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CADTH COMMON DRUG REVIEW

Clinical Review Report

ERTUGLIFLOZIN (STEGLATRO)

(Merck Canada Inc.)

Indication: Type 2 Diabetes Mellitus

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Abbreviations

A1C	glycated hemoglobin
AE	adverse event
AHA	antihyperglycemic agent
BMD	bone mineral density
BMI	body mass index
Cana	canagliflozin
CI	confidence interval
cLDA	constrained longitudinal data analysis
CMQ	custom MedDRA query
CrI	credible interval
CV	cardiovascular
CSR	clinical study report
Dapa	dapagliflozin
DB	double blind
DBP	diastolic blood pressure
DIC	deviance information criterion
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
Empa	empagliflozin
ERT	ertugliflozin
EQ-5D-3L	EuroQol 5-Dimension 3-Level instrument
FAS	full analysis set
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
ITT	intention-to-treat population
LOCF	last observation carried forward
LS	least squares
MACE+	major adverse cardiovascular event plus
MedDRA	Medical Dictionary for Regulatory Activities
MET	metformin
MD	mean difference
NMA	network meta-analysis
NYHA	New York Heart Association
OR	odds ratio
PP	per-protocol
RCT	randomized controlled trial
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SGLT2	sodium-glucose cotransporter-2
SIT	sitagliptin
T2DM	type 2 diabetes mellitus
WDAE	withdrawal due to adverse event

Drug	Ertugliflozin (Steglatro)
Indication	Monotherapy: for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance. Add-on combination: indicated in adult patients with type 2 diabetes mellitus to improve glycemic control in combination with: • metformin • metformin and sitagliptin when the therapy listed above, along with diet and exercise, does not provide adequate glycemic control.
Reimbursement Request	As monotherapy for patients who have inadequate glycemic control and for whom metformin or a sulfonylurea is inappropriate due to contraindications or intolerance Add-on to metformin for patients who have inadequate glycemic control on metformin and have a contraindication or intolerance to a sulfonylurea
Dosage Form(s)	5 mg and 15 mg oral tablets
NOC Date	May 9, 2018
Manufacturer	Merck Canada Inc.

Executive Summary

Introduction

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels on a microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (peripheral artery disease, cardiovascular [CV] disease) level. Diabetes is one of the most common chronic diseases in Canada. Diabetes Canada estimated that there were 3.4 million people (9.3% of the population) with diabetes in 2015, and by 2025 this number will have increased to five million people (12.1%).[1]

The objective was to perform a systematic review of the beneficial and harmful effects of ertugliflozin (ERT) 5 mg and 15 mg tablets to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance (as monotherapy); or in combination with metformin, or metformin and sitagliptin, when these therapies, along with diet and exercise, do not provide adequate glycemic control.

This review was conducted in tandem with an evaluation of the ERT/metformin fixed-dose combination product, Segluromet.

Results and Interpretation

Included Studies

A total of five double-blind randomized controlled trials (RCTs) met the inclusion criteria for this systematic review (N = 461 to 1,326 per study). These trials evaluated the safety and efficacy of ERT 5 mg daily and ERT 15 mg daily (alone or in combination with metformin, or metformin plus sitagliptin), compared with placebo or active comparators, in adults with type 2 diabetes and inadequate glycemic control. Four trials were 26 weeks in duration (MONO, MET, SITA2, FACTORIAL), and one active-controlled, noninferiority trial was 52 weeks in duration (SU).

The primary outcome in all trials was the change from baseline in glycated hemoglobin (A1C). Other outcomes evaluated were the proportion of patients with A1C < 7% or who required glycemic rescue therapy, and the change from baseline in fasting plasma glucose (FPG), body weight, and blood pressure.

The patients enrolled had a mean age per treatment group ranging from 54.8 to 59.7 years and 43% to 65% per treatment group were male. The patients were predominantly white (65% to 86%) with a mean body mass index (BMI) per group ranging from 30.3 kg/m^2 to 33.3 kg/m^2 and baseline A1C of 7.8% to 8.6%. The mean duration of diabetes varied across trials and was lowest for the MONO study (4.6 to 5.2 years) and highest for the SITA2 study (9.2 to 9.9 years per treatment group). The median dose of metformin was 2,000 mg per day (MET, SU, FACTORIAL, SITA2) and for glimepiride, the median dose was 3 mg daily (SU).

The available evidence on the efficacy of ERT was limited by the relatively short duration of the five trials (26 to 52 weeks) for a chronic condition, and the examination of surrogate outcomes (A1C, weight, and blood pressure). The primary analysis in all trials excluded any outcome data after the start of rescue therapy. In addition, no efficacy data were collected for patients who stopped treatment early. Considering the differential frequency of rescue and early discontinuation in the placebo and ERT groups, the ERT treatment effects may be overestimated. Although the manufacturer and FDA conducted additional sensitivity analyses to address the issue, these cannot fully account for the impact of the missing data. With respect to the magnitude of change observed in the studies, the Health Canada Reviewer's Report classified the treatment effect size differences as modest.[2]

Efficacy

ERT as monotherapy was associated with statistically significant reductions in A1C from baseline compared with placebo in the MONO trial. The least squares (LS) mean differences were –1.0%; 95% confidence interval (CI), –1.2% to –0.8% for ERT 5 mg and –1.2%; 95% CI, –1.4% to –0.9% for ERT 15 mg versus placebo (Table 1). ERT as add-on therapy to metformin (≥ 1,500 mg/day) also showed statistically significant differences compared with placebo for the change from baseline in A1C with LS mean differences of –0.7%; 95% CI, –0.9 to –0.5% for ERT 5 mg, and –0.9%; 95% CI, [redacted] for ERT 15 mg groups (MET study).

In the SU study, ERT 15 mg daily as add-on therapy to metformin was noninferior to glimepiride (mean dose 3 mg per day) for the change from baseline in A1C to 52 weeks based on a 0.3% noninferiority margin (LS mean difference 0.1%; 95% CI, –0.02% to 0.22%). Noninferiority was not met for ERT 5 mg versus glimepiride as the upper bound of

the 95% CI for the difference between groups was not below 0.3% (LS mean difference 0.18%; 95% CI, 0.06% to 0.30%).

In the FACTORIAL study, ERT (5 mg and 15 mg) in combination with sitagliptin (100 mg daily) and metformin (≥ 1,500 mg/day), was superior to ERT 5 mg, 15 mg daily, or sitagliptin 100 mg (plus metformin), for the change from baseline in A1C. The LS mean differences between groups were similar and ranged from –0.43% to –0.47% (see Table 1 for details).

The SITA2 trial evaluated the use of ERT versus placebo as add-on therapy to metformin plus sitagliptin. The mean difference between groups for the change from baseline in A1C was statistically significant for ERT 5 mg (LS mean difference –0.7%; 95% CI, –0.9% to –0.5%) and ERT15 mg groups (mean difference –0.8%; 95% CI, –1.0% to –0.6%) versus placebo.

In the MONO, MET, and SITA2 trials, at 26 weeks, a statistically significant number of patients in the ERT groups (28% to 40%) achieved an A1C of less than 7%, compared with placebo (13% to 17%). In the FACTORIAL study, more patients who received ERT plus sitagliptin (49% to 52%) achieved their glycemic target than patients who received ERT (26% to 32%) or sitagliptin (33%) alone, and these differences were statistically significant. In the SU trial, 34%, 38%, and 44% of patients achieved an A1C of less than 7% in the ERT 5 mg, ERT 15 mg, and glimepiride groups, respectively, at 52 weeks.

The percentage of patients who received glycemic rescue therapy ranged from [redacted] in the placebo groups, from [redacted] among groups who received ERT, and from [redacted] in the active control groups. Also of note, more patients in the placebo group than the ERT groups stopped treatment early in the MONO study ([redacted] versus [redacted], respectively). As the primary efficacy analysis excluded any outcome data after stopping study drug or starting rescue therapy, the differences in the frequency of missing data may have influenced the results, as the patients most likely to show a favourable treatment response were followed for the entire study period. However, the manufacturer and the FDA conducted a number of sensitivity analyses in an attempt to address this potential bias, and these data appear to support the primary analysis findings.

ERT was associated with statistically significant reductions in weight in all five trials. At baseline, the mean weight per treatment group ranged from 84.5 kg to 94.2 kg. After 26 weeks, the LS mean change from baseline in weight observed was –1.3 kg to –1.4 kg for placebo, –2.5 kg to –3.7 kg for the ERT groups, –0.7 kg for sitagliptin, and +0.9 kg for the glimepiride groups. Statistically significant differences were detected between ERT and placebo in the MONO, MET, and SITA2 trials with differences between groups ranging from –1.6 kg to –2.2 kg after 26 weeks. Similarly, ERT 5 mg and 15 mg plus sitagliptin was associated with statistically significant mean differences in weight compared with sitagliptin alone (mean difference –1.9 kg and –2.3 kg, respectively). In the SU trial, ERT 15 mg was associated with statistically significant differences in body weight compared with glimepiride (mean difference –4.3 kg; 95% CI, –4.8 to –3.8). Similar treatment effects were noted for ERT 5 mg versus glimepiride (mean difference –3.9 kg), but due to failure in an earlier outcome in the statistical hierarchy, these results should be interpreted as inconclusive. Although any reduction in weight may be viewed as positive by patients, it is not known if these changes translate into longer-term health benefits.

With respect to changes in blood pressure, the results were inconclusive (due to failure of a previous outcome in the statistical testing procedure) or not statistically significant for ERT versus placebo on the change from baseline in systolic blood pressure (SBP) or diastolic

blood pressure (DBP) in the MONO study. ERT 5 mg and ERT 15 mg, as add-on to metformin, were associated with statistically significant differences in SBP (mean difference –3.7 mm Hg to –4.5 mm Hg) and DBP (mean difference –1.8 mm Hg to –2.4 mm Hg) compared with placebo in the MET study. In the SITA2 study, ERT 5 mg and 15 mg as add-on therapy to metformin and sitagliptin was associated with statistically significant differences in SBP (mean difference –2.9 mm Hg and –3.9 mm Hg) but not DBP, compared with placebo. Statistically significant differences were also detected between ERT plus sitagliptin versus sitagliptin alone for the change from baseline in SBP with mean differences of –2.8 mm Hg and –3.0 mm Hg, respectively. No statistically significant differences were observed for the change from baseline in DBP for the ERT plus sitagliptin groups compared with sitagliptin alone in the FACTORIAL study. Data for SBP and DBP from the SU trial comparing ERT versus glimepiride were inconclusive.

No statistically significant differences were detected between ERT and placebo for changes in health-related quality of life based on the EuroQol 5-Dimension (EQ-5D) instrument in the SITA2 study. The MET study found no statistically significant changes in bone mineral density (BMD) after 26 weeks of therapy for ERT versus placebo; however the duration of follow-up may have been insufficient to detect meaningful changes.

The manufacturer submitted two indirect treatment comparisons which compared short-term use of ERT (24 to 26 weeks) as monotherapy, or as add-on therapy with metformin, to the three SGLT2 inhibitors approved in Canada (canagliflozin, dapagliflozin, and empagliflozin). While the methods used to conduct the analyses seem to be adequate, the limited scope of the review meant that not all potentially relevant literature was used to inform the network. The results suggest that ERT as monotherapy, or in combination with metformin, for the treatment of T2DM is likely more efficacious than placebo; however little can be elucidated on the comparative efficacy of ERT to other SGLT2 inhibitors, or on the relative safety of the product. Other than the SU study, direct evidence of the comparative efficacy of ERT with other diabetes treatments is lacking, and without additional direct or indirect evidence, uncertainty remains.

Harms

The frequency of adverse events ranged from 42% to 56% in the 26-week studies and from 59% to 62% across treatment groups in the 52-week trial. Serious adverse events were reported by [redacted] of patients who receive placebo, [redacted] of those who received ERT (alone or with sitagliptin), and [redacted] for those who received sitagliptin or glimepiride based on the analysis that excluded follow-up time after the start of glycemic rescue therapy. Similarly, the proportion of patients who stopped treatment due to adverse events was generally low (placebo: [redacted] ERT: [redacted] active control: [redacted] No deaths were reported in the MONO, MET, FACTORIAL, and SITA2 trials. In the SU study, five patients died in the ERT 5 mg group and one patient died in the ERT 15 mg group. None of the deaths were considered to be related to the study medication. No deaths were reported during the study period among those who received glimepiride.

The frequency of documented or symptomatic hypoglycemia was highest in the glimepiride group ([redacted]), compared with [redacted] among those who received ERT, and [redacted] among those who received placebo. Severe hypoglycemia was reported infrequently in the placebo, ERT, or sitagliptin groups (0 to 2 patients per group [0% to 1.3%]), and was reported in 10 patients (2.3%) in the glimepiride group. Symptomatic hypoglycemia was included in the ordered statistical testing procedure for the SU trial. The frequency of symptomatic hypoglycemia was 19%, 3%, and 5% in the glimepiride, ERT 5 mg, and ERT

15 mg groups, respectively. The absolute difference between the ERT 15 mg and glimepiride groups was –14%; 95% CI, –18% to –10% ($P < 0.001$). For ERT 5 mg versus glimepiride, the absolute difference reported was –16%; 95% CI, –20% to –12%, although this comparison should be interpreted as inconclusive due to failure of a previous outcome in the testing sequence.

In women, genital mycotic infections were reported by 5% to 23% of patients who received ERT compared with 1% to 6% of patients who received placebo, glimepiride, or sitagliptin. In males, 2% to 6% in the ERT groups reported genital mycotic infections compared with 0% to 1% of those in the control groups. The occurrence of other harms of special interest to this review was infrequent, or the frequency was generally similar between ERT and control groups. Although no new safety signals were identified in the extension studies, the included trials were of insufficient duration and sample size to capture rare events such as low trauma fractures or lower limb amputations that have been identified as possible risks with the SGLT2 inhibitors. Additional data will be available once the ongoing CV safety trial (VERTIS CV) is published. Limited data were available on adverse effects from the indirect treatment comparisons submitted by the manufacturer due to the limited scope of the analyses, the scarcity of adverse event data, and poor model performance.

Potential Place in Therapy[a]

ERT is an SGLT2 inhibitor that works by decreasing renal reabsorption of sodium and glucose. In addition to lowering blood glucose, this mechanism of action may be responsible for desirable reductions in SBP and weight. ERT will be the fourth SGLT2 inhibitor on the market in Canada. The 2018 Diabetes Canada guidelines maintain that metformin should be the first-line therapy if lifestyle modifications fail to bring hemoglobin A1C into target, which for most patients would be A1C < 7%.[3] The second-line therapy choice includes a multitude of options; however, in those with known clinical CV disease there is a strong recommendation to use a medication that has clinical trial evidence of CV protection (empagliflozin, canagliflozin, or liraglutide).[4-6]

Deciding on the second-line treatment should involve shared decision-making with patient taking insurance coverage, renal function, weight, blood pressure, and adverse effect profiles into consideration. For many patients with diabetes, weight loss is a challenge and traditional second- and third-line therapies like sulfonylureas, thiazolidinediones, and insulin lead to weight gain. The newer classes of medications are weight neutral (DPP-4 inhibitors) or promote weight loss (SGLT2 inhibitors and GLP-1 agonists). When patients have insurance coverage for their medications, the decision between these three agents is based on the patient's desire for weight loss and willingness to accept adverse effects. Again, if the patient has clinical CV disease, then a drug with CV clinical trial evidence will be prioritized.

Another important consideration with this class of medications is adverse effects. Genitourinary tract infections, hypovolemia, fractures, lower extremity amputations, and euglycemic diabetic ketoacidosis have all been reported with some, if not all, of the medications in this class. Review of the currently available evidence shows the risk of hypovolemia and genital infections to be similar to other available SGLT2 inhibitors. There is no significant signal yet for increased risk of fractures or amputations, but the data from the CV outcome trial due out in 2019 will be important to understand if these unexpected adverse events seen with canagliflozin[4] are a class effect.

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

Renal disease is another important consideration in patients with diabetes. The SGLT2 inhibitors do not work as well at lower estimated glomerular filtration rates (eGFRs), and the ERT renal study showed it to be no different than the other available therapies. In earlier stages of renal disease both empagliflozin and canagliflozin have been shown to reduce progression,[4,7] but there is no data to support that yet for ertugliflozin.

Given that ERT does not yet have evidence of clinical CV or renal benefit (it has an ongoing trial with results expected in fall of 2019) and its glucose lowering potential and adverse effect profile appears to be similar to the currently available SGLT2 inhibitors, it does not appear to offer any significant benefit over the currently available SGLT2 inhibitors.

Conclusions

ERT as monotherapy, or as add-on therapy to metformin or metformin plus sitagliptin, was associated with statistically significant short-term (six month) reductions in A1C and body weight as compared with placebo plus add-on therapies. Statistically significant differences in SBP were observed for ERT as add-on therapy to metformin or metformin plus sitagliptin versus placebo plus add-on therapies.

In addition, ERT 15 mg daily, as add-on to metformin, was noninferior to glimepiride plus metformin for the change from baseline in A1C after 52 weeks. Noninferiority, however, was not met for ERT 5 mg versus glimepiride based on a 0.3% noninferiority margin. Statistically significant short-term reductions in A1C, body weight, and SBP were observed for ERT plus sitagliptin, as add-on therapy to metformin, versus sitagliptin plus metformin.

No differences were detected in health-related quality of life or BMD for ERT versus placebo, based on data from one RCT, although ability to detect differences may have been limited by the short duration of the treatment.

No new safety signals were identified for ERT that were not already known for other SGLT2 inhibitors, however the sample size and treatment duration limited the ability to detect infrequent adverse events, such as fractures or amputations, that have been identified as events of interest. Data on adjudicated major CV adverse events were not reported but are expected to be released once the longer-term CV safety study (VERTIS CV) is published.

The results of the manufacturer-submitted indirect treatment comparisons suggest that ERT as monotherapy, or in combination with metformin, for the treatment of T2DM is likely more efficacious than placebo; however little can be elucidated on the comparative efficacy of ERT to other SGLT2 inhibitors, or on the relative safety of the product.

Table 1: Summary of Primary Outcome

Population/Study	Treatment	N	Baseline A1C (%) Mean (SD)	Change From Baseline A1C LS Mean (95% CI)[a]	Difference in LS Mean (95% CI)[a]	*P* Value
No background AHA				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**
MONO	Placebo	153	8.1 (0.92)	0.20 (0.02 to 0.37)		
	ERT 5 mg	156	8.2 (0.88)	–0.79 (–0.95 to –0.63)	–0.99 (–1.22 to –0.76)	< 0.001
	ERT 15 mg	151	8.4 (1.1)	–0.96 (–1.12 to –0.80)	–1.16 (–1.39 to –0.93)	< 0.001
Add-on to metformin				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**
MET	Placebo	209	8.2 (0.90)	–0.03 (–0.15 to 0.10)		
	ERT 5 mg	207	8.1 (0.89)	–0.73 [redacted])	–0.70 (–0.87 to –0.53)	< 0.001
	ERT 15 mg	205	8.1 (0.93)	–0.91 (–1.03 to –0.78)	–0.88 [redacted])	< 0.001
Add-on to metformin				**Change from baseline to week 52**	**ERT vs. glimepiride at 52 weeks**	***P* value**
SU	Glimepiride	437	[redacted]	–0.74 (–0.83 to –0.65)		
(FAS)	ERT 5 mg	448	[redacted]	–0.56 (–0.65 to –0.47)	0.18 (0.06 to 0.30)	NI not met
	ERT 15 mg	440	[redacted]	–0.64 (–0.73 to –0.55)	0.10 (–0.02 to 0.22)	NI met
SU	Glimepiride	[redacted]	[redacted]	[redacted]		
(PP)	ERT 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ERT 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on to metformin				**Change from baseline to week 26**	**ERT+SIT vs. SIT at 26 weeks, *P* value**	**ERT+SIT vs. ERT at 26 weeks, *P* value**
FACTORIAL	ERT 5 mg	250	8.6 (1.0)	–1.02 (–1.14 to –0.90)		
	ERT 15 mg	248	8.6 (1.0)	–1.08 (–1.20 to –0.96)		
	SIT	247	8.5 (1.0)	–1.05 (–1.17 to –0.93)		
	ERT 5 mg + SIT	243	8.6 (1.0)	–1.49 (–1.61 to –1.36)	–0.43 (–0.60 to –0.27), *P* < 0.001	–0.46 (–0.63 to –0.30), *P* < 0.001
	ERT 15 mg + SIT	244	8.6 (1.0)	–1.52 (–1.64 to –1.40)	–0.47 (–0.63 to –0.30), *P* < 0.001	–0.44 (–0.61 to –0.27), *P* < 0.001
Add-on to metformin + SIT				**Change from baseline to week 26**	**ERT vs. placebo at 26 weeks**	***P* value**
SITA2	Placebo	153	8.0 (0.9)	–0.09 (–0.23 to 0.04)		
	ERT 5 mg	156	8.1 (0.9)	–0.78 (–0.91 to –0.65)	–0.69 (–0.87 to –0.50)	< 0.001
	ERT 15 mg	153	8.0 (0.8)	–0.86 (–0.99 to –0.72)	–0.76 (–0.95 to –0.58)	< 0.001

A1C = glycated hemoglobin; AHA = antihyperglycemic agent; CI = confidence interval; ERT = ertugliflozin; FAS = full analysis set; LS = least squares; MET = metformin; NA = not applicable; NI = noninferiority; PP = per-protocol; SD = standard deviation; SIT = sitagliptin.

[a] Excludes any data after the initiation of rescue glycemic therapy. Based on constrained longitudinal data analysis model with treatment, time (categorical), treatment by time interaction, baseline eGFR (continuous), and study-specific stratification factors as variables (see Table 12).

Source: Clinical Study Reports.[8-12]

Table 2: Summary of Harms

Population/ Study	Treatment	N	Patients With ≥ 1 SAE, n (%)[a]	Stopped Treatment Due to AEs, n (%)[a]	Documented Hypoglycemia, n (%)[a]	Symptomatic Hypoglycemia, n (%)[a]	Genital Mycotic Infection in Females, n (%)[a]
No background AHA							
MONO	Placebo	153	2 (1)	[redacted]	1 (1)	2 (1)	4 (6)
	ERT 5 mg	156	7 (5)	4 (3)	4 (3)	2 (1)	11 (16)
	ERT 15 mg	151	2 (1)	3 (2)	4 (3)	4 (3)	14 (23)
Add-on to metformin							
MET	Placebo	209	8 (4)	3 (1)	9 (4)	4 (2)	1 (1)
	ERT 5 mg	207	3 (1)	3 (1)	15 (7)	7 (3)	6 (6)
	ERT 15 mg	205	7 (3)	3 (1)	16 (8)	7 (3)	7 (6)
Add-on to metformin							
SU	Glimepiride	437	12 (3)	17 (4)	119 (27)	84 (19)	3 (1)
	ERT 5 mg	448	[redacted]	[redacted]	25 (6)	14 (3)[b]	17 (8)
	ERT 15 mg	440	17 (4)	23 (5)	36 (8)	23 (5)[c]	25 (10)
Add-on to metformin							
FACTORIAL	ERT 5 mg	250	8 (3)	6 (2)	14 (6)	6 (2)	6 (5)
	ERT 15 mg	248	3 (1)	3 (1)	13 (5)	6 (2)	8 (7)
	SIT	247	[redacted]	1 (< 1)	9 (4)	6 (2)	1 (1)
	ERT 5 mg + SIT	243	6 (2)	3 (1)	13 (5)	6 (2)	6 (5)
	ERT 15 mg + SIT	244	4 (2)	7 (3)	22 (9)	12 (5)	9 (8)
Add-on to metformin + SIT							
SITA2	Placebo	153	[redacted]	1 (1)	5 (3)	4 (3)	1 (2)
	ERT 5 mg	156	7 (5)	5 (3)	7 (5)	6 (4)	6 (8)
	ERT 15 mg	153	3 (2)	1 (1)	3 (2)	1 (1)	9 (13)

AE = adverse event; AHA = antihyperglycemic agent; ERT = ertugliflozin; SAE = serious adverse events: SIT = sitagliptin.

[a] Excludes events that occurred after the start of rescue therapy.

[b] Absolute difference between ERT 5 mg and glimepiride: –16%; 95% CI, –20% to –12%; $P < 0.001$, however this should be interpreted as inconclusive as the statistical testing failed for a previous outcome.

[c] Absolute difference between ERT 15 mg and glimepiride: –14%; 95% CI, –18% to –10%; $P < 0.001$ (secondary outcome included in the ordered statistical testing procedure).

Source: Clinical Study Reports.[8-12]

Introduction

Disease Prevalence and Incidence

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels on a microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (peripheral artery disease, cardiovascular [CV] disease) level. There are two main subtypes of diabetes mellitus: type 1 diabetes mellitus, in which the primary problem is a lack of adequate insulin secretion from pancreatic beta cells; and type 2 diabetes mellitus, in which cells are unresponsive to insulin. Type 2 diabetes mellitus is more common than type 1 diabetes mellitus, accounting for approximately 90% of cases of diabetes mellitus.[13] The etiology of type 1 diabetes mellitus is unknown, although onset is typically early in life. In contrast, onset of type 2 diabetes mellitus is typically later in life, although this is changing with the current epidemic of childhood obesity in Western societies. Poor diet and minimal exercise, and associated weight gain, are considered to be important risk factors for type 2 diabetes mellitus.[14] The social determinants of health play an important role in developing diabetes and its complications, with the lowest income groups showing the highest risk.[15]

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. This number is projected to increase to 642 million by 2040.[14,16] Diabetes is one of the most common chronic diseases in Canada. Diabetes Canada estimated that there were 3.4 million people (9.3% of the population) with diabetes in 2015, and by 2025 this number will have increased to five million people (12.1%).[1] People with diabetes are more likely to be hospitalized and to experience complications requiring specialist care. Diabetes-associated costs to the Canadian health care system are estimated to be C$16.9 billion per year by 2020.[17]

Standards of Therapy

Treatment regimens and therapeutic targets should be individualized in patients with type 2 diabetes mellitus. 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.[3] There are many classes of antihyperglycemic agents (AHAs) used in treating type 2 diabetes mellitus, including insulin. Metformin is indicated for most patients, and it is considered to be the first-line drug of choice. When initial therapy with lifestyle intervention and metformin monotherapy fails to achieve adequate glycemic control, a second or third drug can be added to metformin. Several oral antidiabetic agents can be used with metformin, such as sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DDP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT2). Injectable agent (glucagon-like peptide-1 [GLP-1] receptor agonists; insulin and insulin analogues in rapid-acting, intermediate or longer-acting forms) can be added to metformin when metformin monotherapy fails, or patients are switched to insulin.[3] In deciding upon which drug to add after metformin, there must be consideration of multiple factors, 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.[3]

Drug

Ertugliflozin (ERT) belongs to the SGLT2 inhibitor class of drugs, which increases glucose excretion from the kidneys. It is approved as monotherapy as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance; and as combination therapy in adult patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, or metformin and sitagliptin, when the therapy listed above, along with diet and exercise, does not provide adequate glycemic control.[18] It is available as a 5 mg and 15 mg tablet, as well as a fixed-dose combination tablet with metformin (ERT/metformin 2.5 mg/500 mg; 2.5 mg/1,000 mg; 7.5 mg/500 mg; 7.5 mg/1,000 mg).[18,19] The recommended dose is 5 mg daily, which may be increased to 15 mg daily if additional glycemic control is needed. The fixed-dose combination product is dosed as one tablet twice daily. Patients should be switched to the nearest therapeutically appropriate dose of metformin. The maximum daily dose is 15 mg ERT and 2,000 mg of metformin. [19] ERT was co-developed by Pfizer Inc. and Merck & Co., Inc.[8]

Table 3: Key Characteristics of SGLT2 Inhibitors, DPP-4 Inhibitors, and GLP-1 Analogues

	SGLT2 Inhibitors	DPP-4 Inhibitors	GLP-1 Analogues
Mechanism of Action	Inhibits the SGLT2 transporter in the kidney, leading to increased glucose excretion	Increase GLP-1 by inhibiting the DPP-4 enzyme, which inactivates GLP-1, leads to: • insulin secretion • inhibits glucagon release • delays gastric emptying • reduces food intake	Mimic GLP-1, which leads to: • insulin secretion • inhibits glucagon release • delays gastric emptying • reduces food intake
Indication[a]	See Table 4	See Table 4	See Table 4
	Oral	Oral	Subcutaneous
Recommended Dose	Varies by drug	Varies by drug	Varies by drug
Serious Side Effects / Safety Issues	Contraindications: Renal impaired patients with eGFR: • less than 60 mL/min/1.73 m^2 (dapagliflozin); • less than 45 mL/min/1.73 (canagliflozin, ertugliflozin); or • less than 30 mL/min/1.73 m^2 (empagliflozin). Warnings or precautions: • ketoacidosis • volume depletion, hypotension or electrolyte imbalances • increase in LDL-C, hemoglobin • impaired renal function • genital mycotic infections • urinary tract infection • lower limb amputation • fractures	Contraindications: Not for the treatment of type 1 diabetes mellitus or those with diabetic ketoacidosis Warnings or precautions: • heart failure • pancreatitis • immune suppression • hypersensitivity reactions • bullous pemphigoid	Contraindications: Personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2 Warnings or precautions: • thyroid cancer • prolonged PR interval • pancreatitis • gastrointestinal disorders

DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; LDL-C = low-density lipoprotein-cholesterol; SGLT2 = sodium-glucose cotransporter-2.

[a] Health Canada indication.

Source: Product monographs.[18,20-32]

Table 4: Indication for SGLT2 Inhibitors, DPP-4 Inhibitors, and GLP-1 Analogues

	SGLT2 Inhibitors				DPP-4 Inhibitor				GLP-1 Analogues					
	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Dulaglutide	Exenatide (b.i.d.)	Exenatide (weekly)	Liraglutide	Semaglutide	Lixisenatide
Glycemic control														
Monotherapy: in patients for whom metformin is inappropriate due to contraindications or intolerance	x	x	x	x	x	x		x	x		x	x	x	
Combination therapy: in combination with the following treatments when diet and exercise plus the treatments do not provide adequate glycemic control														
Metformin	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Sulfonylurea	x	x			x	x	x			x	x			x
Sitagliptin		x												
Pioglitazone			x		x			x						x
Metformin + sulfonylurea	x	x	x			x	x	x	x	x	x	x	x	x
Metformin + sitagliptin.	x	x		x										
Metformin + pioglitazone	x		x		x			x						x
Insulin (with or without metformin)	x	x	x		x		x	x	x	x	x	x	x	x
Cardiovascular														
As an adjunct to diet, exercise, and standard care therapy to reduce the incidence of CV death in patients with type 2 diabetes mellitus and established CV disease who have inadequate glycemic control.			x									x		

b.i.d. = twice daily; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose cotransporter-2.

[a] In combination with sitagliptin (with or without metformin).

Source: Product monographs.[18,20-32]

Table 5: Key Characteristics of Metformin, Sulfonylureas, and Insulin

	Biguanides (Metformin)	Sulfonylurea	Insulin/ Insulin Analogues
Mechanism of Action	Reduces gluconeogenesis. Increases insulin-mediated glucose utilization in peripheral tissues. Antilipolytic effects.	Promotes insulin secretion by binding to the sulfonylurea receptor (SUR-1).	Substitute for endogenously secreted insulin.
Indication	T2DM which cannot be controlled by dietary management, exercise, and weight reduction or when insulin therapy is not appropriate. Treatment of obese patients with diabetes.	T2DM in adults, alone or in combination with other AHAs, as an adjunct to exercise and diet.	Patients with DM who require insulin for control of hyperglycemia.
Route of Administration	Oral	Oral	Subcutaneous
Usual Dose	1,500 mg to 2,000 mg per day	Varies by drug	Titrated
Serious Side Effects / Safety Issues	Contraindications: • acute or chronic metabolic acidosis including diabetic ketoacidosis • severe renal impairment (eGFR < 30 mL/min/1.73m^2) Warnings and precautions: • lactic acidosis (rare) • use in patients with acute heart failure, active liver disease, or alcohol abuse	Contraindications: • ketoacidosis • renal impairment Precautions: • hypoglycemia	Warnings and precautions: • hypoglycemia • immune responses

AHA = antihyperglycemic agent; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus.

[a] Health Canada indication.

Source: Up-To-Date.[33-35]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of ERT 5 mg and 15 mg tablets to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance (as monotherapy); or in combination with metformin, or metformin and sitagliptin, when these therapies, along with diet and exercise, do not provide adequate glycemic control.

This review was conducted in tandem with an evaluation of the ERT/metformin fixed-dose combination product, Segluromet.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CADTH Common Drug Review (CDR) and Health Canada, as well as those meeting the selection criteria presented in Table 6.

