CADTH

CADTH COMMON DRUG REVIEW

Common Drug Review New Combination Product

Ertugliflozin/Metformin Fixed-Dose Combination (SEGLUROMET)

Merck Canada Inc.

Indication: Type 2 Diabetes Mellitus

Service Line:	CADTH Common Drug Review
Version:	Final (with redactions)
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Abbreviations

A1C	glycated hemoglobin
AE	adverse event
AHA	antihyperglycemic agent
BE	bioequivalence
BMI	body mass index
CDR	CADTH Common Drug Review
cLDA	constrained longitudinal data analysis
CI	confidence interval
CSBE	Comprehensive Summary: Bioequivalence
DBP	diastolic blood pressure
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol 5-Dimensions questionnaire
FAS	full analysis set
FDC	fixed-dose combination
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide 1
LS	least squares
MMTT	mixed-meal tolerance test
RCT	randomized controlled trial
SGLT2	sodium-glucose cotransporter-2
SBP	systolic blood pressure
UTI	urinary tract infection

Drug	Ertugliflozin / metformin hydrochloride fixed-dose combination (Segluromet)
Indication	As an adjunct to diet and exercise, to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM) who are: • inadequately controlled on metformin or • already controlled with metformin and ertugliflozin as individual components. For use in combination with sitagliptin as an adjunct to diet and exercise, to improve glycemic control in adult patients with type 2 diabetes mellitus who are: • inadequately controlled on metformin and sitagliptin or • already controlled with metformin, sitagliptin, and ertugliflozin, as individual components
Reimbursement Request	Add-on to metformin for patients who have inadequate glycemic control on metformin and have a contraindication or intolerance to a sulfonylurea. To replace the individual components of ertugliflozin and metformin for those patients who are on both therapies.
Dosage Form(s)	Tablets for oral administration: 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, and 7.5 mg/1,000 mg tablets
NOC Date	May 30, 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 disease) level. Diabetes is one of the most common chronic diseases in Canada. Diabetes Canada estimated there were 3.4 million people (9.3% of the population) with diabetes in 2015 and, by 2025, this number will increase to five million people (12.1%).[1]

The objective was to perform a systematic review of the beneficial and harmful effects of ertugliflozin 5 mg and 15 mg tablets in combination with metformin, or metformin and sitagliptin, to improve glycemic control in adult patients with type 2 diabetes mellitus when these therapies, along with diet and exercise, do not provide adequate glycemic control.

This review was conducted in tandem with the evaluation of ertugliflozin 5 mg and 15 mg tablets (Steglatro), which includes additional study data and an appraisal of the manufacturer-submitted indirect treatment comparison that are not included in this report.

Results and Interpretation

Included Studies

A total of four double-blind randomized controlled trials (RCTs) were included in this review (N = 463 to 1,326 per study). These trials evaluated the safety and efficacy of ertugliflozin 5 mg daily and ertugliflozin 15 mg daily (in combination with metformin, or metformin plus sitagliptin), compared with placebo or active comparators, in adults with type 2 diabetes and inadequate glycemic control. Three trials were 26 weeks in duration (MET, SITA2, FACTORIAL), and one active-controlled, noninferiority trial was 52 weeks in duration (SU study).

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 [redacted] per treatment group were male. The patients were predominantly white ([redacted] with a mean body mass index per group ranging from 30.3 kg/m^2 to 32.5 kg/m^2 and a baseline A1C of 7.8% to 8.6%. The mean duration of diabetes ranged from 6.2 to 9.9 years per treatment group. The median dose of metformin in all studies was 2,000 mg per day and, in the SU trial, the median dose of glimepiride was 3 mg per day.

Efficacy

Ertugliflozin as add-on therapy to metformin (≥ 1,500 mg/day) showed statistically significant differences compared with placebo for the change from baseline in A1C with least squares (LS) mean differences of −0.7% (95% confidence interval [CI] −0.9% to −0.5%) for ertugliflozin 5 mg and −0.9% (95% CI, −1.1% to −0.7%) for ertugliflozin 15 mg groups (MET study).

In the SU study, ertugliflozin 15 mg daily as add-on therapy to metformin was noninferior to glimepiride (mean dose 3 mg per day) for the change from baseline to 52 weeks 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 ertugliflozin 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, ertugliflozin 5 mg and 15 mg in combination with sitagliptin (100 mg daily) and metformin (≥ 1,500 mg/day), was superior to ertugliflozin 5 mg and 15 mg daily, and 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%.

The SITA2 trial evaluated the use of ertugliflozin 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 ertugliflozin 5 mg (LS mean difference: −0.7%; 95% CI, −0.9% to −0.5%) and ertugliflozin 15 mg groups versus placebo (mean difference: −0.8%; 95% CI, −1.0% to −0.6%)

At 26 weeks, statistically significantly more patients in the ertugliflozin groups (32% to 40%) in the MET and SITA2 trials achieved an A1C of less than 7% compared with placebo (16%

to 17%). In the FACTORIAL study, more patients who received ertugliflozin plus sitagliptin (49% to 52%) achieved their glycemic target than those who received ertugliflozin (26% to 32%) or sitagliptin alone (33%), and these differences were statistically significant. In the SU trial at 52 weeks, 34%, 38%, and 44% of patients achieved an A1C of less than 7% in the ertugliflozin 5 mg, ertugliflozin 15 mg, and glimepiride groups, respectively.

The percentage of patients who received glycemic rescue therapy ranged from [redacted] in the placebo groups, from [redacted] among groups who received ertugliflozin, and from [redacted] in the active-control groups. As the primary efficacy analysis excluded any outcome data after stopping the 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.

Ertugliflozin was associated with statistically significant reductions in weight in all four trials. At baseline, the mean weight per treatment group ranged from 84.5 kg to 89.8 kg and, after 26 weeks, the LS mean change from baseline in weight observed was −1.3 kg for placebo, −2.5 kg to –3.7 kg for the ertugliflozin (± sitagliptin) groups, −0.7 kg for sitagliptin, and +0.9 kg for the glimepiride groups. Statistically significant differences were detected between ertugliflozin and placebo in the MET and SITA2 trials, with differences between groups ranging from −1.6 kg to −2.0 kg after 26 weeks. Similarly, ertugliflozin 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, ertugliflozin 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 ertugliflozin 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, ertugliflozin 15 mg and ertugliflozin 5 mg, as add-on to metformin, were associated with statistically significant differences in systolic blood pressure (SBP) (mean difference: −3.7 mm Hg to −4.5 mm Hg) and diastolic blood pressure (DBP) (mean difference: −1.8 mm Hg to −2.4 mm Hg) compared with placebo in the MET study. Ertugliflozin 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 ertugliflozin 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 ertugliflozin plus sitagliptin groups compared with sitagliptin alone in the FACTORIAL study. Data for SBP and DBP from the SU trial comparing ertugliflozin with glimepiride were inconclusive.

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

the reporting of bone mineral density as raw scores, rather than T-scores, makes interpretation difficult.

The manufacturer submitted an indirect treatment comparison that compared ertugliflozin, as add-on therapy to metformin, with the three sodium-glucose cotransporter-2 (SGLT2) inhibitors approved in Canada (canagliflozin, dapagliflozin, and empagliflozin) (see the CADTH Common Drug Review [CDR] Clinical Report on Steglatro for details). 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 greater than 7% who received an SGLT2 inhibitor. The results of the Bayesian network meta-analysis (NMA) suggest that ertugliflozin has similar effects on A1C, weight, and blood pressure as other SGLT2 inhibitors in the short term. Although the NMA 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 have increased the chances of finding no difference between drugs. Based on the results of the submitted indirect treatment comparison, ertugliflozin in combination with metformin for the treatment of type 2 diabetes mellitus is likely more efficacious than placebo. Little can be elucidated on the comparative efficacy of ertugliflozin in combination with metformin versus other SGLT2 inhibitors or the relative safety of the product. Other than the SU study, direct evidence of the comparative efficacy of ertugliflozin versus other diabetes treatments is lacking.

The available evidence on the efficacy of ertugliflozin was limited by the relatively short duration (26 to 52 weeks) of four trials designed to study treatments 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 generated 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 therapy and early discontinuation in the placebo and ertugliflozin groups, the ertugliflozin treatment effects may be overestimated. Although the manufacturer and the 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, changes in A1C have been classified as modest.[2]

While none of the pivotal trials were conducted using the fixed-dose combination (FDC) product of ertugliflozin plus metformin, the manufacturer provided bioequivalence data for the combination product that suggested the pharmacokinetics of the combination are similar to those of the individual components. Bioequivalence between ertugliflozin plus metformin and co-administration of corresponding doses of ertugliflozin and metformin tablets is reported in the product monograph for ertugliflozin plus metformin.[3]

Harms

The frequency of adverse events ranged from 42% to 51% 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 received placebo, [redacted] of those who received ertugliflozin, and [redacted] of 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]; ertugliflozin: [redacted] active control: [redacted]. No deaths were reported in the MET, FACTORIAL, or SITA2 trials. In the SU study, five patients died in the ertugliflozin 5 mg group and one patient died in the ertugliflozin 15 mg group; none of these deaths were considered to be related to 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 ertugliflozin, and [redacted] among those who received placebo. Severe hypoglycemia was reported infrequently in the placebo, ertugliflozin, and sitagliptin groups (0 to 1 patient per group [0% to 0.7%]), 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, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. The absolute difference between the ertugliflozin 15 mg and glimepiride groups was −14% (95% CI, −18% to −10% [$P < 0.001$]). For ertugliflozin 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 the failure of a previous outcome in the testing sequence.

In women, genital mycotic infections were reported by 5% to 13% of patients who received ertugliflozin compared with 1% to 2% of patients who received placebo, glimepiride, or sitagliptin. In males, 2% to 5% in the ertugliflozin groups reported genital mycotic infections compared with 0% 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 the ertugliflozin and control groups. 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. Although adverse cardiovascular events were captured during the trials, data on these events will not be reported until after the completion of the ongoing cardiovascular safety trial (VERTIS CV). Limited data were available on adverse effects from the indirect treatment comparison 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[1]

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 an A1C below 7%; however, if patients present with an A1C that is more than 1.5% above their glycemic target, then the recommended initial therapy is metformin plus a second-line therapy.[4] The second-line therapy choice includes a multitude of options; however, in those with known clinical cardiovascular disease, there is a strong recommendation to use a medication that has clinical trial evidence of cardiovascular protection (e.g., empagliflozin, canagliflozin, or liraglutide).[5-7] There are a number of studies that suggest that combinations of submaximal doses of two drugs produce better glycemic control with fewer adverse effects than monotherapy at maximal doses.[8]

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

Deciding on the second-line treatment should involve shared decision-making with the 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 glucagon-like peptide 1 [GLP-1] agonists). When patients have insurance coverage for their medications, choosing between these three drugs is based on patients' desire for weight loss and willingness to accept adverse effects. Again, if the patient has clinical cardiovascular disease, then a drug with clinical trial evidence of cardiovascular protection 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. A review of the currently available evidence shows the risk of hypovolemia and genital infections with ertugliflozin 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 VERTIS CV outcome trial due out in 2019 will be important to understand if the unexpected adverse events seen with canagliflozin[6] are a class effect.

