	21 (9.8)	24 (10.7)	18 (8.0)	21 (9.7)	11 (6.7)	9 (5.5)	15 (8.9)
Dizziness	< 5%			16 (7.1)	14 (6.3)	18 (8.3)	6 (3.6)	6 (3.6)	14 (8.3)
Headache	< 5%			13 (5.8)	17 (7.6)	10 (4.6)	8 (4.8)	10 (6.1)	13 (7.7)
Back pain	10 (4.9)	9 (4.1)	11 (5.1)	11 (4.9)	15 (6.7)	12 (5.5)	9 (5.5)	10 (6.1)	7 (4.2)
A1C increased	< 5%			12 (5.3)	6 (2.7)	11 (5.1)	< 5%		
Bronchitis	< 5%			8 (3.6)	12 (5.4)	8 (3.7)	< 5%		
Influenza	< 5%			4 (1.8)	7 (3.1)	11 (5.1)	< 5%		
Cough	< 5%			3 (1.3)	13 (5.8)	6 (2.8)	< 5%		
Anemia	< 5%			< 5%			13 (7.9)	7 (4.2)	11 (6.5)
Dyslipidemia	7 (3.4)	16 (7.4)	8 (3.7)	< 5%			26 (15.8)	23 (13.9)	21 (12.5)
Hypertension	6 (2.9)	8 (3.7)	11 (5.1)	< 5%			16 (9.7)	6 (3.6)	3 (1.8)
Hypercholesterolemia	< 5%			< 5%			3 (1.8)	9 (5.5)	7 (4.2)
Dyspepsia	< 5%			< 5%			2 (1.2)	10 (6.1)	4 (2.4)
Arthralgia	< 5%			< 5%			9 (5.5)	11 (6.7)	10 (6.0)
Confirmed	7 (3.4)	9 (4.1)	9 (4.2)	35 (15.6)	53 (23.7)	42 (19.4)	7 (4.2)	3 (1.8)	5 (3.0)

AEs, n (%)	MET			MET + SU			PIO ± MET		
	PL	EMPA 10 mg	EMPA 25 mg	PL	EMPA 10 mg	EMPA 25 mg	PL	EMPA 10 mg	EMPA 25 mg
hypoglycemia									
Requiring assistance	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
Events consistent with UTI	28 (13.6)	31 (14.3)	22 (10.3)	36 (16.0)	38 (17.0)	35 (16.1)	44 (26.7)	37 (22.4)	37 (22.0)
Male	5 (4.3)	2 (1.6)	4 (3.3)	10 (8.9)	7 (6.2)	4 (3.5)	6 (8.2)	7 (8.4)	6 (7.1)
Female	23 (25.3)	29 (31.5)	18 (19.4)	26 (23.0)	31 (27.9)	31 (30.1)	38 (41.3)	30 (36.6)	31 (37.3)
Genital infection	1 (0.5)	18 (8.3)	20 (9.3)	2 (0.9)	10 (4.5)	13 (6.0)	5 (3.0)	17 (10.3)	7 (4.2)
Male	0 (0.0)	4 (3.2)	4 (3.3)	1 (0.9)	5 (4.4)	3 (2.6)	1 (1.4)	7 (8.4)	1 (1.2)
Female	1 (1.1)	14 (15.2)	16 (17.2)	1 (0.9)	5 (4.5)	10 (9.7)	4 (4.3)	10 (12.2)	6 (7.2)

A1C = glycated hemoglobin; AE = adverse event; EMPA = empagliflozin; MET = metformin; PIO = pioglitazone; PL = placebo; SAE = serious adverse event; SU = sulfonylurea; URTI = upper respiratory tract infection; UTI = urinary tract infection; WDAE = withdrawal due to adverse event

Source: Adapted from Merker L, Haring HU, Christiansen AV, Roux F, Salsali A, Kim G, et al. Empagliflozin as add-on to metformin in people with Type 2 diabetes. Diabet Med. 2015 Dec;32(12):1555-67. Copyright 2015, with permission of John Wiley and Sons.