Table 6: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance, or Adult patients with type 2 diabetes mellitus with inadequate glycemic control with metformin, or metformin and sitagliptin. Subgroups • Age • Baseline A1C • Type 2 diabetes duration • BMI • Renal function • Background diabetes therapy • History of heart failure • History of cerebrovascular or CV disease
Intervention	Ertugliflozin 5 mg to 15 mg daily, alone or in combination with metformin or metformin plus sitagliptin
Comparators	One or more of the following: • Sulfonylureas • SGLT2 inhibitors • Incretin mimetics (DPP-4 inhibitors, GLP-1 analogues) • Thiazolidinediones • Insulin secretagogues (meglitinides) • Metformin • Insulin/Insulin analogues (including basal and prandial regimens) • Alpha-glucosidase inhibitors • Placebo

Outcomes	***Efficacy outcomes:*** • Glycemic control (e.g., A1C, FPG)[a] • Mortality (all-cause, CV-related) [a] • Myocardial infarction (fatal and non-fatal) • Stroke (fatal and non-fatal) • Heart failure • Peripheral vascular disease • Hospitalization (CV-related, all-cause) • Diabetes-related microvascular morbidity [a] • Health-related quality of life [a] • Blood pressure [a] • Body weight [a] • BMD • Health care resource utilization ***Harms outcomes:*** • AEs • SAEs • WDAEs • Mortality • Notable harms: ketoacidosis, hypoglycemia,[a] volume depletion, renal impairment, lower limb amputation, genital or urinary tract infections, fractures
Study Design	Published and unpublished phase III or IV RCTs

A1C = glycated hemoglobin; AE = adverse event; BMD = bone mineral density; BMI = body mass index; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; PPG = postprandial glucose; RCT = randomized controlled trial; SAE = serious adverse event; SGLT2 = sodium-glucose cotransporter-2; WDAE = withdrawal due to adverse events.

[a] Patient group input stated these were important to patients.

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 ALL (1946–) Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Steglatro (ertugliflozin).

No methodological filters were applied to limit retrieval to study type. 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 28, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on September 19, 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 device regulatory approvals, advisories and warnings, drug class reviews and databases. 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 7 and excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of five studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 7. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

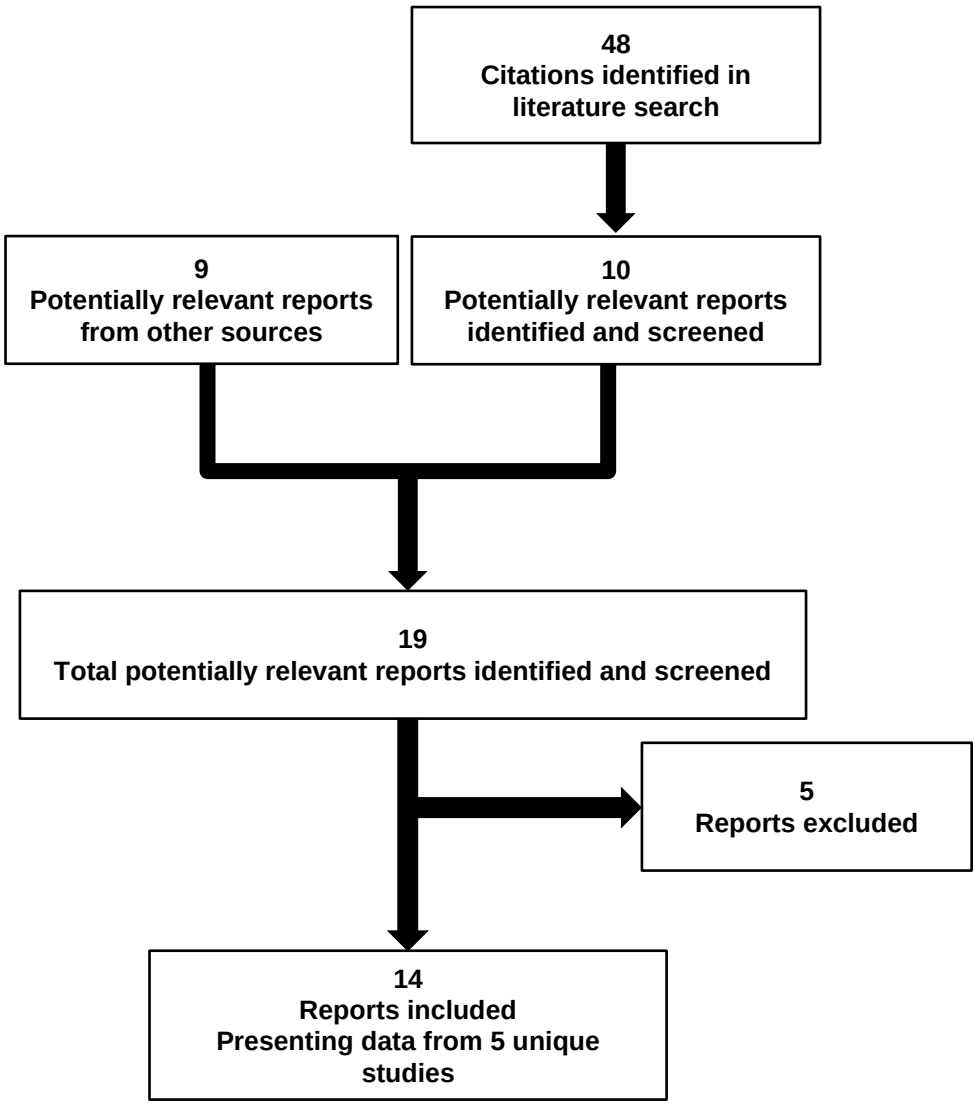


Table 7: Details of Included Studies

		MONO	MET	SU
Designs & Populations	**Study Design**	DB RCT	DB RCT	DB RCT noninferiority
	Locations	Canada, US, Mexico, Italy, UK, Israel, South Africa	US, Europe, Australia, South Africa, Israel, Asia	North America, Europe, Asia, South Africa, Argentina
	Randomized (N)	461	621	1,326
	Inclusion Criteria	• ≥ 18 years of age with T2DM • no prior oral AHA for ≥ 8 weeks prior with A1C 7.0% to 10.5% or on monotherapy with allowable AHA with an A1C 6.5% to 9.5% (see Table 9) • BMI ≥ 18 kg/m^2	• ≥ 18 years of age with T2DM and inadequate glycemic control (A1C 7% to 10.5%) on ≥ 1,500 mg per day metformin for ≥ 8 weeks (see Table 9) • BMI 18.0 kg/m^2 to 40 kg/m^2	• ≥ 18 years of age with T2DM and inadequate glycemic control (A1C ≥ 7.0% and ≤ 9.0%) on stable metformin monotherapy ≥ 1,500 mg/day for ≥ 8 weeks (see Table 9) • BMI ≥ 18.0 kg/m^2
	Exclusion Criteria	• less than 80% adherent during placebo run-in period (pill counts) • history of ketoacidosis, T1DM, or other form of diabetes • history of MI, unstable angina, revascularization, stroke, TIA, NYHA class III or IV heart failure within 3 months, clinically significant ECG abnormality • SBP > 160 mm Hg or DBP > 90 mm Hg not controlled with medication • consumes > 2 alcoholic drinks per day or > 14 per week • patients who were not weight stable due to a weight loss program, bariatric surgery, or medications • abnormal laboratory values including FPG > 15.0 mmol/L, triglyceride > 6.78 mmol/L, elevated liver enzymes, or low hemoglobin levels • elevated serum creatinine or eGFR < 55 mL/min/1.73 m^2 • currently treated for hyperthyroidism, or has an unstable thyroid condition; active liver disease; recent major surgical procedure; HIV or blood dyscrasia; pregnant or breast-feeding; malabsorption condition; obstructive uropathy or indwelling catheter; malignancy ≤ 5 years prior • may require oral corticosteroids for ≥ 14 days or other prohibited medications		
	Additional Exclusion Criteria		• gender specific BMD T-score < –2.5 at any site • osteoporosis or other bone disorders • rheumatoid arthritis • previous atraumatic vertebral fracture or high- and low-impact fracture of the hip or wrist	
Drugs	**Intervention**	ERT 5 mg daily ERT 15 mg daily	ERT 5 mg daily ERT 15 mg daily	ERT 5 mg daily ERT 15 mg daily
	Comparator(s)	placebo	placebo	Glimepiride: initiated at 1 mg and titrated up to the maximum approved dose (6 mg or 8 mg daily) or maximum tolerated dose

		MONO	MET	SU
DURATION	**Phase**			
	Screening/dose-stabilization	3 to 9 weeks	Up to 9 weeks	
	Placebo run-in	2 weeks	2 weeks	2 weeks
	Treatment	26 week (Phase A)	26 weeks (Phase A)	52 weeks (Phase A)
	Follow-up	2 weeks	2 weeks	2 weeks
OUTCOMES	**Primary End Point**	Change from baseline to week 26 in A1C for: • ERT 15 mg vs. placebo • ERT 5 mg vs. placebo	Change from baseline to week 26 in A1C for: • ERT 15 mg vs. placebo • ERT 5 mg vs. placebo	Noninferiority of ERT 15 mg versus glimepiride for the change from baseline in A1C at week 52
	Other End Points	Change from baseline in: • FPG • Body weight • 2-hour PPG • SBP • DBP Proportion of patients with: • A1C < 7.0% • Received rescue therapy Time to rescue therapy	Change from baseline in: • FPG • Body weight • SBP • DBP • BMD Proportion of patients with: • A1C < 7.0% • Received rescue therapy Time to rescue therapy	Change from baseline in: • body weight • SBP • FPG • DBP Proportion of patients with: • A1C < 7% • Receiving glycemic rescue treatment • Durability of glycemic efficacy • Composite (0.5% decrease in A1C, no symptomatic hypoglycemia, and no body weight gain) • Composite (A1C < 7% with no symptomatic hypoglycemia) • Lipid profile • Harms • Incidence of symptomatic hypoglycemia
NOTES	**Publications**	Terra et al.[36]	Rosenstock et al.[37]	Hollander et al.[38]

A1C = glycated hemoglobin; ADA = American Diabetes Association; AHA = antihyperglycemic agent; BMD = bone mineral density; DB = double blind; DBP = diastolic blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ERT = ertugliflozin; FPG = fasting plasma glucose; MI = myocardial infarction; NYHA = New York Heart Association; PPG = postprandial glucose; RCT = randomized controlled trial; SBP = systolic blood pressure; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack.

Note: Nine additional reports were included (FDA Medical and Statistical Reports,[39,40] HC Reviewer's Report,[2] CDR Submission,[41] Clinical Study Reports[8-12]).

Source: Clinical Study Reports.[8-12]

Table 7: Details of Included Studies (continued)

		FACTORIAL	SITA2
Designs & Populations	**Study Design**	DB RCT	DB RCT
	Locations	North America, South America, Europe, Israel, Asia, New Zealand	US, South America, Europe, Asia, Israel
	Randomized (N)	1,233	463
	Inclusion Criteria	• T2DM and ≥ 18 years of age and inadequate glycemic control (A1C ≥ 7.5% and ≤ 11.0%) on stable metformin monotherapy ≥ 1,500 mg/day for ≥ 8 weeks (see Table 9) • BMI ≥ 18.0 kg/m^2	• ≥ 18 years of age with T2DM and inadequate glycemic control (A1C 7% to 10.5%) on ≥ 1,500 mg per day metformin plus sitagliptin 100 mg daily for ≥ 8 weeks (see Table 9) • BMI ≥ 18.0 kg/m^2
	Exclusion Criteria	• < 80% adherent during placebo run-in period (pill counts) • history of ketoacidosis, T1DM, or other form of diabetes • history of MI, unstable angina, revascularization, stroke, TIA, NYHA class III or IV heart failure within 3 months, clinically significant ECG abnormality • SBP > 160 mm Hg or DBP > 90 mm Hg not controlled with medication • consumes > 2 alcoholic drinks per day or > 14 per week • patients who were not weight stable due to a weight loss program, bariatric surgery, or medications • abnormal lab values including triglyceride > 6.78 mmol/L, elevated liver enzymes, or low hemoglobin levels; consistent FPG > 14.4 mmol/L (SITA2) or > 16.6 mmol/L (FACTORIAL) • elevated serum creatinine or eGFR < 60 mL/min/1.73 m^2 • currently treated for hyperthyroidism, or has an unstable thyroid condition; active liver disease; recent surgical procedure; HIV or blood dyscrasia; pregnant or breast-feeding; malabsorption condition; obstructive uropathy or indwelling catheter; malignancy ≤ 5 years prior • may require oral corticosteroids for ≥ 14 days or other prohibited medications	
Drugs	**Intervention**	ERT 5 mg daily ERT 15 mg daily ERT 5 mg + SIT 100 mg daily ERT 15 mg + SIT 100 mg daily	ERT 5 mg daily ERT 15 mg daily
	Comparator(s)	SIT 100 mg daily	Placebo
Duration	**Phase**		
	Washout/dose-stabilization	Up to 12 weeks	Up to 12 weeks
	Placebo run-in	2 weeks	2 weeks
	Treatment	26 weeks (Phase A)	26 weeks (Phase A)
	Follow-up	2 weeks	2 weeks
Outcomes	**Primary End Point**	Change from baseline in A1C at week 26	Change from baseline to week 26 in A1C for: • ERT 15 mg vs. placebo • ERT 5 mg vs. placebo
	Other End Points	Change from baseline in: • bodyweight; • FPG; • sitting SBP; • beta cell function. Proportion of patients with A1C < 7.0% Additional analyses from the MMTT subgroup Harms	Change from baseline in: • FPG • Body weight • SBP • DBP • EQ-5D-3L Proportion of patients with: • A1C < 7.0% • Received rescue therapy

		FACTORIAL	SITA2
			Time to rescue therapy Harms
NOTES	**Publications**	Pratley et al.[42]	Dagogo-Jack et al.[43]

A1C = glycated hemoglobin; ADA = American Diabetes Association; AHA = antihyperglycemic agent; BMD = bone mineral density; DB = double blind; DBP = diastolic blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-3L = EuroQol 5-Dimension 3-level instrument; ERT = ertugliflozin; FPG = fasting plasma glucose; MI = myocardial infarction; MMTT = mixed-meal tolerance test; NYHA = New York Heart Association; PPG = postprandial glucose; RCT = randomized controlled trial; SBP = systolic blood pressure; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack.

Note: Nine additional reports were included (FDA Medical and Statistical Reports,[39,40] HC Reviewer's Report,[2] CDR Submission,[41] Clinical Study Reports[8-12]).

Source: Clinical Study Reports.[8-12]

Included Studies

Description of Studies

A total of five double-blind randomized controlled trials (RCTs) met the inclusion criteria (MONO, MET, SU, FACTORIAL, SITA2) (Table 8). These trials evaluated the safety and efficacy of ERT 5 mg daily and ERT 15 mg daily (alone or in combination with metformin, or metformin plus sitagliptin), compared with placebo or active comparators, in adults with type 2 diabetes and inadequate glycemic control.

All trials included a randomized double-blind treatment period (Phase A), that was 26 weeks in duration (MONO, MET, SITA2, FACTORIAL) or 52 weeks in duration (SU), as well as a 26- to 78-week extension period (Phase B) (see Appendix 4, Figure 2 to Figure 6 for a schematic of the trial designs). Data from Phase A of all studies will be summarized in the main body of this report. Supplemental data from the extension studies will be presented in Appendix 5.

In all trials, the patients who met the entry criteria underwent a period of dose-stabilization or a washout period for background medications, according to the protocol for each trial (see Population section for details), followed by a two-week, single-blind placebo run-in period before randomization. Randomization was conducted using an interactive voice or interactive Web response system (Table 8). Study-specific details are listed in Table 7, and figures of the study conduct of each trial are included in Appendix 4.

Table 8: Study Design of Ertugliflozin Studies

Study	N	Population	Interventions (Daily Dose)	Randomization Methods	Design/ Duration (Phase A)
VERTIS MONO	461	Inadequate glycemic control with diet and exercise	ERT 5 mg ERT 15 mg Placebo No background AHA	1:1:1 using a computer-generated randomization schedule and random permuted blocks Stratified by region	DB RCT 26 weeks
VERTIS MET	621	Inadequate glycemic control with MET ≥ 1,500 mg/day	ERT 5 mg ERT 15 mg Placebo Background AHA: MET ≥ 1,500 mg/day	1:1:1 using random using a computer-generated randomization schedule and random permuted blocks Stratified based on geographic region and four postmenopausal status categories (men; premenopausal women; women perimenopausal or postmenopausal for < 3 years; women postmenopausal for ≥ 3 years)	DB RCT 26 weeks
VERTIS SU	1,326	Inadequate glycemic control with MET ≥ 1,500 mg/day	ERT 5 mg ERT 15 mg Glimepiride 1 mg to 8 mg Background AHA: MET ≥ 1,500 mg/day	1:1:1 using a computer-generated randomization schedule	DB RCT 52 weeks
VERTIS FACTORIAL	1,233	Inadequate glycemic control with MET ≥ 1,500 mg/day	ERT 5 mg ERT 15 mg SIT 100 mg ERT 5 mg + SIT 100 mg ERT 15 mg + SIT 100 mg Background AHA: MET ≥ 1,500 mg/day	1:1:1:1:1 using a computer-generated randomization schedule. Stratified by patients who agreed to participate in additional analyses during a mixed meal tolerance test	DB RCT 26 weeks
VERTIS SITA2	464	Inadequate glycemic control with MET ≥ 1,500 mg/day and SIT 100 mg/day	ERT 5 mg ERT 15 mg Placebo Background AHA: MET ≥ 1,500 mg/day + SIT 100 mg/day	1:1:1 using a computer-generated randomization schedule, Stratified by use of sulfonylurea at screening	DB RCT 26 weeks

AHA = antihyperglycemic agent; CKD = chronic kidney disease; DB = double blind; eGFR = estimated glomerular filtration rate; ERT = ertugliflozin; MET = metformin; RCT = randomized controlled trial; SIT = sitagliptin.

Source: Clinical Study Reports.[8-12]

Populations

Inclusion and exclusion criteria

Patients enrolled in the ERT trials were adults (≥ 18 years of age) with type 2 diabetes mellitus, diagnosed according to the American Diabetes Association (ADA) guidelines with inadequate glycemic control with diet and exercise (MONO), and metformin greater than and equal to 1,500 mg/day (MET, SU, FACTORIAL), or metformin greater than and equal to 1,500 mg/day plus sitagliptin 100 mg daily (SITA2). Each trial had specific inclusion criteria related to A1C levels and background medications at screening (see Table 9). Patients on other background medications or other doses of the protocol-specified background medications (i.e., metformin and/or sitagliptin) were required to undergo a washout period, or dose-stabilization period for at least eight weeks. At the end of this washout period, patients on stable doses of background therapies who met the trial's A1C inclusion criteria were eligible to enter a two-week, single-blind placebo run-in period, and those that had at least 80% adherence based on pill counts, were randomized.

Exclusion criteria were similar across studies and those with recent CV events, history of ketoacidosis, significant alcohol use, or specific laboratory values outside of range, were not eligible for enrolment (Table 7).

Table 9: A1C and Background Therapy Inclusion Criteria

Study	Background Diabetes Medication and A1C Inclusion Criteria at Screening	Change in Background Diabetes Medication During Washout or Dose-Stabilization Period	Inclusion Criteria for Entry into Placebo Run-In
MONO	Monotherapy with single allowable AHA (metformin, sulfonylureas, DPP-4 inhibitors, glinides or alpha-glucosidase inhibitors) and A1C 6.5% to 9.5%	Discontinue AHA for ≥ 8 weeks	No AHA for ≥ 8 weeks and A1C 7.0% to 10.5%
	No AHA for at least 8 weeks prior with A1C 7.0% to 10.5%	No change	
MET	Metformin monotherapy ≥ 1,500 mg/day for ≥ 8 weeks and A1C 7.0% to 10.5%	No change	Metformin ≥ 1,500 mg/day for ≥ 8 weeks and A1C 7.0% to 10.5%
	Metformin monotherapy ≥ 1,500 mg/day for < 8 weeks and A1C 7.0% to 10.5%	Enter placebo run-in after metformin dose had been stable for ≥ 8 weeks	
	Metformin monotherapy < 1,500 mg/day and A1C 7.5% to 11.0%	Titrate metformin dose to ≥ 1,500 mg/day and maintain metformin dose for ≥ 8 weeks	
	Dual therapy: metformin plus sulfonylurea, DPP-4 inhibitor, meglitinide, or alpha-glucosidase inhibitor, and A1C 6.5% to 9.5%	Discontinue non-metformin AHA, titrate metformin dose to ≥ 1,500 mg/day and maintain stable metformin dose for ≥ 8 weeks	
SU	Metformin monotherapy ≥ 1,500 mg/day for ≥ 8 weeks and A1C 7.0% to 9.0%	No change	Metformin ≥ 1,500 mg/day for ≥ 8 weeks and A1C 7.0% to 9.0%
	Metformin monotherapy ≥ 1,500 mg/day for < 8 weeks and A1C 7.0% to 9.0%	Enter placebo run-in after metformin dose had been stable for ≥ 8 weeks	
	Metformin monotherapy < 1,500 mg/day and A1C 7.5% to 9.5%	Titrate metformin dose to ≥ 1,500 mg/day and maintain metformin dose for ≥ 8 weeks	

Study	Background Diabetes Medication and A1C Inclusion Criteria at Screening	Change in Background Diabetes Medication During Washout or Dose-Stabilization Period	Inclusion Criteria for Entry into Placebo Run-In
	Metformin in combination with a single allowable AHA (i.e., SUs at < 50% the maximum approved dose in the local country label, DPP-4 inhibitors, meglitinides, or alpha-glucosidase inhibitors) and A1C 6.5% to 8.5%	Discontinue non-metformin AHA, titrate metformin dose to ≥ 1,500 mg/day and maintain stable metformin dose for ≥ 8 weeks (≥ 10 weeks for patients stopping SU)	
FACTORIAL	Metformin monotherapy ≥ 1,500 mg/day for ≥ 8 weeks and A1C 7.5% to 11%	No change	Metformin ≥ 1,500 mg/day for ≥ 8 weeks and A1C 7.5% to 11%
	Metformin monotherapy ≥ 1,500 mg/day for < 8 weeks and A1C 7.5% to 11%	Enter placebo run-in after metformin dose had been stable for ≥ 8 weeks	
	Metformin monotherapy < 1,500 mg/day and A1C 8% to 11.5%	Titrate metformin dose to ≥ 1,500 mg/day and maintain metformin dose for ≥ 8 weeks	
SITA2	Metformin ≥ 1,500 mg/day plus sitagliptin 100 mg daily for ≥ 8 weeks and A1C 7.0% to 10.5%	No change	Metformin ≥ 1,500 mg/day plus sitagliptin 100 mg daily for ≥ 8 weeks and A1C 7.0% to 10.5%
	Metformin ≥ 1,500 mg/day plus sitagliptin 100 mg daily for < 8 weeks and A1C 7.0% to 10.5%	Maintain metformin and sitagliptin for total of ≥ 8 weeks	
	Metformin ≥ 1,500 mg/day plus other DPP-4 inhibitor and A1C 7.0% to 10.5%	Maintain metformin; switch DPP-4 inhibitor to sitagliptin 100 mg daily; continue with metformin and sitagliptin for total of ≥ 8 weeks	
	Metformin ≥ 1,500 mg/day plus sulfonylurea and A1C 7.0% to 10.5%	Maintain metformin; stop sulfonylurea and add sitagliptin 100 mg daily; continue with metformin and sitagliptin for total of ≥ 8 weeks	
	Metformin < 1,500 mg/day plus any DPP-4 inhibitor and A1C 7.5% to 11.0%	Titrate metformin dose to ≥ 1,500 mg/day and switch DPP-4 inhibitor to sitagliptin 100 mg day; continue with metformin and sitagliptin for total of ≥ 8 weeks	

A1C = glycated hemoglobin; AHA = antihyperglycemic agent; DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium-glucose cotransporter-2; SU = sulfonylurea.

Source: Clinical Study Reports.[8-12]

Baseline characteristics

The proportion of patients who were male ranged from 43% to 65% per treatment group and the mean age per treatment group was 54.8 to 59.7 years (Table 10). The patients enrolled were predominantly white (65% to 86%) with a mean BMI per group ranging from 30.3 kg/m^2 to 33.3 kg/m^2 and baseline A1C of 7.8% to 8.6%.The mean duration of diabetes varied across trials and was lowest for the MONO study (4.6 to 5.2 years), and highest for the SITA2 study (9.2 to 9.9 years). The mean estimated glomerular filtration rate (eGFR) at baseline was above 85 mL/min/1.73 m^2 for all treatment groups.

Baseline characteristics were generally similar between groups within trials although some differences in the proportion of males were noted in the FACTORIAL and SITA2 studies, as well as differences in the duration of diabetes in the MONO and FACTORIAL studies.

Table 10: Summary of Baseline Characteristics

Characteristics	MONO			MET		
	Placebo N = 153	ERT 5 mg N = 156	ERT 15 mg N = 152	Placebo N = 209	ERT 5 mg N = 207	ERT 15 mg N = 205
Male, n (%)	82 (54)	89 (57)	90 (59)	98 (47)	97 (47)	93 (45)
Age, mean years (SD)	56.1 (10.9)	56.8 (11.4)	56.2 (10.8)	56.5 (8.7)	56.6 (8.1)	56.9 (9.4)
Race, n (%)						
White	126 (82)	134 (86)	126 (83)	144 (69)	134 (65)	133 (65)
Black	9 (6)	10 (6)	10 (7)	19 (9)	22 (11)	23 (11)
Asian	15 (10)	10 (6)	14 (9)	31 (15)	34 (16)	35 (17)
Other	3 (2)	2 (1)	2 (1)	15 (7)	17 (8)	14 (7)
Mean duration of diabetes, years (SD)	4.6 (4.5)	5.1 (5.1)	5.2 (5.6)	8.0 (6.3)	7.9 (6.1)	8.1 (5.5)
Mean body weight, kg (SD)	94.2 (25.2)	94.0 (25.4)	90.6 (18.3)	84.5 (17.1)	84.8 (17.2)	85.3 (16.5)
Mean BMI, kg/m^2 (SD)	33.3 (6.8)	33.2 (7.4)	32.5 (5.7)	30.7 (4.7)	30.8 (4.8)	31.1 (4.5)
A1C (%)						
Mean, (SD)	8.1 (0.92)	8.2 (0.88)	8.4 (1.12)	8.2 (0.9)	8.1 (0.9)	8.1 (0.9)
< 8.0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.0 to < 9.0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 9.0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean FPG, mg/dL (SD)	180.2 (45.8)	180.9 (48.5)	179.1 (48.2)	169.1 (41.7)	168.1 (45.5)	167.9 (44.4)
Mean FPG, mmol/L (SD)[a]	10.0 (2.5)	10.1 (2.7)	10.0 (2.7)	9.4 (2.3)	9.3 (2.5)	9.3 (2.5)
Mean eGFR, mL/min/1.73 m^2 (SD)	86.2 (19.4)	88.5 (18.4)	88.3 (18.0)	91.6 (19.8)	88.9 (17.5)	91.0 (20.6)
30 to < 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 to < 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background AHA therapy at screening, n (%)						
None	[redacted]	[redacted]	[redacted]	0	0	0
Biguanides	[redacted]	[redacted]	[redacted]	209 (100)	207 (100)	204 (99.5)
DPP-4 inhibitor	[redacted]	[redacted]	[redacted]	7 (3)	6 (3)	8 (4)
Sulfonamides	[redacted]	[redacted]	[redacted]	62 (30)	57 (28)	45 (22)
Other AHA	[redacted]	[redacted]	[redacted]	0	3 (1)	2 (1)
Medical History (SOC)						
Cardiac disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutritional disorders[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; AHA = antihyperglycemic agent; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; ERT = ertugliflozin; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide 1; SD = standard deviation; SOC = system organ class.

[a] Converted by CDR.

[b] Metabolic disorders SOC include dyslipidemia, hypercholesterolemia, hyperlipidemia, and obesity, as well as gout, hyperuricemia, etc.

Source: Clinical Study Reports.[8-12]

Table 10: Summary of Baseline Characteristics (continued)

Characteristics	SU			FACTORIAL				
	GLIM N = 437	ERT 5 mg N = 448	ERT 15 mg N = 440	ERT 5 mg N = 250	ERT 15 mg N = 248	SIT 100 mg N = 247	ERT 5 mg + SIT N = 243	ERT 15 mg + SIT N = 244
Male, n (%)	224 (51)	227 (51)	191 (43)	127 (51)	134 (54)	154 (62)	123 (51)	126 (52)
Age, mean years (SD)	57.8 (9.2)	58.8 (9.7)	58.0 (9.9)	55.1 (10.1)	55.3 (9.5)	54.8 (10.7)	55.2 (10.4)	55.1 (9.8)
Race, n (%)								
White	318 (73)	332 (74)	316 (72)	206 (82)	205 (83)	193 (78)	197 (81)	188 (77)
Black	25 (6)	17 (4)	19 (4)	7 (3)	6 (2)	11 (5)	12 (5)	10 (4)
Asian	73 (17)	81 (18)	85 (19)	22 (9)	22 (9)	29 (12)	22 (9)	36 (15)
Other	21 (5)	18 (4)	20 (5)	15 (6)	15 (6)	14 (6)	12 (5)	10 (4)
Mean duration of diabetes, years (SD)	7.5 (5.6)	7.4 (5.7)	7.5 (5.7)	7.1 (5.4)	7.3 (5.4)	6.2 (5.2)	7.0 (5.6)	6.9 (5.2)
Mean body weight, kg (SD)	86.8 (20.7)	87.9 (18.9)	85.6 (19.1)	88.6 (22.2)	88.0 (20.3)	89.8 (23.5)	89.5 (20.8)	87.5 (20.5)
Mean BMI, kg/m^2 (SD)	31.2 (6.4)	31.7 (5.5)	31.3 (6.2)	31.8 (6.2)	31.5 (5.8)	31.7 (6.5)	32.5 (6.7)	31.8 (6.5)
A1C (%)								
Mean (SD)	7.8 (0.6)	7.8 (0.6)	7.8 (0.6)	8.6 (1.1)	8.6 (1.0)	8.5 (1.0)	8.6 (1.0)	8.6 (1.0)
< 8.0, n (%)	285 (65)	279 (62)	283 (64)	68 (27)	77 (31)	80 (32)	68 (28)	70 (29)
≥8.0, n (%)	152 (35)	168 (38)	157 (36)					
8.0 to < 9.0, n (%)				99 (40)	86 (35)	84 (34)	92 (38)	97 (40)
≥ 9.0, n (%)				77 (31)	84 (34)	78 (32)	77 (32)	74 (30)
Mean FPG, mg/dL (SD)	157.9 (33.8)	161.8 (34.2)	163.2 (36.3)	184.1 (52.2)	179.5 (45.7)	177.4 (46.6)	183.8 (44.3)	177.2 (49.4)
Mean FPG, mmol/L (SD)[a]	8.8 (1.9)	9.0 (1.9)	9.1 (2.0)	10.2 (2.9)	10.0 (2.5)	9.9 (2.6)	10.2 (2.5)	9.8 (2.7)
Mean eGFR, mL/min/1.73 m^2 (SD)	86.6 (18.5)	88.3 (18.7)	86.7 (18.3)	91.9 (20.6)	92.8 (21.4)	92.6 (18.2)	91.9 (20.4)	92.6 (19.2)
30 to < 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 to < 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background AHA therapy at screening, n (%)								
None	0	0	0	0	0	0	0	0
Biguanides	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DPP-4 inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sulfonamides	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	SU			FACTORIAL				
	GLIM N = 437	ERT 5 mg N = 448	ERT 15 mg N = 440	ERT 5 mg N = 250	ERT 15 mg N = 248	SIT 100 mg N = 247	ERT 5 mg + SIT N = 243	ERT 15 mg + SIT N = 244
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical History								
Cardiac disorders (SOC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutritional disorders (SOC)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders (SOC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; AHA = antihyperglycemic agent; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; ERT = ertugliflozin; FPG = fasting plasma glucose; GLIM = glimepiride; SD = standard deviation; SIT = sitagliptin; SOC = system organ class.

[a] Converted by CDR.

[b] Metabolic disorders SOC include dyslipidemia, hypercholesterolemia, hyperlipidemia, and obesity, as well as gout, hyperuricemia, etc.