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 ertugliflozin renal study showed it to be no different than the other available therapies. In the earlier stages of renal disease, both empagliflozin and canagliflozin have been shown to reduce progression,[6,9] but there is no data to support that yet for ertugliflozin.

Given that ertugliflozin does not yet have evidence of clinical cardiovascular or renal benefit (it has an ongoing trial with results expected in the 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. If ertugliflozin is reimbursed as monotherapy, however, then it would make sense to reimburse the combination product given that many patients require more than one drug to manage their hyperglycemia, and patients appreciate the reduced pill burden offered by combination products.

Conclusions

Ertugliflozin as add-on therapy to metformin, or metformin plus sitagliptin, was associated with statistically significant short-term (six- month) reductions in A1C, body weight, and SBP compared with placebo plus add-on therapies. In addition, ertugliflozin 15 mg daily was noninferior to glimepiride for the change from baseline in A1C after 52 weeks. Noninferiority, however, was not met for ertugliflozin 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 ertugliflozin plus sitagliptin, as add-on therapy to metformin, versus sitagliptin plus metformin.

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

No new safety signals were identified for ertugliflozin 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 cardiovascular adverse events were not reported but are expected to be released once the longer-term cardiovascular safety study (VERTIS CV) is published.

The results of the manufacturer-submitted indirect treatment comparisons suggest that ertugliflozin in combination with metformin for the treatment of type 2 diabetes mellitus is likely more efficacious than placebo; however, little can be elucidated on the comparative efficacy of ertugliflozin in combination with metformin versus other SGLT2 inhibitors or the relative safety of the product.

Ertugliflozin/metformin FDC may provide cost savings versus other SGLT2/metformin FDC drugs and newer second- and third-line drugs in combination with metformin, but appears to be more costly than most older second- and third-line drugs in combination with metformin. However, there is uncertainty related to the comparative clinical evidence for ertugliflozin/metformin FDC versus other antidiabetic therapies, precluding definitive conclusions on the comparative costs.

1. Product Information

1.1 Health Canada–Approved Indications

Indication(s) to be Reviewed by the CADTH Common Drug Review
Segluromet (ertugliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are: • inadequately controlled on metformin, or • already on metformin and ertugliflozin as individual components. Segluromet (ertugliflozin and metformin hydrochloride) is indicated for use in combination with sitagliptin, as an adjunct to diet and exercise, to improve glycemic control in adult patients with type 2 diabetes mellitus who are: • inadequately controlled on metformin and sitagliptin, or • already on metformin, sitagliptin, and ertugliflozin, as individual components.[10]

1.2 Requested Reimbursement Criteria

Requested Reimbursement Criteria
• Added on to metformin for patients who have inadequate glycemic control on metformin and have a contraindication or intolerance to a sulfonylurea, or • To replace the individual components of ertugliflozin and metformin for those patients who are on both therapies.

1.3 Manufacturer's Rationale and Place in Therapy for the Combination

1.3.1 Rationale

A very important factor to consider when trying to individualize and optimize the type 2 diabetes mellitus treatment regimen is pill burden, since a high pill burden may negatively impact adherence.[11-13] Individuals with type 2 diabetes mellitus often take multiple medications, including glucose-lowering drugs and medications to manage hypertension and dyslipidemia.[14] In Canada, 90% of individuals with type 2 diabetes mellitus aged 65 years and older were taking four or more prescriptions and over-the-counter medications.[15] Multiple daily-dosing regimens can be challenging for type 2 diabetes mellitus patients, and fixed-dose combinations (FDCs) may improve adherence to type 2 diabetes mellitus medication, as demonstrated by a Canadian study.[16] This retrospective study was conducted in Ontario using the LMC Diabetes Registry and recruited 568 adults with type 2 diabetes mellitus who switched from a dual therapy of metformin and a dipeptidyl peptidase-4 (DPP-4) inhibitor to an FDC of the two drugs. Individuals with a baseline A1C of between 7% and 10% had an A1C that was 0.4% lower ($P < 0.01$) after the switch, with 31% of these individuals reaching a post-switch target A1C of 7% or lower. This study demonstrated that switching to an FDC improved A1C goal achievement, especially in patients with high pill burden. Furthermore, as per a meta-analysis of observational studies, good medication adherence is associated with a reduced risk of all-cause mortality and hospitalization in individuals with type 2 diabetes mellitus.[17]

Observational studies demonstrated that treatment modification or intensification in patients with inadequate glycemic control on monotherapy is frequently delayed.[18,19] In addition, patients with high A1C levels often require combination therapy to further reduce their A1C and help them reach their treatment goals.[4]

As the pathogenesis of type 2 diabetes mellitus involves multiple metabolic defects, combination therapy with antihyperglycemic agents (AHAs) that have different mechanisms of action can achieve further reductions in A1C and help more patients reach treatment goals. An FDC therapy may also help to improve treatment adherence.[20] The ertugliflozin/metformin FDC combines two AHAs with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus.

In short, pill burden may be a significant contributor to nonadherence to medications in patients with type 2 diabetes mellitus.[15] FDC therapies may help patients with type 2 diabetes mellitus to achieve their A1C targets and result in potentially greater adherence to therapy via a reduced pill burden, simplification of the treatment regimen, and favourable cost factors.[21]

1.3.2 Place in Therapy

As per the Health Canada–approved indications, ertugliflozin/metformin FDC should be used when metformin alone does not provide adequate glycemic control, or in patients already being treated with the combination of ertugliflozin and metformin as individual components.

Ertugliflozin/metformin FDC tablets are available as 2.5 mg ertugliflozin combined with 500 mg or 1,000 mg metformin, and as
7.5 mg ertugliflozin combined with 500 mg or 1,000 mg metformin. The recommended dose is one tablet twice daily.

The starting dose of ertugliflozin and metformin FDC needs to be individualized based on the patient's current regimen:

- Patients on metformin are switched to ertugliflozin and metformin FDC tablets containing 2.5 mg ertugliflozin and the nearest therapeutically appropriate dose of metformin.
- Patients switching from separate tablets of ertugliflozin and metformin to the ertugliflozin/metformin FDC tablet should receive the same daily dose of ertugliflozin and metformin they are already taking, or the nearest therapeutically appropriate dose of metformin. The maximum daily dose is 15 mg ertugliflozin and 2,000 mg metformin.

The components are metformin and ertugliflozin. According to the clinical practice guidelines developed by Diabetes Canada, metformin is recommended as first-line pharmacotherapy for the initial management of type 2 diabetes mellitus. If glycemic targets are not met with metformin and lifestyle changes alone, another drug can be added.[4] Therefore, metformin is the drug of choice in starting a patient on pharmacotherapy.

Choosing a second drug, such as ertugliflozin, is based on the AHA that is best suited to the patient based on clinical considerations. According to Diabetes Canada guidelines, individuals without clinical cardiovascular disease who are concerned about hypoglycemia and weight gain and who do not achieve their A1C target may prefer an incretin agent (DPP-4 inhibitor or GLP-1 receptor agonist) and/or a sodium-glucose cotransporter-2 (SGLT2) inhibitor over other drugs, as they improve glycemic control with a low risk of hypoglycemia and weight gain.[4]

Overall, people with type 2 diabetes mellitus are a heterogeneous group and the choice of drug will have to be individualized according to the desired A1C lowering, risk of hypoglycemia, effect on weight, cardiovascular effects, other side effects, and accessibility.[4]

The available dosage formulations for ertugliflozin/metformin FDC are:

- 2.5 mg/500 mg film-coated tablets. Each tablet contains 2.5 mg of ertugliflozin and 500 mg of metformin hydrochloride.
- 2.5 mg/1,000 mg film-coated tablets. Each tablet contains 2.5 mg of ertugliflozin and 1,000 mg of metformin hydrochloride.
- 7.5 mg/500 mg film-coated tablets. Each tablet contains 7.5 mg of ertugliflozin and 500 mg of metformin hydrochloride.
- 7.5 mg/1,000 mg film-coated tablets. Each tablet contains 7.5 mg of ertugliflozin and 1,000 mg of metformin hydrochloride.

The recommended dose of ertugliflozin and metformin (FDC) is one tablet twice daily with meals; therefore, the daily dose ranges from 5 mg/1,000 mg to 15 mg/2,000 mg (ertugliflozin/metformin FDC), which are the common doses of metformin used in Canada.[22]

The ertugliflozin/metformin FDC should not be used for initiating therapy. As per the indications in the product monograph and requested reimbursement criteria, ertugliflozin/metformin FDC should be used when metformin alone does not provide adequate glycemic control, or in patients already being treated with the combination of ertugliflozin and metformin as individual components.[22]

1.3.3 Dosing Considerations

As per the product monograph, ertugliflozin/metformin (FDC) is to be initiated as a switch.[22] Specifically:

- Patients on metformin are switched to ertugliflozin and metformin (FDC) tablets containing 2.5 mg ertugliflozin and the nearest therapeutically appropriate dose of metformin.
- Patients switching from separate tablets of ertugliflozin and metformin to ertugliflozin/metformin (FDC) should receive the same daily dose of ertugliflozin and metformin they are already taking, or the nearest therapeutically appropriate dose of metformin. The maximum daily dose is 15 mg ertugliflozin and 2,000 mg metformin.

The daily dose permitted for the ertugliflozin/metformin FDC is as follows: 5 mg/1,000 mg, 5 mg/2,000 mg, 15 mg/1,000 mg, and 15 mg/2,000 mg. These doses allow for titration within these dosing ranges.

The daily dose of ertugliflozin and metformin should be individualized to the patient's need. The ertugliflozin/metformin (FDC) doses permitted with the FDC are 5 mg/1,000 mg, 5 mg/2,000 mg, 15 mg/1,000 mg, and 15 mg/2,000 mg, which allow titration within these dosing ranges. Therefore, increasing the dose of one component does not result in an unnecessary dose increase of the other component.

2. Clinical Evidence

Information and data in this section were provided by the manufacturer of ertugliflozin/metformin while completing the CADTH Common Drug Review (CDR) FDC review template. Additional information and/or data have been included by CDR reviewers.

2.1 Pivotal Clinical Studies

The ertugliflozin/metformin FDC clinical program assessed the safety and efficacy of ertugliflozin in combination with metformin across a broad population of patients with type 2 diabetes mellitus, including those treated with metformin as background therapy. In the phase III studies, ertugliflozin and metformin were administered as separate tablets. No phase III studies have been performed with the ertugliflozin/metformin FDC tablet. However, data obtained from the phase III studies that assessed combination treatment with ertugliflozin and metformin can be bridged to the FDC tablet, based on the established bioequivalence of the FDC and the individual components and equivalence of once-daily and twice-daily dosing of ertugliflozin[23] (see Common Technical Document 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, section 3, page 33). Additionally, a phase I drug–drug interaction study demonstrated no pharmacokinetic interaction between ertugliflozin and metformin. Thus, data from studies utilizing combination treatment with ertugliflozin and metformin extrapolate directly to the to-be-marketed combination tablet at corresponding doses.[23]

The following are three pivotal clinical trials (MET, SU, and FACTORIAL) in which ertugliflozin was added on to patients taking metformin. The published studies can be found in the Clinical Studies section of the submission. In addition, CDR has added information on a fourth trial evaluating ertugliflozin as add-on therapy to metformin plus sitagliptin (SITA2) that was considered pivotal by Health Canada.