Critical appraisal

The primary limitation of Study 1245.31 is the high proportion of patients who discontinued at the end of the core phase or during the extension phase (i.e., 52.7% to 41.5% with placebo, 43.6% to 25.3% with EMPA 10 mg, and 44.0% to 30.6% with EMPA 25 mg). LOCF was used for evaluations of the efficacy end points, which can be problematic given the high proportion of patients who discontinued the study. Although these were supported by similar results from sensitivity analyses using a completers data set, all analyses are still subject to bias due to the high losses to follow-up, which may overestimate the true effect of EMPA. There was pre-specified primary end point in Study 1245.31. Exploratory efficacy analyses were conducted; however, there was no adjustment for multiple comparisons.

Summary

Study 1245.31 was a large extension study that enrolled 1856 patients who had completed four 24-week DB trials: 1245.19, 1245.20, 1245.23$_{MET}$, or 1245.23$_{MET+SU}$. Patients who enrolled in Study 1245.31 continued to receive DB study treatments in accordance with their randomized allocation in the core DB trials. Overall, the improvements in A1C, body weight, SBP, and DBP that were observed in the 24-week core studies appeared to be maintained through the 76-week extension phase. The frequency and severity of the AEs reported during the extension study were similar to those reported during the core studies.

APPENDIX 8: SUMMARY OF BRIDGING STUDY

1. Objective

To summarize the results of a phase IIb, double-blind (DB), randomized, placebo-controlled trial conducted to evaluate the efficacy and safety of empagliflozin (EMPA) twice daily versus once daily.

2. Results

2.1 Study characteristics

Study 1276.10 was a five-group, phase IIb, 16-week, DB, randomized, placebo-controlled trial conducted to evaluated the efficacy and safety of EMPA twice daily versus once daily in patients with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin (MET). Adults with T2DM were eligible to participate if they met the following criteria: BMI (body mass index) ≤ 45 kg/m^2; A1C ≥ 7% and ≤ 10%; treated with a stable dose of at least 1,500 mg per day of MET immediate release (IR) for at least 12 weeks before randomization.

Enrolled patients underwent a two-week, single-blinded, placebo run-in period, where they could be removed from the study if they demonstrated non-compliance (at the discretion of the investigator). Those who completed the run-in period were randomized (2:2:2:2:1) to receive EMPA 12.5 mg twice daily, 25 mg once daily, 5 mg twice daily or 10 mg once daily, or placebo. All treatments were provided in addition to the patient's background therapy with MET. Randomization was stratified by region, (hemoglobin A1C) A1C at screening, and estimated glomerular filtration rate (eGFR) at screening.

2.2 End points

The primary end point of 1276.10 was change from baseline in A1C at 16 weeks. Secondary end points included the following: Changes from baseline in fasting plasma glucose (FPG), body weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at week 16, and the proportion of patients with A1C < 7% at week 16.

The primary analysis of Study 1276.10 consisted of the following noninferiority comparisons for change from baseline in A1C at 16 weeks:[53]

- EMPA 12.5 mg twice daily versus 25 mg once daily
- EMPA 5 mg twice daily versus 10 mg once daily.

A noninferiority margin of 0.35% was used for the primary analysis. The primary analysis was conducted using a full analysis set (FAS) which consisted of all patients who received at least one dose of study drug and had a baseline and on-treatment A1C value. Sensitivity analyses were conducted using per-protocol (PP) and observed case data sets.[54] Superiority of EMPA doses versus placebo was tested to demonstrate assay sensitivity. Safety was assessed in patients who received at least one dose of the study drug.[53]

2.3 Study population

Baseline and demographic data are summarized in Table 38. Overall, 53.9% of the patients were male and the mean age was 58 years. The majority of participants were white (80%) and were located in Europe (62.9%). Mean baseline A1C was 7.77% and the majority of patients (64.9%) had an A1C below 8.0%. Mean body weight and BMI were 89.04 kg and 31.77 kg/m^2, respectively. The mean SBP was 131.3 mm Hg and the mean DBP (standard deviation [SD]) was 78.6 mm Hg.