Source: Clinical Study Reports.[8-12]

Table 10: Summary of Baseline Characteristics (continued)

Characteristics	SITA2		
	Placebo N =153	ERT 5 mg N = 156	ERT 15 mg N = 153
Male, n (%)	100 (65)	81 (52)	82 (54)
Age, mean years (SD)	58.3 (9.2)	59.2 (9.3)	59.7 (8.6)
Race, n (%)			
White	108 (71)	114 (73)	115 (75)
Black	3 (2)	2 (1)	4 (3)
Asian	33 (22)	33 (21)	28 (18)
Other	9 (6)	7 (4)	6 (4)
Mean duration of diabetes, years (SD)	9.4 (5.6)	9.9 (6.1)	9.2 (5.3)
Mean body weight, kg (SD)	86.4 (20.8)	87.6 (18.6)	86.6 (19.5)
Mean BMI, kg/m^2 (SD)	30.3 (6.4)	31.2 (5.5)	30.9 (6.1)
A1C (%)			
Mean (SD)	8.0 (0.9)	8.1 (0.9)	8.0 (0.8)
< 8.0, n (%)	83 (54)	82 (53)	84 (55)
8.0 to < 9.0, n (%)	43 (28)	47 (30)	44 (29)
≥ 9.0, n (%)	26 (17)	26 (17)	24 (16)
Mean FPG, mg/dL (SD)	169.6 (37.8)	167.7 (37.7)	171.7 (39.1)
Mean FPG, mmol/L (SD)[a]	9.5 (2.1)	9.3 (2.1)	9.5 (2.2)
Mean eGFR, mL/min/1.73 m^2 (SD)	89.9 (17.5)	87.0 (17.5)	86.9 (15.9)
30 to < 60	[redacted]	[redacted]	[redacted]
60 to < 90	[redacted]	[redacted]	[redacted]
≥ 90	[redacted]	[redacted]	[redacted]
Background AHA therapy at screening, n (%)			

Characteristics	SITA2		
	Placebo N =153	ERT 5 mg N = 156	ERT 15 mg N = 153
None	0	0	0
Biguanides	153 (100)	156 (100)	153 (100)
DPP-4 inhibitor	102 (67)	107 (69)	100 (65)
Sulfonamides	52 (34)	52 (33)	54 (35)
Medical History			
Cardiac disorders (SOC)	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Metabolism and nutritional disorders (SOC)[b]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders (SOC)	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; AHA = antihyperglycemic agent; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; ERT = ertugliflozin; FPG = fasting plasma glucose; SD = standard deviation; SOC = system organ class.

[a] Converted by CDR.

[b] Metabolic disorders SOC include dyslipidemia, hypercholesterolemia, hyperlipidemia, and obesity, as well as gout, hyperuricemia, etc.

Source: Clinical Study Reports.[8-12]

Interventions

All trials used double-dummy design to maintain blinding, with matching placebo for active treatments. In the MONO, MET, and SITA2 studies patients were randomized 1:1:1 to ERT 5 mg daily, ERT 15 mg daily, or placebo. Patients were randomized to five treatment groups in the FACTORIAL study including ERT 5 mg daily, ERT 15 mg daily, sitagliptin 100 mg daily, ERT 5 mg plus sitagliptin 100 mg daily, or ERT 15 mg plus sitagliptin 100 mg daily.

In the SU trial, patients were randomized 1:1:1 to ERT 5 mg, ERT 15 mg, or glimepiride, daily. Glimepiride was initiated at 1 mg per day and titrated up to 6 mg or 8 mg per day depending on the local country label, or the maximum tolerated dose. The criteria for up-titration of glimepiride (or glimepiride placebo) was fasting finger-stick glucose greater than and equal to 6.1 mmol/L at a clinic visit or reported twice in the prior week with no hypoglycemic episodes since last dose change, and if the dose increase would not place the patient at risk of hypoglycemia. Patients who experienced hypoglycemia could have their glimepiride dose down-titrated or interrupted at the investigator's discretion. To maintain blinding for patients in the ERT groups, glimepiride placebo tablets were also titrated based on the same criteria as the glimepiride active-treatment group.

Background medications were continued during the double-blind study treatment in five of the trials including metformin greater than and equal to 1,500 mg per day in the MET, SU, and FACTORIAL studies, and metformin greater than and equal to 1,500 mg per day plus sitagliptin 100 mg per day in the SITA2 study. All patients were counselled on dietary, exercise, and lifestyle guidelines for T2DM according to local treatment standards.

In all studies, patients who met the glycemic rescue criteria (Table 11) were administered open-label rescue therapy of metformin (MONO), glimepiride (MET, FACTORIAL, SITA2), or sitagliptin (SU). In three studies, patients could receive insulin if they continued to meet rescue criteria after maximum glimepiride dose for two weeks (MET) or if glimepiride was not suitable treatment in the investigator's opinion (FACTORIAL, SITA2). Rescue therapy was dosed at the investigator's discretion and according to the local label. Patients initiated

on rescue therapy continued to receive the blinded study drug treatment and any background AHA therapies.

Glycemic measurements were masked at randomization and throughout the studies for the sponsor and investigative sites unless the results met pre-specified criteria (i.e., glycemic rescue criteria, or FPG 3.9 mmol/L). Patients who met glycemic rescue criteria had FPG and A1C unmasked for the rest of the study.

Table 11: Glycemic Rescue Criteria

Glycemic Rescue Criteria[a]	
Day 1 to week 6	FPG > 270 mg/dL (15.0 mmol/L)
Week 6 to 12	FPG > 240 mg/dL (13.3 mmol/L)
Week 12 to 26	FPG > 200 mg/dL (11.1 mmol/L)
After week 26	FPG > 200 mg/dL (11.1 mmol/L) or A1C > 8.0% (64 mmol/mol)

A1C = glycated hemoglobin; FPG = fasting plasma glucose.

[a] Based on repeated, confirmed FPG values from a central laboratory.

Source: Clinical Study Reports.[8-12]

In the trials, patients were permitted to receive blood pressure or lipid lowering drugs, provided that their dosages were stable for at least four weeks before enrolment. Other drugs allowed included hormone or thyroid replacement therapy and birth control pills. In the MET study, patients receiving calcium supplements at enrolment were to continue this at the same dosage. Prohibited medications in all trials included insulin (other than short-term use for acute illnesses), pioglitazone or rosiglitazone, or any other AHA that was not specified on each study protocol's approved list (Table 9) or glycemic rescue therapy. Other prohibited drugs were bromocriptine, colesevelam, corticosteroids (≥ 14 days duration), and initiation of weight loss medications. In the MET study, bisphosphonates or drugs that affect bone turnover were also prohibited.

Patients were discontinued from the studies if they met protocol-specified stopping criteria that included recurrent hyperglycemia despite study drug and rescue AHA therapy, repeated hypoglycemia episodes, abnormal liver function, elevated serum creatinine or reduced eGFR, hypersensitivity reaction, pregnancy, need for a prohibited medication, underwent bariatric surgery, or other condition where continued participation in the trial might place the patient at risk. Patients who stopped study drug treatment, and provided they had not withdrawn consent, completed an early termination visit, and were followed up via telephone to monitor for serious adverse events.

Outcomes

The primary outcome in all trials was the change from baseline in A1C to week 26 (MONO, MET, FACTORIAL, SITA) or week 52 (SU). Other outcomes tested included the change from baseline in FPG, body weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (sitting), and the proportion of patients who met glycemic targets (i.e., A1C < 7% or < 6.5%) or who required rescue glycemic therapy. The MET trial also analyzed the change in bone mineral density (BMD) and the SITA2 study reported data for the EuroQol 5-Dimension 3-level instrument (EQ-5D-3L). In the SU trial, symptomatic hypoglycemia was part of the statistical testing hierarchy and was analyzed as per the efficacy outcomes.

Bone densitometry was measured using standardized dual-energy X-ray absorptiometry procedures and all scans were centrally analyzed. BMD was assessed for the lumbar spine, femoral neck, total hip, and distal forearm at baseline and week 26.

The EQ-5D-3L[44,45] is a generic quality of life instrument that has been applied to a wide range of health conditions and treatments including diabetes. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing “no problems,” “some problems,” and “extreme problems,” respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system.[44,45] Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores of less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states “dead” and “perfect health,” respectively. The minimal clinically important difference (MCID) for the EQ-5D-3L index score ranges from 0.033 to 0.074 for general use.[46] Although validation information of EQ-5D-3L in patients with diabetes has been reported,[47,48] the MCID specifically in patients with diabetes mellitus has not been identified.

Adverse events were analyzed using “excluding rescue” as the primary analysis; except for deaths, SAEs, and adverse events leading to discontinuation of study drug. These outcomes were analyzed including the rescue follow-up period.

An adverse event was defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with the study drug. It can be any unfavourable and unintended sign, symptom, or disease, or any worsening of a pre-existing condition temporally associated with the use of a medicinal product, A serious adverse event was defined as an event that was life threatening, or that resulted in: death, persistent or significant disability, hospitalization or prolongation of hospitalization, a congenital anomaly or birth defect, or other important medical event. Other events considered serious were cancer or overdose.

Patients were provided with glucose meters to self-monitor glucose levels and were to complete a Hypoglycemia Assessment Log for any potential hypoglycemia-related events. Documented hypoglycemia was defined as any episode with a glucose level less than 3.9 mmol/L, with or without symptoms. Symptomatic hypoglycemia included events with clinical symptoms (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), regardless of biochemical documentation. Severe hypoglycemia was defined as any event for which assistance was required.

Urine samples were collected routinely and monitored for blood, nitrites, leukocytes, or protein with microscopic urinalysis or culture and sensitivity done on samples showing positive results on a dipstick test. Any patients with symptoms of a urinary tract infection were investigated and treated at the discretion of the treating physician. Patients were to report any suspected genital mycotic infections.

A blinded, independent clinical adjudication committee evaluated potential CV events and all deaths. The composite of adjudicated major adverse CV events (MACE+) was reported, which included CV death, non-fatal myocardial infarction, non-fatal stroke, and

hospitalization for unstable angina. Also adjudicated were venous thromboembolic events and hospitalization for heart failure. The committee also adjudicated fractures, pancreatitis, renal events, and hepatic events. Key adverse events (genital mycotic infection, UTI, and hypovolemia) were collected using pre-specified sponsor-generated custom Medical Dictionary for Regulatory Activities (MedDRA) queries (CMQ).

Statistical Analysis

The change from baseline in A1C, FPG, body weight, blood pressure, and BMD were analyzed using similar methods across all trials. A constrained longitudinal data analysis model was used that included treatment, time (categorical), treatment by time interaction, baseline eGFR (continuous), and study-specific stratification factors (see Table 12 for details). Sensitivity analyses were conducted to assess the impact of missing data including a tipping point analysis, a jump-to-reference analysis or an analysis of covariance (ANCOVA) with last observation carried forward (LOCF) analysis. The tipping point analysis assessed how large the difference between the non-missing and the missing data would need to be to alter the conclusions of the trial. The jump-to-reference analysis assumes that missing data in the ERT group would follow the same distribution as the control group.

The proportion of patients with A1C < 7% was analyzed using a logistic regression model with treatment and baseline A1C (continuous) as variables (Table 12). Missing data were imputed using multiple imputation methods, or with missing data assuming that the patient did not achieve the glycemic target.

In all trials, the efficacy analyses were conducted in two ways. In the excluding rescue analysis, all data obtained after the initiation of glycemic rescue or bariatric surgery were censored (i.e., treated as missing). This was considered the primary analysis. In the including rescue analysis, all outcome measures were included (i.e., data after the start of rescue therapy were included in the analysis). Of note, patients who discontinued treatment early underwent a final study visit, and then were followed by phone for adverse events.

The MONO, MET, SITA2, and FACTORIAL studies were superiority trials. The primary hypothesis in the SU trial was the noninferiority of ERT 15 mg versus glimepiride in the change from baseline in A1C at week 52. ERT 15 mg was considered noninferior to glimepiride if the upper limit of the two-sided 95% CI for the mean difference in change from baseline in A1C was less than 0.3% (based on a constrained longitudinal data analysis model). Sensitivity analyses were conducted based on an ANCOVA model for the per-protocol population. No justification was provided to support the 0.3% noninferiority margin.

All trials used an ordered testing procedure to control for multiplicity (Table 13). Beginning with the first hypothesis, a test was conducted at a 5% level of significance and if significance was not achieved (i.e., *P* value > 0.05), then no further hypothesis testing was conducted. If significance was achieved, the next hypothesis was then tested at a 5% level of significance with the decision process repeated. Details on the statistical testing procedure and power estimates are listed in Table 13.

The trials conducted subgroup analyses of which the following were of interested to this review: baseline A1C categories, age, BMI, baseline AHA, time since diagnosis of diabetes. A minimum of 20 patients required per subgroup. Subgroup data were analyzed using an ANCOVA model with treatment by subgroup and treatment by subgroup by time as interaction terms.

Table 12: Summary of Statistical Testing Methods

Study	Outcome	Statistical Model	Imputation of Missing Data
MONO	Change from baseline in A1C to week 26 and other continuous outcome measures	Primary: constrained longitudinal data analysis model, excluding data obtained after initiation of glycemic rescue or bariatric surgery, with treatment, time (categorical), treatment by time interaction, AHA status at study entry, and baseline eGFR (continuous) as variables. Secondary: same model but data from after the initiation of glycemic rescue therapy was included.	None. Sensitivity analyses for missing data based on tipping point analysis and a jump-to-reference analysis.
	Proportion of patients with A1C < 7%	Logistic regression model with treatment, baseline A1C (continuous), ADA status at study entry, and baseline eGFR (continuous) as variables.	Multiple imputation based on cLDA prediction modelling, and imputing “not at goal” for missing data.
MET	Change from baseline in A1C to week 26 and other continuous outcome measures	Primary: constrained longitudinal data analysis model, excluding data obtained after initiation of glycemic rescue, with treatment, time (categorical), treatment by time interaction, menopausal status stratum, AHA status at study entry, and baseline eGFR (continuous) as variables. Secondary: same model but data from after the initiation of glycemic rescue therapy were included.	None. Sensitivity analyses for missing data based on tipping point analysis and a jump-to-reference analysis.
	Proportion of patients with A1C < 7% or < 6.5%	Logistic regression model with treatment, baseline A1C (continuous), menopausal status stratum, ADA status at study entry, and baseline eGFR (continuous) as variables.	Multiple imputation based on cLDA prediction modelling, and imputing “not at goal” for missing data.
	Per cent change from baseline in BMD	Constrained longitudinal data analysis model, with treatment, time (categorical), treatment by time interaction, menopausal status stratum, AHA status at study entry, and baseline eGFR (continuous) as variables. Data after the initiation of rescue therapy for bone loss or bariatric surgery were excluded (set to missing). Primary analysis based on raw BMD data with corrected data[a] as secondary.	Sensitivity analyses based on ANCOVA model.
SU	Change from baseline in A1C to week 52 and other continuous outcome measures	Primary: constrained longitudinal data analysis model, excluding data obtained after initiation of glycemic rescue, with treatment, time (categorical), treatment by time interaction, prior AHA (mono or dual therapy), and baseline eGFR (continuous) as variables. ERT 15 mg was noninferior to glimepiride for the change from baseline in A1C at week 52 if the upper bound of the 95% CI of the mean difference between treatments was less than the noninferiority margin of 0.3%.	None. Sensitivity analyses for missing data based on ANCOVA model with tipping point analysis, and ANCOVA with LOCF.
	Sensitivity analysis: PP analysis of change from baseline in A1C	ANCOVA model including treatment, prior AHA medication, baseline eGFR, and baseline value.	None (by definition there were no missing data in PP population).
	Proportion of patients	Logistic regression model with treatment, baseline	Multiple imputations based on

Study	Outcome	Statistical Model	Imputation of Missing Data
	with A1C < 7% or < 6.5%	A1C (continuous) as variables.	cLDA model, and with missing data assumed to be not at goal.
FACTORIAL	Change from baseline in A1C to week 26 and other continuous outcome measures	Primary: constrained longitudinal data analysis model, excluding data obtained after initiation of glycemic rescue, with treatment, time (categorical), treatment by time interaction, and baseline eGFR (continuous) as variables. Secondary: same model but data from after the initiation of glycemic rescue therapy was included.	None. Sensitivity analyses for missing data based on tipping point analysis and a jump-to-reference analysis; ANCOVA with LOCF.
	Proportion of patients with A1C < 7%	Logistic regression model with treatment, baseline A1C (continuous) as variables.	Multiple imputation based on cLDA model, and with missing data assumed to be not at goal.
SITA2	Change from baseline in A1C to week 26 and other continuous outcome measures	Constrained longitudinal data analysis model, excluding data obtained after initiation of glycemic rescue, with treatment, time (categorical), treatment by time interaction, prior AHA (MET+DPP-4 or MET+SU), and baseline eGFR (continuous) as variables.	None. Sensitivity analyses for missing data based on tipping point analysis and a jump-to-reference analysis; ANCOVA with LOCF.
	Proportion of patients with A1C < 7%	Logistic regression model with treatment, baseline A1C (continuous) as variables.	Multiple imputations based on cLDA model, and with missing data assumed to be not at goal.

A1C = glycated hemoglobin; ADA = American Diabetes Association; AHA = antihyperglycemic agent; ANCOVA = analysis of covariance; BMD = bone mineral density; CI = confidence interval; cLDA = constrained longitudinal data analysis; DBP = diastolic blood pressure; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; ERT = ertugliflozin; LOCF = last observation carried forward; MET = metformin; PP = per-protocol.

[a] Correction factors were applied to the measured (raw) BMD data, with the intent to account for drifts or shifts in instrument calibration during the study (Instrument Quality Control [IQC]), as well as to standardize the calibration across the study scanners (Instrument Cross-Calibration [X-cal]).

Source: Clinical Study Reports.[8-12]

Table 13: Statistical Testing Hierarchy and Power Estimates

Study	Statistical Testing Hierarchy	Statistical Power
MONO	Change from baseline to week 26 or proportion or patients with outcome were tested in order as listed below for ERT 15 mg versus placebo first, then ERT 5 mg versus placebo second: 1. A1C (primary) 2. FPG 3. Body weight 4. Proportion of patients with A1C < 7.0% 5. 2-hour PPG 6. SBP (sitting) 7. DBP (sitting)	Planned enrolment of 450 patients with 360 remaining at week 26 (20% dropout) would have 99% power to detect a 0.6% difference the change from baseline in A1C between ERT and placebo, based on a 2-sided test at a 5% level of significance. The estimate assumed an SD of 1% for the change in baseline in A1C after 24 to 26 weeks based on data from dapagliflozin and canagliflozin monotherapy trials.
MET	Change from baseline to week 26 or proportion of patients with outcome were tested in order as listed below for ERT 15 mg versus placebo first, then ERT 5 mg versus placebo second: 1. A1C (primary) 2. FPG 3. Body weight 4. Proportion of patients with A1C < 7.0% 5. SBP (sitting)	With 600 patients enrolled and an estimated 160 per group at week 26, the study would have 99% power to detect a 0.5% difference in A1C between each ERT dose and placebo using a 2-sided test with alpha of 0.05. These estimates assumed a 20% dropout rate and A1C standard deviation of 1%.

Study	Statistical Testing Hierarchy	Statistical Power
	6. DBP (sitting)	
SU	Ordered testing procedure combined with the Hochberg procedure as follows: ERT 15 mg versus glimepiride 1. A1C for noninferiority (primary) 2. Symptomatic hypoglycemia superiority 3. body weight superiority ERT 5 mg versus glimepiride 4. A1C for noninferiority 5. Symptomatic hypoglycemia superiority 6. body weight superiority 7. ERT 15 mg versus glimepiride and ERT 5 mg versus glimepiride (Hochberg adjustment) for SBP superiority 8. A1C superiority (ERT 15 mg versus glimepiride) 9. A1C superiority (ERT 5 mg versus glimepiride)	An estimated 1,230 patients enrolled (337 per group at week 52) will provide 97% power to determine noninferiority in A1C at week 52 based on a 0.3% noninferiority margin assuming the true mean difference in 0% for a given ERT dose versus glimepiride (alpha 0.05, 2-sided).
FACTORIAL	Ordered testing procedure combined with the Hochberg procedure as follows: Change from baseline in A1C 1. ERT 15 mg+SIT vs SIT 2. ERT 15 mg+SIT vs ERT 15 mg 3. ERT 5 mg+SIT vs SIT 4. ERT 5 mg+SIT vs ERT 5 mg Change from baseline in body weight 5. ERT 15 mg+SIT vs SIT 6. ERT 5 mg+SIT vs SIT Change from baseline in FPG 7. ERT 15 mg+SIT vs SIT 8. ERT 15 mg+SIT vs ERT 15 mg 9. ERT 5 mg+SIT vs SIT 10. ERT 5 mg+SIT vs ERT 5 mg Change from baseline in SBP 11. ERT 15 mg+SIT vs SIT 12. ERT 5 mg+SIT vs SIT Proportion of patients with A1C < 7% 13. ERT 15 mg+SIT vs SIT 14. ERT 15 mg+SIT vs ERT 15 mg 15. ERT 5 mg+SIT vs SIT 16. ERT 5 mg+SIT vs ERT 5 mg Change from baseline in beta cell function (Hochberg procedure) 17. ERT 15 mg+SIT vs SIT 18. ERT 15 mg+SIT vs ERT 15 mg 19. ERT 5 mg+SIT vs SIT 20. ERT 5 mg+SIT vs ERT 5 mg	With 1,250 patients enrolled (250 per group), the study would have 94% power to detect a 0.4% difference in A1C between each ERT+SIT dose and SIT monotherapy using a 2-sided test with alpha of 0.05 (based on an assumed SD of 1.2%).
SITA2	Change from baseline to week 26 or proportion with outcome as listed below for ERT 15 mg versus placebo first, then ERT 5 mg versus placebo second: 1. A1C 2. FPG 3. Body weight	405 patients were planned for enrolment (135 per group; 120 per group at week 26) to provide 97% power to detect a 0.5% difference in A1C in the change from baseline to week 26 for ERT versus placebo (2-sided test, alpha 0.05).

Study	Statistical Testing Hierarchy	Statistical Power
	4. Proportion of patients with A1C < 7.0% 5. SBP	

A1C = glycated hemoglobin; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate: ERT = ertugliflozin; FPG = fasting plasma glucose; PPG = postprandial glucose; SD = standard deviation; SIT = sitagliptin; SBP = systolic blood pressure; SD = standard deviation; SIT = sitagliptin.

Source: Clinical Study Reports.[8-12]

Analysis populations

For all trials, the efficacy analyses were conducted based on the full analysis set (FAS) which was defined as all randomized patients who took at least one dose of study drug and had at least one measurement of the outcome (baseline or post-baseline). Safety analyses were based on all randomized patients who took at least one dose of study drug (based on treatment received).

In the SU study noninferiority was also analyzed based on the per-protocol population which included all randomized patients who took at least one dose of study drug and who had an outcome measurement at baseline and the analysis end point, with no major protocol violations (i.e., adherence < 75%; use of prohibited medication or corticosteroids for ≥ 2 weeks, incorrect study medication received, or a change in metformin dosage for ≥ 14 days).

Patient Disposition

Among the patients screened for enrolment, 40% (MET) to 48% (FACTORIAL) completed the washout or dose-stabilization period and had 80% adherence during the placebo run-in period and were randomized to study drug. The randomized sample size per study ranged from 461 to 1,326 patients, with 152 to 250 patients per treatment group in the 26-week trials and 437 to 448 patients per group in the 52-week trial.

The proportion of patients who discontinued study drug was highest in the 52-week SU study (19% to 24% per group) compared with 14% to 22% in the MONO study and 3% to 11% in the MET, FACTORIAL, and SITA2 studies. The withdrawal rate was general similar between groups within studies except for the MONO trial where 14% in the ERT groups stopped treatment compared with 22% in the placebo group. Withdrawal by patient, adverse events, and lost to follow-up were generally the most common reasons for stopping study drug.

Table 14: Patient Disposition

	MONO			MET			SU		
	Placebo	ERT 5 mg	ERT 15 mg	Placebo	ERT 5 mg	ERT 15 mg	ERT 5 mg	ERT 15 mg	GLIM
Screened, N	1,067			1,535			2,985		
Randomized, N (%)	461 (43)[a]			621 (40)[b]			1,326 (44)[c]		
	153	156	152	209	207	205	448	441	437
Not treated	0	0	0	0	0	0	0	1	0
Discontinued study drug, n (%)	34 (22)	22 (14)	21 (14)	19 (9)	6 (3)	15 (7)	108 (24)	83 (19)	89 (20)
Adverse event	5 (3)	4 (3)	3 (2)	5 (2)	2 (1)	3 (2)	15 (3)	22 (5)	13 (3)
Withdrawal by patient	10 (7)	9 (6)	8 (5)	6 (3)	2 (1)	6 (3)	20 (5)	23 (5)	18 (4)
Lost to follow-up	4 (3)	3 (2)	5 (3)	3 (1)	0	3 (2)	16 (4)	8 (2)	14 (3)
Lack of efficacy	6 (4)	3 (2)	0	0	0	0	0	0	3 (1)
Excluded medication	1 (1)	1 (1)	1 (1)	2 (1)	0	1 (< 1)	2 (< 1)	1 (< 1)	4 (1)
Non-compliance	1 (1)	0	1 (1)	1 (< 1)	1 (< 1)	0	10 (2)	2 (< 1)	3 (1)
Physician decision	0	1 (1)	1 (1)	1 (< 1)	0	0	3 (1)	2 (< 1)	3 (1)
Protocol violation	0	0	1 (1)	0	1 (< 1)	0	2 (< 1)	4 (1)	3 (1)
Study terminated by sponsor	1 (1)	1 (1)	0	0	0	0	6 (1)	4 (1)	10 (2)
Hyperglycemia	4 (3)	0	0	0	0	0	24 (5)	13 (3)	10 (2)
Hypoglycemia	0	0	0	0	0	1 (< 1)	0	0	1 (< 1)
Pregnancy	1 (1)	0	0	0	0	0	1 (< 1)	0	0
Patient moved	1 (1)	0	1 (1)	1 (< 1)	0	1 (< 1)	5 (1)	4 (1)	6 (1)
Death	0	0	0	0	0	0	4 (1)	0	1 (< 1)
FAS, N	153	156	151	209	207	205	448	440	437
PP, N	NA	NA	NA	NA	NA	NA	331	345	342
Safety, N	153	156	152	209	207	205	448	440	437

Table 14: Patient Disposition (continued)

	FACTORIAL					SITA2		
	ERT 5 mg	ERT 15 mg	SIT 100 mg	ERT 5 mg + SIT	ERT 15 mg + SIT	Placebo	ERT 5 mg	ERT 15 mg
Screened, N	2,582					987		
Randomized, N (%)	1,233 (48)[d]					463 (47)[e]		
	250	248	247	243	245	153	156	154
Not treated	0	0	0	0	1	0	0	1
Discontinued study drug, n (%)	17 (7)	22 (9)	26 (11)	17 (7)	23 (9)	12 (8)	13 (8)	13 (8)
Adverse event	3 (1)	3 (1)	1 (< 1)	3 (1)	6 (2)	1 (1)	5 (3)	1 (< 1)
Withdrawal by patient	4 (2)	10 (4)	14 (6)	6 (3)	11(5)	8 (5)	5 (3)	6 (4)
Lost to follow-up	3 (1)	6 (2)	4 (2)	2 (1)	1 (< 1)	0	0	1 (< 1)
Excluded medication	0	0	2 (1)	0	0	0	0	0
Non-compliance	1 (< 1)	1 (< 1)	0	1 (< 1)	0	2 (1)	1 (< 1)	0
Physician decision	1 (< 1)	1 (< 1)	1 (< 1)	2 (1)	2 (1)	0	1 (< 1)	1 (< 1)

	FACTORIAL					SITA2		
Protocol violation	1 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)	1 (< 1)	0	1 (< 1)
Hyperglycemia	0	0	2 (1)	0	0	0	0	0
Creatinine/eGFR	3 (1)	0	1 (< 1)	1 (< 1)	1 (< 1)	0	0	3 (2)
Patient moved	1 (< 1)	0	1 (< 1)	1 (< 1)	1 (< 1)	0	1 (< 1)	0
Death	0	0	0	0	0	0	0	0
FAS, N	250	248	247	243	244	153	156	153
Safety, N	250	248	247	243	244	153	156	153

eGFR = estimated glomerular filtration rate; ERT = ertugliflozin; FAS = full analysis set; GLIM = glimepiride; NA = not applicable; PP = per-protocol; SIT = sitagliptin.

[a] MONO Study: Reasons for exclusion: screen failure (96%); withdrawal by patient (2%); lost to follow-up (1%); other (1%).

[b] MET Study: the most common reason for screen failure was did not meet A1C inclusion criteria (32%), unstable thyroid condition (13%), BMD score <–2.5 (10%), creatinine or eGFR (9%).

[c] SU Study: The most common reason for screen failure were: did not meet prior therapy or A1C inclusion criteria (68%); exclusionary lab value (26%), and unwilling to comply with study procedures (7%).

[d] The most common reason for screening failure were not meeting background therapy or A1C criteria (60%), or exclusionary lab values (33%).

[e] SITA2 Study: The most common reason for patients not being randomized was screening failure (98%), including not meeting A1C criteria (55%) or exclusionary lab values (34%).

Source: Clinical Study Reports.[8-12]

Exposure to Study Treatments

In the 26-week trials, the mean treatment duration ranged from 137.9 to 163.2 days among patients who received placebo, and 163.9 to 175.7 days among those who receive ERT (Table 15). In the SU study, the mean treatment duration was 317.6 days for glimepiride and 323.6 days for ERT groups. The mean duration of treatment was shorter for placebo than ERT groups in the MONO. MET, and SITA2 trials.

The median dosage of metformin background therapy was 2,000 mg per day in the MET, SU, FACTORIAL, and SITA2 trials (Table 15). In the SU study the mean dose of glimepiride was 3 mg (SD 1.5; median 3.0; range 0.0 to 6.8).

Table 15: Extent of Exposure and Background Therapy Dose

Study / Study Duration	Treatment	Treatment Duration	Background Metformin Dose[c]
		Mean, Days (SD)[a,b]	Median (Range)
MONO	Placebo	[redacted]	[redacted]
26 weeks	ERT 5 mg	[redacted]	[redacted]
	ERT 15 mg	[redacted]	[redacted]
MET	Placebo	[redacted]	[redacted]
26 weeks	ERT 5 mg	[redacted]	[redacted]
	ERT 15 mg	[redacted]	[redacted]
SU	Glimepiride	[redacted]	[redacted]
52 weeks	ERT 5 mg	[redacted]	[redacted]
	ERT 15 mg	[redacted]	[redacted]
FACTORIAL	ERT 5 mg	[redacted]	[redacted]
26 weeks	ERT 15 mg	[redacted]	[redacted]
	SIT	[redacted]	[redacted]
	ERT 5 mg + SIT	[redacted]	[redacted]

Study / Study Duration	Treatment	Treatment Duration	Background Metformin Dose[c]
		Mean, Days (SD)[a,b]	Median (Range)
	ERT 15 mg + SIT	[redacted]	[redacted]
SITA2	Placebo	[redacted]	[redacted]
26 weeks	ERT 5 mg	[redacted]	[redacted]
	ERT 15 mg	[redacted]	[redacted]

ERT = ertugliflozin; NA = not applicable; SD = standard deviation; SIT = sitagliptin.

[a] Excluding rescue.

[b] Standard deviation not reported in all trials.

[c] At randomization.

[redacted]

Source: Clinical Study Reports.[8-12]

Critical Appraisal

Internal Validity

All trials were randomized double-blind studies that appear to have used acceptable methods to randomize patients to groups and to conceal allocation. These methods included computer-generated randomization via an interactive voice or Web response. The treatment groups appeared to be balanced with respect to baseline characteristics within studies although some differences in the proportion of males were noted in the FACTORIAL and SITA2 studies, as well as differences in the duration of diabetes in the MONO and FACTORIAL studies. The trials used an enrichment design, where only those patients who were greater than 80% adherent to placebo during a 2-week run-in period were enrolled. While placebo run-in may be commonly used in diabetes trials, this process may select patients who are more likely to respond to treatment. All trials used a double-dummy design with identical placebo tablets in order to maintain blinding. Although the overall frequency of adverse events was similar between ERT and control groups, it is possible that some unblinding may have occurred due to the increased frequency of specific adverse events that are known to be associated with certain drugs. This may include hypoglycemia, which was reported more frequently among those who received glimepiride, and genital mycotic infections among those who received ERT.

Four of the trials were 26 weeks in duration and one was 52 weeks, which met the minimum guidelines for diabetes trials that were set by the European Medicines Agency.[40] All trials evaluated the change from baseline in A1C as the primary outcome and were not designed to test for longer-term diabetes-related morbidity or mortality. There is, however, a CV safety trial underway for ERT (VERTIS CV), and although all the included studies used an independent adjudication committee to evaluate deaths and CV events, no data on these outcomes were available at the time this report was written. Health-related quality of life was reported in only one trial, and as an exploratory outcome. The MET trial reported data on BMD, as fractures have been identified as a possible adverse effect of SGLT2 inhibitors; however the trial was of insufficient duration to show differences between treatments. Furthermore, the reporting of BMD as raw scores, rather than T-scores, makes interpretation difficult. Although multiple outcomes were tested in each trial, all trials used an ordered statistical testing procedure to control for family-wise type I error for the key outcomes (A1C, FPG, weight, and blood pressure). Health-related quality of life, the proportion of patients requiring rescue therapy and change in BMD outcomes, however, were outside the statistical testing procedure.

The primary outcome of the SU trial was noninferiority of ERT versus glimepiride, based on a 0.3% noninferiority margin for the change from baseline in A1C. No justification was provided to support the 0.3% noninferiority margin; however the FDA states this may be an acceptable margin and it has been used in other diabetes trials.[39,49] The primary analysis was based on the FAS population, but the per-protocol population was also tested and showed similar results.