Table 1: Study Characteristics

Study Name	Design	Objectives	Population
Effect of Ertugliflozin on Glucose Control, Body Weight, Blood Pressure, and Bone Density in Type 2 Diabetes Mellitus Inadequately Controlled on Metformin Monotherapy (VERTIS MET)	This was a double-blind, 26-week, multi-centre study with an ongoing 78-week extension. A total of 621 participants were randomized 1:1:1 to placebo, or ertugliflozin 5 mg/day, or 15 mg/day.	The primary end point was change from baseline at week 26 in A1C. Secondary efficacy end points were change from baseline at week 26 in FPG, body weight, SBP, and DBP, and number of participants with A1C < 7.0% (53 mmol/mol). Pre-specified AEs of special interest and percentage change from baseline in bone mineral density were also assessed at week 26.	Men and women aged ≥ 18 years with type 2 diabetes mellitus inadequately controlled (A1C of 7.0% to 10.5% [53 mmol/mol to 91 mmol/mol] inclusive) with metformin monotherapy (≥ 1,500 mg/day for ≥ 8 weeks), and with a BMI of 18.0 kg/m^2 to 40.0 kg/m^2.

Study Name	Design	Objectives	Population
Ertugliflozin Compared With Glimepiride in Patients With Type 2 Diabetes Mellitus Inadequately Controlled on Metformin: The VERTIS SU Randomized Study	This phase III, double-blind, noninferiority study randomized 1,326 patients 1:1:1 to ertugliflozin 15 mg or 5 mg once daily (q.d.), or glimepiride (titrated from 1 mg q.d.). The primary and secondary hypotheses were pre-specified for testing at week 52 (phase A); treatment was continued for another 52 weeks (phase B) to evaluate longer-term safety and efficacy of ertugliflozin. Phase A results have been reported.	The primary hypothesis was that ertugliflozin 15 mg was noninferior to glimepiride on A1C (noninferiority criterion: upper bound of the 95% CI around the treatment difference < 0.3%).	Patients aged at least 18 years with type 2 diabetes mellitus and inadequate glycemic control (A1C ≥ 7.0% and ≤ 9.0%) on ≥ 1,500 mg per day of metformin monotherapy for at least 8 weeks.
Ertugliflozin Plus Sitagliptin Versus Either Individual Agent Over 52 Weeks in Patients With Type 2 Diabetes Mellitus Inadequately Controlled With Metformin: The VERTIS FACTORIAL Randomized Trial	In this study, 1,233 patients were randomized to ertugliflozin 5 mg or 15 mg/day, sitagliptin 100 mg/day, or to co-administration of ertugliflozin 5 mg/day and sitagliptin 100 mg/day, or ertugliflozin 15 mg/day and sitagliptin 100 mg/day. Phase A: 26-week randomized, double-blind treatment period assessing the primary and key secondary hypotheses. Phase B: 26-week active-controlled treatment period assessing the longer-term efficacy and safety.	To evaluate the efficacy and safety of ertugliflozin and sitagliptin co-administration versus the individual drugs in patients with type 2 diabetes who are inadequately controlled with metformin. The primary end point was change in A1C from baseline to week 26. Key secondary end points evaluated at week 26 were: change from baseline in FPG, body weight, and SBP; proportion of patients with A1C < 7.0% (< 53 mmol/mol).	≥ 18 years of age with type 2 diabetes and A1C ≥ 7.5 and ≤ 11.0% with stable (≥ 8 weeks) metformin monotherapy ≥ 1,500 mg/day.
Effect of Ertugliflozin on Glucose Control, Body Weight, and Blood Pressure in Type 2 Diabetes Mellitus Inadequately Controlled on Metformin Plus Sitagliptin (VERTIS SITA2)[24]	This was a double-blind, 26-week, multi-centre study with a 26-week extension. A total of 463 participants were randomized 1:1:1 to placebo, or ertugliflozin 5 mg/day or 15 mg/day.	The primary end point was change from baseline at week 26 in A1C. Secondary efficacy end points were change from baseline at week 26 in FPG, body weight, SBP, and number of participants with A1C < 7.0%.	Men and women aged ≥ 18 years with type 2 diabetes mellitus inadequately controlled (A1C, 7.0% to 10.5% inclusive) with metformin (≥ 1,500 mg/day for ≥ 8 weeks) plus sitagliptin 100 mg/day and with a BMI ≥ 18.0 kg/m2.

A1C = glycated hemoglobin; AE = adverse event; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; FPG = fasting plasma glucose; q.d. = once daily; SBP = systolic blood pressure.

2.1.1 VERTIS MET (P007)[25]

A. Study Characteristics

This is a 104-week, multi-centre, randomized, parallel-group study with a 26-week, double-blind, placebo-controlled treatment period (phase A) followed by a 78-week active-controlled treatment period (phase B) in men and women ≥ 18 years of age with type 2 diabetes mellitus, diagnosed in accordance with the American Diabetes Association guidelines, and inadequate glycemic control (A1C 7.0% to 10.5% [53 mmol/mol to 91 mmol/mol], inclusive) on metformin monotherapy at a dose of ≥ 1,500 mg/day. Approximately 600 patients were planned to be randomized. Patients will participate in the study for up to approximately 119 weeks. The study includes a screening period of one week, a minimum eight-week metformin stable-dose period (when patients discontinue and remain off any previous allowable background diabetes therapy, except for metformin), and a two-week single-blind placebo run-in period prior to randomization; a double-blind treatment period of up to 104 weeks (the 26-week phase A herein reported, plus the 78-week phase B extension), and a post-treatment telephone contact 14 days after the last dose of blinded study medication. The study included a two-week single-blind placebo run-in from screening visit 3 to day 1 / visit 4 which had the explicit purpose of familiarizing the patients with the study treatment regimen and excluding patients who were not adherent with the blinded placebo prior to randomization.

Table 2: VERTIS MET Details

Characteristics		Details for VERTIS MET
Study Design	**Objective**	Pivotal efficacy and safety study
	Blinding	Double-blind
	Study Period	Beginning and end dates of phase A (weeks 0 to 26): January 10, 2014 to January 26, 2016
	Study Centres (Number of Centres)	Australia (4), Czech Republic (4), Hong Kong (5), Hungary (10), Israel (5), Mexico (2), Poland (3), Romania (8), Russian Federation (5), Slovakia (10), South Africa (12), Taiwan (8), UK (1), US (26)
	Design	Ertugliflozin is superior to placebo in A1C reduction at week 26
Study Population	**Randomized (N)**	621
	Inclusion Criteria	• Diagnosis of type 2 diabetes mellitus in accordance with guidelines and 18 years and older. • Patients receiving one of the following diabetes therapy regimens at the time of screening visit 1 and with an A1C within the following range: ○ metformin monotherapy: ≥ 1,500 mg/day and A1C 7.0% to 10.5% (53 mmol/mol to 91 mmol/mol) inclusive OR ○ metformin monotherapy: < 1,500 mg/day and A1C 7.5% to 11.0% (58 mmol/mol to 97 mmol/mol) inclusive OR ○ dual combination therapy with metformin + sulfonylurea, DPP-4 inhibitor, meglitinide, or alpha-glucosidase inhibitor and A1C 6.5% to 9.5% (48 mmol/mol to 80 mmol/mol), inclusive. • To remain eligible to participate in the trial, participants must have been receiving metformin monotherapy for ≥ 8 weeks prior to study participation or required a change in their diabetes regimen (including discontinuing antihyperglycemic agent therapy) and must have had an A1C of 7.0% to 10.5% (53 mmol/mol to 91 mmol/mol) after at least 8 weeks on a regimen of metformin monotherapy. ○ Stable doses of blood pressure and/or lipid-altering medication for at least 4 weeks prior to randomization.
	Exclusion Criteria	[redacted]

Characteristics		Details for VERTIS MET
		[redacted] • [redacted] • The following therapeutic drugs were prohibited for the duration of the study. Specific time length restrictions for each medication/drug class were as follows: Bisphosphonates (e.g., alendronate, risedronate, ibandronate): [redacted] bazedoxifene (or another selective estrogen receptor modulators [SERM]), tibolone, denosumab, aromatase inhibitor, strontium, or corticosteroid treatment (oral, inhaled, parenteral at any dose) within 12 months of screening visit 1. Pioglitazone or rosiglitazone within 12 months of screening visit 1. Growth hormone within 12 months of screening visit 1. Phenytoin or phenobarbital within 12 months of screening visit 1. Medroxyprogesterone acetate (Depo-Provera) within 24 months of screening visit 1. • Treatment adherence < 80% during placebo run-in period. • History of diabetic ketoacidosis or type 1 diabetes mellitus.
Drugs	**Intervention**	Dosing regimen in phase A for 26 weeks: • ertugliflozin 15 mg orally once daily for 26 weeks OR • ertugliflozin 5 mg orally once daily for 26 weeks OR • ertugliflozin-matching placebo orally once daily.
	Comparator(s)	See interventions
Duration	**Run-in**	2 weeks
	Treatment	Phase A (26 weeks)
	Follow-up	Patients who discontinued treatment with study medication for reasons other than withdrawn consent and did not continue into phase B were to attend the clinic for a study medication discontinuation visit followed by a post-treatment telephone call 14 days after the last dose of study medication.
Outcomes	**Primary End Point(s)**	Primary efficacy end point: Change from baseline in A1C at week 26.
	Other End Points	Secondary efficacy end points: Change from baseline in FPG and body weight at week 26, the proportion of patients with A1C < 7.0% at week 26, and change from baseline in systolic blood pressure and diastolic blood pressure at week 26. [redacted] Safety evaluations included clinical monitoring, vital signs (heart rate and blood pressure [both sitting and postural]), 12-lead ECGs, adverse events (including urinary tract infections, genital mycotic infections, symptomatic hypoglycemia, hypovolemia, and adjudicated events: cardiovascular events and deaths, fractures, and pancreatitis, and renal and hepatic events meeting pre-specified criteria were adjudicated to assess causality relative to study medication), physical examinations, hypoglycemia episodes, and safety laboratory tests (including lipids, apolipoproteins, and urinary albumin/creatinine ratio). Bone mineral density of lumbar spine (L1 to L4), femoral neck, total hip, and distal forearm was also measured by DXA.
Notes	**Publications**	ClinicalTrials.gov identifier: NCT02033889 Rosenstock et al. 2018[26]

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; DXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; FPG = fasting plasma glucose.

Intervention and Comparators

The study utilized a double-dummy approach to maintain double blinding, with a placebo tablet matching the ertugliflozin 5 mg tablet and another placebo tablet matching the ertugliflozin 10 mg tablet. Patients were instructed to take one ertugliflozin 5 mg tablet (or matching placebo) and one ertugliflozin 10 mg tablet (or matching placebo) daily.

Patients were to remain on their stable dose of metformin (≥ 1,500 mg/day) while receiving study medication during the double-blind treatment period. Patients who were initiated on open-label glimepiride rescue therapy and who reached the maximum allowed dose (or tolerated dose, if lower), and met glycemic rescue fasting plasma glucose (FPG) criteria (after at least two weeks on the maximum dose of glimepiride), had additional glycemic rescue therapy with basal insulin initiated.