TABLE 38: POPULATION CHARACTERISTICS OF STUDY 1276.10

Characteristics	EMPA 12.5 mg b.i.d.	EMPA 25 mg q.d.	EMPA 5 mg b.i.d.	EMPA 10 mg q.d.	PL
Number of patients, N (%)	215 (100.0)	214 (100.0)	215 (100.0)	214 (100.0)	107 (100.0)
Age, mean (SD)	57.6 (9.9)	58.2 (10.2)	58.8 (9.8)	58.5 (10.8)	57.9 (11.2)
Sex, n (%)					
Male	123 (57.2)	114 (53.3)	120 (55.8)	108 (50.5)	55 (51.4)
Female	92 (42.8)	100 (46.7)	95 (44.2)	106 (49.5)	52 (48.6)
Race, N (%)					
White	176 (81.9)	191 (89.3)	189 (87.9)	180 (84.1)	93 (86.9)
Black	17 (7.9)	10 (4.7)	17 (7.9)	14 (6.5)	8 (7.5)
Asian	15 (7.0)	9 (4.2)	6 (2.8)	10 (4.7)	2 (1.9)
American Indian	6 (2.8)	3 (1.4)	3 (1.4)	10 (4.7)	4 (3.7)
eGFR, mean (SD)	88.62 (20.07)	88.90 (19.43)	89.66 (22.35)	89.45 (20.57)	89.54 (18.46)
Region, N (%)					
Europe	138 (64.2)	134 (62.6)	135 (62.8)	133 (62.1)	67 (62.6)
North America	60 (27.9)	63 (29.4)	62 (28.8)	63 (29.4)	31 (29.0)
Latin America	17 (7.9)	17 (7.9)	18 (8.4)	18 (8.4)	9 (8.4)
A1C, mean (SD) [%]	7.78 (0.79)	7.73 (0.79)	7.79 (0.88)	7.84 (0.75)	7.69 (0.72)
Weight, mean (SD) [kg]	89.42 (19.02)	88.72 (18.58)	88.30 (17.40)	89.17 (18.96)	90.10 (18.43)
BMI, mean (SD) [kg/m^2]	31.57 (5.13)	32.06 (5.26)	31.46 (5.22)	31.85 (5.41)	32.03 (4.95)
SBP, mean (SD) [mm Hg]	130.2 (14.8)	131.0 (15.2)	132.4 (14.4)	131.6 (14.4)	131.5 (14.2)
DBP, mean (SD) [mm Hg]	78.5 (8.7)	79.1 (8.3)	78.5 (8.8)	78.6 (8.4)	78.3 (9.6)

b.i.d. = twice daily; BMI = body mass index; DBP = diastolic blood pressure; EMPA = empagliflozin; eGFR = estimated glomerular filtration rate; q.d. = once daily; PL = placebo; SBP = systolic blood pressure; SD = standard deviation.
Source: Clinical Study Report for 1276.10.[54]

2.4 Efficacy results

Results for the primary, secondary, and exploratory end points of Study 1276.10 are summarized in Table 39. EMPA administered twice daily was noninferior to EMPA administered once daily for change from baseline in A1C at 16 weeks. The adjusted mean differences in the FAS analysis were −0.11% (95% CI, −0.26 to 0.03) for 12.5 mg twice daily compared with 25 mg once daily and −0.02% (95% CI, −0.16 to 0.13) for 5 mg twice daily versus 10 mg once daily.[53] Similar results were demonstrated with the per-protocol (PP) analysis (−0.12 [95% CI, −0.27 to 0.03] for 12.5 mg twice daily compared with 25 mg once daily and −0.03 [95% CI, −0.18 to 0.12] for 5 mg twice daily versus 10 mg once daily).[54]

Compared with placebo, the twice daily and once daily EMPA regimens were associated with statistically significant reductions from baseline in FPG, body weight, and SBP. Three out of four EMPA groups also demonstrated a statistically significant reduction in DBP compared with placebo (Table 39).[53]