In the SU trial, the mean dosage of glimepiride was 3 mg per day, which may be considered low, given that the maximum daily dosage is 6 mg to 8 mg per day. However, the reduction in A1C was numerically higher in the glimepiride group than in the ERT groups, thus the dose appears to be sufficient, and increased doses may have led to a higher incidence of hypoglycemia (reported frequency of documented hypoglycemia was 27%). In the trials where ERT was used as add-on therapy to metformin, the dose of metformin was titrated to at least 1,500 mg per day and the median dosage was 2,000 mg per day. The sitagliptin dosage of 100 mg per day is consistent with the approved dosage in Canada.

In all trials, the change from baseline in A1C, weight, and blood pressure were analyzed using a constrained longitudinal data analysis model with no imputation for missing data. Efficacy analyses were based on a modified intention-to-treat (ITT) population, rather than a full ITT, and included all patients who received at least one dose of study drug and had one or more baseline or post-baseline outcome measures. However, the modified intention-to-treat and ITT populations were the same or similar in the trials and any differences were unlikely to have affected the results as the vast majority of patients were included. For patients who stopped study drug treatment early there was no efficacy outcome data collected after treatment was discontinued. These patients were followed by telephone for adverse events. In addition, outcome data from any patients who met the glycemic rescue therapy criteria were excluded from the primary analysis after they started on rescue AHA treatments. While this analysis method avoids potential confounding effects of rescue therapy, the FDA expressed concerns with this method.[39,40] There were more patients in the placebo group with missing or excluded A1C data at week 26 in the MONO (42%), MET (27%), and SITA2 (22%) trials compared with ERT groups (MONO: 15% and 18%; MET 8% and 9%; SITA2: 12% and 10%). Given that the missing data were associated with treatment discontinuation and poor glycemic control, it would not be considered missing at random, and may potentially impact the results of the studies in favour of ERT. The FDA Statistical Review stated that the preferred analysis would follow an ITT approach and include outcome data collected regardless of treatment adherence or need for rescue therapy.[40] The manufacturer had conducted sensitivity analyses (i.e., tipping point and jump-to-reference) to examine the impact of missing data as well as analyses that included data collected after the start of rescue therapy. The FDA statistical reviewer also conducted analyses that included all available outcome data and used a return to baseline approach for patients with missing data. Although these analyses showed similar results as the primary data analysis, these analyses cannot fully account for the impact of missing data. Despite concerns regarding the missing data, dropouts, and rescue rates, the FDA concluded that the available evidence supported the new drug application.[40]

All trials conducted pre-planned subgroup analyses for the primary outcome. Although *P* values for interactions for subgroups were not presented to allow full evaluation of differences in subgroups, the overall results seemed consistent across subgroups.

External Validity

The population enrolled in the studies was middle-aged and predominantly white, with diabetes on average for 4.6 to 9.9 years, and a low rate of cardiac disorders (≤ 25%). All trials were multinational and, except for the MONO trial in which 30% of patients enrolled were from Canada, few Canadians were enrolled (0% to 8%). A substantial proportion of patients screened were excluded from the trials (52% to 60%), which may affect the generalizability of the studies. As all trials included a placebo run-in period, the patients selected were highly adherent to medications, which may not be the case in the general diabetes population. The clinical expert consulted for this review stated that the race of the patients enrolled was more homogeneous than the Canadian diabetes population, but otherwise the patient characteristics were similar to those seen in clinical practice.

The trials did not address the approved indication of ERT for monotherapy, which is in patients who are intolerant of, or have contraindications to, metformin. Although the results of the MONO trial may be extrapolated to the Health Canada–approved population, the trial did not explicitly enroll patients who were unable to take metformin. Approximately half the patients in the MONO study were on metformin at screening. The SU study was the only head-to-head trial.

Limited data were available for subgroups of interest in this review, specifically older adults who may have a higher risk of adverse events. Except for the SU study, which was 52 weeks in duration, the trials were limited to 26 weeks, and were not designed to assess longer-term outcomes or harms that are important to patients. A CV safety study is under way and is expected to be completed in 2019.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See Appendix 4 for additional efficacy data. Limited data were available on diabetes-related morbidity and health-related quality of life. None of the trials evaluated health care resource utilization or hospitalizations.

Diabetes-Related Morbidity or Mortality

All deaths and CV events were adjudicated by an independent blinded committee and will be included in the meta-analysis of phase II and III clinical trials. These data were requested from the manufacturer but were not available at the time of this review as the meta-analysis also includes events from the ongoing CV safety study (VERTIS CV, P004/1021). The FDA, however, had access to interim meta-analysis data and stated that the upper bound of the adjusted 95% CI for the hazard ratio for the composite major adverse CV event plus (MACE+) end point (CV death, non-fatal myocardial infarction, non-fatal stroke, or unstable angina requiring hospitalization) was less than 1.8.[40] Data from the VERTIS CV trial are expected in 2019.

Deaths and renal-related events that occurred during the trials are described in the Harms section of this report. There was no assessment of retinopathy or peripheral neuropathy in the trials.

Glycemic Control

Data for the change from baseline in A1C, the proportion of patients with A1C < 7%, and the proportion who received rescue AHA therapy, are presented in Table 16, Table 17, and Table 18. The change from baseline in FPG is listed in Appendix 4, Table 27.

Subgroup data for the change from baseline in A1C are presented in Appendix 4 (Figure 7 to Figure 12).

No background AHA therapy

In the MONO trial, the mean A1C at baseline ranged from 8.1% to 8.4%. The placebo group showed a least squares (LS) mean increase in A1C of 0.2% at week 26 compared with a 0.8% and 1.0% decrease in the ERT 5 mg and 15 mg groups respectively. The mean differences were statistically significant for both ERT groups versus placebo (ERT 5 mg: –1.0%; 95% CI, –1.2% to –0.8%; ERT 15 mg: –1.2%; 95% CI, –1.4% to –0.9%) (Table 16). At 26 weeks, 28% and 36% of patients who received ERT 5 mg and 15 mg, respectively, achieved an A1C < 7%, compared with 13% of those in the placebo group (Table 17) and these differences were statistically significant. Similarly, statistically significant differences were detected between ERT and placebo for the change from baseline in FPG with mean differences of –1.9 mmol/L for ERT 5 mg, and –2.4 mmol/L for ERT 15 mg versus placebo (Appendix 4, Table 27).

In the MONO study, 4%, 12%, and 13% of patients in the placebo, ERT 5 mg, and ERT 15 mg groups, respectively, achieved an A1C < 6.5% at week 26.

Over 26 weeks, 2% and 3% of patients in the ERT groups received rescue glycemic therapy, whereas 26% of patients in the placebo group required rescue. As per the protocol, any outcome measures after the start of rescue therapy were set to missing, thus the proportion of placebo patients with A1C data reported at 26 weeks were lower than the ERT groups. Overall, 15% to 18% of patients in the ERT groups had missing or excluded data at week 26, compared with 42% of patients in the placebo group (Appendix 4 Table 26).

Add-on therapy to metformin

ERT, as add-on therapy to metformin, showed statistically significant differences versus placebo in the change from baseline in A1C in the MET study. At baseline, the mean A1C was 8.1% to 8.2% per group, and at 26 weeks, the LS mean change from baseline was 0%, –0.7%, and –0.9% in the placebo, ERT 5 mg, and ERT 15 mg groups, respectively. The mean differences observed were –0.7% (95% CI, –0.9% to –0.5%) for ERT 5 mg; and –0.9% (95% CI, –1.1% to –0.7%) for ERT 15 mg versus placebo (Table 16).

Statistically significantly more patients in the ERT groups achieved an A1C < 7% at 26 weeks (ERT 5 mg: 35%; ERT 15 mg: 40%; placebo: 16%) (Table 17). The MET study also reported the proportion of patients with A1C < 6.5% at week 26. In the placebo, ERT 5 mg, and ERT 15 mg groups, [redacted] of patients met this glycemic target. The adjusted OR was [redacted] for ERT 5 mg versus placebo [redacted] for ERT 15 mg versus placebo; however this outcome was [redacted]. Mean differences of –1.5 mmol/L and –2.1 mmol/L were reported for the change from baseline in FPG for the ERT 5 mg and 15 mg groups versus placebo. These differences were statistically significant (Appendix 4, Table 27). Of note, there were more

patients in the placebo group who had missing A1C data at week 26 in the MET study (28%) compared with the ERT groups (8% and 9%).

In the SU trial, ERT as add-on therapy to metformin was compared with glimepiride (median dosage 3 mg per day). In all groups the A1C was 7.8% at baseline and showed a decrease after 52 weeks (LS mean –0.6% to –0.7%; FAS population). The mean difference for ERT 15 mg versus glimepiride was 0.10% (95% CI, –0.02 to 0.22%) and noninferiority was met, as the upper bound of the 95% CI was less than the 0.3% noninferiority margin (Table 16). Similar results were reported for the per-protocol population (LS mean difference 0.12%; 95% CI, –0.01 to 0.24). Noninferiority was not met for ERT 5 mg versus glimepiride (LS mean difference 0.18; 95% CI, 0.06 to 0.30) based on the FAS (designated as the primary analysis) but was met based on the sensitivity analysis for the per-protocol population (0.17%; 95% CI, 0.04% to 0.29%). The proportion of patients with A1C < 7% was 44% for glimepiride, 38% for ERT 15 mg, and 34% for ERT 5 mg, and the LS mean difference in the change from baseline in FPG was –0.4 mmol/L for ERT 15 mg and –0.1 mmol/L for the ERT 5 mg group versus glimepiride (Table 17, Appendix 4 Table 27). Three per cent, 4%, and 6% of patients required glycemic rescue therapy in the glimepiride, ERT 15 mg, and ERT 5 mg groups, respectively (Table 18). At week 52 in the SU trial, A1C data were missing for [redacted] of patients in the ERT 5 mg, ERT 15 mg, and glimepiride groups respectively.

ERT alone or in combination with sitagliptin was evaluated as add-on therapy to metformin in the FACTORIAL study. In all groups at baseline the mean A1C was 8.5% to 8.6%. After 26 weeks, the LS mean A1C had decreased 1% to 1.5% (Table 16). The mean difference in the change from baseline in A1C was statistically significant for the ERT plus sitagliptin combination groups versus sitagliptin alone or versus ERT alone. ERT 15 mg plus sitagliptin showed a mean difference in A1C of –0.47% (95% CI, –0.63 to –0.30), and ERT 5 mg plus sitagliptin showed a mean difference of –0.43 (95% CI, –0.60 to –0.27) compared with sitagliptin alone. Statistically significantly more patients achieved A1C < 7% while on ERT plus sitagliptin (52% and 49%) compared with ERT alone (26% and 32%), or sitagliptin alone (33%) (Table 17). In addition, statistically significant differences were noted between ERT plus sitagliptin versus sitagliptin alone in the change from baseline in FPG ([redacted]) and versus ERT alone [redacted]) (Appendix 4 Table 27). In the ERT plus sitagliptin groups, 0% to 3% of patients required glycemic rescue therapy compared with [redacted] in the sitagliptin group and [redacted] and [redacted] in the ERT groups (Table 18). A1C data were missing at week 26 for [redacted] of patients who received ERT monotherapy, [redacted] who received sitagliptin, and [redacted] of patients who received ERT plus sitagliptin in the FACTORIAL study. No comparisons were made between the ERT and sitagliptin monotherapy treatment groups.

Add-on therapy to metformin plus sitagliptin

The SITA2 trial evaluated the use of ERT versus placebo as add-on therapy to metformin plus sitagliptin. In the placebo group, the LS mean change from baseline observed was 0.1% compared with –0.8% and –0.9% for the ERT groups (baseline A1C: 8.0% to 8.1%). The difference between groups was statistically significant for ERT 5 mg (mean difference –0.7%; 95% CI, –0.9% to –0.5%) and ERT15 mg groups versus placebo (mean difference –0.8%; 95% CI, –1.0% to –0.6%) (Table 16). Statistically significantly more patients achieved an A1C of < 7% at 26 weeks in the ERT 15 mg (40%) and ERT 5 mg (32%) groups than in the placebo group (17%) (Table 17). The change from baseline in FPG was also statistically significantly lower in the ERT groups than placebo (mean difference 1.4 mmol/L to 1.7 mmol/L) (Appendix 4, Table 27). Rescue glycemic therapy was required in 1% and 2% of

patients in the ERT groups, compared with 16% in the placebo group (Table 18). At week 26; 22%, 12%, and 10% of patients were missing A1C data in the placebo, ERT 5 mg, and ERT 15 mg groups, respectively.

Table 16: Change From Baseline in A1C (%)

Population/ Study	Treatment	N	Baseline Mean (SD)	Change From Baseline LS Mean (95% CI)[a]	Difference in LS Mean (95% CI)[a]	*P* Value
No background AHA				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**
MONO	Placebo	153	8.1 (0.92)	0.20 (0.02 to 0.37)		
	ERT 5 mg	156	8.2 (0.88)	–0.79 (–0.95 to –0.63)	–0.99 (–1.22 to –0.76)	< 0.001
	ERT 15 mg	151	8.4 (1.1)	–0.96 (–1.12 to –0.80)	–1.16 (–1.39 to –0.93)	< 0.001
Add-on to metformin				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	**P value**
MET	Placebo	209	8.2 (0.90)	–0.03 (–0.15 to 0.10)		
	ERT 5 mg	207	8.1 (0.89)	–0.73 (–0.85 to –0.61)	–0.70 (–0.87 to –0.53)	< 0.001
	ERT 15 mg	205	8.1 (0.93)	–0.91 (–1.03 to –0.78)	–0.88 (–1.05 to –0.71)	< 0.001
Add-on to metformin				**Change from baseline to week 52**	**ERT vs. glimepiride at 52 weeks**	***P* value**
SU (FAS)	Glimepiride	437	7.8 (0.60)	–0.74 (–0.83 to –0.65)		
	ERT 5 mg	448	7.8 (0.60)	–0.56 (–0.65 to –0.47)	0.18 (0.06 to 0.30)	NI not met
	ERT 15 mg	440	7.8 (0.60)	–0.64 (–0.73 to –0.55)	0.10 (–0.02 to 0.22)	NI met
SU (PP)	Glimepiride	342	7.8 (0.60)	–0.76 (–0.86 to –0.66)		
	ERT 5 mg	331	7.8 (0.59)	–0.59 (–0.69 to –0.49)	0.17 (0.04 to 0.29)	NI met
	ERT 15 mg	345	7.8 (0.59)	–0.64 (–0.74 to –0.55)	0.12 (–0.01 to 0.24)	NI met
Add-on to metformin				**Change from baseline to week 26**	**ERT+SIT vs. SIT at 26 weeks, *P* value**	**ERT+SIT vs. ERT at 26 weeks, *P* value**
FACTORIAL	ERT 5 mg	250	8.6 (1.0)	–1.02 (–1.14 to –0.90)		
	ERT 15 mg	248	8.6 (1.0)	–1.08 (–1.20 to –0.96)		
	SIT	247	8.5 (1.0)	–1.05 (–1.17 to –0.93)		
	ERT 5 mg + SIT	243	8.6 (1.0)	–1.49 (–1.61 to –1.36)	–0.43 (–0.60 to –0.27) *P* < 0.001	–0.46 (–0.63 to –0.30), *P* < 0.001
	ERT 15 mg + SIT	244	8.6 (1.0)	–1.52 (–1.64 to –1.40)	–0.47 (–0.63 to –0.30) to *P* < 0.001	–0.44 (–0.61 to –0.27), *P* < 0.001
Add-on to metformin + SIT				**Change from baseline to week 26**	**ERT vs. placebo at 26 weeks**	***P* value**
SITA2	Placebo	153	8.0 (0.9)	–0.09 (–0.23 to 0.04)		
	ERT 5 mg	156	8.1 (0.9)	–0.78 (–0.91 to –0.65)	–0.69 (–0.87 to –0.50)	< 0.001
	ERT 15 mg	153	8.0 (0.8)	–0.86 (–0.99 to –0.72)	–0.76 (–0.95 to –0.58)	< 0.001

A1C = glycated hemoglobin; AHA = antihyperglycemic agent; CI = confidence interval; ERT = ertugliflozin; FAS = full analysis set; LS = least squares; MET = metformin; NI = noninferiority; PP = per-protocol; SD = standard deviation; SIT = sitagliptin.

[a] Excludes any data after the initiation of rescue glycemic therapy. Based on constrained longitudinal data analysis model with treatment, time (categorical), treatment by time interaction, baseline eGFR (continuous), and study-specific stratification factors as variables (Table 12).

Source: Clinical Study Reports.[8-12]

Table 17: Proportion of Patients With A1C < 7.0%

Study	Treatment	N	Number (%) with A1C < 7.0%[a]	Adjusted OR (95% CI)[a]	*P value*
No background AHA			**Week 26**	**ERT vs. placebo**	***P* value**
MONO	Placebo	153	[redacted] (13)		
	ERT 5 mg	156	[redacted] (28)	3.59 (1.85 to 6.95)	< 0.001
	ERT 15 mg	151	[redacted] (36)	6.77 (3.46 to 13.24)	< 0.001
Add-on to metformin			**Week 26**	**ERT vs. placebo**	***P* value**
MET	Placebo	209	[redacted] (16)		
	ERT 5 mg	207	[redacted] (35)	3.03 (1.81 to 5.06)	< 0.001
	ERT 15 mg	205	[redacted] (40)	4.48 (2.64 to 7.62)	< 0.001
Add-on to metformin			**Week 52**	**ERT vs. glimepiride**	***P* value**
SU	Glimepiride	437	190 (44)		
	ERT 5 mg	448	154 (34)	0.68 (0.50 to 0.91)	0.01[b]
	ERT 15 mg	440	167 (38)	0.79 (0.59 to 1.05)	[redacted][b]
Add-on to metformin			**Week 26**	**ERT+SIT vs. SIT, *P* value**	**ERT+SIT vs. ERT, *P* value**
FACTORIAL	ERT 5 mg	250	[redacted] (26)		
	ERT 15 mg	248	[redacted] (32)		
	SIT	247	[redacted] (33)		
	ERT 5 mg + SIT	243	[redacted] (52)	2.95 (1.92 to 4.54), *P* < 0.001	4.14 (2.68 to 6.40), *P* < 0.001
	ERT 15 mg + SIT	244	[redacted] (49)	2.56 (1.69 to 3.89), *P* < 0.001	2.53 (1.68 to 3.83), *P* < 0.001
Add-on to metformin+SIT			**Week 26**	**ERT vs. placebo**	***P* value**
SITA2	Placebo	153	[redacted] (17)		
	ERT 5 mg	156	[redacted] (32)	3.16 (1.74 to 5.72)	< 0.001
	ERT 15 mg	153	[redacted] (40)	4.43 (2.44 to 8.02)	< 0.001

A1C = glycated hemoglobin; AHA = antihyperglycemic agent; CI = confidence interval; ERT = ertugliflozin; OR = odds ratio; SIT= sitagliptin.

[a] Excludes any data after the initiation of rescue glycemic therapy. Based on logistic regression model with treatment, baseline A1C (continuous) as variables (SU, FACTORIAL, and SITA2). MONO study also included AHA status at baseline as a variable and baseline eGFR (continuous) as variables. The MET study also included AHA status, baseline eGFR (continuous), and menopausal stratification groups as variables.

[b] Outside the statistical testing procedure thus should be interpreted as inconclusive.

Source: Clinical Study Reports.[8-12]

Table 18: Proportion of Patients Requiring Glycemic Rescue Therapy

Study	Treatment	N	Number (%) Requiring Rescue Therapy	Difference in % (95% CI)	*P* value
No background AHA			**Week 26**	**ERT vs. placebo**	***P* value**
MONO	Placebo	153	39 (26)		
	ERT 5 mg	156	3 (2)	–24% (–31 to –17)	< 0.001[ab]
	ERT 15 mg	152	4 (3)	–23% (–31 to –16)	< 0.001[ab]
Add-on to metformin			**Week 26**	**ERT vs. placebo**	***P* value**
MET	Placebo	209	37 (18)		
	ERT 5 mg	207	6 (3)	–15% (–21 to –9)	< 0.001[ab]
	ERT 15 mg	205	3 (2)	–16% (–22 to –11)	< 0.001[ab]
Add-on to metformin			**Week 52**	**ERT vs. glimepiride**	***P* value**
SU	Glimepiride	437	14 (3)	NR	
	ERT 5 mg	448	25 (6)	NR	NR
	ERT 15 mg	440	16 (4)	NR	NR
Add-on to metformin			**Week 26**	**ERT+SIT vs. SIT, P value**	**ERT+SIT vs. ERT, *P* value**
FACTORIAL	ERT 5 mg	250	16 (6)		
	ERT 15 mg	248	7 (3)		
	SIT	247	16 (7)		
	ERT 5 mg + SIT	243	6 (3)	–4% (–8 to –0.4), *P* = 0.032[ab]	4% (–8 to –0.3), *P* = 0.035[ab]
	ERT 15 mg + SIT	244	0	–7% (–10 to –4), *P* < 0.001[ab]	–3% (–6 to –1), *P* = 0.008[ab]
Add-on to metformin+SIT			**Week 26**	**ERT vs. placebo**	***P* value**
SITA2	Placebo	153	25 (16)		
	ERT 5 mg	156	2 (1)	–15% (–22 to –9)	< 0.001[ab]
	ERT 15 mg	153	3 (2)	–14% (–21 to –9)	< 0.001[ab]

A1C = glycated hemoglobin; AHA = antihyperglycemic agent; CI = confidence interval; ERT = ertugliflozin; LS = least squares; NR = not reported; SIT = sitagliptin.

[a] *P* value based on Miettinen & Nurminen method.

[b] Outside the statistical testing hierarchy thus statistically significant results should be interpreted as inconclusive.

Source: Clinical Study Reports.[8-12]

Subgroup and sensitivity analyses

All five trials conducted subgroup analyses for the change from baseline in A1C (Appendix 4, Figure 7 to Figure 12). Although *P* values for the treatment by subgroup interaction terms were not reported, the treatment effects appear to be generally similar across subgroups.

In all trials for the change from baseline in A1C, sensitivity analyses were conducted to explore the impact of missing data (i.e., tipping point and jump-to-reference analyses), as well as analyses that included data after the initiation of rescue therapy. The results of these analyses were similar to the primary analyses.

Body Weight

Across the included studies, the mean baseline weight ranged from 84.5 kg to 94.2 kg (Table 19). The LS mean change from baseline in weight ranged from –1.3 kg to –1.4 kg for placebo, –2.5 kg to –3.7 kg for the ERT groups, –0.7 kg for sitagliptin, and +0.9 kg for the glimepiride groups. Statistically significant differences were detected between ERT and placebo in the MONO, MET, and SITA2 trials with differences between groups ranging from –1.6 kg to –2.2 kg after 26 weeks. Similarly, ERT plus sitagliptin was associated with statistically significant mean differences in weight compared with sitagliptin alone (mean difference –1.9 kg and –2.3 kg). In the SU trial, ERT 15 mg was associated with statistically significant differences in body weight compared with glimepiride (mean difference –4.3 kg; 95% CI, –4.8 to –3.8). Similar treatment effects were noted for ERT 5 mg versus glimepiride (mean difference –3.9 kg), but due to failure in an earlier outcome in the statistical hierarchy, these results should be interpreted as inconclusive.

Table 19: Change From Baseline in Body Weight (kg)

Population/ Study	Treatment	N	Baseline Mean (SD)	Change From Baseline LS Mean (95% CI)[a]	Difference in LS Mean (95% CI)[a]	*P* Value
No background AHA				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**
MONO	Placebo	153	94.2 (25.2)	–1.4 (–2.0 to –0.8)		
	ERT 5 mg	156	94.0 (25.4)	–3.2 (–3.7 to –2.6)	–1.8 (–2.6 to –1.0)	< 0.001
	ERT 15 mg	152	90.6 (18.3)	–3.6 (–4.1 to –3.0)	–2.2 (–3.0 to –1.3)	< 0.001
Add-on to metformin				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**
MET	Placebo	209	84.5 (17.1)	–1.3 (–1.7 to –0.9)		
	ERT 5 mg	207	84.9 (17.2)	–3.0 (–3.4 to –2.6)	–1.7 (–2.2 to –1.1)	< 0.001
	ERT 15 mg	205	85.3 (16.5)	–2.9 (–3.3 to –2.5)	–1.6 (–2.2 to –1.0)	< 0.001
Add-on to metformin				**Change from baseline to week 52**	**ERT vs. glimepiride at 52 weeks**	***P* value**
SU	Glimepiride	437	86.8 (20.7)	0.9 (0.6 to 1.3)		
	ERT 5 mg	448	88.0 (19.0)	–3.0 (–3.3 to –2.6)	–3.9 (–4.4 to –3.4)	< 0.001[b]
	ERT 15 mg	440	85.6 (19.1)	–3.4 (–3.7 to –3.0)	–4.3 (–4.8 to –3.8)	< 0.001
Add-on to metformin				**Change from baseline to week 26**	**ERT+SIT vs. SIT at 26 weeks, *P* value**	**ERT+SIT vs. ERT at 26 weeks, *P* value**
FACTORIAL	ERT 5 mg	250	88.6 (22.2)	–2.7 (–3.0 to –2.3)		
	ERT 15 mg	248	88.0 (20.3)	–3.7 (–1.2 to –3.3)		
	SIT	247	89.8 (23.5)	–0.7 (–1.1 to –0.2)		
	ERT 5 mg + SIT	243	89.5 (20.8)	–2.5 (–3.0 to –2.1)	–1.9 (–2.5 to –1.2), P < 0.001	(not tested according to statistical plan)
	ERT 15 mg + SIT	244	87.5 (20.5)	–2.9 (–3.4 to –2.5)	–2.3 (–2.9 to –1.6), *P* < 0.001	(not tested according to statistical plan)
Add-on to metformin + SIT				**Change from baseline to week 26**	**ERT vs. placebo at 26 weeks**	***P* value**
SITA2	Placebo	153	86.5 (20.8)	–1.3 (–1.8 to –0.9)		
	ERT 5 mg	156	87.6 (18.6)	–3.4 (–3.8 to –2.9)	–2.0 (–2.7 to –1.4)	< 0.001

Population/ Study	Treatment	N	Baseline Mean (SD)	Change From Baseline LS Mean (95% CI)[a]	Difference in LS Mean (95% CI)[a]	*P* Value
	ERT 15 mg	153	86.6 (19.5)	–3.0 (–3.5 to –2.6)	–1.7 (–2.4 to –1.1)	< 0.001

AHA = antihyperglycemic agent; CI = confidence interval; ERT = ertugliflozin; LS = least squares; MET = metformin; SD = standard deviation; SIT = sitagliptin.

[a] Excludes any data after the initiation of rescue glycemic therapy. Based on constrained longitudinal data analysis model with treatment, time (categorical), treatment by time interaction, baseline eGFR (continuous), and study-specific stratification factors as variables (Table 12).

[b] Statistical testing failed at a previous outcome in the ordered statistical testing procedure, thus any statistically significant results should be interpreted as inconclusive.

Source: Clinical Study Reports.[8-12]

Blood Pressure

A summary of the baseline, LS mean change from baseline and mean difference between groups for SBP and DBP are presented in Table 20 and Table 21.

In the MONO study, no statistically significant differences were detected between ERT 15 mg and placebo groups on the change from baseline in SBP or DBP, and any differences observed between ERT 5 mg and placebo should be interpreted as inconclusive due to failure of a previous outcome in the statistical testing procedure.

ERT 15 mg and ERT 5 mg were associated with statistically significant differences in SBP (mean difference –3.7 mm Hg to –4.5 mm Hg) and DBP (mean difference –1.8 mm Hg to –2.4 mm Hg) compared with placebo in the MET study. ERT as add-on therapy to metformin and sitagliptin was associated with statistically significant differences in SBP (mean difference –2.9 mm Hg and –3.9 mm Hg) but not DBP, compared with placebo in the SITA2 study.

Statistically significant differences were also detected between ERT plus sitagliptin versus sitagliptin alone for the change from baseline in SBP with mean differences of –2.8 mm Hg and –3.0 mm Hg. No statistically significant differences were observed for the change from baseline in DBP for the ERT plus sitagliptin groups compared with sitagliptin alone in the FACTORIAL study.

Data from the SU trial comparing ERT versus glimepiride should be interpreted as inconclusive due to failure of a prior outcome and because SBP was outside of the statistical testing hierarchy.

Table 20: Change From Baseline in Systolic Blood Pressure (mm Hg)

Population/ Study	Treatment	N	Baseline Mean (SD)	Change From Baseline LS Mean (95% CI)[a]	Difference in LS Mean (95% CI)[a]	*P* Value
No background AHA				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**
MONO	Placebo	152	129.8 (14.5)	–2.2 (–4.3 to –1.1)		
	ERT 5 mg	156	130.5 (13.5)	–5.5 (–7.3 to –3.8)	–3.3 (–6.0 to –0.7)	0.015[b]
	ERT 15 mg	152	129.7 (14.2)	–3.9 (–5.7 to –2.1)	–1.7 (–4.4 to 1.0)	0.21
Add-on to metformin				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**
MET	Placebo	209	129.3 (15.4)	–0.7 (–2.5 to 1.1)		
	ERT 5 mg	207	130.5 (13.8)	–4.4 (–6.0 to –2.8)	–3.7 (–6.0 to –1.4)	0.002
	ERT 15 mg	204	130.2 (11.9)	–5.2 (–6.9 to –3.5)	–4.5 (–6.8 to –2.2)	< 0.001

Population/ Study	Treatment	N	Baseline Mean (SD)	Change From Baseline LS Mean (95% CI)[a]	Difference in LS Mean (95% CI)[a]	*P* Value
Add-on to metformin				**Change from baseline to week 52**	**ERT vs. glimepiride at 52 weeks**	***P* value**
SU	Glimepiride	437	129.9 (12.0)	1.0 (–0.2 to 2.1)		
	ERT 5 mg	448	130.2 (12.8)	–2.3 (–3.4 to –1.1)	–3.2 (–4.7 to –1.7)	< 0.001[b]
	ERT 15 mg	440	130.8 (12.4)	–3.8 (–4.9 to –2.7)	–4.8 (–6.3 to –3.3)	< 0.001[b]
Add-on to metformin				**Change from baseline to week 26**	**ERT+SIT vs. SIT at 26 weeks, *P* value**	**ERT+SIT vs. ERT at 26 weeks, *P* value**
FACTORIAL	ERT 5 mg	250	129.7 (12.5)	–3.9 (–5.3 to –2.5)		
	ERT 15 mg	248	128.9 (12.5)	–3.7 (–5.1 to –2.3)		
	SIT	247	128.3 (12.2)	–0.7 (–2.1 to 0.8)		
	ERT 5 mg + SIT	243	130.2 (12.6)	–3.4 (–4.8 to –2.0)	–2.8 (–4.7 to –0.8), *P* = 0.005	Not analyzed as per statistical plan
	ERT 15 mg + SIT	244	129.1 (13.3)	–3.7 (–5.1 to –2.3)	–3.0 (–4.9 to –1.1), *P* = 0.002	Not analyzed as per statistical plan
Add-on to metformin + SIT				**Change from baseline to week 26**	**ERT vs. placebo at 26 weeks**	***P* value**
SITA2	Placebo	153	130.2 (13.3)	–0.9 (–2.7 to 0.9)		
	ERT 5 mg	156	132.1 (12.5)	–3.8 (–5.5 to –2.1)	–2.9 (–5.4 to –0.5)	0.019
	ERT 15 mg	153	131.6 (13.2)	–4.8 (–6.6 to –3.1)	–3.9 (–6.4 to –1.5)	0.002

AHA = antihyperglycemic agent; CI = confidence interval; ERT = ertugliflozin; LS = least squares; SBP = systolic blood pressure; SD = standard deviation; SIT = sitagliptin.

[a] Excludes any data after the initiation of rescue glycemic therapy. Based on constrained longitudinal data analysis model with treatment, time (categorical), treatment by time interaction, baseline eGFR (continuous), and study-specific stratification factors as variables (Table 12).

[b] Statistical testing failed at a previous outcome in the ordered statistical testing procedure, thus any statistically significant results should be interpreted as inconclusive.