Outcomes

Efficacy

A1C: The primary glycemic efficacy end point was the change from baseline in A1C at week 26. A1C reflects average glucose concentrations over the past three to four months and, therefore, provides an index of the glycemic control. It is a standard efficacy end point used to assess the glycemic efficacy of AHAs. A1C is also a glycemic parameter that correlates with reduction of risk of diabetic microvascular complications.

The FPG secondary glycemic efficacy end point was the change from baseline in FPG at week 26. FPG was assessed to characterize the earlier time course of glucose control with ertugliflozin treatment.

Body weight and blood pressure: Blood pressure and body weight were measured as described subsequently to assess the potential benefit of ertugliflozin treatment on these parameters. Sitting blood pressure (and pulse rate) was measured in triplicate using an automated, oscillometric blood pressure measuring [redacted]. Body weight was measured in duplicate using a standardized digital scale provided by the manufacturer.

Rescue: The proportion of patients who received glycemic rescue therapy and time to initiation of rescue were assessed.

Safety End Points (Definitions and Measurement)

[redacted] physical examinations including vital signs and sitting and postural blood pressures. Laboratory safety studies included blood chemistry, lipid panel, [redacted], biochemical markers of bone turnover, [redacted] and bone mineral densitometry. Tier 1 safety end points which consist of adverse events (AEs) of special interest are AEs or collections of AEs related to urinary tract infection (UTI), genital mycotic infection (gender-specific), symptomatic hypoglycemia, and hypovolemia. Part of the assessment of laboratory safety was accomplished by defining limits of change for particular tests such that occurrences of patient values beyond these bounds were considered abnormal.

Statistical Analyses[25]

- An ordered testing procedure was used to assess a collection of primary and secondary hypothesis tests. Beginning with the first hypothesis, a test was conducted at a two-sided 5% level of significance (comparing 15 mg versus placebo followed by 5 mg versus placebo). 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 two-sided 5% level of significance with the decision process repeated. A constrained longitudinal data analysis (cLDA) model (Liang and Zeger, 2000), based on the full analysis set (FAS), which included all randomized patients who took at least one dose of study medication and had at least one measurement of the outcome variable [baseline or post-baseline]) was used to evaluate the change from baseline in A1C levels at week 26 as the primary efficacy analysis, excluding data obtained after the initiation of glycemic rescue therapy. This model assumed a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. The statistical model included terms for treatment (categorical), time (categorical), the treatment by time interaction, menopausal status randomization stratum, AHA status at study entry (binary), and baseline estimated glomerular filtration rates (eGFRs) (continuous). No imputation of missing data was performed. All other continuous efficacy end points were analyzed using the cLDA method for A1C described previously.
- With respect to the primary end point of reduction in A1C from baseline to week 26 and assuming a standard deviation of 1.0%, the sample size of approximately 600 patients (200 per arm) provided at least 99% power to detect a difference of 0.5% between each ertugliflozin dose and placebo ([redacted]) using a two-sided 0.05 alpha level test, [redacted]. To control the overall type I error rate at 0.05, a sequential testing approach was used across the primary and secondary efficacy end points for which hypotheses were tested, and for the two doses of ertugliflozin.

B. Results

Baseline Characteristics

Table 3: VERTIS MET Patient Characteristics: All Patients Treated – Gender, Age, Race, Ethnicity, Region, Height, Weight, BMI, and Stratification Factors

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Region								
North America (excluding Central America)	55	(26.3)	61	(29.5)	53	(25.9)	169	(27.2)
South America (including Central America)	9	(4.3)	4	(1.9)	8	(3.9)	21	(3.4)
Europe (including Russia)	76	(36.4)	74	(35.7)	74	(36.1)	224	(36.1)
Asia	26	(12.4)	27	(13.0)	32	(15.6)	85	(13.7)
South Africa	39	(18.7)	35	(16.9)	37	(18.0)	111	(17.9)
Australia/New Zealand	4	(1.9)	6	(2.9)	1	(0.5)	11	(1.8)
Height (cm)								
Patients with data	[redacted]		[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]		[redacted]	
Weight (kg)								
Patients with data	209		207		205		621	
Mean	84.5		84.8		85.3		84.9	
BMI (kg/m^2)								
Patients with data	209		207		205		621	
Mean	30.7		30.8		31.1		30.9	
Stratification Factor: Menopausal Status								
Male	97	(46.4)	97	(46.9)	93	(45.4)	287	(46.2)
Premenopausal women	16	(7.7)	17	(8.2)	16	(7.8)	49	(7.9)
Women who are perimenopausal or < 3 years postmenopausal	9	(4.3)	10	(4.8)	11	(5.4)	30	(4.8)
Women who are ≥ 3 years postmenopausal	87	(41.6)	83	(40.1)	85	(41.5)	255	(41.1)

BMI = body mass index; IVR/IWR = interactive voice recognition / interactive Web recognition; n = number of patients.

Note: The stratification factor in the baseline characteristics summary is sourced from the original entry in the IVR/IWR system. This summary does not account for the incorrectly stratified patients. For height, weight, and BMI summary, baseline value is used if available; otherwise, the last pre-randomization value is used for summarization.

Table 4: VERTIS MET Baseline Age, Sex, and Race[a]

Characteristics		MET	
	Placebo N = 209	Ertugliflozin 5 mg N = 207	Ertugliflozin 15 mg N = 205
Male, n (%)	98 (47)	97 (47)	93 (45)
Age, mean years (SD)	56.5 (8.7)	56.6 (8.1)	56.9 (9.4)
Race, n (%)			
White	144 (69)	134 (65)	133 (65)
Black	19 (9)	22 (11)	23 (11)
Asian	31 (15)	34 (16)	35 (17)
Other	15 (7)	17 (8)	14 (7)
Metformin daily dose, median mg (range)	[redacted]	[redacted]	[redacted]

CDR = CADTH Common Drug Review; SD = standard deviation.

[a] Additional data added by CDR from Clinical Study Report.[27]

Similarity among groups and across studies:

- Overall, 53.6% of patients were female. The majority of female patients (76.6%) had been postmenopausal for three years or more. The percentage of female patients, including the percentage of patients who were postmenopausal, was similar across treatment groups.

Concomitant conditions, medications, and other relevant issues:

[redacted]

Patient Disposition

Patient disposition from the 26-week phase A treatment period is shown subsequently. A high completion rate was observed for all treatment groups (> 90% of patients) during phase A of the study. The proportion of patients who discontinued the study medication in phase A was numerically higher in the placebo group compared with the ertugliflozin groups. In the ertugliflozin 15 mg group and placebo group, the most common reason for study medication discontinuation was withdrawal by patient; in the ertugliflozin 5 mg group, the most common reasons were withdrawal by patient and AEs. Reasons for study medication discontinuation were generally similar between groups. For the numbers of patients who discontinued the study medication due to an AE, there were two patients in the placebo group who discontinued in phase A due to pre-existing AEs.

Table 5: Summary of Patient Disposition for VERTIS MET[25,27,28]

Disposition	VERTIS MET: Placebo-Controlled Add-On to Metformin Study		
	Placebo	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Screened, N (overall not per treatment arm)	[redacted]	[redacted]	[redacted]
Randomized, N	[redacted]	[redacted]	[redacted]
Discontinued, N (%)	[redacted]	[redacted]	[redacted]
WDAEs, N (%)	[redacted]	[redacted]	[redacted]
Withdrawal due to SAEs, N (%)	[redacted]	[redacted]	[redacted]
Withdrawal by patient[a]	[redacted]	[redacted]	[redacted]
Lost to follow-up[a]	[redacted]	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]	[redacted]
Intention to treat, N	[redacted]	[redacted]	[redacted]
Per-protocol, N	[redacted]	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]	[redacted]

CDR = CADTH Common Drug Review; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Additional data added by CDR from Clinical Study Report.[27]

Efficacy

Table 6: Key Efficacy End Points[25]

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) Versus Placebo[a]	*P* Value
Change From Baseline in A1C at Week 26: cLDA				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ertugliflozin 5 mg	[redacted]	[redacted]		
Ertugliflozin 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Change From Baseline in FPG (mg/dL) at Week 26: cLDA				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ertugliflozin 5 mg	[redacted]	[redacted]		
Ertugliflozin 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Change From Baseline in Body Weight (kg) at Week 26: cLDA				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ertugliflozin 5 mg	[redacted]	[redacted]		
Ertugliflozin 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Change From Baseline in Sitting Systolic Blood Pressure (mm Hg) at Week 26: cLDA				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ertugliflozin 5 mg	[redacted]	[redacted]		
Ertugliflozin 15 mg	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) Versus Placebo[a]	*P* Value
Change From Baseline in Sitting Diastolic Blood Pressure (mm Hg) at Week 26: cLDA				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ertugliflozin 5 mg	[redacted]	[redacted]		
Ertugliflozin 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Treatment	**N**	**n (%)**	**Odds ratio (95% CI) vs. placebo**	***P* value**
A1C < 7.0% at Week 26 (Logistic Regression With Multiple Imputation Based on cLDA Model)[b]				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ertugliflozin 5 mg	[redacted]	[redacted]		
Ertugliflozin 15 mg	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; AHA = antihyperglycemic agent; CI = confidence interval; cLDA = constrained longitudinal data analysis; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; LS =least squares; N = number of subjects in the analysis population; vs. = versus.

[a] The cLDA model is fitted with fixed effects for treatment, time, interaction of time by treatment. Time was treated as a categorical variable.

[b] Logistic regression model fitted with terms for treatment and baseline A1C. For the analyses with multiple imputations, missing data imputed using the fitted cLDA model.

Note: All model-based analyses fitted with terms for prior antihyperglycemic medication (metformin alone or metformin plus another AHA), baseline eGFR (continuous), menopausal status randomization stratum (men, premenopausal women, women who are perimenopausal or < 3 years postmenopausal, women who are ≥ 3 years postmenopausal).

Change from baseline in A1C at week 26: The least squares (LS) mean reduction from baseline in A1C at week 26 was significantly greater in the ertugliflozin groups compared with the placebo group ($P < 0.001$ for both comparisons).

Change from baseline in FPG at week 26: The LS mean reductions from baseline in FPG at week 26 were significantly greater in the 15 mg and 5 mg ertugliflozin groups compared with the placebo group ($P < 0.001$ for both comparisons).

Change from baseline in body weight at week 26: The LS mean reductions from baseline in body weight at week 26 were significantly greater in the ertugliflozin groups compared with the placebo group ($P < 0.001$ for both comparisons).

Change from baseline in sitting systolic blood pressure (SBP) at week 26: The LS mean reductions from baseline in SBP at week 26 were significantly greater in the ertugliflozin 15 mg group and the ertugliflozin 5 mg group compared with the placebo group ($P < 0.001$ and $P = 0.002$ versus placebo, respectively).

Change from baseline in sitting diastolic blood pressure (DBP) at week 26: The LS mean reductions from baseline in DBP at week 26 were significantly greater in the ertugliflozin 15 mg group and the ertugliflozin 5 mg group compared with the placebo group ($P = 0.001$ and $P = 0.013$ versus placebo, respectively).