TABLE 39: SUMMARY OF EFFICACY RESULTS FROM STUDY 1276.10

	PL (n = 107)	EMPA 12.5 mg b.i.d. (n = 215)	EMPA 25 mg q.d. (n = 214)	EMPA 5 mg b.i.d. (n = 215)	EMPA 10 mg q.d. (n = 214)
A1C at week 16					
A1C at BL (SE), %	7.69 (0.07)	7.78 (0.05)	7.73 (0.05)	7.79 (0.06)	7.83 (0.05)
Change from BL (SE), %	−0.22 (0.07)	−0.83 (0.05)	−0.72 (0.05)	−0.66 (0.05)	−0.64 (0.05)
EMPA b.i.d. vs. q.d. (MD [95% CI])[a]		−0.11 (−0.26 to 0.03)		−0.02 (−0.16 to 0.13)	
P value for noninferiority		< 0.001		< 0.001	
FPG at week 16					
FPG at BL, mmol/L	8.9 (0.2)	8.7 (0.1)	8.7 (0.1)	9.0 (0.2)	8.9 (0.2)
Change from BL, mmol/L	0.0 (0.2)	−1.5 (0.1)	−1.3 (0.1)	−1.2 (0.1)	−1.0 (0.1)
EMPA vs. PL (MD [95% CI])[b]		−1.5 (−1.9 to −1.2)	−1.3 (−1.6 to −0.9)	−1.2 (−1.5 to −0.8)	−1.0 (−1.3 to −0.6)
P value for superiority		< 0.001	< 0.001	< 0.001	< 0.001
Body weight at week 16					
Weight at BL (SE), kg	90.10 (1.78)	89.42 (1.30)	88.72 (1.27)	88.30 (1.19)	89.10 (1.30)
Change from BL (SE), kg	−0.97 (0.25)	−3.20 (0.18)	−2.89 (0.18)	−2.93 (0.18)	−2.71 (0.18)
EMPA vs. PL (MD [95% CI])[b]		−2.2 (−2.8 to −1.6)	−1.9 (−2.5 to −1.3)	−2.0 (−2.6 to −1.4)	−1.7 (−2.4 to −1.1)
P value for superiority		< 0.001	< 0.001	< 0.001	< 0.001
Systolic blood pressure at week 16					
SBP at BL (SE), mm Hg	131.5 (1.4)	130.2 (1.0)	131.0 (1.0)	132.4 (1.0)	131.6 (1.0)
Change from BL (SE), mm Hg	1.6 (1.1)	−4.1 (0.7)	−3.8 (0.7)	−4.2 (0.7)	−2.5 (0.8)
EMPA vs. PL (MD [95% CI])[b]		−5.8 (−8.3 to −3.2)	−5.5 (−8.0 to −2.9)	−5.8 (−8.3 to −3.3)	−4.1 (−6.7 to −1.6)
P value for superiority		< 0.001	< 0.001	< 0.001	0.002
Diastolic blood pressure at week 16					
DBP at BL (SE), mm Hg	78.3 (0.9)	78.5 (0.6)	79.1 (0.6)	78.5 (0.6)	78.6 (0.6)
Change from BL (SE), mm Hg	0.4 (0.6)	−2.1 (0.5)	−2.6 (0.5)	−1.6 (0.5)	−0.8 (0.5)
EMPA vs. PL (MD [95% CI])[b]		−2.5 (−4.0 to −0.9)	−3.1 (−4.6 to −1.5)	−2.1 (−3.6 to −0.5)	−1.2 (−2.8 to 0.3)
P value for superiority		0.002	< 0.001	0.009	0.117

A1C = glycated hemoglobin; b.i.d. = twice daily; BL = baseline; CI = confidence interval; EMPA = empagliflozin; FPG = fasting plasma glucose; MD = mean difference; PL = placebo; q.d. = once daily; SE = standard error; vs. = versus.

[a] Model included treatment, baseline A1C and the number of previous antidiabetic medications as fixed effects, and country as a random effect.

[b] Model included baseline value of end point, treatment, number of previous antidiabetic med, country as fixed effects and country as a random effect.

Source: Adapted from Ross S, Thamer C, Cescutti J, Meinicke T, Woerle HJ, Broedl UC. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. Diabetes Obes Metab. 2015 Jul;17(7):699-702. Copyright 2015, with permission of John Wiley and Sons.