Source: Clinical Study Reports.[8-12]

Table 21: Change From Baseline in Diastolic Blood Pressure (mm Hg)

Population/ Study	Treatment	N	Baseline Mean (SD)	Change from Baseline LS Mean (95% CI)[a]	Difference in LS Mean (95% CI)[a]	*P* value
No background AHA				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**
MONO	Placebo	152	78.1 (7.5)	–0.7 (–2.1 to 0.6)		
	ERT 5 mg	156	78.5 (8.1)	–2.5 (–3.7 to –1.4)	–1.8 (–3.5 to –0.1)	0.039[b]
	ERT 15 mg	152	78.5 (7.7)	–1.1 (–2.2 to 0.05)	–0.4 (–2.1 to 1.4)	0.67 [b]
Add-on to metformin				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**
MET	Placebo	209	77.5 (7.5)	0.2 (–0.9 to 1.3)		
	ERT 5 mg	207	78.5 (8.3)	–1.6 (–2.6 to –0.6)	–1.8 (–3.2 to –0.4)	0.013
	ERT 15 mg	204	78.1 (7.5)	–2.2 (–3.2 to –1.2)	–2.4 (–3.9 to –1.0)	0.001
Add-on to metformin				**Change from baseline to week 52**	**ERT vs. glimepiride at 52 weeks**	***P* value**
SU	Glimepiride	437	77.8 (7.3)	0.3 (–0.4 to 1.0)		
	ERT 5 mg	448	77.8 (7.6)	–0.9 (–1.6 to –0.2)	–1.2 (–2.2 to –0.2)	0.015[c]
	ERT 15 mg	440	77.7 (7.2)	–1.2 (–1.9 to –0.5)	–1.6 (–2.5 to –0.6)	0.002[c]
Add-on to metformin				**Change from baseline to week 26**	**ERT+SIT vs. SIT at 26 weeks, *P* value**	**ERT+SIT vs. ERT at 26 weeks, *P* value**
FACTORIAL	ERT 5 mg	250	77.9 (7.8)	–1.1 (2.0 to –0.3)		
	ERT 15 mg	248	77.5 (7.3)	–1.0 (–1.8 to –0.1)		
	SIT	247	77.3 (6.7)	–0.3 (–1.2 to 0.5)		
	ERT 5 mg + SIT	243	77.8 (7.7)	–0.7 (–1.5 to 0.2)	–0.3 (–1.5 to 0.9), *P* = 0.59[c]	NR
	ERT 15 mg + SIT	244	77.4 (7.1)	–1.3 (–2.2 to –0.5)	–1.0 (–2.2 to 0.2), *P* = 0.11[c]	NR
Add-on to metformin + SIT				**Change from baseline to week 26**	**ERT vs. placebo at 26 weeks**	***P* value**
SITA2	Placebo	153	78.5 (7.6)	–0.4 (–1.7 to 0.8)		
	ERT 5 mg	156	78.4 (7.3)	–1.7 (–2.9 to –0.5)	–1.2 (–3.0 to 0.5)	0.16[c]
	ERT 15 mg	153	78.8 (7.3)	–1.8 (–3.0 to –0.6)	–1.4 (–3.1 to 0.4)	0.12[c]

AHA = antihyperglycemic agent; CI = confidence interval; ERT = ertugliflozin; LS = least squares; NR = not reported; SD = standard deviation; SIT = sitagliptin.

[a] Excludes any data after the initiation of rescue glycemic therapy. Based on constrained longitudinal data analysis model with treatment, time (categorical), treatment by time interaction, baseline eGFR (continuous), and study-specific stratification factors as variables (Table 12).

[b] Statistical testing failed at a previous outcome in the ordered statistical testing procedure, thus any statistically significant results should be interpreted as inconclusive.

[c] Outside the ordered statistical testing procedure, thus statistically significant findings should be interpreted as inconclusive.

Source: Clinical Study Reports.[8-12]

Bone Mineral Density

The per cent change from baseline to week 26 in BMD (as raw scores) was reported in the MET study; however this outcome was outside the ordered statistical testing procedure. No statistically significant differences in BMD were detected between the ERT and placebo groups for the lumbar spine, femoral neck, total hip, or distal forearm (Appendix 4, Table 28).

Health-Related Quality of Life

One study, SITA2, collected data on health-related quality of life using the EQ-5D instrument. At baseline the EQ-5D index scores ranged from 0.88 to 0.90, and an LS mean change from baseline of 0.0 to 0.02 points was reported across the treatment groups. No statistically significant differences were detected between groups. Of note, 26-week data were missing for 22%, 10%, and 11% of patients in the placebo, ERT 5 mg, and ERT 15 mg groups, respectively.

Table 22: Change From Baseline in EQ-5D-3L Index Scores

Population/Study	Treatment	N	Baseline Mean (SD)	Change From Baseline LS Mean (95% CI)[a]	Difference in LS Mean (95% CI)[a]	*P* value
Add-on to metformin + SIT				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**
SITA2	Placebo	153	[redacted]	0.01 (–0.01 to 0.04)		
	ERT 5 mg	155	[redacted]	0.0 (–0.02 to 0.03)	–0.01 (–0.04 to 0.02)	[redacted]
	ERT 15 mg	151	[redacted]	0.02 (–0.0 to 0.04)	0.01 (–0.02 to 0.04)	[redacted]

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimension, 3-level instrument; ERT = ertugliflozin; LS = least squares; SD = standard deviation; SIT = sitagliptin.

[a] Excludes any data after the initiation of rescue glycemic therapy. Based on constrained longitudinal data analysis model with treatment, time (categorical), treatment by time interaction, prior AHA (metformin+DPP-4 or metformin+SU), and baseline eGFR (continuous) as variables.

[redacted]

Source: Clinical Study Report.[12]

Harms

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

Adverse Events

Adverse events were reported by 42% to 56% of patients in the 26-week trials, and by 59% to 62% of patients in the 52-week study (Table 23). The overall frequency of adverse events was similar between groups within studies. Among patients who received ERT, nasopharyngitis, hypoglycemia, urinary tract infections, and upper respiratory tract infections were the most commonly reported adverse events (< 7%). Hypoglycemia was the most frequently reported adverse event among patients who received glimepiride (22%).

Serious Adverse Events

Serious adverse events were reported by 1% to 4% of patients who receive placebo, 1% to 6% of those who received ERT (alone or with sitagliptin), 3% for glimepiride, and 1% for sitagliptin groups (Table 23) based on the analysis that excluded rescue therapy. The data were similar for analysis that included the entire study period. Most specific events were reported in one patient per group; however two patients in the ERT 5 mg group experienced a serious adverse event of pneumonia and cerebrovascular accident in the SU trial, and two patients suffered myocardial infarction in the ERT 15 mg plus sitagliptin group in the FACTORIAL study.

Withdrawals Due to Adverse Events

The proportion of patients who stopped treatment due to adverse events ranged from 1% to 3% in the placebo, 1% to 5% in the ERT groups, 4% for glimepiride, and 0.4% for sitagliptin groups. Two patients in the ERT 5 mg group stopped treatment due to urinary tract infections in the SU trial. Nausea, decreased glomerular filtration rate (GFR), acute kidney injury, or pollakiuria was reported as the reason for stopping therapy for two or more patients in the ERT 15 mg group of the SU trial. Other adverse events that led to discontinuation of ERT were reported in one patient per group.

Mortality

In the SU study, five patients died in the ERT 5 mg group and one patient died in the ERT 15 mg group. No deaths were reported during the study period among those who received glimepiride, although one patient died of congestive heart failure in the post-treatment period. The cause of death for those in the ERT 5 mg group was as follows: multiple organ failure following auto collision, cerebrovascular accident, depression and suicide, pneumonia, respiratory failure due to chronic obstructive pulmonary disease, sudden cardiac death. The patient in the ERT 15 mg group died due to an acute myocardial infarction.

No deaths were reported in the MONO, MET, FACTORIAL, and SITA2 trials.

Table 23: Summary of Harms

Adverse Events	MONO			MET			SU		
Excluding rescue	**Placebo N = 153**	**ERT 5 mg N = 156**	**ERT 15 mg N = 152**	**Placebo N = 209**	**ERT 5 mg N = 207**	**ERT 15 mg N = 205**	**Glimepiride N = 437**	**ERT 5 mg N = 448**	**ERT 15 mg N = 440**
Patients with ≥ 1 AE, n (%)[a]	80 (52)	82 (53)	85 (56)	94 (45)	88 (43)	103 (50)	269 (62)	263 (59)	262 (60)
Most common AEs[b]									
Nasopharyngitis	3 (2)	6 (4)	4 (3)	5 (2)	4 (2)	4 (2)	27 (6)	23 (5)	15 (3)
Urinary tract infection	12 (8)	7 (5)	5 (3)	2 (1)	5 (2)	5 (2)	24 (6)	23 (5)	20 (5)
Hypoglycemia	2 (1)	2 (1)	5 (5)	6 (3)	8 (4)	10 (5)	96 (22)	17 (4)	25 (6)
Upper respiratory tract infection	7 (5)	6 (4)	6 (4)	12 (6)	5 (2)	12 (6)	15 (3)	20 (5)	11 (3)
Vulvovaginal mycotic infection	1 (1)	7 (5)	6 (4)	0	3 (1)	3 (2)	NR	NR	NR
Constipation	0	10 (6)	1 (1)	NR	NR	NR	7 (2)	10 (2)	7 (2)
Headache	6 (4)	6 (4)	7 (5)	3 (1)	9 (4)	6 (3)	NR	NR	NR
Back pain				3 (1)	3 (1)	10 (5)	13 (3)	11 (3)	10 (2)
Patients with ≥ 1 SAE, n (%)	2 (1)	7 (5)	2 (1)	8 (4)	3 (1)	7 (3)	12 (3)	27 (6)	17 (4)
Stopped treatment due to AEs, n (%)	4 (3)	4 (3)	3 (2)	3 (1)	3 (1)	3 (1)	17 (4)	17 (4)	23 (5)
Number of deaths, n (%)	0	0	0	0	0	0	0	5 (1)	1 (< 1)

Adverse Events	MONO			MET			SU		
Excluding rescue	**Placebo N = 153**	**ERT 5 mg N = 156**	**ERT 15 mg N = 152**	**Placebo N = 209**	**ERT 5 mg N = 207**	**ERT 15 mg N = 205**	**Glimepiride N = 437**	**ERT 5 mg N = 448**	**ERT 15 mg N = 440**
Including Rescue									
Patients with ≥ 1 SAE, n (%)	2 (1)	7 (5)	2 (1)	8 (4)	3 (1)	7 (3)	12 (3)	28 (6)	17 (4)
Stopped treatment due to AEs, n (%)	5 (3)	4 (3)	3 (2)	3 (1)	3 (1)	3 (1)	17 (4)	18 (4)	25 (6)
Number of deaths, n (%)	0	0	0	0	0	0	0	5 (1)	1 (< 1)

AE = adverse event; ERT = ertugliflozin; NR = not reported; SAE = serious adverse event: SIT = sitagliptin.

[a] Excludes events that occurred after the start of rescue therapy.

[b] Frequency ≥ 5% per group in one or more studies.

Source: Clinical Study Reports.[8-12]

Table 23: Summary of Harms (continued)

Adverse Events	FACTORIAL					SITA2		
Excluding rescue	**ERT 5 mg N = 250**	**ERT 15 mg N = 248**	**SIT N = 247**	**ERT 5 mg + SIT N = 243**	**ERT 15 mg + SIT N = 244**	**Placebo N = 153**	**ERT 5 mg N = 156**	**ERT 15 mg N = 153**
Patients with ≥ 1 AEs, n (%)[a]	128 (51)	107 (43)	103 (42)	111 (46)	114 (47)	74 (48)	65 (42)	67 (44)
Most common AEs[b]								
Nasopharyngitis	2 (1)	6 (2)	2 (1)	6 (3)	5 (2)	3 (2)	3 (2)	2 (1)
Urinary tract infection	11 (4)	11 (4)	8 (3)	7 (3)	7 (3)	1 (1)	2 (1)	1 (1)
Hypoglycemia	8 (3)	9 (4)	6 (2)	7 (3)	17 (7)	4 (3)	6 (4)	1 (1)
Upper respiratory tract infection	5 (2)	4 (2)	9 (4)	5 (2)	2 (1)	7 (5)	3 (2)	4 (3)
Vulvovaginal mycotic infection	2 (1)	5 (2)	0	4 (2)	3 (1)	1 (1)	4 (3)	5 (3)
Constipation	6 (2)	6 (2)	1 (< 1)	4 (2)	1 (< 1)	2 (1)	0	5 (3)
Headache	1 (< 1)	6 (2)	9 (4)	4 (2)	5 (2)	1 (1)	3 (2)	2 (1)
Back pain	5 (2)	0	4 (2)	5 (2)	2 (1)	4 (3)	4 (3)	2 (1)
Patients with ≥ 1 SAEs, n (%)	8 (3)	3 (1)	3 (1)	6 (2)	4 (2)	4 (3)	7 (5)	3 (2)
Stopped treatment due to AEs, n (%)	6 (2)	3 (1)	1 (< 1)	3 (1)	7 (3)	1 (1)	5 (3)	1 (1)
Number of deaths, n (%)	0	0	0	0	0	0	0	0
Including Rescue								
Patients with ≥ 1 SAEs, n (%)	8 (3)	3 (1)	4 (2)	6 (2)	4 (2)	5 (3)	7 (5)	3 (2)
Stopped treatment due to AEs, n (%)	6 (2)	3 (1)	(< 1)	3 (1)	7 (3)	1 (1)	5 (3)	1 (1)
Number of deaths, n (%)	0	0	0	0	0	0	0	0

AE = adverse event; ERT = ertugliflozin; NR = not reported; SAE = serious adverse event: SIT = sitagliptin.

[a] Excludes events that occurred after the start of rescue therapy.

[b] Frequency ≥ 5% per group in one or more studies.

Source: Clinical Study Reports.[8-12]

Notable Harms

The frequency of documented and symptomatic hypoglycemia was highest in the glimepiride group (27% and 19%, respectively), compared with 2% to 9% (documented hypoglycemia), and 1% to 5% (symptomatic hypoglycemia) among those who received ERT, and 1% to 4% (documented or symptomatic) among those who received placebo (Table 24). Severe hypoglycemia was reported infrequently in the placebo, ERT, or sitagliptin groups (0 to 2 patients per group [0% to 1.3%]), and was reported in 10 patients (2.3%) in the glimepiride group.

Symptomatic hypoglycemia was included in the ordered statistical testing procedure for the SU trial. The frequency of symptomatic hypoglycemia was 19%, 3%, and 5% in the glimepiride, ERT 5 mg, and ERT 15 mg groups respectively (Table 24). The absolute difference between the ERT 15 mg and glimepiride groups was –14%; 95% CI, –18% to –10% ($P < 0.001$). For ERT 5 mg versus glimepiride, the absolute difference reported was –16%, 95% CI, –20% to –12%, although this comparison should be interpreted as inconclusive due to failure of a previous outcome in the testing sequence.

In women, genital mycotic infections were reported by 5% to 23% of patients who received ERT compared with 1% to 6% of patients who received placebo, glimepiride, or sitagliptin (Table 24). In males, 2% to 6% in the ERT groups reported genital mycotic infections compared with 0% to 1% of those in the control groups. Urinary tract infections were reported by 3% to 7% of those on ERT and 1% to 9% of those in the placebo, glimepiride, or sitagliptin groups.

The occurrence of other harms of special interest to this review was infrequent. Although no lower limb amputations were reported in the clinical study reports (CSRs) for the five trials, pooled study data from the FDA reported a total of 11 non-traumatic limb amputations among 3,409 patients who received ERT (0.3%) compared with 1/1,450 (0.1%) of those who received a control treatment.[40]

Table 24: Notable Harms

Adverse Events	MONO			MET			SU		
Excluding Rescue	**Placebo N = 153**	**ERT 5 mg N = 156**	**ERT 15 mg N = 152**	**Placebo N = 209**	**ERT 5 mg N = 207**	**ERT 15 mg N = 205**	**Glimepiride N = 437**	**ERT 5 mg N = 448**	**ERT 15 mg N = 440**
Notable Harms, n (%)[a]									
Documented hypoglycemia	1 (1)	4 (3)	4 (3)	9 (4)	15 (7)	16 (8)	119 (27)	25 (6)	36 (8)
Symptomatic hypoglycemia	2 (1)	2 (1)	4 (3)	4 (2)	7 (3)	7 (3)	84 (19)	14 (3)[b]	23 (5)[c]
Severe hypoglycemia	0	0	2 (1)	1 (< 1)	1 (< 1)	0	10 (2)	1 (< 1)	1 (< 1)
Hypovolemia (CMQ)[d]	6 (4)	2 (1)	3 (2)	1 (< 1)	1 (< 1)	2 (1)	3 (1)	6 (1)	3 (1)
Genital mycotic infection (CMQ) [d]									
Males	1 (1)	3 (3)	5 (6)	0	3 (3)	3 (3)	0	10 (4)	4 (2)
Females	4 (6)	11 (16)	14 (23)	1 (1)	6 (6)	7 (6)	3 (1)	17 (8)	25 (10)
Urinary tract infection (CMQ) [d]	13 (9)	11 (7)	6 (4)	2 (1)	6 (3)	7 (3)	30 (7)	30 (7)	28 (6)
Fractures (adjudicated)[e]	0	0	0	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)

Adverse Events	MONO			MET			SU		
Excluding Rescue	Placebo N = 153	ERT 5 mg N = 156	ERT 15 mg N = 152	Placebo N = 209	ERT 5 mg N = 207	ERT 15 mg N = 205	Glimepiride N = 437	ERT 5 mg N = 448	ERT 15 mg N = 440
Low trauma fracture				0	0	1 (< 1)	1 (< 1)	0	1 (< 1)
Renal and urinary disorders (SOC)	5 (3)	11 (7)	9 (6)	2 (1)	6 (3)	8 (4)	15 (3)	24 (5)	33 (8)
Adjudicated renal events[e]	0	0	0	0	0	2 (1)	0	0	1 (< 1)
Ketoacidosis or metabolic acidosis	NR	NR	NR	NR	NR	NR	0	0	1 (< 1)
Lower limb amputation	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 24: Notable Harms (continued)

Adverse Events	FACTORIAL					SITA2		
Excluding Rescue	ERT 5 mg N = 250	ERT 15 mg N = 248	SIT N = 247	ERT 5 mg + SIT N = 243	ERT 15 mg + SIT N = 244	Placebo N = 153	ERT 5 mg N = 156	ERT 15 mg N = 153
Notable Harms, n (%)[a]								
Documented hypoglycemia	14 (6)	13 (5)	9 (4)	13 (5)	22 (9)	5 (3)	7 (5)	3 (2)
Symptomatic hypoglycemia	6 (2)	6 (2)	6 (2)	6 (2)	12 (5)	4 (3)	6 (4)	1 (1)
Severe hypoglycemia	0	1 (< 1)	0	0	1 (< 1)	1 (1)	1 (1)	0
Hypovolemia (CMQ)[d]	4 (2)	2 (1)	0	0	0	1 (1)	1 (1)	0
Genital mycotic infection (CMQ)[d]								
Males	6 (5)	5 (4)	0	5 (4)	3 (2)	0	4 (5)	3 (4)
Females	6 (5)	8 (7)	1 (1)	6 (5)	9 (8)	1 (2)	6 (8)	9 (13)
Urinary tract infection (CMQ)[d]	13 (5)	14 (6)	8 (3)	8 (3)	9 (4)	3 (2)	4 (3)	7 (5)
Fractures (adjudicated)[e]	0	2 (1)	1 (< 1)	0	0	1 (1)	1 (1)	1 (1)
Low trauma fracture	0	1 (< 1)	0	0	0	0	0	1 (1)
Renal and urinary disorders (SOC)	9 (4)	6 (2)	4 (2)	13 (5)	12 (5)	4 (3)	5 (3)	7 (5)
Adjudicated renal events[e]	0	2 (1)	0	0	0	0	0	0
Ketoacidosis or metabolic acidosis	NR	NR	NR	NR	NR	NR	NR	NR
Lower limb amputation	NR	NR	NR	NR	NR	NR	NR	NR

CMQ = custom MedDRA query; ERT = ertugliflozin; NR = not reported; SIT = sitagliptin; SOC = system organ class.

[a] Excludes events that occurred after the start of rescue therapy.

[b] Absolute difference between ERT 5 mg and glimepiride: –16%; 95% CI, –20% to –12%; $P < 0.001$, however this should be interpreted as inconclusive as the statistical testing failed for a previous outcome.

[c] Absolute difference between ERT 15 mg and glimepiride: –14%; 95% CI, –18% to –10%; $P < 0.001$ (secondary outcome included in the ordered statistical testing procedure).

[d] Based on a pre-specified custom MedDRA query (CMQ) of preferred terms associated with hypovolemia, urinary tract infection, genital mycotic infections.

[e] Adjudicated events, based on events reported for the total study period (including time on rescue therapy).

Source: Clinical Study Reports.[8-12]

Discussion

Summary of Available Evidence

A total of five double-blind RCTs provided evidence on the efficacy and safety of ERT in adults with type 2 diabetes and inadequate glycemic controlled with diet and exercise (MONO), metformin (MET, SU, FACTORIAL) or metformin plus sitagliptin (SITA2). These trials examined shorter-term (26 to 52 weeks) surrogate outcomes including A1C, FPG, body weight, and blood pressure for ERT 5 mg and 15 mg daily versus placebo (MONO, MET, SITA2) or glimepiride (SU). The FACTORIAL trial compared 5 mg and 15 mg ERT daily plus sitagliptin with ERT or sitagliptin alone.

Interpretation of Results

Efficacy

ERT as monotherapy, as add-on therapy to metformin, or in combination with metformin and sitagliptin, was associated with statistically significant reductions in A1C after 26 weeks compared with placebo (LS mean difference –0.7% to –1.2%). ERT plus sitagliptin (as add-on to metformin) also showed statistically significant differences in A1C or compared with ERT or sitagliptin (plus metformin) (LS mean difference –0.4% to –0.5%). More patients on ERT achieved glycemic targets (A1C < 7%) and fewer required rescue therapy than placebo. In the head-to-head study, ERT 15 mg daily as add-on therapy to metformin was noninferior to glimepiride for the change from baseline in A1C based on a 0.3% noninferiority margin (LS mean difference 0.1%; 95% CI –0.02% to 0.22%). Noninferiority was not met for ERT 5 mg versus glimepiride as the upper bound of the 95% CI for the difference between groups was not below 0.3%.

Input from patient groups reported weight loss and lowered blood pressure as important outcomes, however it is unclear what degree of change may be considered clinically significant. The mean differences in the change from baseline in body weight ranged from –1.6 kg to –2.2 kg for ERT versus placebo and from –1.9 kg to –2.3 kg for ERT plus sitagliptin versus sitagliptin after 26 weeks of therapy, which were statistically significant. Somewhat larger mean differences were noted between ERT and glimepiride (–3.9 kg to –4.3 kg) at week 52, which was not unexpected as the sulfonylureas are associated with weight gain. The mean differences in SBP between ERT and comparator groups in the MET, FACTORIAL, and SITA2 studies ranged from –2.8 mm Hg to –4.5 mm Hg, which the clinical expert consulted for this review considered was clinically relevant. SBP data from the MONO or SU trials were either not statistically significant or inconclusive due to failure of a previous outcome in the statistical testing procedure. The differences between ERT and control groups for the change from baseline in DBP were not statistically significant or inconclusive in four of the five studies (MONO, SU, FACTORIAL, and SITA2). Although any reduction in weight or blood pressure may be viewed as positive by patients, it is not known if these changes translate into longer-term health benefits. The extension data suggests that the reduction in body weight may extend beyond 26 weeks, but given the limitations of these studies (attrition and exclusion of non-responders) it is difficult to draw conclusions from these data.

No statistically significant differences were detected between ERT and placebo for changes in health-related quality of life based on the EQ-5D instrument in the SITA2 study. The MET study found no statistically significant changes in BMD after 26 weeks of therapy for ERT

versus placebo; however the duration of follow-up may have been insufficient to detect meaningful changes. Furthermore, the reporting of BMD as raw scores, rather than T-scores, makes interpretation difficult.

The manufacturer submitted two indirect treatment comparisons which compared ERT as monotherapy, or as add-on therapy with metformin to the three SGLT2 inhibitors approved in Canada (canagliflozin, dapagliflozin, and empagliflozin).[50,51] The inclusion criteria for this focused review were limited to English language RCTs that were 24 to 26 weeks in duration in adults with type 2 diabetes with an A1C > 7% who received an SGLT2 inhibitor. The results of the Bayesian network meta-analysis (NMA) suggest that ERT has similar effects on A1C, weight, and blood pressure as other SGLT2 inhibitors in the short-term. Although both NMAs planned to examine hypoglycemia, urinary tract infections, genital infections, and overall adverse events, some of the models did not converge due to the low frequency of events. Thus limited data were available on adverse effects. While the methods used to conduct the analyses seem to be adequate, the limited scope of the review meant that not all potentially relevant literature was used to inform the network. It is impossible to know what impact this may have had on the results but the smaller sample size may increase the chances of finding no difference between drugs. Based on the results of the submitted indirect treatment comparison, ERT as monotherapy or in combination with metformin for the treatment of T2DM is likely more efficacious than placebo. Little can be elucidated on the comparative efficacy of ERT to other SGLT2 inhibitors, or on the relative safety of the product. Direct evidence of the comparative efficacy of ERT with other diabetes treatments is limited. Although the FACTORIAL study included ERT and sitagliptin control groups, the trial was not designed to test for differences between these drugs, and no between-group statistical comparison was reported. Thus the only head-to-head study compares ERT to a sulfonylurea, with no direct evidence comparing ERT to DPP-4 inhibitors or GLP-1 analogues. Based on data reported in the CADTH Therapeutic Review of second-line therapies,[52] the treatment effects of ERT appear to be similar to the SGLT2 inhibitor class but without additional direct or indirect evidence, uncertainty remains.

The available evidence on the efficacy of ERT was limited by the relatively short duration of the five trials (26 to 52 weeks) for a chronic condition, and the examination of surrogate outcomes (A1C, weight, and blood pressure). The primary analysis in all trials excluded any outcome data after the start of rescue therapy. In addition, no efficacy data were collected for patients who stopped treatment early. Considering the differential frequency of rescue and early discontinuation in the placebo and ERT groups, the ERT treatment effects may be overestimated. Although the manufacturer and FDA conducted additional sensitivity analyses to address the missing data, these cannot fully account for the impact of missing data. With respect to the magnitude of change observed in the studies, the Health Canada Reviewer's Report classified the effect size differences as modest.[2]

Limited data were available for the subgroups of interest for this review. One study that did not meet the systematic review inclusion criteria (population enrolled was not consistent with Health Canada indication), found no statistically significant differences in A1C for ERT versus placebo among patients with stage III chronic kidney disease. [53] This trial enrolled 468 patients with eGFR greater than and equal to 30 mL/min/1.73m^2 and less than 60 mL/min/1.73m^2 who were randomized to receive 26 weeks of placebo, ERT 5 mg, or ERT 15 mg daily as add-on therapy to standard AHAs. The trial failed on the primary outcome (change from baseline in A1C) and based on these data, the product monograph states that ERT should not be initiated in patients with eGFR less than 60 mL/min/1.73m^2 and is contraindicated in those with an eGFR less than 45 mL/min/1.72m.[2,18]

Harms

The adverse event profile of ERT appears to be similar to other drugs in the class and no new safety signals were identified based on the RCT and extension data available. The overall frequency of adverse events was generally similar between groups within studies, and the proportion of patients who stopped study drug due to adverse events was low (≤ 5% per group). Serious adverse events were reported by 1% to 4% of patients who received placebo, 1% to 6% of those who received ERT (alone or with sitagliptin), 1% to 3% who received sitagliptin or glimepiride. Genital mycotic infections were reported more frequently among patients who received ERT than other therapies. Changes in BMD and an increased risk of fractures has been raised as a possible concern with other SGLT2 inhibitors. Few fractures were reported during Phase A of the RCTs, but by the end of Phase B, 28 of 2,894 (1.0%) patients who received ERT had reported a fracture compared with 5 of 1,187 patients (0.4%) who received placebo or active control drug. Pooled study data from the FDA reported a total of 11 non-traumatic limb amputations among 3,409 patients who received ERT (0.3%) compared with 1/1450 (0.1%) of those who received a control treatment.[40] Additional data on these adverse events may be available from the ERT CV safety study, as the included trials were of insufficient duration and sample size to detect and quantify rare events. Although adverse CV events were captured during the trials, data on these events will not be reported until after the completion of the VERTIS CV study.

Potential Place in Therapy[a]

Ertugliflozin is an SGLT2 inhibitor that works by decreasing renal reabsorption of sodium and glucose. In addition to lowering blood glucose, this mechanism of action may be responsible for desirable reductions in SBP and weight. Ertugliflozin will be the fourth SGLT2 inhibitor on the market in Canada. The 2018 Diabetes Canada guidelines maintain that metformin should be the first-line therapy if lifestyle modifications fail to bring hemoglobin A1C into target, which for most patients would be A1C < 7%.[3] The second-line therapy choice includes a multitude of options; however, in those with known clinical CV disease there is a strong recommendation to use a medication that has clinical trial evidence of CV protection (empagliflozin, canagliflozin, or liraglutide).[4-6]

Deciding on the second-line treatment should involve shared decision-making with the patient, taking into consideration insurance coverage, renal function, weight, blood pressure, and adverse effect profiles. For many patients with diabetes, weight loss is a challenge and traditional second- and third-line therapies like sulfonylureas, thiazolidinediones, and insulin lead to weight gain. The newer classes of medications are weight neutral (DPP-4 inhibitors) or promote weight loss (SGLT2 inhibitors and GLP-1 agonists). When patients have insurance coverage for their medications, the decision between these three drugs is based on the patient's desire for weight loss and willingness to accept adverse effects. Again, if the patient has clinical CV disease then a drug with CV clinical trial evidence will be prioritized.

Another important consideration with this class of medications is adverse effects. Genitourinary tract infections, hypovolemia, fractures, lower extremity amputations, and euglycemic diabetic ketoacidosis have all been reported with some, if not all, of the medications in this class. Review of the currently available evidence shows the risk of hypovolemia and genital infections to be similar to other available SGLT2 inhibitors. There

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

is no significant signal yet for increased risk of fractures or amputations, but the data from the CV outcome trial due out in 2019 will be important to understand if the unexpected adverse events seen with canagliflozin[4] are a class effect.

Renal disease is another important consideration in patients with diabetes. The SGLT2 inhibitors do not work as well at lower eGFRs and ERT renal study showed it to be no different than the other available therapies. In earlier stages of renal disease both empagliflozin and canagliflozin have been shown to reduce progression[4,7] but there is no data to support that yet for ERT.

Given that ERT does not yet have evidence of clinical CV or renal benefit (it has an ongoing trial with results expected in fall of 2019) and its glucose lowering potential and adverse effect profile appears to be similar to the currently available SGLT2 inhibitors, it does not appear to offer any significant benefit over the currently available SGLT2 inhibitors.

Conclusions

ERT as monotherapy, or as add-on therapy to metformin or metformin plus sitagliptin, was associated with statistically significant short-term (six month) reductions in A1C and body weight as compared with placebo plus add-on therapies. Statistically significant differences in SBP were observed for ERT as add-on therapy to metformin or metformin plus sitagliptin versus placebo plus add-on therapies.

In addition, ERT 15 mg daily, as add-on to metformin, was noninferior to glimepiride plus metformin for the change from baseline in A1C after 52 weeks. Noninferiority, however, was not met for ERT 5 mg versus glimepiride based on a 0.3% noninferiority margin. Statistically significant short-term reductions in A1C, body weight, and SBP were observed for ERT plus sitagliptin, as add-on therapy to metformin, versus sitagliptin plus metformin.

No differences were detected in health-related quality of life or BMD for ERT versus placebo, based on data from one RCT, although ability to detect differences may have been limited by the short duration of the treatment.

No new safety signals were identified for ERT that were not already known for other SGLT2 inhibitors, however the sample size and treatment duration limited the ability to detect infrequent adverse events, such as fractures or amputations, that have been identified as events of interest. Data on adjudicated major CV adverse events were not reported but are expected to be released once the longer-term CV safety study (VERTIS CV) is published.

The results of the manufacturer-submitted indirect treatment comparisons suggest that ERT as monotherapy, or in combination with metformin, for the treatment of T2DM is likely more efficacious than placebo; however little can be elucidated on the comparative efficacy of ERT to other SGLT2 inhibitors, or on the relative safety of the product.

Appendix 1: Patient Input Summary

This section was summarized by CADTH staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

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

One patient group, Diabetes Canada, provided the input for this submission. Diabetes Canada is a national health charity representing 11 million Canadians living with diabetes or prediabetes. The priorities of Diabetes Canada's mission are diabetes prevention, care, and cure. Diabetes Canada focuses on research and policy initiatives for better prevention and treatment strategies. The organization received funding from multiple pharmaceutical companies and organizations, including Merck, who was one of 12 companies that provided more than $100,000 over the past two years. They had no help from outside their organization to collect and analyze data, or to complete the submission.

2. Condition-Related Information

Information was gathered through online surveys of patients with type 2 diabetes and their caregivers. Surveys were conducted in October 2016 and April/May 2018. The 2018 survey posed a number of questions specifically about the drug under review, ertugliflozin (Steglatro), as well as the combination drug ertugliflozin and metformin hydrochloride. A total of 847 people responded to the October 2016 survey: 790 patients with type 2 diabetes and 57 caregivers. Of those who responded to questions about age and time since diagnosis (n = 379), 70% were over the age of 55, with the largest number of respondents (56%, n = 211) in the 55- to 69-year-old category; and 60% had been living with diabetes for over 10 years. In the April/May 2018 survey (n = 52), 47 respondents were patients with type 2 diabetes and five were caregivers. A total of 15 people provided age and date of diagnosis data: 100% of respondents were over the age of 40 years, with the largest number (60%, n = 9) in the 40- to 54-year-old category, and 67% having lived with diabetes for six years or more.