Proportion of patients with an A1C value < 7.0% (< 53 mmol/mol) at week 26: The raw proportions of patients with an A1C < 7.0% in the ertugliflozin 15 mg group (40.0% of patients) and the ertugliflozin 5 mg group (35.3% of patients) were approximately 2.5 times greater than in the placebo group (15.8% of patients). The model-based odds of having an A1C of < 7.0% at week 26, using multiple imputations for patients with missing week 26 data, were significantly greater in both ertugliflozin groups compared with the placebo group ($P < 0.001$ for both comparisons).

CDR reviewer: The per cent change from baseline to week 26 in bone mineral density (as raw scores) was reported in the MET study; however, this outcome was outside the ordered statistical testing procedure. No statistically significant differences in bone mineral density were detected between the ertugliflozin and placebo groups for the lumbar spine, femoral neck, and total hip or distal forearm (data not included in this report).[27]

In the ertugliflozin 5 mg and ertugliflozin 15 mg groups, [redacted] of patients required glycemic rescue therapy compared with [redacted] of those in the placebo group.[27]

2.1.2 VERTIS SU (P002)[25]

A. Study Characteristics

This was a multi-centre randomized, double-blind, active-comparator, controlled parallel-group clinical trial of ertugliflozin in patients ≥ 18 years of age with type 2 diabetes mellitus and inadequate glycemic control (A1C ≥ 7.0% and ≤ 9.0% [≥ 53 mmol/mol and ≤ 75 mmol/mol]) on ≥ 1,500 mg/day metformin monotherapy for at least 8 weeks. The double-blind treatment period was 104 weeks in duration and divided into two 52-week phases (phase A: weeks 0 to 52; phase B: weeks 52 to 104). Patients on ≥ 1,500 mg/day of metformin for ≥ 8 weeks with an A1C of ≥ 7.0% and ≤ 9.0% (≥ 53 and ≤ 75 mmol/mol) at screening were eligible to directly enter a two-week, single-blind placebo run-in period. Patients on ≥ 1,500 mg/day of metformin for < 8 weeks with an A1C of ≥ 7.0% and ≤ 9.0% (≥ 53 and ≤ 75 mmol/mol) at screening received diet and exercise counselling and entered a two-week, single-blind, placebo run-in period after their metformin dose had been stable for ≥ 8 weeks. Patients on < 1,500 mg/day of metformin with an A1C of ≥ 7.5% and ≤ 9.5% (≥ 58 and ≤ 80 mmol/mol) received diet/exercise counselling, titrated their dose of metformin to ≥ 1,500 mg/day, and underwent a metformin dose-stabilization period ≥ 8 weeks in duration. Patients on any dose of metformin in combination with a single allowable AHA who had an A1C of ≥ 6.5% and ≤ 8.5% (≥ 48 and ≤ 69 mmol/mol) received diet/exercise counselling, discontinued the non-metformin AHA, titrated their dose of metformin to ≥ 1,500 mg/day (if necessary), and underwent a metformin dose-stabilization period ≥ 8 weeks in duration. Allowable AHAs included sulfonylureas administered at < 50% the maximum approved dose (per local country label), DPP-4 inhibitors, meglitinides, and alpha-glucosidase inhibitors. The metformin dose-stabilization period was ≥ 10 weeks in duration for patients who discontinued a sulfonylurea.

Table 7: VERTIS SU Details

Characteristics		Details for VERTIS SU
Study Design	**Objective**	Pivotal efficacy and safety study
	Blinding	Double-blind
	Study Period	Beginning and end dates of phase A (weeks 0 to 52): December 17, 2013 to April 28, 2016
	Study Centres	The trial was conducted in 16 countries at 232 trial centres: 9 in Argentina, 16 in Canada, 11 in the Czech Republic, 14 in Hungary, 18 in South Korea, 7 in Lithuania, 10 in Mexico, 10 in the Philippines, 14 in Poland, 18 in Romania, 14 in Russia, 12 in Slovakia, 10 in South Africa, 7 in Taiwan, 5 in Ukraine, and 57 in the US.
	Design	Noninferiority
Study Population	**Randomized (N)**	1,326
	Inclusion Criteria	Have type 2 diabetes mellitus in accordance with guidelines and be ≥ 18 years of age on the day of signing the informed consent form. Meet one of the following criteria: • on metformin monotherapy ≥ 1,500 mg/day for ≥ 8 weeks with a visit 1 / screening A1C ≥ 7.0% and ≤ 9.0% (≥ 53 mmol/mol and ≤ 75 mmol/mol) **or** • on metformin monotherapy ≥ 1,500 mg/day for < 8 weeks with a visit 1 / screening A1C ≥ 7.0% and ≤ 9.0% (≥ 53 mmol/mol and ≤ 75 mmol/mol) **or** [redacted] (≥ 58 mmol/mol and ≤ 80 mmol/mol) **or** • on metformin in combination with a single allowable AHA (i.e., sulfonylureas at < 50% the maximum approved dose in the local country label — DPP-4 inhibitors, meglitinides, or alpha-glucosidase inhibitors) with a visit 1 / screening A1C ≥ 6.5% and ≤ 8.5% (≥ 48 mmol/mol and ≤ 69 mmol/mol). • have a body mass index ≥ 18.0 kg/m^2 • male; **or** female not of reproductive potential **or** female of reproductive potential practising abstinence **or** using one of the multiple listed birth control methodologies.
	Exclusion Criteria	• Estimated glomerular filtration rate using the four-variable Modification of Diet in Renal Disease study equation < 60 mL/min/1.73 m^2 • Serum creatinine ≥ 1.3 mg/dL (115 µmol/L) for males and ≥ 1.2 mg/dL (106 µmol/L) for females [redacted]
Drugs	**Intervention**	Dosing regimen in phase A (all treatments were given orally, once daily for 52 weeks): • ertugliflozin 5 mg **or** • ertugliflozin 15 mg.
	Comparator(s)	Glimepiride: Initiated at 1 mg and titrated up to the maximum approved dose (6 mg or 8 mg based on the local country label) or maximum tolerated dose
Duration	**Run-In**	2 weeks
	Treatment	Phase A (52 weeks)
	Follow-Up	Patients who discontinued treatment with study medication for reasons other than withdrawn consent and who did not continue into phase B, were to attend the clinic for a study medication discontinuation visit followed by a post-treatment telephone call 14 days after the last dose of study medication.
Outcomes	**Primary End Point(s)**	Primary efficacy end point: Change from baseline in A1C at week 52
	Other End Points	Secondary efficacy end points: • body weight minus change from baseline in body weight at week 52 • change from baseline in systolic blood pressure at week 52. Safety end points: • Tier 1 events: tier 1 (%) of patients with at least one AE of symptomatic hypoglycemia, **or** AE associated with urinary tract infections or male and female genital mycotic infections, or

Characteristics		Details for VERTIS SU
		hypovolemia. • Tier 2 and tier 3: Number (%) of patients with at least one AE (for AE summary measures and specific AEs, other hypoglycemia end points) **or** value meeting pre-defined limits of change criteria for various [redacted].
Notes	**Publications**	ClinicalTrials.gov number: NCT01999218 Hollander et al. 2018[29]

A1C = glycated hemoglobin; AE = adverse event; AHA = antihyperglycemic agent; DPP-4 = dipeptidyl peptidase-4.

Intervention and Comparators

Ertugliflozin 5 mg and 10 mg tablets or matching placebos were administered as either 5 mg or 15 mg (5 mg and 10 mg tablets together) once daily or as glimepiride. Glimepiride or matching placebo was initiated at 1 mg once daily and titrated up to the maximum approved dose (6 mg or 8 mg once daily based on the local country label) or maximum tolerated dose. Glimepiride or matching placebo could be down-titrated to avoid or manage hypoglycemia. The treatment period for phase A was 52 weeks.

Patients were on metformin ≥ 1,500 mg daily as background therapy. Patients who met progressively more stringent glycemic rescue criteria were to receive open-label sitagliptin.

Outcomes

- Efficacy (definitions and measurement): A1C and FPG: Glycemic efficacy end points included the changes from baseline in A1C and FPG at week 52. A1C reflects average glucose concentrations over the past three to four months and, therefore, provided an index of the glycemic control of treatment with ertugliflozin over that time period. It is a standard efficacy end point used to assess the glycemic efficacy of AHAs. A1C is also a glycemic parameter that correlates with a reduced risk of diabetic microvascular complications. FPG was assessed to characterize the earlier time course of glucose control with the ertugliflozin treatment.
- Body weight and blood pressure: Blood pressure and body weight were measured as described subsequently to assess the potential benefit of ertugliflozin treatment on these parameters. Sitting blood pressure (and pulse rate) was measured in triplicate using automated, oscillometric blood pressure measuring. [redacted]. Body weight was measured in duplicate using a standardized, digital scale (provided by the manufacturer).
- Safety end points (definitions and measurement): [redacted]. Tier 1 safety end points, which consist of AEs of special interest, are AEs or collections of AEs related to UTI, genital mycotic infection (gender-specific), symptomatic hypoglycemia, and hypovolemia. Part of the assessment of laboratory safety was accomplished by defining limits of change for particular tests such that occurrences of patient values beyond these bounds were considered abnormal.

Statistical Analyses

The primary population for efficacy analyses was the FAS, which included all randomized patients who took at least one dose of study medication and had at least one measurement of the outcome variable (baseline or post-baseline). The primary analysis model for continuous efficacy end points was a cLDA model proposed by Liang and Zeger. This model assumed a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. The model included terms for treatment, prior AHAs (monotherapy or dual therapy), baseline eGFR, time, and the interaction of time by treatment. The primary approach for efficacy analyses excluded results after initiation of glycemic rescue therapy.

The primary hypothesis regarding the noninferiority of ertugliflozin 15 mg versus glimepiride in decreasing A1C was assessed using the estimated treatment difference obtained from the cLDA model. Ertugliflozin 15 mg was to be declared noninferior to glimepiride in terms of A1C reduction if the upper limit of the two-sided 95% confidence interval (CI) for the mean difference between ertugliflozin 15 mg and glimepiride at week 52 was less than the noninferiority margin, δ = 0.3%.

All hypotheses were evaluated separately for each ertugliflozin dose level. The primary and key secondary hypotheses were tested using an ordered testing procedure combined with the Hochberg procedure. The ordered testing procedure included the tests of A1C noninferiority, hypoglycemia superiority (defined as symptomatic hypoglycemia, which included events with clinical symptoms [e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion], regardless of biochemical documentation), and body weight superiority, all beginning with ertugliflozin 15 mg versus glimepiride and continuing to ertugliflozin 5 mg versus glimepiride. If the success criterion was achieved for all of the above tests, the Hochberg procedure was to be used for tests of superiority on SBP for ertugliflozin 15 mg versus glimepiride and ertugliflozin 5 mg versus glimepiride. If the SBP tests were both successful, then A1C superiority of ertugliflozin 15 mg versus glimepiride followed by ertugliflozin 5 mg versus glimepiride were to be tested (alpha = 0.05).