2.5 Safety results

A summary of key adverse event (AE) data from Study 1276.10 is provided in Table 40. The proportion of patients who experienced at least one AE was similar across the EMPA groups, though there was a numerical increase in events within the EMPA 10 mg once daily group. This was also observed for the proportion of patients who discontinued treatment as a result of the study drug, where the proportion was greater in the EMPA 10 mg once daily group (5.9%) compared with the other EMPA groups (1.4% to 2.3%) and the placebo group (0.9%). The manufacturer noted that no specific pattern of events leading to discontinuation could be identified.[54] Serious adverse events (SAEs) and events of hypoglycemia were relatively rare across the groups. The proportion of patients who experienced urogenital AEs were numerically similar or lower in the EMPA twice daily groups compared with the once daily groups.

TABLE 40: SUMMARY OF SAFETY RESULTS FROM STUDY 1276.10

AEs, N (%)	EMPA 12.5 MG B.I.D.	EMPA 25 MG Q.D.	EMPA 5 MG B.I.D.	EMPA 10 MG Q.D.	PL
Number of patients	219 (100.0)	218 (100.0)	219 (100.0)	220 (100.0)	107 (100.0)
Any AE	100 (45.7)	91 (41.7)	96 (43.8)	110 (50.0)	51 (47.7)
WDAE	5 (2.3)	3 (1.4)	4 (1.8)	13 (5.9)	1 (0.9)
SAE	5 (2.3)	2 (0.9)	7 (3.2)	5 (2.3)	1 (0.9)
Confirmed hypoglycemia	0	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.9)
Urinary tract infection	10 (4.6)	10 (4.6)	8 (3.7)	15 (6.8)	4 (3.7)
Vulvovaginal mycotic	2 (0.9)	5 (2.3)	1 (0.5)	2 (0.9)	0

AE = adverse event; b.i.d. = twice daily; EMPA = empagliflozin; PL = placebo; q.d. = once daily; SAE = serious adverse event; WDAE = withdrawal from treatment due to adverse event.
Source: Clinical Study Report for 1276.10.[54]

3. Critical appraisal

3.1 Internal validity

Participants in Study 1276.10 were randomized using an interactive voice and/or Web response system that adequately concealed the allocation of participants.[54] Randomization was stratified by relevant factors, including A1C at screening, renal function, and geographical region.[54] The inclusion and exclusion criteria were similar to those used in the pivotal studies (reviewed in section 3.5 of the report). Treatment groups were well balanced with respect to key demographic and disease characteristics. Treatments were administered in a DB manner using matching placebo and EMPA tablets.[54] It is unclear from the study protocols if changes in glycemic parameters (e.g., A1C or FPG), body weight, or blood pressure were available to investigators and/or discussed with participants during study visits.

Study end points were appropriately measured and consistent with guidance from the European Medicines Agency (EMA) for antihyperglycemic treatments.[21] The EMA noted that the primary end point (change from baseline in A1C after 16 weeks of treatment) was consistent with regulatory guidance.[21] The statistical approach used in Study 1276.10 was well described and appropriate. The noninferiority margin (i.e., A1C level 0.35%) is consistent with other studies evaluating changes in A1C and was considered appropriate by the EMA and Health Canada.[21,42]

3.2 External validity

The patients enrolled in Study 1276.10 are representative of the target Canadian population in terms of demography, comorbidities, and disease characteristics. The twice-daily dosages of EMPA reflect those that are available in the EMPA/MET fixed-dose combination (FDC) product. EMPA was administered as an add-on treatment to MET for which the dosage was required to be stable for at least 12 weeks.[54] Twelve weeks of stable doses of background medication is at the upper end of the range recommended by the EMA (i.e., eight to 12 weeks) to ensure the maximal effect of the previous medication has been achieved and that A1C is stabilized at baseline.[21]

Study 1276.10 involved extensive patient contact with health care professionals (i.e., seven visits from screening to end point). In addition, the trial included an open-label (OL) two-week run-in period to ensure compliance with the study protocol and dosage regimen.[54] This is not reflective of routine clinical practice in Canada and may, therefore, reduce generalizability of results to the general population with T2DM.

4. Conclusions

One 16-week, DB RCT (Study 1276.10; N = 983) demonstrated the EMPA administered twice daily at a dose of 5 mg or 12.5 mg is noninferior to once daily administration of 10 mg or 25 mg (respectively) for improving glycemic control.

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