The patient group highlighted that diabetes is a chronic, progressive disease without cure. The common symptoms of diabetes include extreme fatigue, unusual thirst, frequent urination, and weight change (gain or loss). Diabetes requires considerable self-management, including eating well, engaging in regular physical activity, maintaining a healthy body weight, taking medications (oral and/or injectable) as prescribed, monitoring blood glucose, and managing stress. Poor glucose control is serious and problematic. Low blood glucose can precipitate an acute crisis, such as confusion, coma, or seizure. High blood glucose over time can irreversibly damage blood vessels and nerves, resulting in blindness, heart disease, kidney problems, and lower limb amputations, among other issues. The goal of diabetes management is to keep glucose levels within a target range to minimize symptoms and avoid or delay complications.

Patients describe their diabetic conditions as "manageable but a bother," "a constant battle every day," "terrible," "inconvenient," "frustrating," and "exhausting." Most patients surveyed talked about the adverse effect diabetes has had on their lives. Their diabetes affects all aspects of their lives from eating and exercising, to working and socialization. Patients are anxious and fearful of complications of the disease, and face stigma due to diabetes. Patients who responded to the surveys indicated that they experienced the following symptoms or comorbidities: hyperglycemia; hypoglycemia; high blood pressure; high cholesterol; heart problems; mental health problems; kidney symptoms or disease; foot

problems; eye problems; nerve damage; damage to blood vessels; heart or brain; liver disease; weight gain; and sexual dysfunction.

Below are some quotes from survey respondents:

"I am more focused on healthy lifestyle...eating well and exercising and I now have regular medical appointments and blood work. These are the positives but they are far outweighed by the impact of long-term stress and challenges of remaining healthy with diabetes. Everything is just harder and I feel like I am continually juggling all the pieces… I most definitely experience more frequent "blues" or period of depression and hopelessness. This is especially so if I let myself dwell on the future."

"I had a heart attack due to having diabetes so it has changed my life in so many ways."

"Life is tougher to manage now with the loss of limbs."

"Reduced happiness, increase in depression, increase worry about complications in future."

"I am a mother and hate the fact that I have developed diabetes and have to take medications for it… My kids have to know what to do if I pass out…"

"I have neuropathy in my legs and hands. I have diabetic neuropathy in my eyes. I can't drive anymore and have to rely on help from family…"

3. Current Therapy-Related Information

Patients (n = 668) reported that they have used (in the past or currently) the following antihyperglycemic agents (AHA): metformin; glucagon-like peptide-1 (GLP-1) receptor agonists; sodium-glucose cotransporter-2 (SGLT2) inhibitors; combination of SGLT2 inhibitors and metformin; dipeptidyl peptidase-4 (DPP-4) inhibitors; combination of DPP-4 inhibitors and metformin; sulfonylureas; thiazolidinediones; combination of thiazolidinediones and metformin; combination of thiazolidinediones and glimepiride; meglitinides; acarbose; and insulin. More than 60% of respondents from the October 2016 survey, and more than 45% of respondents from the 2018 survey, noted improvements in meeting target blood glucose levels (fasting, postprandial, upon waking) and glycated hemoglobin (A1C) levels after initiation on their current medication regimen, compared with before (when they were not on treatment). From the survey administered in October 2016, about 46% patients said they were "better" or "much better" able to avoid hypoglycemia, and 39% said their current regimen helped them maintain or lose weight more effectively than in the past. Gastrointestinal side effects were "neither better nor worse" than previously in 39% of respondents. About two-thirds indicated they were either "satisfied" or "very satisfied" with the medication or combination of medications they were taking for their diabetes management. The factors that were considered "quite important" or "very important" in choosing diabetes medications among respondents of both surveys were, among others: keeping blood glucose at satisfactory level, avoiding low blood sugar, avoiding weight gain or facilitating weight loss, reducing risk of heart problems, avoiding gastrointestinal issues (nausea, vomiting, diarrhea, pain), and avoiding urinary tract and/or yeast infections.

4. Expectations About the Drug Being Reviewed

Patients who participated in the survey reported no experience of using ertugliflozin or were not sure whether they had or not. However, respondents (patients and caregivers) expressed a strong desire for medications that can normalize or stabilize blood glucose

levels and improve hemoglobin A1c without causing weight gain or hypoglycemia. They wish for new treatments that have been proven to be safe, enhance weight loss, and improve health outcomes. They want affordable drug options; ideally, they'd like medications to be covered by public and private plans, and in a timely manner. They want treatments that are easily administered, with few side effects, and medications that minimize the risk of diabetes-related complications, help avoid polypharmacy, and eliminate the need for injections.

Below are a few examples of quotes from patients:

"Help with managing my levels and avoiding nerve damage"

"Minimal side effects"

"Less meds mean less preparation time and less time per day for glucose level testing"

"It would be nice to not have to take shots anymore. Would be nice to be able to just take pills again"

"… Losing weight would just make everything easier and move overall health into a positive trend"

"Expectations are that eventually there will be a medication that can be taken once a day that will help my pancreas produce the right amount of insulin to keep up with me ..."

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 28, 2018
Alerts:	Weekly search updates until September 19, 2018
Study Types: Limits:	No search filters were applied 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#	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
.rn	CAS registry number
.nm .dq	Name of substance word Candidate Term Word (Embase)
medall	Ovid database code; MEDLINE ALL 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(6C282481IP or MLU731K321).rn,nm.
2	(steglatro* or ertugliflozin* or "PF 04971729" or PF04971729 or MK 8835 or MK8835).ti,ab,ot,kf,hw,rn,nm.
3	or/1-2
4	3 use medall
5	*ertugliflozin/
6	(steglatro* or ertugliflozin* or "PF 04971729" or PF04971729 or MK 8835 or MK8835).ti,ab,kw,dq.
7	or/5-6
8	7 use oemezd
9	conference abstract.pt.
10	8 not 9
11	4 or 10
12	remove duplicates from 11

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 2018
Keywords:	Steglatro (ertugliflozin), type 2 diabetes
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for 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.

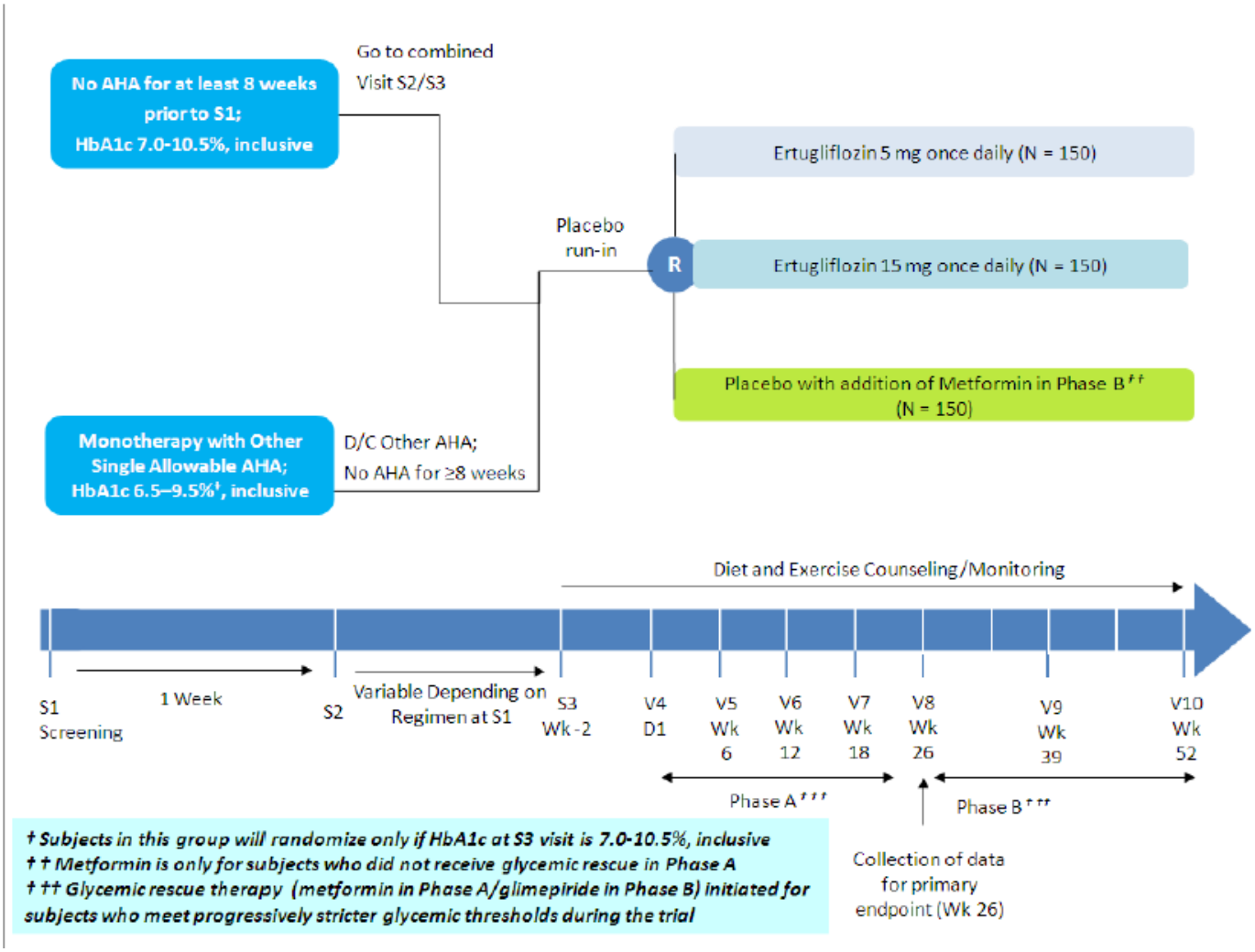
Appendix 3: Excluded Studies

Table 25: Excluded Studies

Reference	Reason for Exclusion
Amin NB, Wang X, Mitchell JR, Lee DS, Nucci G, Rusnak JM. Blood pressure-lowering effect of the sodium glucose co-transporter-2 inhibitor ertugliflozin, assessed via ambulatory blood pressure monitoring in patients with type 2 diabetes and hypertension. Diabetes Obes Metab. 2015;17(8):805-808. Amin NB, Wang X, Jain SM, Lee DS, Nucci G, Rusnak JM. Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. Diabetes Obes Metab. 2015;17(6):591-598.	Phase II study[54,55]
Aronson R, Frias J, Goldman A, Darekar A, Lauring B, Terra SG. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. Diabetes Obes Metab. 2018;20(6):1453-1460.	Extension study[56]
Miller S, Krumins T, Zhou H, et al. Ertugliflozin and Sitagliptin Co-initiation in Patients with Type 2 Diabetes: The VERTIS SITA Randomized Study. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders. 2018;9(1):253-268.	Wrong intervention[57]
Grunberger G, Camp S, Johnson J, et al. Ertugliflozin in Patients with Stage 3 Chronic Kidney Disease and Type 2 Diabetes Mellitus: The VERTIS RENAL Randomized Study. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders. 2018;9(1):49-66.	Wrong population[53]

Appendix 4: Detailed Outcome Data

Figure 2: Trial Design for MONO Study



Source: Clinical Study Report.[8]

Figure 3: Trial Design for MET Study

Figure redacted at the request of the manufacturer

Source: Clinical Study Report.[9]

Figure 4: Trial Design for SU Study

Figure redacted at the request of the manufacturer

Source: Clinical Study Report.10

Figure 5: Trial Design for FACTORIAL Study

Figure redacted at the request of the manufacturer

Source: Clinical Study Report.[11]

Figure 6: Trial Design for SITA2 Study

Figure redacted at the request of the manufacturer

Source: Clinical Study Report.[12]

Table 26: Percentage of Patients With Missing A1C Data at End of Study

Treatment	MONO	MET	SU	FACTORIAL	SITA2
Time Point	**26 Weeks**	**26 Weeks**	**52 Weeks**	**26 Weeks**	**26 Weeks**
Placebo	42%	28%			22%
Glimepiride			20%		
SIT				17%	
ERT 5 mg	15%	8%	25%	13%	12%
ERT 15 mg	18%	9%	21%	13%	10%
ERT 5 mg + SIT				10%	
ERT 15 mg + SIT				10%	

A1C = glycated hemoglobin; ERT = ertugliflozin; SIT = sitagliptin.

Source: Clinical Study Reports.[8-12]

Table 27: Change From Baseline in FPG (mg/dL)

Population/ Study	Treatment	N	FPG (mg/dL)				FPG (mmol/L)[a]	
			Baseline Mean (SD)	Change from Baseline LS Mean (95% CI)[b]	Difference in LS Mean (95% CI)[b]	*P* value	Difference in LS Mean (95% CI)[b]	*P* value
No background AHA				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**	**ERT vs. placebo at week 26**	***P* value**
MONO	Placebo	153	[redacted]	0.6 (–6.0 to 7.2)				
	ERT 5 mg	155	[redacted]	–34.0 (–39.9 to –28.1)	–34.5 (–42.8 to –26.3)	< 0.001	–1.9 (–2.4 to –1.5)	< 0.001
	ERT 15 mg	152	[redacted]	–43.4 (–49.4 to –37.5)	–44.0 (–52.3 to –35.7)	< 0.001	–2.4 (–2.9 to –2.0)	< 0.001
Add-on to metformin				**Change from baseline to week 26**	**ERT vs. placebo at week 26**	***P* value**	**ERT vs. placebo at week 26**	***P* value**
MET	Placebo	[redacted]	[redacted]	[redacted]				
	ERT 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ERT 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on to metformin				**Change from baseline to week 52**	**ERT vs. glimepiride at 52 weeks**	***P* value**	**ERT vs. glimepiride at 52 weeks**	***P* value**
SU	Glimepiride	437	[redacted]	[redacted]				
(FAS)	ERT 5 mg	448	[redacted]	[redacted]	[redacted]	[redacted]	–0.1 (–0.4 to 0.1)	0.25[c]
	ERT 15 mg	440	[redacted]	[redacted]	[redacted]	[redacted]	–0.4 (–0.7 to –0.2)	< 0.001[b]
Add-on to metformin				**Change from baseline to week 26**	**ERT+SIT vs. SIT at 26 weeks, *P* value**	**ERT+SIT vs. ERT at 26 weeks, *P* value**	**ERT+SIT vs. SIT at 26 weeks, *P* value**	**ERT+SIT vs. ERT at 26 weeks, *P* value**
FACTORIAL	ERT 5 mg	250	[redacted]	–35.7 (–40.0 to –31.4)				
	ERT 15 mg	248	[redacted]	–36.9 (–41.2 to –32.6)				
	SIT	247	[redacted]	–25.6 (29.9 to –21.2)				
	ERT 5 mg + SIT	243	[redacted]	–44.0 (–48.3 to –39.6)	–18.4 (–20.0 to –12.8), *P* < 0.001	–8.2 (–13.8 to –2.7), *P* = 0.004	–1.0 (–1.1 to –0.7), *P* = 0.004	-0.5 (–0.8 to –0.2), *P* = 0.004
	ERT 15 mg + SIT	244	[redacted]	–48.7 (–53.0 to –44.4)	–23.1 (–28.8 to –17.5), *P* < 0.001	–11.8 (–17.4 to –6.2), *P* < 0.001	–1.3 (–1.6 to –1.0), *P* < 0.001	–0.7 (–1.0 to –0.3), *P* < 0.001

Population/ Study	Treatment	N	FPG (mg/dL)				FPG (mmol/L)[a]	
			Baseline Mean (SD)	Change from Baseline LS Mean (95% CI)[b]	Difference in LS Mean (95% CI)[b]	*P* value	Difference in LS Mean (95% CI)[b]	*P* value
Add-on to metformin + SIT				**Change from baseline to week 26**	**ERT vs. placebo at 26 weeks**	***P* value**	**ERT vs. placebo at week 26**	***P* value**
SITA2	Placebo	153	[redacted]	–1.8 (–7.7 to 4.2)				
	ERT 5 mg	156	[redacted]	–26.9 (–32.6 to –21.2)	–25.2 (–32.8 to –17.5)	< 0.001	–1.4 (–1.8 to –1.0)	< 0.001
	ERT 15 mg	153	[redacted]	–33.0 (–38.7 to –27.4)	–31.3 (–38.9 to –23.7)	< 0.001	–1.7 (–2.2 to –1.3)	< 0.001

AHA = antihyperglycemic agent; CI = confidence interval; ERT = ertugliflozin; FPG = fasting plasma glucose; LS = least squares; SD = standard deviation; SIT = sitagliptin.

[a] Converted to mmol/L by CDR (FPG in mg/dL divided by 18).

[b] Excludes any data after the initiation of rescue glycemic therapy. Based on constrained longitudinal data analysis model with treatment, time (categorical), treatment by time interaction, baseline eGFR (continuous), and study-specific stratification factors as variables (Table 12).

[c] Outside the statistical testing procedure, thus should be interpreted as inconclusive.

Source: Clinical Study Reports.[8-12]

Figure 7: Change From Baseline in A1C by Subgroups (MONO Study)

Figure redacted at the request of the manufacturer

A1C = glycated hemoglobin; LS = least squares.

Source: Clinical Study Report.[8]

Figure 8: Change From Baseline in A1C by Subgroups (MET Study)

Figure redacted at the request of the manufacturer

A1C = glycated hemoglobin; LS = least squares.

Source: Clinical Study Report.[9]

Figure 9: Change From Baseline in A1C by Subgroups — A1C, Age, Sex, Race (SU Study)

Figure redacted at the request of the manufacturer

A1C = glycated hemoglobin; LS = least squares.

Source: Clinical Study Report SU study.[10]

Figure 10: Change From Baseline in A1C by Subgroups — Ethnicity, BMI, Duration of Diabetes, Prior AHA (SU Study)

Figure redacted at the request of the manufacturer

A1C = glycated hemoglobin; AHA = antihyperglycemic agent; BMI = body mass index; LS = least squares.

Source: Clinical Study Report SU study.[10]

Figure 11: Change from Baseline in A1C by Subgroups (FACTORIAL Study)

Figure redacted at the request of the manufacturer

A1C = glycated hemoglobin; LS = least squares.

Source: Clinical Study Report.[11]

Figure 12: Change From Baseline in A1C by Subgroups (SITA2 Study)

Figure redacted at the request of the manufacturer

A1C = glycated hemoglobin; LS = least squares.

Source: Clinical Study Report.[12]

Table 28: Per Cent Change From Baseline in Bone Mineral Density (MET Study)

Site/Study	Treatment	N	Baseline Mean (SD)	% Change From Baseline to week 26 LS Mean (95% CI)	Difference in LS Mean (95% CI)[a]
Lumbar spine					
MET	Placebo	[redacted]	[redacted]	[redacted]	
	ERT 5 mg	[redacted]	[redacted]	[redacted]	[redacted]
	ERT 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Femoral neck					
MET	Placebo	[redacted]	[redacted]	[redacted]	
	ERT 5 mg	[redacted]	[redacted]	[redacted]	[redacted]
	ERT 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Total hip					
MET	Placebo	[redacted]	[redacted]	[redacted]	
	ERT 5 mg	[redacted]	[redacted]	[redacted]	[redacted]
	ERT 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Distal forearm					
MET	Placebo	[redacted]	[redacted]	[redacted]	
	ERT 5 mg	[redacted]	[redacted]	[redacted]	[redacted]
	ERT 15 mg	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ERT = ertugliflozin; LS = least squares; SD = standard deviation.

[a] Based on constrained longitudinal data analysis model with treatment, time (categorical), treatment by time interaction, menopausal status stratum, AHA status at study entry, and baseline eGFR (continuous) as variables.

Source: Clinical Study Report.[9]

Appendix 5: Summary of Extension Studies

Aim

To summarize the efficacy and safety results of long-term extension period (Phase B) of included studies (i.e., MONO, MET, SU, FACTORIAL, and SITA 2). [58-62]

Findings

Study Design and Baseline Disease Characteristics

The overall study design (Phase A) is described in the main text (see the Results section in main text). The overall study design (Phase A + Phase B) is also presented in Appendix 4, Figure 2 to Figure 6, and in Table 29. In the MONO study, during the 26-week Phase B treatment period following completion of week 26 of Phase A, non-rescued patients in the placebo group received blinded metformin in addition to placebo (the placebo/metformin group). Non-rescued patients in the ertugliflozin (ERT) groups received placebo in addition to ERT 15 mg or ERT 5 mg. Patients rescued with metformin in Phase A entered into Phase B and continued to receive open-label metformin in addition to their original randomized treatment.[61] In the MET study, during the 78-week Phase B treatment period following completion of week 26 of Phase A, patients remained on randomized treatment. Non-rescue patients in the placebo group received the addition of treatment with glimepiride (the placebo/glimepiride group), providing their fasting finger-stick glucose was greater than and equal to 110 mg/dL (6.1 mmol/L). The study was a couble-blind, double-dummy design and matching placebo was used to maintaining the double-blinding.[62] In the SU study, during the 52-week Phase B treatment period following completion of week 52 of Phase A, patients remained on their randomized treatment.[58] In both the FACTORIAL and SITA 2 studies, patients remained on their randomized treatment during the 26-week Phase B treatment period following completion of week 26 of Phase A.[59,60]

Table 29: Summary of PICOS of Included Studies (Phase A + Phase B)

Study	Population	Intervention	Outcomes	Design
MONO				
Phase A	Inadequate glycemic control with diet and exercise	ERT 5 mg ERT 15 mg Placebo	Primary: Change in A1C at week 26	DB RCT 26 weeks
Phase B	–	Placebo patients who did not receive rescue therapy were switched to blinded MET	Secondary: Safety, A1C etc., at week 52	Randomization and blind remained Extension: Active-controlled trial for 26 weeks
MET				
Phase A	Inadequate glycemic control with MET ≥ 1,500 mg/day	ERT 5 mg ERT 15 mg Placebo	Primary: Change in A1C at week 26	DB RCT 26 weeks
Phase B	–	ERT 5 mg ERT 15 mg Placebo patients who did not receive rescue therapy were switched to blinded glimepiride	Secondary: Safety, A1C etc., at Week 104	Randomization and blind remained Extension: 78 weeks

Study	Population	Intervention	Outcomes	Design
SU				
Phase A	Inadequate glycemic control with MET ≥ 1,500 mg/day	ERT 5 mg ERT 15 mg Glimepiride 1 mg to 8 mg	Primary: Change in A1C at week 52	DB RCT 52 weeks
Phase B	–	The same as Phase A	Secondary: Safety, A1C etc., at week 104	Randomization and blind remained Extension: 52 weeks
FACTORIAL				
Phase A	Inadequate glycemic control with MET ≥ 1,500 mg/day	ERT 5 mg ERT 15 mg SIT 100 mg ERT 5 mg + SIT 100 mg ERT 15 mg + SIT 100 mg	Primary: Change in A1C at week 26	DB RCT 26 weeks
Phase B	–	The same as Phase A	Secondary: Safety, A1C etc., at week 52	Randomization and blind remained Extension: 26 weeks
SITA2				
Phase A	Inadequate glycemic control with MET ≥ 1,500 mg/day and SIT 100 mg/d	ERT 5 mg ERT 15 mg Placebo	Primary: Change in A1C at week 26	DB RCT 26 weeks
Phase B	–	The same as Phase A	Secondary: Safety, A1C etc., at week 52	Randomization and blind remained Extension: 26 weeks

A1C = glycated hemoglobin; DB = double blind; ERT = ertugliflozin; MET = metformin; RCT = randomized controlled trial; SIT = sitagliptin.

Source: Clinical Study Reports.[8-12,58-62]

Baseline Demographics and Clinical Characteristics

The baseline study and patient characteristics are described in the main text and summarized in Table 10.

Patient Disposition

The patient disposition (Phase A and Phase B) is presented in Table 30 and Table 31. The discontinuation rate ranged from 10.9% to 41.6% in the individual treatment group across the studies. The discontinuation due to adverse events ranged from 2.9% to 8.5% in the individual treatment group across the studies.

Table 30: Patient Disposition for Studies MONO, MET, and SU (Phase A + Phase B)

	MONO			MET			SU		
Phase A	**Placebo**	**ERT 5 mg**	**ERT 15 mg**	**Placebo**	**ERT 5 mg**	**ERT 15 mg**	**ERT 5 mg**	**ERT 15 mg**	**GLIM**
Screened, N									
Randomized, N (%)									
Not treated									
Discontinued study drug, n (%) the end of Phase A									
Discontinuation due to adverse event									
Death									
	MONO			**MET**			**SU**		
Phase B	**Placebo/MET**	**ERT 5 mg**	**ERT 15 mg**	**Placebo/GLIM**	**ERT 5 mg**	**ERT 15 mg**	**ERT 5 mg**	**ERT 15 mg**	**GLIM**
Discontinued study drug, n (%) at the end of Phase B									
Discontinuation due to adverse event									
Death									

ERT = ertugliflozin; GLIM = glimepiride; MET = metformin.

Source: Clinical Study Reports.[58,61,62]

Table 31: Patient Disposition for FACTORIAL and SITA2 Studies (Phase A + Phase B)

Phase A	**FACTORIAL**					**SITA2**		
	ERT 5 mg	**ERT 15 mg**	**SIT 100 mg**	**ERT 5 mg + SIT**	**ERT 15 mg + SIT**	**Placebo**	**ERT 5 mg**	**ERT 15 mg**
Screened, N								
Randomized, N (%)								
Not treated								
Discontinued study drug, n (%) at the end of Phase A								
Discontinuation due to adverse event								
Death								
Phase B	**FACTORIAL**					**SITA2**		
	ERT 5 mg	**ERT 15 mg**	**SIT 100 mg**	**ERT 5 mg + SIT**	**ERT 15 mg + SIT**	**Placebo**	**ERT 5 mg**	**ERT 15 mg**
Discontinued study drug, n (%) at the end of Phase B								
Discontinuation due to adverse event								
Death								

ERT = ertugliflozin; SIT = sitagliptin.

Source: Clinical Study Reports.[59,60]

Results: Efficacy and Harms

Efficacy

A1C

The results of the change from baseline in A1C to the end of Phase B for all five studies are presented in Table 32. The change in A1C during the course of Phase A and Phase B are shown in Figure 13 to Figure 17.

In the MONO study, at the end of Phase B (week 52; n = 83 [53%] in the ERT 5 mg group, and n = 97 [64%] in the ERT 15 mg group), both doses of ERT lowered A1C compared with baseline. In both ERT groups, the reductions in A1C through week 26 were maintained through week 52. The magnitude of the reduction in A1C was numerically greater in the ERT 15 mg group than in the ERT 5 mg group at each time point. LS mean (95% CI) reductions from baseline in A1C to week 52 in the ERT groups based on the excluding rescue approach were –0.7 (–0.9 to –0.6) and –0.9 (–1.0 to –0.7) in the ERT 5 mg group and ERT 15 mg group respectively.(Table 32, Figure 13).

Figure 13: LS Mean Change From Baseline A1C Over Time (cLDA) at Week 52 — Excluding Rescue Approach (MONO Study — Ertugliflozin Arms Only)

Figure redacted at the request of the manufacturer

A1C = glycated hemoglobin; cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error.

Source: Clinical Study Report.[61]

In the MET study at week 104 (n = 148 [72%] in the ERT 5 mg group, and n=144 [71%] in the ERT 15 mg group), A1C in both of the ERT groups showed a reduction compared with baseline. Both ERT groups mean reductions in A1C through week 26 were maintained through week 104. The observed estimate of the reduction in A1C was greater in the ERT 15 mg group than in the ERT 5 mg group (Figure 14). The observed estimates of the mean reduction in A1C were greater in the ERT groups than in the placebo/glimepiride group at each time point through week 104, except at week 39 and week 104, where the mean reductions were similar for the ERT 5 mg and placebo/glimepiride groups.

Figure 14: LS Mean Change From Baseline A1C Over Time (cLDA) at Week 104 — Excluding Rescue Approach (MET Study — Ertugliflozin Arms Only)

Figure redacted at the request of the manufacturer

A1C = glycated hemoglobin; cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error.

Source: Clinical Study Report.[62]

In the SU study, the LS mean reductions from baseline in A1C at week 104 (n = 255 [57%] in the ERT 5 mg group; n = 267 [61%] for the ERT 15 mg group; and n = 267 [61%] in the GLIM group, respectively) were similar in the ERT groups and glimepiride group (Table 32). The reduction of A1C responses achieved at week 52 was gradually attenuated through week 104 in all treatment groups (Figure 15).

Figure 15: LS Mean Change From Baseline A1C Over Time (cLDA) at Week 104 — Excluding Rescue Approach (SU Study)

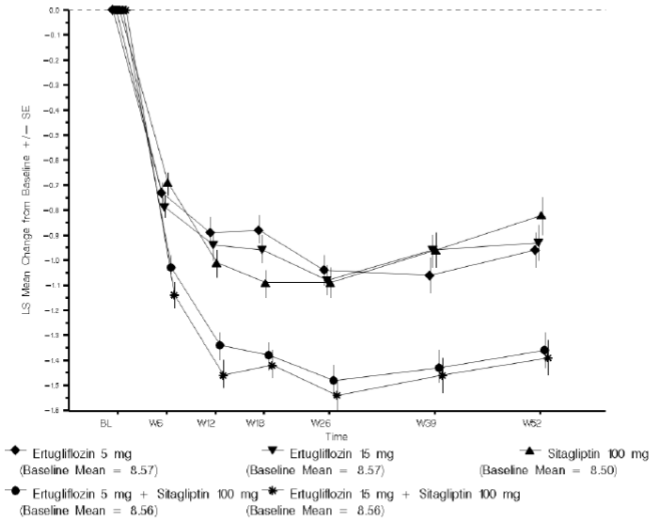
Figure redacted at the request of the manufacturer

A1C = glycated hemoglobin; cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error.

Source: Clinical Study Report.[58]

In the FACTORIAL study, the reductions from baseline (LS) mean in A1C at week 52 (n = 176 [72%] in the ERT 5 mg group; n = 151 [61%] for the ERT 15 mg group; n = 138 [57%] for the SITA group; n = 173 [73%] for the ERT 5mg+SITA group; and n= 177 [73%] for the ERT 15mg +SITA group, respectively) were greater in the ERT15 mg /SITA100 mg and ERT5 mg/SITA 100 mg groups compared with ERT 15 mg and ERT 5 mg monotherapy, respectively (Table 32). In all treatment groups, reductions from baseline in A1C through week 26 were followed by a slight increase toward baseline at week 52 (Figure 16).

Figure 16: LS Mean Change From Baseline A1C Over Time (cLDA) at Week 52 — Excluding Rescue Approach (FACTORIAL Study)

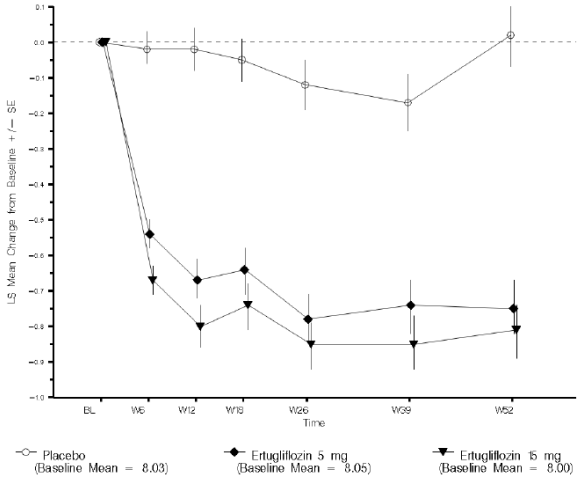


A1C = glycated hemoglobin; cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error.

Source: Clinical Study Report.[59]

In the SITA 2 Study, the least squares (LS) mean reductions from baseline in A1C at week 52 were greater in the ERT 15 mg (n = 155 [75%]) and ERT 5 mg groups (n = 120 [77%]) than in the placebo group (n = 73 [48%]). For both ERT groups, reductions from baseline in A1C achieved at week 26 were maintained through week 52. It was observed that there were numerically greater improvements in A1C reduction over time in the ERT 15 mg group compared with the ERT 5 mg group (see Table 32 and Figure 17).

Figure 17: LS Mean Change from Baseline A1C Over Time (cLDA) at Week 52 — Excluding Rescue Approach (SITA2 Study)



A1C = glycated hemoglobin; cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error.