Approximately 1,230 patients were to be randomized equally among the three treatment groups. A sample size of 410 per arm provided 97% power to declare noninferiority in A1C reduction at week 52 between a given ertugliflozin dose and glimepiride using a noninferiority margin of 0.3%, assuming the true mean difference in A1C is 0%, based on the primary analysis population (FAS). The half-width of the 95% CI was expected to be 0.15%. The probability of meeting the noninferiority criterion for both ertugliflozin doses in the FAS was 95%.

B. Results

Baseline Characteristics

Table 8: VERTIS SU Patient Characteristics: All Patients Treated – Gender, Age, Race, Ethnicity, Region, Height, Weight, BMI, and Stratification Factors

	Ertugliflozin 5 mg		Ertugliflozin 15 mg		Glimepiride		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	448		440		437		1,325	
Gender								
Male	227	(50.7)	191	(43.4)	224	(51.3)	642	(48.5)
Female	221	(49.3)	249	(56.6)	213	(48.7)	683	(51.5)
Age (Years)								
< 45	[redacted]							
45 to 64	[redacted]							
≥ 65	[redacted]							
Mean	58.8		58.0		57.8		58.2	
Race								
American Indian or Alaska Native	[redacted]							
Asian	81	(18.1)	85	(19.3)	73	(16.7)	239	(18.0)
Black or African American	17	(3.8)	19	(4.3)	25	(5.7)	61	(4.6)
Multiple	[redacted]							
White	332	(74.1)	316	(71.8)	318	(72.8)	966	(72.9)
Ethnicity								
Hispanic or Latino	[redacted]							
Not Hispanic or Latino	[redacted]							
Not reported	[redacted]							
Age Categories (Years)								
< 75	[redacted]							
≥ 75	[redacted]							
Region								
North America (excluding Central America)	[redacted]							
South America (including Central America)	[redacted]							
Europe (including Russia)	[redacted]							
Asia	[redacted]							
South Africa	[redacted]							
Height (cm)								
Patients with data	[redacted]							
Mean	[redacted]							
Weight (kg)								
Patients with data	[redacted]							
Mean	87.9		85.6		86.8		86.8	
BMI (kg/m^2)								
Patients with data	[redacted]							
Mean	31.7		31.3		31.2		31.4	

BMI = body mass index.

Note: For weight, and BMI summary, baseline value is used if available; otherwise, the last pre-randomization value is used for summarization.

Baseline demographic and anthropometric characteristics were generally similar between treatment groups except for fewer male patients in the ertugliflozin 15 mg group (43.4%) relative to the two other groups, where approximately 51% of the patients were male.

Following randomization, patients were to remain on a stable dose of metformin during the study; therefore, 100% of patients were taking drugs used for diabetes. [redacted].

CDR reviewer: [redacted].

Patient Disposition

The number of randomized patients was balanced across the three treatment groups. One randomized patient (in the ertugliflozin 15 mg group) did not receive treatment. The proportion of patients who discontinued study medication in phase A was similar in the ertugliflozin 15 mg and glimepiride groups, and numerically higher in the ertugliflozin 5 mg group (primarily related to discontinuations for hyperglycemia and nonadherence to the study drug). The number of patients who discontinued due to an AE was numerically higher in the ertugliflozin 15 mg group relative to the other two groups. The most common reason for study medication discontinuation in each treatment group was withdrawal by patient.

Table 9: Summary of Patient Disposition for VERTIS SU[28,30]

Disposition	VERTIS SU: Active-Controlled (Glimepiride) Add-on to Metformin Study (Noninferiority)		
	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride
Screened, N (overall, not per treatment arm)	2,985	2,985	2,985
Randomized, N[a]	448	441	437
Discontinued, N (%)	108 (24.1)	83 (18.8)	89 (20.4)
WDAEs, N (%)	15 (3.3)	22 (5.0)	13 (3)
Withdrawal due to SAEs, N (%)	[redacted]	[redacted]	[redacted]
Lost to follow-up, N (%)	16 (3.6)	8(1.8)	14 (3.2)
Withdrawal by patient[a]	20 (5)	23 (5)	18 (4)
Hyperglycemia[a]	24 (5)	13 (3)	10 (2)
Other reason[a]	33 (7)	17 (4)	34 (8)
FAS, N[a]	448	440	437
Per-protocol, N[a]	[redacted]	[redacted]	[redacted]
Safety, N	448	440	437

CDR = CADTH Common Drug Review; FAS = full analysis set; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Data added or edited by CDR reviewer based on information from Clinical Study Report.[30]

Efficacy

Table 10: Key Efficacy End Points[25]

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means Versus Glimepiride[a] (95% CI)	*P* Value
Change From Baseline in A1C at Week 52: cLDA				
Ertugliflozin 5 mg	448	−0.56 (−0.65 to −0.47)	0.18 (0.06 to 0.30)	
Ertugliflozin 15 mg	440	−0.64 (−0.73 to −0.55)	0.10 (−0.02 to 0.22)	
Glimepiride	437	−0.74 (−0.83 to −0.65)		
Change From Baseline in Body Weight (kg) at Week 52: cLDA				
Ertugliflozin 5 mg	448	−2.96 (−3.31 to −2.61)	−3.87 (−4.36 to −3.38)	< 0.001[b]
Ertugliflozin 15 mg	440	−3.38 (−3.73 to −3.03)	−4.29 (−4.77 to −3.80)	< 0.001
Glimepiride	437	0.91 (0.56 to 1.25)		
Change From Baseline in Sitting Systolic Blood Pressure (mm Hg) at Week 52: cLDA				
Ertugliflozin 5 mg	448	−2.25 (−3.36 to −1.13)	−3.20 (−4.73, to −1.67)	< 0.001[b]
Ertugliflozin 15 mg	440	−3.81 (−4.91 to −2.71)	−4.77 (−6.29 to −3.25)	< 0.001[b]
Glimepiride	437	0.95 (−0.15 to 2.06)		

A1C = glycated hemoglobin; CI = confidence interval; cLDA = constrained longitudinal data analysis; eGFR = estimated glomerular filtration rate; LS = least squares; N = number of patients in the analysis population.

[a] Based on a cLDA model, with fixed effects for treatment, time, interaction of time by treatment, prior antihyperglycemic medication (monotherapy or dual therapy), and baseline eGFR (continuous).

[b] CDR reviewer: Results should be interpreted as inconclusive due to failure of a previous outcome in the ordered statistical testing procedure (i.e., *P* values are nominal).

Primary End Point

Glycated Hemoglobin: Change From Baseline, Ertugliflozin 15 mg Versus Glimepiride

The LS mean difference (95% CI) between ertugliflozin 15 mg and glimepiride (ertugliflozin minus glimepiride) at week 52 was 0.10% (95% CI, −0.02 to 0.22). Since the upper bound of the CI around the treatment difference was less than the noninferiority margin of 0.3%, ertugliflozin 15 mg met the pre-specified criterion for noninferiority to glimepiride in reducing A1C.

CDR reviewer comment: Noninferiority was also met for the per-protocol population (LS mean difference: 0.12% [95% CI, −0.01 to 0.24]) for ertugliflozin 15 mg versus glimepiride.[30]

Secondary End Points

Body Weight: Change From Baseline

The LS mean reduction from baseline in body weight was significantly greater (*P* < 0.001) in the ertugliflozin 15 mg group relative to the glimepiride group, where an LS mean increase from baseline in body weight was observed (*P* < 0.001). The reduction from baseline in body weight was greater in the ertugliflozin 5 mg group relative to the glimepiride group (nominal *P* value: < 0.001). The *P* value is considered nominal for the ertugliflozin 5 mg group because formal hypothesis testing was stopped earlier in the testing sequence.

CDR reviewer: Nominal *P* values should be interpreted as inconclusive.

A1C: Change From Baseline Ertugliflozin 5 mg Versus Glimepiride

The LS mean difference (95% CI) between ertugliflozin 5 mg and glimepiride (ertugliflozin minus glimepiride) at week 52 was 0.18% (95% CI, 0.06 to 0.30). Since the upper bound of

the CI around the treatment difference did not exclude the margin of 0.3%, ertugliflozin 5 mg did not meet the pre-specified criterion for noninferiority to glimepiride in reducing A1C.

Sitting Systolic Blood Pressure: Change From Baseline

The LS mean reductions from baseline in SBP at week 52 were greater in the ertugliflozin 15 mg and ertugliflozin 5 mg groups relative to the glimepiride group, where an LS mean increase from baseline in SBP was observed (nominal $P < 0.001$ for both comparisons). The *P* values are considered nominal for the ertugliflozin 15 mg and 5 mg comparisons with glimepiride because formal hypothesis testing was stopped earlier in the testing sequence.

CDR reviewer: Other outcomes reported included the proportion of patients with A1C < 7%, the proportion who required glycemic rescue therapy, and the change from baseline in DBP, all of which were outside the ordered statistical testing procedure.

Other Outcomes

- A1C < 7%: Proportion at week 52
- Ertugliflozin 5 mg: 34%; ertugliflozin 15 mg: 38%; glimepiride: 44%[30]
- Received glycemic rescue therapy: Proportion at week 52
- Ertugliflozin 5 mg: [redacted]; ertugliflozin 15 mg: [redacted]; glimepiride: [redacted][30]
- Sitting DBP: Change from baseline
- LS mean difference ertugliflozin 5 mg versus glimepiride: −1.2 mm Hg (95% CI, −2.2 to −0.2); ertugliflozin 15 mg versus glimepiride. [redacted].[30]

2.1.3 VERTIS FACTORIAL (P005)[25]

A. Study Characteristics

This was a randomized double-blind, parallel-group, factorial study of the co-administration of ertugliflozin and sitagliptin and administration of the individual drugs in patients with type 2 diabetes mellitus and inadequate glycemic control on a stable dose of metformin monotherapy (≥ 1,500 mg/day). The duration of the study was up to 69 weeks (with 10 clinic visits) for each patient. This included a one-week screening period (visit 1 to visit 2), an up to 12-week metformin titration / dose-stabilization period (visit 2 to visit 3); a two-week single-blind placebo run-in period (visit 3 to visit 4); a 52-week double-blind, active-controlled treatment period (consisting of a 26-week phase A [visit 4 to visit 8] period followed by a 26-week phase B [visit 8 to visit 10] period); and a post-treatment telephone contact 14 days after the last dose of study medication. Approximately 1,250 patients ≥ 18 years of age with type 2 diabetes mellitus, diagnosed in accordance with American Diabetes Association guidelines, with inadequate glycemic control (A1C ≥ 7.5% and ≤ 11% [≥ 58 mmol/mol and ≤ 97 mmol/mol]) while on a stable dose of metformin monotherapy (≥ 1,500 mg/day for ≥ 8 weeks) and who met all other enrolment criteria, were planned to be randomized.

Table 11: ABCD

	Characteristics	Details for VERTIS FACTORIAL
Study Design	**Objective**	Pivotal efficacy and safety stud.
	Blinding	Double-blind
	Study Period	Beginning and end dates of phase A (weeks 0 to 26): April 29, 2014 to November 11, 2015.
	Study Centres	The trial was conducted in 21 countries, including 242 trial centres: 19 in Argentina, 7 in Bulgaria, 4 in Canada, 7 in Chile, 8 in Colombia, 9 in the Czech Republic, 4 in Finland, 11 in Hungary, 10 in Israel, 4 in Italy, 7 in Malaysia, 15 in Mexico, 6 in New Zealand, 7 in the Philippines, 13 in Poland, 13 in Romania, 19 in Russia, 12 in Slovakia, 3 in Thailand, 12 in Ukraine, and 52 in the US.
	Design	The combination of ertugliflozin and sitagliptin is superior to sitagliptin alone and ertugliflozin alone in A1C reduction at week 26.
Study Population	**Randomized (N)**	1,233
	Inclusion Criteria	• Type 2 diabetes mellitus as per American Diabetes Association guidelines and 18 years and older • On metformin monotherapy (≥ 1,500 mg/day) for ≥ 8 weeks with a visit 1 / screening A1C ≥ 7.5% and ≤ 11.0% (≥ 58 mmol/mol and ≤ 97 mmol/mol); OR on metformin monotherapy (≥ 1,500 mg/day) for < 8 weeks with a visit 1 / screening A1C ≥ 7.5% and ≤ 11.0% (≥ 58 mmol/mol and ≤ 97 mmol/mol); OR on metformin monotherapy < 1,500 mg/day with a visit 1 / screening A1C ≥ 8.0% and ≤ 11.5% (≥ 64 mmol/mol and ≤ 102 mmol/mol) • Body mass index ≥ 18.0 kg/m^2 • Male, or female not of reproductive potential • Female of reproductive potential who agrees to remain abstinent from heterosexual activity or to use two acceptable combinations of contraception
	Exclusion Criteria	• eGFR (using the four-variable MDRD study equation) < 60 mL/min/1.73 m^2 • Serum creatinine ≥ 1.3 mg/dL (115 µmol/L) for males and ≥ 1.2 mg/dL (106 µmol/L) for females [redacted]
Drugs	**Intervention**	Dosing regimen in phase A (all treatments were given orally once daily for 26 weeks): • ertugliflozin 5 mg + sitagliptin 100 mg **or** • ertugliflozin 15 mg + sitagliptin 100 mg **or** • ertugliflozin 5 mg **or** • ertugliflozin 15 mg.
	Comparator(s)	Sitagliptin 100 mg orally once daily for 26 weeks
Duration	**Run-in**	2 weeks
	Treatment	Phase A (26 weeks)
	Follow-Up	Patients who discontinued treatment with study medication for reasons other than withdrawn consent and did not continue into phase B were to attend the clinic for a study medication discontinuation visit followed by a post-treatment telephone call 14 days after the last dose of study medication.

	Characteristics	Details for VERTIS FACTORIAL
Outcomes	**Primary End Point(s)**	Primary efficacy end point: Change from baseline in A1C at week 26
	Other End Points	Secondary efficacy end points with hypotheses: • body weight minus change from baseline in body weight at week 26; FPG minus change from baseline in FPG at week 26; sitting systolic blood pressure minus change from baseline in sitting systolic blood pressure at week 26; A1C minus proportion of patients with A1C < 7.0% (53 mmol/mol) at week 26; β-cell responsivity static component (Φ_S) minus change from baseline in Φ_S at week 26. Safety end points: • tier 1 events: Number (%) of patients with at least one AE of symptomatic hypoglycemia **or** an AE associated with urinary tract infections or male and female genital mycotic infections or hypovolemia. [redacted]
Notes	**Publications**	Provide references for all publications related to this study: • Eldor R, Pratley R, Golm G, et al. Effect of ertugliflozin plus sitagliptin on glycemic control versus either treatment alone in patients with type 2 diabetes mellitus inadequately controlled with metformin. Presented at the American Diabetes Association 76th Scientific Sessions, New Orleans, LA, June 10–14, 2016. http://diabetes.diabetesjournals.org/content/diabetes/suppl/2016/06/20/65.Supplement_1.DC1/2016_ADA_LB_Abstracts_HiRes_FINAL_5_11_16.pdf. Accessed 8 July 2016. • ClinicalTrials.gov number: NCT02099110 • Pratley et al., 2018.[31]

A1C = glycated hemoglobin; AE = adverse event; eGFR = Estimated glomerular filtration rate; FPG = fasting plasma glucose; MDRD = Modification of Diet in Renal Disease.

Intervention and Comparators

- At visit 4 / day 1, patients entered phase A (weeks 0 to 26) of the 52-week, double-blind treatment period. Patients were randomized in a 1:1:1:1:1 ratio to one of five treatment groups:
  - ertugliflozin 5 mg once daily + sitagliptin 100 mg once daily (E5/S100) group
  - ertugliflozin 15 mg once daily + sitagliptin 100 mg once daily (E15/S100) group
  - ertugliflozin 5 mg once daily (E5) group
  - ertugliflozin 15 mg once daily (E15) group
  - sitagliptin 100 mg once daily (S100) group.
- During the placebo run-in and double-blind treatment periods, patients were to take three oral tablets of study medication once daily in the morning, including ertugliflozin 5 mg or matching placebo tablet, ertugliflozin 10 mg or matching placebo tablet, and sitagliptin 100 mg or matching placebo tablet.
- Patients were to remain on their stable dose of metformin (≥ 1,500 mg/day) while receiving study medication during the double-blind treatment period.
- During the double-blind treatment period, patients who met progressively more stringent protocol-specified glycemic rescue criteria were to receive open-label glimepiride as the glycemic rescue medication in accordance with the local country label. However, in the event that an investigator considered the use of glimepiride to be inappropriate for a patient meeting rescue criteria, insulin glargine could have been initiated as the rescue medication and managed by the investigator according to the local clinical practice

guidelines of the country. After initiation of rescue therapy, the background metformin (same dose and regimen) and study medication were to be continued.

Outcomes

Efficacy (Definitions and Measurement)

A1C and FPG: Glycemic efficacy end points included the changes from baseline in A1C and FPG at week 26. A1C reflects average glucose concentrations over the past three to four months and, therefore, provided an index of the glycemic control of combination treatment with ertugliflozin and sitagliptin over that time period. It is a standard efficacy end point used to assess the glycemic efficacy of AHAs. A1C is also a glycemic parameter that correlates with reduced risk of diabetic microvascular complications, and FPG was assessed to characterize the earlier time course of glucose control with the ertugliflozin and sitagliptin combination treatment.

Body weight and blood pressure: Sitting blood pressure (and pulse rate) was measured in triplicate using an automated, oscillometric blood pressure measuring device. [redacted]. Body weight was measured in duplicate using a standardized, digital scale (provided by the manufacturer).

Efficacy parameters derived from the mixed-meal tolerance test (MMTT): This study included a frequently sampled MMTT at visit 4 / day 1 and visit 8 / week 26 (or the rescue or discontinuation visit occurring in phase A) for a subset of patients who consented to participate. Blood samples (for measurement of glucose, insulin, and C-peptide) were collected at the following time points relative to the start of the meal: −30, 0, 15, 30, 60, 90, 120, and 180 minutes. Patients were to take their double-blind study medication and background metformin approximately one hour before consuming the standard meal at visit 8 / week 26 (or at the rescue or phase A discontinuation visit); double-blind study medication and background metformin were not administered prior to the MMTT procedure at visit 4 / day 1. The standard meal for the MMTT consisted of two nutrition bars and one nutrition drink (~680 kcal; 111 g carbohydrate, 14 g fat, 26 g protein in total). Urine was also collected during the MMTT to assess urinary glucose excretion.

Rescue: The proportion of patients who received glycemic rescue therapy and time to initiation of rescue were assessed.

Safety End Points (Definitions and Measurement)

In addition to evaluation of AEs, [redacted]The tier 1 safety end points, which consisted of AEs of special interest, were AEs or collections of AEs related to UTI, genital mycotic infection (gender-specific), symptomatic hypoglycemia, and hypovolemia. Part of the assessment of laboratory safety was accomplished by defining limits of change for particular tests such that occurrences of patient values beyond these bounds were considered abnormal.

Statistical Analyses

The primary population for efficacy analyses was the FAS, which included all randomized patients who took at least one dose of study medication and had at least one measurement of the outcome variable (baseline or post-baseline). The primary analysis model for continuous efficacy end points was a cLDA model proposed by Liang and Zeger. This model assumed a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. The model included terms for treatment, baseline eGFR, time, and the interaction of time by treatment.

CDR reviewer: The primary analysis excluded any efficacy outcome data after the start of rescue glycemic therapy.

All hypotheses were evaluated separately for each ertugliflozin dose level. The primary and key secondary hypotheses were tested using an ordered testing procedure combined with the Hochberg procedure. The ordered testing procedure included the tests of A1C, body weight, FPG, and SBP, and the percentage of patients with A1C < 7.0% (53 mmol/mol), all beginning with the E15/S100 dose and continuing to the E5/S100 dose within each end point, using alpha = 0.05 (two-sided). If the success criterion was achieved for all of the previously mentioned tests, the Hochberg procedure (starting with alpha = 0.05) was to be used for the two tests of β-cell responsivity static component (Φ_S) for E15/S100 and, if successful for at least one of the preceding two tests, it was to be used for E5/S100, starting with the final alpha level (0.05 or 0.025) from the tests used for E15/S100.

Approximately 1,250 patients were planned to be enrolled in this trial and randomized equally among the five treatment arms. The expected group size of 250 patients per group was estimated to provide approximately 94% power to detect a difference in A1C of 0.4% for each of the pairwise comparisons at a given ertugliflozin dose level, assuming a standard deviation of 1.2% based on a two-sided test at a 5% level of significance. The power for success for both pairwise comparisons at a given ertugliflozin dose level was approximately 89%.

B. Results

Baseline Characteristics

Table 12: VERTIS FACTORIAL Patient Characteristics: All Patients Treated – Gender, Age, Race, Ethnicity, Region, Height, Weight, BMI, and Stratification Factors

	Ertugliflozin 5 mg		Ertugliflozin 15 mg		Sitagliptin 100 mg		Ertugliflozin 5 mg + Sitagliptin 100 mg		Ertugliflozin 15 mg + Sitagliptin 100 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	250		248		247		243		244		1,232	
Gender												
Male	127	(50.8)	134	(54.0)	154	(62.3)	123	(50.6)	126	(51.6)	664	(53.9)
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (Years)												
< 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45 to 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	55.1		55.3		54.8		55.2		55.1		55.1	
Race												
American Indian or Alaska Native	7	(2.8)	4	(1.6)	4	(1.6)	2	(0.8)	4	(1.6)	21	(1.7)
Asian	22	(8.8)	22	(8.9)	29	(11.7)	22	(9.1)	36	(14.8)	131	(10.6)
Black or African American	7	(2.8)	6	(2.4)	11	(4.5)	12	(4.9)	10	(4.1)	46	(3.7)
Multiple	8	(3.2)	11	(4.4)	9	(3.6)	10	(4.1)	6	(2.5)	44	(3.6)
Native Hawaiian or other Pacific Islander	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.1)
White	206	(82.4)	205	(82.7)	193	(78.1)	197	(81.1)	188	(77.0)	989	(80.3)
Ethnicity												
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age Categories (Years)												
< 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region												
North America ([redacted])	76	(30.4)	77	(31.0)	73	(29.6)	74	(30.5)	75	(30.7)	375	(30.4)
South America ([redacted])	43	(17.2)	42	(16.9)	39	(15.8)	44	(18.1)	42	(17.2)	210	(17.0)
Europe ([redacted])	104	(41.6)	105	(42.3)	102	(41.3)	104	(42.8)	95	(38.9)	510	(41.4)

	Ertugliflozin 5 mg		Ertugliflozin 15 mg		Sitagliptin 100 mg		Ertugliflozin 5 mg + Sitagliptin 100 mg		Ertugliflozin 15 mg + Sitagliptin 100 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Asia	23	(9.2)	21	(8.5)	25	(10.1)	18	(7.4)	29	(11.9)	116	(9.4)
Australia / New Zealand	4	(1.6)	3	(1.2)	8	(3.2)	3	(1.2)	3	(1.2)	21	(1.7)
Height (cm)												
Patients with data	[redacted]											
Mean	[redacted]											
Weight (kg)												
Patients with data	[redacted]											
Mean	88.6		88.0		89.8		89.5		87.5		88.7	
BMI (kg/m^2)												
Patients with data	[redacted]											
Mean	31.8		31.5		31.7		32.5		31.8		31.9	
Stratification Factor: Mixed-Meal Tolerance Test												
No	[redacted]											
Yes	[redacted]											

BMI = body mass index.