Source: Clinical Study Report.[60]

Table 32: Change from Baseline A1C at Week 52 or Week 104 (FAS, cLDA) — Excluding Rescue Approach

MONO							
Treatment	Baseline		Week 52		Change From Baseline at Week 52		
	N[a]	Mean (SD)	N (%)[a,b]	Mean (SD)	N[a]	Mean (SD)	LS Mean (95% CI)[c]
ERT 5 mg	[redacted]						
ERT15 mg	[redacted]						
MET							
Treatment	Baseline		Week 104		Change from Baseline at Week 104		
	N[a]	Mean (SD)	N (%)[ab]	Mean (SD)	N[a]	Mean (SD)	LS Mean (95% CI)[c]
ERT 5 mg/ERT 5 mg	[redacted]						
ERT 5 mg/ERT 15 mg	[redacted]						
SU							
Treatment	Baseline		Week 104		Change from Baseline at Week 104		
	N[a]	Mean (SD)	N (%)[ab]	Mean (SD)	N[a]	Mean (SD)	LS Mean (95% CI)[c]
ERT 5 mg	[redacted]						
ERT 15 mg	[redacted]						
GLIM	[redacted]						
Pairwise Comparison							[redacted]
ERT 5 mg vs. GLIM							[redacted]
ERT 15 mg vs. GLIM							[redacted]
FACTORIAL							
Treatment	Baseline		Week 52		Change from Baseline at Week 52		
	N[a]	Mean (SD)	N (%)[ab]	Mean (SD)	N[a]	Mean (SD)	LS mean (95% CI)[c]
ERT 5 mg	[redacted]						
ERT 15 mg	[redacted]						
SIT 100 mg	[redacted]						
ERT 5 mg + SIT 100 mg	[redacted]						
ERT 15 mg + SIT 100 mg	[redacted]						
Pairwise Comparison							Difference in LS Means(95% CI)
ERT 5 mg + SIT 100 mg vs. ERT 5 mg							[redacted]
ERT 5 mg + SIT 100 mg vs. SIT 100 mg							[redacted]
ERT 15 mg + SIT 100 mg vs. ERT 15 mg							[redacted]
ERT 15 mg + SIT 100 mg vs. SIT 100 mg							[redacted]

SITA2							
Treatment	Baseline		Week 52		Change From Baseline at Week 52		
	N[a]	Mean (SD)	N (%)[ab]	Mean (SD)	N[a]	Mean (SD)	LS Mean (95% CI)[c]
PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison							Difference in LS Means(95% CI)
ERT 5 mg vs. PL							[redacted]
ERT 15 mg vs. PL							[redacted]

A1C = hemoglobin A1C; CI = confidence interval; cLDA = constrained longitudinal data analysis; ERT = ertugliflozin; FAS = full analysis set; GLIM = glimepiride; LS = least squares; MET = metformin; PL = placebo; SD = standard deviation; SIT = sitagliptin.

[a] For baseline, week 52, and week 104; N is the number of patients with non-missing assessments at the specific time point; for change from baseline at week 52 and change from baseline at week 104, N is the number of patients in the FAS (i.e., randomized patients who took at least one dose of study medication and had at least one assessment at or after baseline). The mean and SD for the change from baseline are based on non-missing values.

[b] Value of % calculated by CADTH.

[c] Based on cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (yes, no), baseline eGFR (continuous), and the interaction of time by treatment. Time was treated as a categorical variable.

Source: Clinical Study Report.[58-62]

Fasting plasma glucose

In all five studies, the fasting plasma glucose (FPG) change from baseline over the course of study (Phase A + Phase B) to the end of Phase B is presented in Figure 18 to Figure 22. Overall, in all five included studies, the improvements in FPG observed at the end of Phase A (week 26 or week 52) were maintained or gradually attenuated at Phase B (week 52 or week 104).

Figure 18: LS Mean Change from Baseline in FPG Over Time (cLDA) at Week 52 — Excluding Rescue Approach (MONO Study)

Figure redacted at the request of the manufacturer

cLDA = constrained longitudinal data analysis; FPG = fasting plasma glucose; LS = least squares; SE = standard error.

Source: Clinical Study Report.[61]

Figure 19: LS Mean Change from Baseline in FPG Over Time (cLDA) at Week 104 — Excluding Rescue Approach (MET Study)

Figure redacted at the request of the manufacturer

cLDA = constrained longitudinal data analysis; FPG = fasting plasma glucose; LS = least squares; SE = standard error.

Source: Clinical Study Report.[62]

Figure 20: LS Mean Change from Baseline in FPG Over Time (cLDA) at Week 52 — Excluding Rescue Approach (SU Study)

Figure redacted at the request of the manufacturer

cLDA = constrained longitudinal data analysis; FPG = fasting plasma glucose; LS = least squares; SE = standard error.

Source: Clinical Study Report[58]

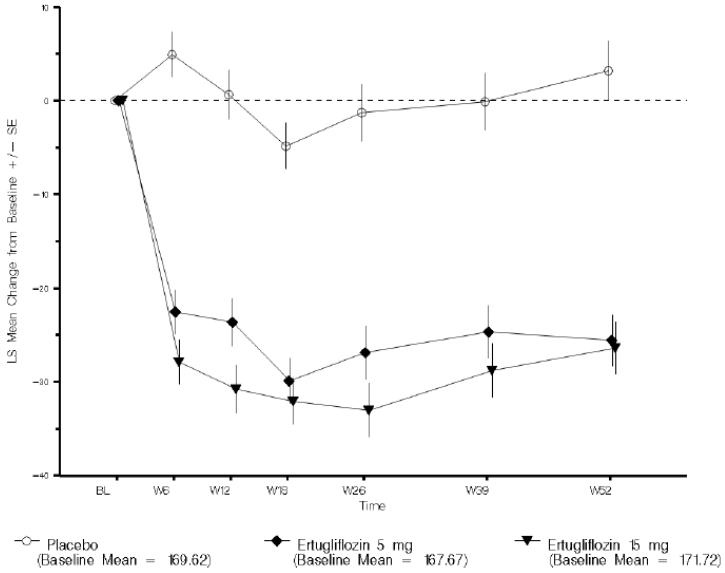
Figure 21: LS Mean Change from Baseline in FPG Over Time (cLDA) at Week 52 — Excluding Rescue Approach (FACTORIAL Study)

Figure redacted at the request of the manufacturer

cLDA = constrained longitudinal data analysis; FPG = fasting plasma glucose; LS = least squares; SE = standard error.

Source: Clinical Study Report.[59]

Figure 22: LS Mean Change from Baseline in FPG Over Time (cLDA) at Week 52 — Excluding Rescue Approach (SITA 2 Study)



cLDA = constrained longitudinal data analysis; FPG = fasting plasma glucose; LS = least squares; SE = standard error.

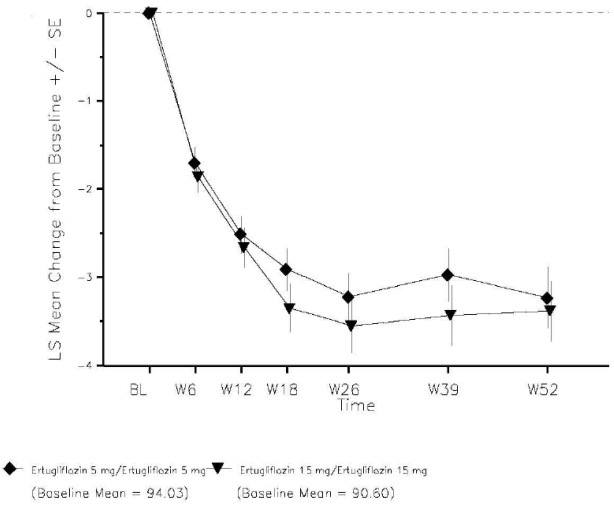
Source: Clinical Study Report.[60]

Body weight

The changes in body weight during the course of the study (Phase A and Phase B) are presented in Figure 23 to Table 27. The reduction from baseline to the end of Phase B (at week 52 or week 104) is presented in Table 33.

In the MONO study at week 52, both ERT groups showed a reduction of body weight compared with baseline. For both ERT groups, LS mean reductions in body weight from baseline observed at week 26 were maintained through week 52. The LS mean changes from baseline at week 52 were similar in the ERT 15 mg and 5 mg groups. (Figure 23)

Figure 23: LS Mean Change from Baseline in Body Weight Over Time (cLDA) at Week 52 — Excluding Rescue Approach (MONO Study)



cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error.

Source: Clinical Study Report.[61]

In the MET study, at week 104, ERT at both doses showed a reduction of body weight compared with baseline. For both ERT groups, LS mean reductions in body weight from baseline to week 26 were maintained through week 104. The observed LS mean changes from baseline at week 104 were similar in the ERT 15 mg and 5 mg groups (Figure 24: LS Mean Change from Baseline in Body Weight Over Time (CLDA) at Week 104 — Excluding Rescue Approach (MET Study)).

The observed mean reduction from baseline in body weight was greater for the ERT treatment groups than for the placebo/glimepiride group at each time point through week 104.

Figure 24: LS Mean Change from Baseline in Body Weight Over Time (CLDA) at Week 104 — Excluding Rescue Approach (MET Study)

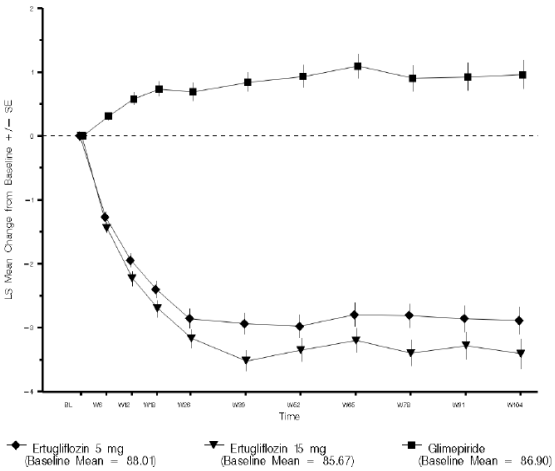
Figure redacted at the request of the manufacturer

cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error.

Source: Clinical Study Report.[62]

In the SU study, the LS mean reductions from baseline in body weight at week 104 were greater in the ERT groups compared with the glimepiride group (Figure 24). Mean body weight reductions in the ERT groups observed at week 52 were maintained through week 104.

Figure 24: LS Mean Change from Baseline in Body Weight Over Time (cLDA) at Week 52 — Excluding Rescue Approach (SU Study)

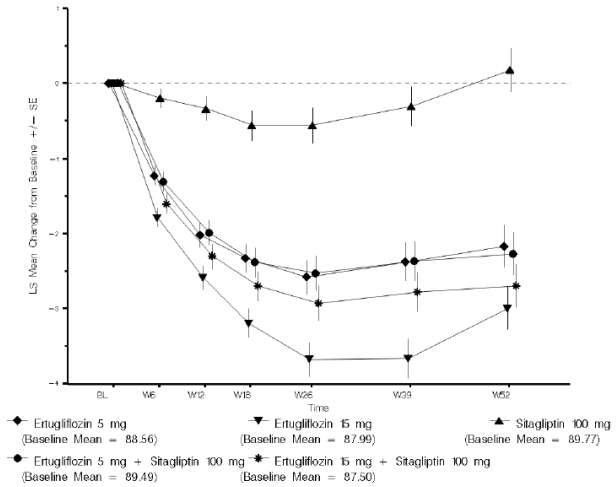


cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error.

Source: Clinical Study Report.[58]

In the FACTORIAL study, at week 52, LS mean reductions from baseline in body weight in the ERT15 mg/SITA100 mg and ERT 5 mg/SITA100 mg groups were greater than in the SITA 100 mg group, and were consistent with those in the ERT5 and ERT15 groups. Reductions observed at week 26 generally were maintained at week 52 in the four ERT groups. No body weight reduction observed at week 52 in the SITA100 mg group compared with baseline (Figure 25).

Figure 25: LS Mean Change from Baseline in Body Weight Over Time (cLDA) at Week 52 — Excluding Rescue Approach (FACTORIAL Study)

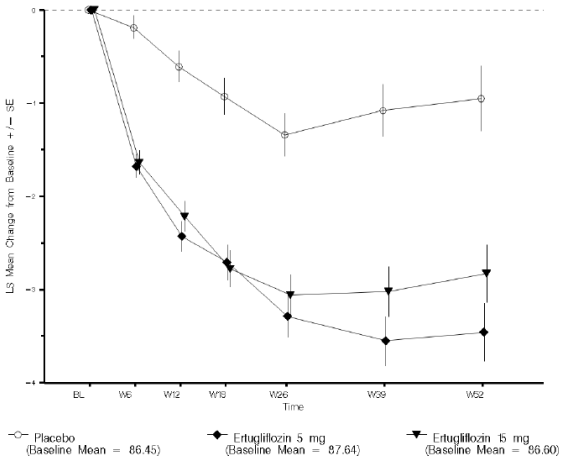


cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error.

Source: Clinical Study Report.[59]

In the SITA2 study, the LS mean reductions from baseline in body weight at week 52 were greater in the ERT 15 mg and 5 mg groups than in the placebo group. In both ERT groups, reductions from baseline in body weight through week 26 were maintained through week 52. There was a small improvement in body weight reduction in the ERT 5 mg group compared with the ERT 15 mg group at week 52 (Figure 26).

Figure 26: LS Mean Change from Baseline in Body Weight Over Time (cLDA) at Week 52 — Excluding Rescue Approach (SITA2 Study)



cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error.

Source: Clinical Study Report.[60]

Table 33: Change from Baseline in Body Weight at Week 52 or Week 104 (cLDA, FAS) — Excluding Rescue Approach

MONO							
Treatment	Baseline		Week 52		Change from Baseline at Week 52		
	N[a]	Mean (SD)	N(%)[ab]	Mean (SD)	N[a]	Mean (SD)	LS Mean (95% CI)[c]
ERT 5 mg	156	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT15 mg	152	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MET							
Treatment	Baseline		Week 104		Change from Baseline at Week 104		
	N[a]	Mean (SD)	N(%)[ab]	Mean (SD)	N[a]	Mean (SD)	LS mean (95% CI)[c]
ERT 5 mg/ERT 5 mg	207	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT 5 mg/ERT 15 mg	205	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SU							
Treatment	Baseline		week 104		Change from Baseline at Week 104		
	N[a]	Mean (SD)	N(%)[ab]	Mean (SD)	N[a]	Mean (SD)	LS mean (95% CI)[c]
ERT 5 mg	445	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT 15 mg	435	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GLIM	435	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison							Difference in LS Means (95% CI)
ERT 5 mg vs. GLIM							[redacted]
ERT 15 mg vs. GLIM							[redacted]

FACTORIAL							
Treatment	Baseline		Week 52		Change from Baseline at Week 52		
	N[a]	Mean (SD)	N(%)[ab]	Mean (SD)	N[a]	Mean (SD)	LS mean (95% CI)[c]
ERT 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SIT 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT 5 mg + SIT 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT 15 mg + SIT 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison							Difference in LS Means (95% CI)
ERT 5 mg + SIT 100 mg vs. ERT 5 mg							[redacted]
ERT 5 mg + SIT 100 mg vs. SITA 100 mg							[redacted]
ERT 15 mg + SIT 100 mg vs. ERT 15 mg							[redacted]
ERT 15 mg + SITA 100 mg vs. SITA 100 mg							[redacted]

FACTORIAL							
Treatment	Baseline		Week 52		Change from Baseline at Week 52		
	N[a]	Mean (SD)	N(%)[ab]	Mean (SD)	N[a]	Mean (SD)	LS mean (95% CI)[c]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERT 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison							Difference in LS Means(95% CI)
ERT 5 mg vs. Placebo							[redacted]
ERT 15 mg vs. Placebo							[redacted]

CI = confidence interval; cLDA = constrained longitudinal data analysis; ERT = ertugliflozin; FAS = full analysis set; GLIM = glimepiride; A1C = hemoglobin A1C; LS = least squares; MET = metformin; SD= standard deviation; SIT = sitagliptin.

[a] For baseline, week 52, and week 104, N is the number of patients with non-missing assessments at the specific time point; for change from baseline at week 52 and change from baseline at week 104, N is the number of patients in the FAS (i.e., randomized patients who took at least one dose of study medication and had at least one assessment at or after baseline). The mean and SD for the change from baseline are based on non-missing values. Treatment time was treated as a categorical variable.

[b] The value of % calculated by CADTH.

[c] Based on cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (yes, no), baseline eGFR (continuous), and the interaction of time by.

Source: Clinical Study Report.[58-62]

Safety

The adverse events, serious adverse events, and notable adverse events reported during the study course (Phase A + Phase B) are presented in Table 34.

At the end of the study (including Phase A + Phase B), the frequency of treatment-emergent adverse events in each individual group ranged from 56% to 76% across the five included studies (Table 34). Patients discontinued study drug due to adverse events in each study arm ranging from 2.4% to 8.2% across all the studies. The number of deaths reported in each study ranged from 0 to 10 (0.08%). The frequency of serious adverse events in each study arm ranged from 2.0% to 19.4% across all the studies. It was observed that several fracture cases (from 0% to 1% in the placebo (control) group, 0% to 2.2% in the ERT 5 mg group, and 1.3% to 3.3% in the ERT 15 mg treatment group) were reported at the end of Phase B (Table 34), which were not reported at the end of Phase A. Overall the safety profile (Phase A + Phase B) was similar to that observed at the end of Phase A.

Table 34: Summary of Harms in Phase A + Phase B (Including Rescue Approach)

MONO	Number of Patients with AEs (Phase A + B) at Week 52, n, (%)		
	Placebo/Metformin n = 153	ERT 5 mg n = 156	ERT 15 mg n = 152
≥ 1 AE	[redacted]	[redacted]	[redacted]
≥ 1 SAE	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]
Discontinued study medication due to AE	[redacted]	[redacted]	[redacted]
Notable AEs			
ketoacidosis	[redacted]	[redacted]	[redacted]
symptomatic hypoglycemia, < 3.9 mmol/L	[redacted]	[redacted]	[redacted]
hypovolemia	[redacted]	[redacted]	[redacted]
renal impairment	[redacted]	[redacted]	[redacted]
lower limb amputation (limb traumatic amputation)	[redacted]	[redacted]	[redacted]
genital or urinary tract infections	[redacted]	[redacted]	[redacted]
genital mycotic infections (male)	[redacted]	[redacted]	[redacted]
genital mycotic infections (female)	[redacted]	[redacted]	[redacted]
complicated UTI	[redacted]	[redacted]	[redacted]
fractures	[redacted]	[redacted]	[redacted]
MET	**Number of Patients with AEs (Phase A + B) at Week 52, n, (%)**		
	Placebo/Glimepiride n = 209	ERT 5 mg n = 207	ERT 15 mg n = 205
≥ 1 AE	[redacted]	[redacted]	[redacted]
≥ 1 SAE	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]
Discontinued study medication due to AE	[redacted]	[redacted]	[redacted]
Notable AEs			
ketoacidosis	[redacted]	[redacted]	[redacted]
symptomatic hypoglycemia, < 3.9 mmol/L	[redacted]	[redacted]	[redacted]
hypovolemia	[redacted]	[redacted]	[redacted]
renal impairment	[redacted]	[redacted]	[redacted]
lower limb amputation (limb traumatic amputation)	[redacted]	[redacted]	[redacted]
genital or urinary tract infections	[redacted]	[redacted]	[redacted]
genital mycotic infections (male)	[redacted]	[redacted]	[redacted]
genital mycotic infections (female)	[redacted]	[redacted]	[redacted]
fractures	[redacted]	[redacted]	[redacted]

SU	Number of Patients with AEs (Phase A + B) at Week 52, n, (%)		
	ERT 5 mg n = 445	ERT 15 mg n = 435	Glimepiride n = 435
≥ 1 AE	[redacted]	[redacted]	[redacted]
≥ 1 SAE	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]
Discontinued study medication due to AE	[redacted]	[redacted]	[redacted]
Notable AEs			
ketoacidosis	[redacted]	[redacted]	[redacted]
symptomatic hypoglycemia, < 3.9 mmol/L	[redacted]	[redacted]	[redacted]
hypovolemia	[redacted]	[redacted]	[redacted]
renal impairment	[redacted]	[redacted]	[redacted]
lower limb amputation (limb traumatic amputation)	[redacted]	[redacted]	[redacted]
genital or urinary tract infections	[redacted]	[redacted]	[redacted]
genital mycotic infections (male)	[redacted]	[redacted]	[redacted]
genital mycotic infections (female)	[redacted]	[redacted]	[redacted]
fractures	[redacted]	[redacted]	[redacted]
FACTORIAL	**Number of Patients with AEs (Phase A + B) at Week 52, n, (%)**		
	ERT 5 mg n = 250	ERT 15 mg n = 248	SIT 100mg n = 247
≥1 AE	[redacted]	[redacted]	[redacted]
≥1 SAE	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]
Discontinued study medication due to AE	[redacted]	[redacted]	[redacted]
Notable AEs			
ketoacidosis	[redacted]	[redacted]	[redacted]
symptomatic hypoglycemia, < 3.9 mmol/L	[redacted]	[redacted]	[redacted]
hypovolemia	[redacted]	[redacted]	[redacted]
renal impairment	[redacted]	[redacted]	[redacted]
lower limb amputation (limb traumatic amputation)	[redacted]	[redacted]	[redacted]
genital or urinary tract infections	[redacted]	[redacted]	[redacted]
genital mycotic infections (male)	[redacted]	[redacted]	[redacted]
genital mycotic infections (female)	[redacted]	[redacted]	[redacted]
fractures	[redacted]	[redacted]	[redacted]

FACTORIAL (continued)	Number of Patients with AEs (Phase A + B) at Week 52, n, (%)		
	ERT 5 mg + SIT 100mg n = 243	ERT 15mg + SIT 100mg n = 244	
≥ 1 AE	[redacted]	[redacted]	
≥ 1 SAE	[redacted]	[redacted]	
Deaths	[redacted]	[redacted]	
Discontinued study medication due to AE	[redacted]	[redacted]	
Notable AEs			
ketoacidosis	[redacted]	[redacted]	
symptomatic hypoglycemia, < 3.9 mmol/L	[redacted]	[redacted]	
hypovolemia	[redacted]	[redacted]	
renal impairment	[redacted]	[redacted]	
lower limb amputation (limb traumatic amputation)	[redacted]	[redacted]	
genital or urinary tract infections	[redacted]	[redacted]	
genital mycotic infections) (male)	[redacted]	[redacted]	
genital mycotic infections) (female)	[redacted]	[redacted]	
fractures	[redacted]	[redacted]	
SITA2	**Number of Patients with AEs (Phase A + B) at Week 52, n, (%)**		
	Placebo n = 153	**ERT 5 mg = 156**	**ERT 15 mg = 153**
≥ 1 AE	[redacted]	[redacted]	[redacted]
≥ 1 SAE	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]
Discontinued study medication due to AE	[redacted]	[redacted]	[redacted]
Notable AEs			
ketoacidosis	[redacted]	[redacted]	[redacted]
symptomatic hypoglycemia, < 3.9 mmol/L	[redacted]	[redacted]	[redacted]
hypovolemia	[redacted]	[redacted]	[redacted]
renal impairment	[redacted]	[redacted]	[redacted]
lower limb amputation (limb traumatic amputation)	[redacted]	[redacted]	[redacted]
genital or urinary tract infections	[redacted]	[redacted]	[redacted]
genital mycotic infections (male)	[redacted]	[redacted]	[redacted]
genital mycotic infections (female)	[redacted]	[redacted]	[redacted]
fractures	[redacted]	[redacted]	[redacted]

AE = adverse event; ERT = ertugliflozin; SAE = serious adverse event; SIT = sitagliptin.

Note: Data are presented as n (%), including rescue therapy. In addition, some of the % values were calculated by the CDR reviewer.

Source: Clinical Study Reports.[58-62]

Limitation

Although in the extension periods (Phase B), patients generally remained in their randomized treatment groups and the blind treatment was maintained, there are several limitations to these data. Only 48% to 75% of patients in each individual treatment group across all five studies were included in the analysis of the change from the baseline in A1C. This was due in part to the excluding rescue approach (Table 32), which excluded any outcome data after the start of rescue therapy. In addition, no efficacy data were collected for patients who stopped treatment early, after treatment had been discontinued. Since the missing data were associated with treatment discontinuation and poor glycemic control, it

would not be considered missing at random, and may potentially impact the results of the studies. Considering the differential frequency of rescue and early discontinuation in the placebo and ERT groups, the ERT treatment effects may be overestimated. Moreover, all of the outcomes measured at end of Phase B were considered as either secondary or other outcomes; no efficacy hypotheses were tested in the Phase A + B analyses, no multiplicity procedures were applied, and the estimation of between-group differences (95% CI) were provided without adjustment for multiplicity; therefore, all results should interpreted with caution.

Summary

The improvements in A1C, FPG, and body weight that were observed at the end of Phase A (week 26 or week 52) of all five included studies were maintained or gradually attenuated at week 52 or week 104. The estimated comparative efficacy findings reported at the end of Phase B should be interpreted with caution because the percentage of patients not included in the analysis by using the excluding rescue approach was high; no efficacy hypotheses were tested in the Phase A + B analyses, and the estimation of the between-group differences (95% CI) were provided without adjustment for multiplicity.

The overall safety profile observed at the end of Phase B was similar to that observed at the end of Phase A. It was observed that a few of patients (0% to 3.3% across the individual treatment groups) reported fracture in the extension period, although fracture rate is very low. The CDR clinical expert consulted for this review indicated that the adverse events of fracture associated with ERT have drawn attention clinically, although it is unclear by what mechanism the SGLT2 inhibitors may cause fractures.

Appendix 6: Summary of Indirect Comparisons

Introduction

Ertugliflozin (ERT) is a sodium-glucose cotransporter-2 (SGLT2) inhibitor that has been approved for treatment in adults with type 2 diabetes mellitus (T2DM) as monotherapy and in combination with metformin or metformin plus sitagliptin. There are presently three other approved SGLT2 inhibitors in Canada. Given that other T2DM treatments are already on the market and there is an absence of head-to-head studies, the objective of this review is to summarize and critically appraise the manufacturer-submitted indirect comparisons (IDCs) that assess the comparative efficacy and safety of ERT either as monotherapy or in combination with other drugs for the treatment of T2DM versus other similar treatments.

Methods

The manufacturer submitted two IDCs which were reviewed, summarized, and critically appraised. They first explored ERT as monotherapy and the second investigated ERT in combination with metformin. The methods and analysis used in both were similar and drew from the same systematic review. They will be reported here in parallel.

Objectives and Rationale for Manufacturer's IDC

The primary aim of the manufacturer's IDCs was to evaluate the efficacy and safety of ERT alone or in combination with metformin versus other available SGLT2 inhibitors for the treatment of T2DM.

Study Eligibility and Selection Process

Literature search

Relevant studies were identified by searches of Embase, MEDLINE, and Cochrane Central Register of Controlled. The search was up to December 19, 2016, and was limited to studies published in English. In addition, abstracts from conference proceedings published from 2012 to 2016 at either the American Diabetes Association or the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) were included. Lastly, the search leveraged a completed National Institute for Health and Care Excellence (NICE) Health Technology Assessment, European Public Assessment Reports, US FDA label documents, and clinical guidelines from 2010.

Table 35: Population, Interventions, Comparisons, Outcomes, and Study Design Criteria for Study Inclusion

Criteria	Monotherapy	Dual Therapy
Population	• Adults (age ≥ 18) with T2DM • All patients with uncontrolled A1C (≥ 7.0%) with no background therapy	• Adults (age ≥ 18) with T2DM • All patients with uncontrolled A1C (≥ 7.0%) and on MET
Interventions	ERT 5 mg , ERT 15 mg	ERT 5 mg + MET, ERT 15 mg + MET
Comparators	SGLT2 inhibitor (Cana 100 mg /300 mg, Dapa 5 mg/10 mg , Empa 10 mg /25 mg), PL	SGLT2 inhibitor (Cana 100 mg/300 mg, Dapa 5 mg/10 mg, Empa 10 mg /25 mg) + MET, PL + MET
Outcomes	**Continuous outcomes:** A1C, weight (kg), SBP, DBP **Binary outcomes:** A1C within target range (A1C < 7.0%), non-severe hypoglycemia event,[a] severe hypoglycemia event,[a] urinary tract infection, genital tract infection, proportion of patients with one or more adverse event	
Study Design and Factors	• RCTs of included medical therapies • Trials 24 to 26 weeks in duration or data reported at this time point • RCTs with a duration of 24 to 26 weeks	
Language	English	
Search Period	Up to December 19, 2016	

A1C = glycated hemoglobin; Cana = canagliflozin, Dapa = dapagliflozin, DBP = diastolic blood pressure: Empa = empagliflozin, ERT = ertugliflozin; MET = metformin; PL = placebo; RCT = randomized controlled trial; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus.

[a] Adverse event definitions may vary across studies.

Source: Adopted from manufacturer's submitted IDCs.[50,51]

Eligibility criteria

Studies were eligible for inclusion that: were RCTs, irrespective of blinding status; enrolled adults (18+ years) with any diagnosis of uncontrolled T2DM (A1C ≥ 7.0%); and had a duration of at least 24 and no more than 26 weeks.

Study selection

Two reviewers independently screened citation titles and abstracts and selected full-text published articles based on predefined eligibility criteria. At each stage, a third independent reviewer resolved any discrepancies that arose between reviewers.

Data extraction

Two independent reviewers conducted the data extraction, which was compared for accuracy. A third independent reviewer resolved any discrepancies. Data were extracted on study characteristics, interventions, patient characteristics, and outcomes in duplicate for the final list of included studies.

Comparators

Comparators of interest were placebo and other currently available SGLT2 inhibitors, including:

- placebo (PL)
- canagliflozin (Cana)
- dapagliflozin (Dapa)
- empagliflozin (Empa).

All comparators were categorized by low- and high-dose and analyzed separately. Dose categories were guided by the approved labelling for each product.

Outcomes

The primary efficacy outcomes were:

- glycated hemoglobin (A1C) change (%)
- weight change (kg)
- systolic blood pressure (SBP) (mm Hg)
- diastolic blood pressure (DBP) (mm Hg)
- A1C within target range (< 7.0%).

Secondary safety outcomes were:

- non-severe hypoglycemic event[a]
- severe hypoglycemic event requiring medical attention a
- urinary tract infections
- genital tract infections
- proportion of patients with one or more adverse event.

Quality assessment of included studies

One independent reviewer assessed study quality using Grades of Recommendation, Assessment, Development and Evaluation Working group (GRADE) guidelines. No sensitivity analysis was conducted applying the quality assessment results to exclude studies.

Indirect Comparison Methods

The submitted IDC used a Bayesian-based analysis to conduct multiple network meta-analyses. Both fixed- and random-effects models were conducted, but only one model was chosen per outcome based on deviance information criterion (DIC) and the total residual deviance. The DIC provides a measure of model fit with lower values of the DIC suggesting a more parsimonious model. The analysis was planned a priori and it was not clear what prior distribution was used. Meta-regression was considered to adjust for differences in key study level effect modifiers (i.e., baseline A1C). However, due to data limitations that prevented convergence of networks, it was not possible to control for differences in effect modifiers via meta-regression. Convergence was assessed by visual inspection of the trace and density plots and the autocorrelation as well as reviewing the 95% credible interval (CrI). Analyses were conducted using a Markov Chain Monte Carlo method. A burn-in of at least 50,000 simulations was discarded and three chains were used. All results presented were based on a sample of at least 100,000 simulations or until convergence was achieved. Monte Carlo error was used to assess the degree of autocorrelation. The analysis was conducted using WinBUGS software package with the selection on models based on suggestions per the NICE Decision Support Unit. The methodology also followed guidance from the ISPOR Task Force on Indirect Treatment Comparisons.

The submitted IDC also included sensitivity analysis in which outlier trials were removed based on A1C inclusion criteria and any trials that were not connected to the network via a

[a] Due to insufficient data and number of zero events, non-severe hypoglycemia and severe hypoglycemia models did not converge and were not reported.

placebo arm. This sensitivity analyses were run for only two outcomes: A1C change and weight change. Additional sensitivity analyses, such as meta-regression, were not possible due to sample size. Violations of inconsistency were assessed. Inconsistency in the network was identified using Bucher tests, which allowed for the comparison of direct and indirect evidence for all closed loops. *P* values less than 0.05 were considered evidence of potential inconsistency.

Results were presented with estimates for treatment effects of each drug relative to the reference treatments. Relative treatment effects were reported by the median and 95% CrIs. The results of the network meta-analyses were presented only using league tables with relative treatment effect estimates between all interventions of interest along with 95% CrI for all outcomes. The analyses conducted consisted of both continuous and binary outcomes. The results corresponding to binary outcomes were represented by median odds ratios (ORs) and 95% CrIs. Continuous values were reported using the median of the mean difference from baseline. The results tables display the median of the mean differences (MD) and OR for continuous and binary outcomes, respectively, with associated CrI for the selected base-case scenario (whether random effects or fixed effects).

Results

Monotherapy

The systematic review identified 10,566 publications identified through Embase, MEDLINE, and Cochrane Central Register of Controlled Trials. One additional citation was identified outside of the database search. Overall, 11 trials met the criteria for inclusion (Table 36). All of the included trials were parallel, double-blind, multi-centre clinical trials; all but two of the studies were multinational studies, and six of the studies included Canadian centres.

The quality assessment conducted found that all studies were of high quality. All trials were randomized; however not all of them report how randomization was achieved or how allocation was concealed. Other patient interventions (i.e., diet and exercise recommendations) were consistent between interventions for all studies. Outcome measures were reported consistently and follow-up time for studies was similar (24 to 26 weeks), by design, to reduce potential heterogeneity from varying intervention lengths.

The majority of trials were limited to treatment-naive patients or at minimum had a treatment washout. A total of 11 trials included a total of 3,927 patients in 25 treatment arms with an average size of 140.3 patients; ranging from 64 to 234. The network was closed with no direct evidence between any of the SGLT2s (Figure 27). The baseline A1C between the different studies ranged from 7.5% to 8.9%. All studies reported age and gender. Age was very similar, with all studies reporting baseline average age of 49.9 to 60.4 years. Baseline weight and BMI were noted to be higher on average in the multinational studies. There was limited variation in SBP and DBP at baseline. Additional details are available in Table 40.

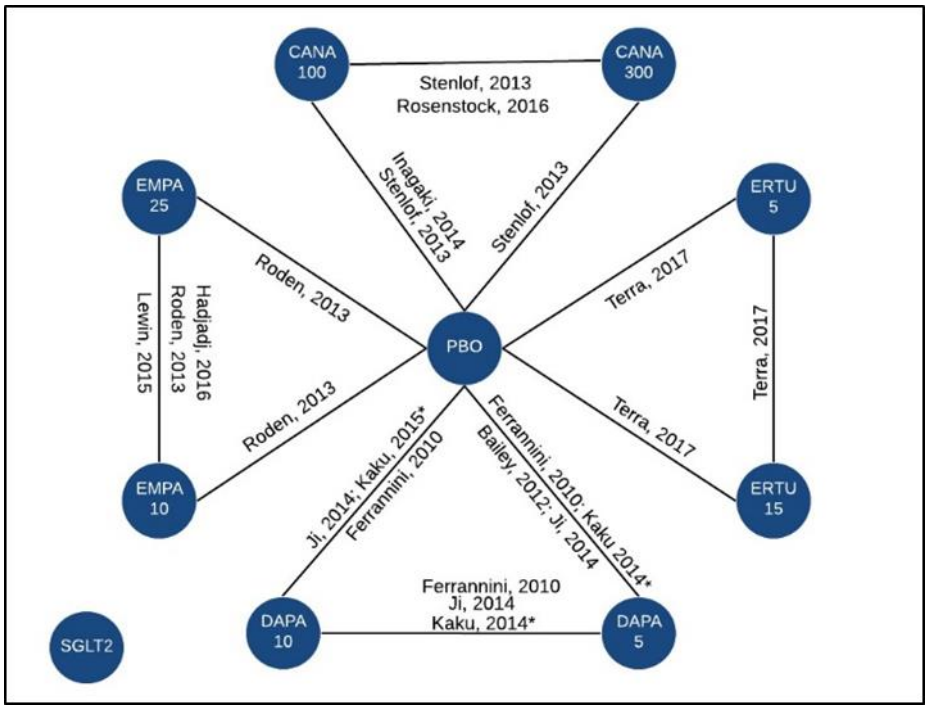
Table 36: Summary of Studies Included and Baseline Characteristics

Characteristics	
Number of Studies	11
Total number of patients	3,927
Average number of patients per treatment arm (range)	140.3 (64 to 234)
Baseline Characteristics (mean [range] per arm)	
Age (years)	54.8 (49.9 to 60.4)
% Female	45% (34% to 59%)
A1C (%)	8.1 (7.5 to 8.9)
Weight (kg)	82.0 (65.8 to 94.2)
BMI (kg/m^2)	29.8 (24.9 to 33.6)
SBP (mm Hg)	127.9 (122.0 to 133.0)
DBP (mm Hg)	78.5 (77.0 to 80.0)
FPG (mg/dL)	165 (138 to 196)
Disease duration (years)	3.2 (0.3 to 5.6)

A1C = glycated hemoglobin; BMI = body mass index; DBP = diastolic blood pressure; FPG = fasting plasma glucose; SBP = systolic blood pressure.

Source: Manufacturer's submitted IDC.[51]

Figure 27: Network of Trials for Network Meta-Analysis for Monotherapy



CANA = canagliflozin, DAPA = dapagliflozin, EMPA = empagliflozin, ERTU = ertugliflozin; PL = placebo; SGLT2 = sodium-glucose cotransporter-2.

Source: Adopted from manufacturer's submitted IDC.[51]

Network Meta-analysis

Overall, ERT doses were as efficacious for reducing A1C and weight loss versus SGLT2 inhibitors of similar doses (Table 37). All 11 included studies reported change in A1C and weight loss. Both low- and high-dose ERT were found to reduce A1C versus placebo which was also true for all other SGLT2 inhibitors. The highest A1C reductions versus placebo were found with ERT and canagliflozin. Comparatively, lower-dose ERT was no different than other low-dose SGLT2 inhibitors. Higher-dose ERT significantly reduced A1C versus high-dose dapagliflozin and empagliflozin. There were no significant differences found between any of the SGLT2 inhibitors and placebo for change in weight. Both low- and high-dose ERT were found to be no different than other SGLT2 inhibitors at equal doses.

Importantly, sensitivity analysis conducted did change results. In sensitivity analyses for A1C, adding the Kaku 2014 Study (an outlier study due to its inclusion of patients with A1C < 7%) resulted in ERT 5 mg becoming statistically significantly more effective versus both low- and high-dose dapagliflozin. In another sensitivity analysis, dropping dapagliflozin 5 mg (a dose that is not commonly used for T2DM) did not impact base-case results. The same sensitivity analyses were run for weight change, but these tests did not impact base-case findings. Also, the limited number of studies meant further sensitivity analyses (i.e., meta-regression) were not possible for all outcomes. For other efficacy outcomes (weight change, blood pressure changes, and reaching A1C targets) there were no statistically significant differences between ERT and similar doses of SGLT2 inhibitors, although ERT was sometimes superior to placebo. These results were found in both base cases and the sensitivity analyses.

In terms of safety, the only outcome of the outcomes studied that had a reliable model converge was urinary tract infection. There were no statistically significant differences between ERT and other SGLT2 inhibitors and placebo. There were no statistically significant differences between SGLT2 inhibitors of similar doses. The authors conclude that there are no differences in adverse events but both non-severe hypoglycemia and genital tract infection models did not produce meaningful results due to non-convergence or poor model performance.

Table 37: Summary of Results for the Outcomes in Monotherapy Network

Outcome	Model		PL	Cana 100/300	Dapa 5/10	Empa 10/25	Summary of Base-Case Results
A1C change (%) MD (95% CrI)	FEM	ERT5 vs low-dose SGLT2	**–0.99 (–1.23 to –0.75)**	0.01 (–0.27 to 0.28)	–0.24 (–0.52 to 0.04)	–0.24 (–0.51 to 0.03)	• Statistically NS differences for ERT5 vs. similar doses. • ERT15 statistically significantly reduces A1C vs. Dapa10 and Empa25.
		ERT15 vs high-dose SGLT2	**–1.16 (–1.4 to –0.93)**	–0.01 (–0.29 to 0.27)	**–0.36 (–0.65 to –0.08)**	**–0.31 (–0.58 to –0.04)**	
Weight change (kg) MD (95% CrI)	REM	ERT5 vs low-dose SGLT2	–1.70 (–4.45 to 1.06)	–1.10 (–4.73 to 2.00)	–0.45 (–3.64 to 2.73)	0.32 (–3.33 to 3.98)	• No statistically significant differences for ERT doses vs. similar dosed SGLT2 inhibitors
		ERT15 vs high-dose SGLT2	–2.1 (–4.83 to 0.62)	–0.19 (–3.91 to 3.12)	–0.42 (–3.77 to 2.84)	–0.04 (–3.70 to 3.59)	
SBP change (mm Hg) MD (95% CrI)	FEM	ERT5 vs low-dose SGLT2	**–3.31 (–6.06 to –0.58)**	1.17 (–2.04 to 4.39)	–0.37 (–3.96 to 3.23)	–0.58 (–4.06 to 2.90)	• ERT5 had no statistically significant differences vs. other SGLT2 inhibitors • ERT15 was statistically significantly less effective in reducing SBP vs. Cana300
		ERT15 vs high-dose SGLT2	–1.70 (–4.46 to 1.05)	**3.45 (0.15 to 6.76)**	1.83 (–1.96 to 5.63)	1.55 (–1.94 to 5.05)	
A1C in target OR (95% CrI)	REM	ERT5 vs low-dose SGLT2	2.66 (0.96 to 7.45)	0.62 (0.17 to 2.10)	1.27 (0.39 to 4.25)	0.58 (0.15 to 2.30)	• No statistically significant differences among SGLT2 inhibitors
		ERT15 vs high-dose SGLT2	**3.78 (1.37 to 10.58)**	0.60 (0.16 to 2.14)	1.36 (0.40 to 4.74)	0.83 (0.21 to 3.25)	
Urinary Tract Infection OR (95% CrI)	FEM	ERT5 vs low-dose SGLT2	0.81 (0.34 to 1.9)	0.52 (0.15 to 1.7)	0.37 (0.11 to 1.26)	0.62 (0.2 to 1.88)	• No statistically significant differences from PL or SGLT2 inhibitors
		ERT15 vs high-dose SGLT2	0.43 (0.14 to 1.14)	0.31 (0.08 to 1.16)	0.31 (0.07 to 1.29)	0.41 (0.11 to 1.41)	
Adverse Events OR (95% CrI)	FEM	ERT5 vs low-dose SGLT2	1.01 (0.65 to 1.58)	0.75 (0.44 to 1.31)	1.11 (0.63 to 1.96)	1.12 (0.63 to 1.97)	• No statistically significant differences from PL or SGLT2 inhibitors
		ERT15 vs high-dose SGLT2	1.16 (0.74 to 1.82)	0.83 (0.47 to 1.46)	1.1 (0.61 to 2.0)	1.39 (0.79 to 2.48)	

A1C = glycated hemoglobin; Cana = canagliflozin, CrI = credible interval; Dapa = dapagliflozin, Empa = empagliflozin, ERT = ertugliflozin; FEM = fixed-effects model; MD = mean difference; NS = not statistically significant; OR = odds ratio; PL = placebo, REM = random-effects model; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter-2.

Note: **Bold indicates statistical significance**. Results are presented as ERT versus comparators. Note that indirect placebo data are presented for completeness. For direct evidence on the performance of ERT versus placebo, please refer to ERT trial data.

Source: Adopted from manufacturer's submitted IDC.[51]

Dual Therapy

The systematic review identified 10,566 publications identified through Embase, MEDLINE, and Cochrane Central Register of Controlled Trials (Table 38). Three additional citations were identified outside of the database search. Overall, eight trials met the criteria for inclusion. All of the included trials were parallel, double-blind, multi-centre clinical trials; all studies were multinational studies, and four of the studies included Canadian centres. The quality assessment conducted found that all studies were of high quality. All base-case studies were double blind and randomized, and randomization allocation concealment was adequate. However, the actual method of allocation concealment was not reported by several studies. Outcome measures were reported consistently and follow-up time for studies were similar (24 to 26 weeks), by design, to reduce potential heterogeneity from varying intervention lengths.

All trials had patients stable on metformin for a minimum of eight weeks on a dosage higher than 1,500 mg daily (Table 38). A total of six trials included a total of 3,951 patients in 19 treatment arms with an average of 188.1 patients per arm, ranging from 89 to 365. The network was closed, with no direct evidence between any of the SGLT2 inhibitors (Figure 28). The baseline A1C between the different studies ranged from 7.2% to 8.6%. All studies reported age and gender. Age was very similar, with all studies reporting baseline average age of 52.7 to 60.8 years. There was limited variation in SBP and at baseline (see Table 41 for additional details).

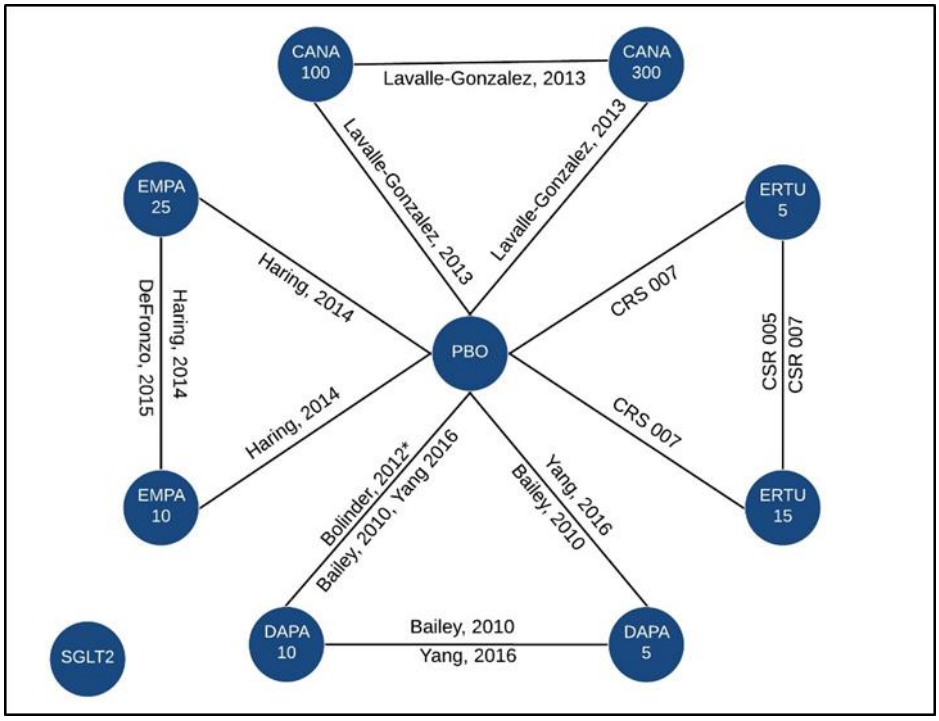
Table 38: Summary of Studies Included and Baseline Characteristics

Characteristics	
Number of Studies	6
Total number of patients	3,951
Average number of patients per study arm (range)	188.1 (89 to 365)
Baseline Characteristics (mean [range] per arm)	
Age (years)	55.6 (52.7 to 60.8)
% Female	48% (41% to 55%)
A1C (%)	8.0 (7.2 to 8.6)
Weight (kg)	84.0 (70.8 to 92.1)
BMI (kg/m^2)	30.4 (25.7 to 32.4)
SBP (mm Hg)	128.8 (126.0 to 132.0)
FPG (mg/dL)	163 (148 to 184)
Disease duration (years)	6.5 (4.2 to 8.1)

A1C = glycated hemoglobin; BMI = body mass index; FPG = fasting plasma glucose; SBP = systolic blood pressure.

Source: Adopted from manufacturer's submitted IDC.[50]

Figure 28: Network of Trials for Network Meta-Analysis for Dual Therapy



CANA = canagliflozin, DAPA = dapagliflozin, EMPA = empagliflozin, ERTU = ertugliflozin; PL = placebo; SGLT2 = sodium-glucose cotransporter-2.

Source: Adopted from manufacturer's submitted IDC.[50]

Network meta-analysis

Overall, ERT was efficacious for lowering A1C (primary outcome) versus placebo and similar to other SGLT2 inhibitors of similar doses (Table 39). All 11 included studies reported change in A1C and weight loss. Both low- and high-dose ERT were found to reduce A1C versus placebo which was also true for all other SGLT2 inhibitors. The highest A1C reductions versus placebo were found with ERT. Comparatively lower-dose ERT significantly reduced A1C versus high-dose dapagliflozin and empagliflozin. Higher-dose ERT was no different than other low-dose SGLT2 inhibitors. Higher-dose ERT significantly reduced baseline weight versus placebo; this was not found for the lower dose. There were no significant differences found between any of the SGLT2 inhibitors and placebo for change in weight. Both low- and high-dose ERT were found to be no different than other SGLT2 inhibitors at equal doses.

Ertugliflozin 15mg was found to be statistically significantly more efficacious versus two of the SGLT2 inhibitors at high-doses, and also, ERT 5mg was statistically significantly more effective versus dapagliflozin 5 mg in the base-case. Importantly, sensitivity analysis conducted did change results. In the first sensitivity analysis, adding Bolinder 2012 Study (an outlier study due to its inclusion of patients with A1C < 7%) ERT 5 mg became statistically significantly more effective versus high-dose dapagliflozin for change in A1C. In the second sensitivity analysis, dropping studies that were not linked to the network via a placebo arm, ERT 5 mg was no longer statistically significantly effective (for an A1C change) versus dapagliflozin, attributed to a wider confidence interval and a reduction in

average effect. For other efficacy outcomes (weight change, blood pressure changes and reaching A1C targets) there were no statistically significant differences between ERT and similar doses of SGLT2 inhibitors and ERT was superior to placebo. These results were found in both base cases and the sensitivity analyses.

In terms of safety outcomes studied the only outcome that had a model converge was urinary tract infection. There were no statistically significant differences between ERT and other SGLT2 inhibitors and placebo. There were no statistically significant differences between SGLT2 inhibitors of similar doses. The authors conclude that there are no differences in adverse events but both non-severe hypoglycemia and genital tract infection models did not produce meaningful results due to non-convergence.

Table 39: Summary of Results for the Outcomes in Dual Therapy Network

Outcome	Model		PL	Cana 100/300	Dapa 5/10	Empa 10/25	Summary of Base-Case Results
A1C change (%) MD (95% CrI)	FEM	ERT5 vs low-dose SGLT2	**–0.73 (–0.89 to –0.57)**	–0.11 (–0.32 to 0.10)	**–0.22 (–0.42 to –0.02)**	–0.14 (–0.34 to 0.07)	• ERT5 point estimate had the highest reduction for low-dose SGLT2 inhibitors and was statistically significantly more effective versus Dapa5 • ERT15 had the highest point estimate reduction and was statistically significantly more effective versus Dapa10 and Empa25
		ERT15 vs high-dose SGLT2	**–0.85 (–1.01 to –0.69)**	–0.08 (–0.29 to 0.13)	**–0.26 (–0.46 to –0.06)**	**–0.23 (–0.44 to –0.03)**	
Weight change (kg) MD (95% CrI)	REM	ERT5 vs low-dose SGLT2	–1.41 (–3.24 to 0.44)	0.79 (–1.88 to 3.49)	0.15 (–2.12 to 2.49)	0.17 (–2.41 to 2.74)	• There were no statistically significant differences among SGLT2 inhibitors of comparable doses
		ERT15 vs high-dose SGLT2	**–1.87 (–3.72 to –0.44)**	0.63 (–2.05 to 3.31)	0.06 (–2.23 to 2.38)	0.19 (–2.38 to 2.78)	
SBP change (mm Hg) MD (95% CrI)	FEM	ERT5 vs low-dose SGLT2	**–3.97 (–6.19 to –1.75)**	1.34 (–1.62 to 4.29)	1.10 (–2.13 to 4.33)	0.13 (–2.82 to 3.07)	• Both doses of ERT were among the most effective SGLT2 inhibitors for this outcome for comparable doses (statistically non-significant)
		ERT15 vs high-dose SGLT2	**–4.2 (–6.43 to –1.96)**	2.42 (–0.55 to 5.37)	0.40 (–2.83 to 3.63)	0.61 (–2.34 to 3.56)	
A1C in target OR (95% CrI)	FEM	ERT5 vs low-dose SGLT2	**2.88 (1.86 to 4.55)**	1.47 (0.82 to 2.64)	0.46 (0.81 to 2.63)	0.70 (0.35 to 1.37)	• Statistically non-significant differences were observed among SGLT2 inhibitors
		ERT15 vs high-dose SGLT2	**3.65 (2.36 to 5.75)**	1.13 (0.63 to 2.04)	1.54 (0.86 to 2.77)	0.81 (0.41 to 1.59)	
Urinary Tract Infection OR (95% CrI)	FEM	ERT5 vs low-dose SGLT2	3.66 (0.89 to 27.48)	1.49 (0.22 to 13.95)	4.24 (0.86 to 35.02)	3.54 (0.66 to 30.37)	• ERT5 had no statistically significant differences versus PL or other SGLT2s SGLT2 inhibitors • ERT15 was statistically significantly more likely to cause the event than PL but no different than other SGLT2 inhibitors
		ERT15 vs high-dose SGLT2	**4.11 (1.01 to 30.81)**	2.37 (0.34 to 22.65)	3.54 (0.74 to 28.91)	3.43 (0.65 to 29)	

Outcome	Model		PL	Cana 100/300	Dapa 5/10	Empa 10/25	Summary of Base-Case Results
Adverse Events OR (95% CrI)	FEM	ERT5 vs low-dose SGLT2	1.08 (0.75 to 1.54)	1.19 (0.71 to 2.01)	0.97 (0.59 to 1.59)	1.23 (0.74 to 2.07)	• No statistically significant differences from PL or SGLT2 inhibitors
		ERT15 vs high-dose SGLT2	1.04 (0.72 to 1.49)	0.8 (0.47 to 1.35)	0.82 (0.5 to 1.35)	1.36 (0.81 to 2.29)	

A1C = glycated hemoglobin; Cana = canagliflozin, CrI = credible interval; Dapa = dapagliflozin, Empa = empagliflozin, ERT = ertugliflozin FEM = fixed-effects model; MD = mean difference; OR = odds ratio; PL = placebo, REM = random-effects model; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter-2.

Note: **Bold indicates significance**. Results are presented as ERT versus comparators. Note that indirect placebo data are presented for completeness, for direct evidence on the performance of ERT versus placebo, please refer to ERT trial data.

Source: Adopted from manufacturer's submitted IDC.[50]

Critical Appraisal

The manufacturer-submitted IDCs were a transparent but limited synthesis of the current evidence. The evidence presented in the two IDCs overall does not refute the conclusion that ERT is more efficacious than placebo, but weakly supports the conclusion that ERT is equivalent to other SGLT2 inhibitors in terms of both safety and efficacy. Importantly, the submitted analyses have limitations that hinder their generalizability and applicability. The major concerns with the submitted IDCs are the utility of the question asked and the limited evidence base utilized. Both of these concerns greatly limit the utility of the results in evaluating the comparative efficacy and safety of the drug both within class and within indication.

The IDCs presented a comprehensive search of multiple databases over a reasonable period. Overall, the methodology presented is in line with current methodological standards for systematic reviews. Screening of studies for eligibility occurred over multiple phases (titles, abstracts, and full texts) by two reviewers working independently. There is concern that conducting quality assessment by only one reviewer would limit the reliability of those results. Importantly, the search was limited to studies that would likely only be of high quality. The review was only conducted up until December 2016, excluding recent evidence which, especially for a newer drug, may limit the inclusion of all available evidence. Although a quality assessment of the studies was completed using the GRADE tool, this information was not applied to any sensitivity analysis.

A significant concern with the evidence presented is that studies included in the analyses were extremely limited by only allowing studies that had a 24- to 26-week follow-up. In limiting the inclusion criteria, the analyses gained a higher level of homogeneity but sacrificed sample size. This limited sample size is also compounded by the fact that the studies were limited to only those that had other SGLT2 inhibitors or placebo. There is a signficant amount of evidence excluded that would be informative, especially for assessing safety that was not included in the analyses. For example, a recently published NMA assessing comparative renal safety of SGLT2 inhibitors[63] had more than 39,741 patients, while the included IDCs only had 3,927 and 3,951, respectively. These limited sample sizes increase the chance that the conclusion of the analysis will be that there is no difference between drugs. Rather than significantly limiting the evidence base, methodologies and analysis could have been leveraged to control for heterogeneity and compare and contrast limited (such as the ones submitted) and expanded networks. Importantly, the limited size of the network sensitivity analyses did sway the results, putting into question the robustness of the analyses.

The second major concern with the evidence presented is the generalizability of the information included. The included IDCs were both limited to within class only. Although this answers a specific question, it is only partially useful in helping address the more critical question of the drug's place in treatment with other T2DM second-line treatments. Importantly, previous CADTH submissions for similar indications and the recent CADTH Therapeutic Review of T2DM was completed for all medications with similar indications. This broader view of the indication not only allows for more information to be included in the network but also improves the clinical generalizability, addressing the primary question of where in practice this drug fits.

Lastly, any assessment of safety is likely inadequate due to the limited evidence included and the rarity of events. Due to the rare instances of adverse events and the high level of statistical heterogeneity, many of the results presented are not informative, as evidenced by extremely wide credible intervals and non-converging models. The majority of outcomes, especially among safety outcomes, were found to be non-informative or with high degrees of inconsistency and wide credible intervals. Additionally, the submitted analysis did not explore other safety outcomes that can assess tolerability. Inclusion of other outcomes such as discontinuation due to adverse events would help allow for a more robust assessment of tolerability and safety. Safety outcomes such as discontinuation due to the adverse event may be more dependable due to their broader definitions. Assessment of safety requires a more nuanced analysis than the ones submitted. Lastly, the safety analyses conducted were limited to six months and thus, similar to most randomized controlled trial (RCT) evidence, the long-term safety of these products is unknown. Overall, there are no signals of potential safety issues presented, however, the evidence does not support any potential superiority of the product, compared with other available products, and it does not evaluate tolerability and long-term or serious adverse events.

Conclusion

The applicability of the manufacturer's IDC is impacted by the limited scope and evidence base included. As described above, the manufacturer's IDC did include an extensive systematic review and robust analyses, but was limited by the tight inclusion criteria and research question, especially regarding comparators and sample size. This restriction significantly limited the utility and the robustness of the results. Results of no difference between drugs may primarily be due to the limited evidence base. Overall, results should be interpreted with caution, given the limitations noted. Based on the results of the submitted IDC, ERT, both as monotherapy and in combination with other drugs for the treatment of T2DM, is likely more efficacious than placebo. Little can be elucidated on the comparative efficacy of ERT to other SGLT2 inhibitors, or on the relative safety of the product.

Table 40: Baseline Patient Demographic and Clinical Characteristics of Included Randomized Controlled Trials in Monotherapy Indirect Comparison

Study	Treatment Arms	N	Age (years)	% Female	A1C (%)	Weight (kg)	BMI (kg/m^2)	SBP (mm Hg)	DBP (mm Hg)	FPG (mg/dL)	Disease Duration (years)
Bailey 2012	PL	65	53.5	46%	7.8	90.0	32.5	129	80	161	1.1
	Dapa5	68	51.3	53%	7.9	85.4	31.0	126	78	157	1.4
	Total/Avg	133	52.4	49%	7.9	87.7	31.7	127	79	159	1.3
Ferrannini 2010	PL	75	52.7	59%	7.8	88.8	32.3	NR	NR	160	0.5
	Dapa5	64	52.6	52%	7.9	87.6	31.9	NR	NR	162	0.3
	Dapa10	70	50.6	51%	8.0	94.2	33.6	NR	NR	167	0.5
	Total/Avg	209	52.0	54%	7.9	90.2	32.6	NA	NA	163	0.4
Hadjadj 2016	Empa25	143	53.3	49%	8.9	83.1	30.6	128	79	176	NR
	Empa10	156	53.1	43%	8.6	83.8	30.3	128	79	169	NR
	Total/Avg	299	53.2	46%	8.7	83.5	30.5	128	79	173	NA
Inagaki 2014	PL	93	58.2	35%	8.0	68.6	25.9	128	78	163	5.6
	Cana100	90	58.4	34%	8.0	69.1	25.6	127	78	158	4.7
	Total/Avg	183	58.3	35%	8.0	68.8	25.7	128	78	160	5.2
Ji 2014	PL	132	49.9	34%	8.4	72.2	25.9	124	79	167	1.3
	Dapa5	128	53.0	34%	8.1	68.9	25.2	124	77	154	1.2
	Dapa10	133	51.2	35%	8.3	70.9	25.8	124	78	162	1.7
	Total/Avg	393	51.4	35%	8.3	70.7	25.6	124	78	161	1.4
Kaku 2014*	PL	87	60.4	40%	7.5	66.0	25.2	127	NR	140	5.3
	Dapa5	86	58.6	42%	7.5	65.8	24.9	122	NR	138	4.6
	Dapa10	88	57.5	40%	7.5	69.7	26.1	126	NR	139	4.9
	Total/Avg	261	58.8	41%	7.5	67.2	25.4	125	NA	139	4.9
Lewin 2015	Empa25	133	56.0	42%	8.0	86.7	31.2	129	79	153	NR
	Empa10	132	53.9	52%	8.1	87.8	31.5	129	79	160	NR
	Total/Avg	265	55.0	47%	8.0	87.3	31.4	129	79	157	NA
Roden 2013	PL	228	54.9	46%	7.9	78.2	28.7	130	79	NR	NR
	Empa10	224	56.2	37%	7.9	78.4	28.3	133	79	NR	NR
	Empa25	224	53.8	35%	7.9	77.8	28.2	130	78	NR	NR
	Total/Avg	676	55.0	39%	7.9	78.1	28.4	131	79	NA	NA
Rosenstock 2016	Cana100	230	54.0	56%	8.8	90.2	32.4	129	79	196	3.5
	Cana300	234	55.8	48%	8.8	93.0	32.6	130	79	193	3.3
	Total	464	54.9	52%	8.8	91.6	32.5	130	79	195	3.4
Stenlof 2013	PL	192	55.7	54%	8.0	87.6	31.8	128	77	167	4.2
	Cana100	195	55.1	58%	8.1	85.8	31.3	127	78	173	4.5

Study	Treatment Arms	N	Age (years)	% Female	A1C (%)	Weight (kg)	BMI (kg/m^2)	SBP (mm Hg)	DBP (mm Hg)	FPG (mg/dL)	Disease Duration (years)
	Cana300	197	55.3	55%	8.0	86.9	31.7	129	79	173	4.3
	Total/Avg	584	55.4	56%	8.0	86.8	31.6	128	78	171	4.3
Terra 2017	PL	153	56.1	46%	8.1	94.2	33.3	130	78	180	4.6
	ERT5	156	56.8	43%	8.2	94.0	33.2	130	78	180	5.1
	ERT15	151	56.2	40%	8.4	90.6	32.5	130	78	178	5.2
	Total/Avg	460	56.4	43%	8.2	92.9	33.0	130	78	179	5.0

A1C = glycated hemoglobin; Avg = average; BMI = body mass index; Cana = canagliflozin; Dapa = dapagliflozin; DBP = diastolic blood pressure; Empa = empagliflozin; ERT = ertugliflozin FPG = fasting plasma glucose; MD = mean difference; NA = not applicable; NR = not reported; PL = placebo; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter-2.

Source: Adopted from manufacturer's submitted IDC.[51]

Table 41: Baseline Patient Demographic and Clinical Characteristics of included Randomized Controlled Trials in Dual Therapy Indirect Comparison

Reference	Treatment Arms	N	Age (years)	% Female	A1C (%)	Weight (kg)	BMI (kg/m^2)	SBP (mm Hg)	FPG (mg/dL)	Disease Duration (years)
Bailey 2010	MET + PL	134	53.7	45%	8.1	87.7	31.8	128	165	5.8
	MET + Dapa5	133	54.3	48%	8.2	84.7	31.4	127	169	6.4
	MET + Dapa10	132	52.7	42%	7.9	86.3	31.2	126	156	6.1
	Total/Avg	399	53.6	45%	8.1	86.2	31.5	127	163	6.1
Bolinder 2012	MET + PL	91	60.8	44%	7.2	90.9	31.7	NR	150	5.5
	MET + Dapa10	89	60.6	45%	7.2	92.1	32.1	NR	148	6.0
	Total/Avg	180	60.7	44%	7.2	91.5	31.9	NR	149	5.7
CSR 005	MET + ERT5	[redacted]								
	MET + ERT15	[redacted]								
	Total/Avg	[redacted]								
CSR 007	MET + ERT5	[redacted]								
	MET + ERT15	[redacted]								
	MET + PL	[redacted]								
	Total/Avg	[redacted]								
DeFronzo 2015	MET + Empa10	137	56.1	43%	8.0	86.1	30.9	132	162	NR
	MET + Empa25	140	55.5	54%	8.0	87.7	31.8	129	160	NR
	Total/Avg	277	55.8	48%	8.0	86.9	31.4	130	161	NR
Häring 2014	MET + PL	207	56.0	44%	7.9	79.7	28.7	129	156	NR
	MET + Empa10	217	55.5	42%	7.9	81.6	29.1	130	154	NR
	MET + Empa25	213	55.6	44%	7.9	82.2	29.7	130	149	NR
	Total/Avg	637	55.7	43%	7.9	81.2	29.2	129	153	NR
Lavalle-	MET + PL	181	55.3	49%	8.0	86.6	31.1	NR	164	6.8

Reference	Treatment Arms	N	Age (years)	% Female	A1C (%)	Weight (kg)	BMI (kg/m^2)	SBP (mm Hg)	FPG (mg/dL)	Disease Duration (years)
González 2013	MET + Cana100	365	55.5	53%	7.9	88.8	32.4	128	167	6.7
	MET + Cana300	360	55.3	55%	7.9	85.4	31.4	129	173	7.1
	Total/Avg	906	55.4	53%	7.9	87.0	31.7	128	169	6.9
Yang 2016	MET + PL	139	53.5	41%	8.1	70.9	25.7	126	166	5.3
	MET + Dapa5	146	53.1	54%	8.1	70.8	26.4	129	162	4.2
	MET + Dapa10	149	54.6	42%	8.2	71.4	26.2	127	162	5.3
	Total/Avg	434	53.7	46%	8.1	71.0	26.1	127	163	4.9

A1C = glycated hemoglobin; Avg = average; BMI = body mass index; Cana = canagliflozin; CSR = Clinical Study Report; Dapa = dapagliflozin; DBP = diastolic blood pressure; Empa = empagliflozin; ERT = ertugliflozin FPG = fasting plasma glucose; MD = mean difference; MET = metformin; NR = not reported; PL = placebo; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter-2.

Source: Adopted from manufacturer's submitted IDC.[50]

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