Note: For weight and BMI summary, baseline value is used, if available; otherwise, last pre-randomization value is used for summarization.

Baseline demographic and anthropometric characteristics and the distribution of patients by stratification factor were generally similar between treatment groups except for small differences in the distribution of patients by race and a higher percentage of male patients in the S100 group.

Following randomization, patients were to remain on a stable dose of metformin during the study; [redacted]

CDR reviewer: The median metformin dose was 2,000 mg per day in all treatment groups.

Patient Disposition

The disposition with regard to continuing or discontinuing study medication among patients in the 26-week phase A treatment period is shown in the following table. The number of randomized patients was balanced across the five treatment groups. One randomized patient (E15/S100 group) did not receive treatment. The proportion of patients who discontinued the study medication in phase A was numerically higher in the S100 group relative to the four ertugliflozin-treated groups, primarily due to a small increase in the proportion of those in the S100 group who discontinued due to withdrawal by patient. The most common reason for study medication discontinuation in each treatment group was withdrawal by patient. A numerically higher proportion of patients in the E15/S100 group discontinued study medication due to an AE; other reasons for study medication discontinuation were generally similar between groups.

Table 13: Summary of Patient Disposition for VERTIS FACTORIAL[28,32]

Disposition	VERTIS FACTORIAL: Factorial Study (5 Arms) of Ertugliflozin and Sitagliptin				
	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Sitagliptin 100 mg	Ertugliflozin 5 mg / Sitagliptin 100 mg	Ertugliflozin 15 mg / Sitagliptin 100 mg
Screened, N, all groups	2,582	2,582	2,582	2,582	2,582
Randomized, N	250	248	247	243	245
Discontinued, N (%)	17 (6.8)	22 (8.9)	26 (10.5)	17 (7.0)	23 (9.4)
Discontinued due to AEs, N (%)	3 (1.2)	3 (1.2)	1 (0.4)	3 (1.2)	6 (2.4)
Discontinued due to SAEs, N (%)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)
Lost to follow-up, N (%)	3 (1.2)	6 (2.4)	4 (1.6)	2 (0.8)	1 (0.4)
Withdrawal by patient[a]	4 (2)	10 (4)	14 (6)	6 (3)	11 (5)
Other reason[a]	7 (3)	3 (1)	7 (3)	6 (3)	5 (2)
FAS, N[a]	250	248	247	243	244
Per-protocol, N	244	247	242	237	241
Safety, N	250	248	247	243	244

CDR = CADTH Common Drug Review; FAS = full analysis set; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Additional data from Clinical Study Report added by CDR.[32]

Efficacy

Table 14: Key Efficacy End Points

Treatment	N	LS Mean (95% CI)	Difference in LS Means (95% CI) Versus Ertugliflozin[a]	*P* Value	Difference in LS Means (95% CI) Versus Sitagliptin[a]	*P* Value
Change From Baseline in A1C at Week 26: cLDA						
Ertugliflozin 5 mg	250	−1.02 (−1.14 to −0.90)	−0.46 (−0.63 to −0.30)	< 0.001	−0.43 (−0.60 to −0.27)	< 0.001
Ertugliflozin 15 mg	248	−1.08 (−1.20 to −0.96)				
Sitagliptin 100 mg	247	−1.05 (−1.17 to −0.93)				
Ertugliflozin 5 mg + sitagliptin 100 mg	243	−1.49 (−1.61 to −1.36)				
Ertugliflozin 15 mg + sitagliptin 100 mg	244	−1.52 (−1.64 to −1.40)	−0.44 (−0.61 to −0.27)	< 0.001	−0.47 (−0.63 to −0.30)	< 0.001
Change From Baseline in FPG (mg/dL) at Week 26: cLDA						
Ertugliflozin 5 mg	250	−35.73 (−40.04 to −31.42)	−8.23 (−13.82 to −2.65)	0.004	−18.40 (−24.03 to −12.77)	< 0.001
Ertugliflozin 15 mg	248	−36.91 (−41.21 to −32.62)				
Sitagliptin 100 mg	247	−25.56 (−29.93 to −21.19)				
Ertugliflozin 5 mg + sitagliptin 100 mg	243	−43.96 (−48.29 to −39.63)				
Ertugliflozin 15 mg + sitagliptin 100 mg	244	−48.70 (−53.01 to −44.39)	−11.79 (−17.35 to −6.23)	< 0.001	−23.14 (−28.76 to −17.53)	< 0.001
Change From Baseline in Body Weight (kg) at Week 26: cLDA						

Treatment	N	LS Mean (95% CI)	Difference in LS Means (95% CI) Versus Ertugliflozin[a]	*P* Value	Difference in LS Means (95% CI) Versus Sitagliptin[a]	*P* Value
Ertugliflozin 5 mg	250	−2.69 (−3.13 to −2.25)			−1.85 (−2.48 to −1.22)	< 0.001
Ertugliflozin 15 mg	248	−3.74 (−4.18 to −3.29)				
Sitagliptin 100 mg	247	−0.67 (−1.12 to −0.22)				
Ertugliflozin 5 mg + sitagliptin 100 mg	243	−2.52 (−2.97 to −2.07)				
Ertugliflozin 15 mg + sitagliptin 100 mg	244	−2.94 (−3.39 to −2.49)			−2.27 (−2.90 to −1.64)	< 0.001
Change From Baseline in Sitting Systolic Blood Pressure (mm Hg) at Week 26: cLDA						
Ertugliflozin 5 mg	250	−3.89 (−5.28 to −2.50)			−2.76 (−4.69 to −0.83)	0.005
Ertugliflozin 15 mg	248	−3.69 (−5.08 to −2.30)				
Sitagliptin 100 mg	247	−0.66 (−2.07 to 0.76)				
Ertugliflozin 5 mg + sitagliptin 100 mg	243	−3.42 (−4.82 to −2.03)				
Ertugliflozin 15 mg + sitagliptin 100 mg	244	−3.67 (−5.06 to −2.29)			−3.01 (−4.94 to −1.09)	0.002
Change From Baseline in β-Cell Responsivity Static Component (φ_s) ($10^{-9}min^{-1}$) From the Eight-Point Meal Tolerance Test at Week 26: cLDA						
Ertugliflozin 5 mg	66	8.62 (1.28 to 15.96)	7.61 (−2.90 to 18.13)	0.155	−4.87 (−15.54 to 5.80)	0.369
Ertugliflozin 15 mg	67	9.71 (2.29 to 17.13)				
Sitagliptin 100 mg	63	21.11 (13.55 to 28.67)				
Ertugliflozin 5 mg + sitagliptin 100 mg	55	16.24 (8.36 to 24.11)				
Ertugliflozin 15 mg + sitagliptin 100 mg	61	11.51 (3.76 to 19.26)	1.81 (−8.66 to 12.27)	0.734	−9.59 (−20.17 to 0.98)	0.075

A1C = glycated hemoglobin; CI = confidence interval; cLDA = constrained longitudinal data analysis; LS = least squares; N = number of patients in the analysis population.

[a] The cLDA model is fitted with fixed effects for treatment, time, and interaction of time by treatment. Time was treated as a categorical variable.

Treatment	N	n (%)	Odds Ratio (95% CI) Versus Sitagliptin	*P* Value	Odds Ratio (95% CI) Versus Ertugliflozin	*P* Value
A1C < 7.0% at Week 26 (Logistic Regression With Multiple Imputation Based on cLDA Model)[a]						
Ertugliflozin 5 mg	250	[redacted] (26.4)	4.14 (2.68 to 6.40)	< 0.001	2.95 (1.92 to 4.54)	< 0.001
Ertugliflozin 15 mg	248	[redacted] (31.9)				
Sitagliptin 100 mg	247	[redacted] (32.8)				
Ertugliflozin 5 mg + sitagliptin 100 mg	243	[redacted] (52.3)				
Ertugliflozin 15 mg + sitagliptin 100 mg	244	[redacted] (49.2)	2.53 (1.68 to 3.83)	< 0.001	2.56 (1.69 to 3.89)	< 0.001

A1C = glycated hemoglobin; CI = confidence interval; cLDA = constrained longitudinal data analysis; eGFR = estimated glomerular filtration rate LS = least squares; N = number of patients in the analysis population.

[a] Logistic regression model fitted with terms for treatment and baseline A1C. For the analyses with multiple imputations, missing data imputed using the fitted cLDA model. All model-based analyses fitted with terms for baseline eGFR (continuous).

Primary End Point

Glycated Hemoglobin: Change From Baseline

The LS mean reductions from baseline in A1C at week 26 were significantly greater in the E15/S100 and E5/S100 groups relative to the individual component treatment groups at corresponding dose strengths ($P < 0.001$ for all comparisons).

Secondary End Points

Fasting Plasma Glucose: Change From Baseline

The LS mean reductions from baseline in FPG at week 26 were significantly greater in the E15/S100 and E5/S100 groups relative to the individual component treatment groups at corresponding dose strengths ($P = 0.004$ for E5/S100 versus E5; $P < 0.001$ for all other comparisons).

Body Weight: Change From Baseline

The LS mean reductions from baseline in body weight at week 26 were significantly greater in the E15/S100 and E5/S100 groups relative to the S100 group ($P < 0.001$ for both comparisons).

Sitting Systolic Blood Pressure: Change From Baseline

The LS mean reductions from baseline in SBP at week 26 were significantly greater in the E15/S100 and E5/S100 groups relative to the S100 group ($P = 0.002$ and $P = 0.005$, respectively).

Proportion of Patients With Glycated Hemoglobin Below 7.0%

The model-based odds of having an A1C value < 7.0% (< 53 mmol/mol) at week 26, using multiple imputation for patients with missing week 26 data, were significantly greater in the E15/S100 and E5/S100 groups relative to the individual component treatment groups at corresponding dose strengths ($P < 0.001$ for all comparisons).

β-Cell Responsivity Static Component (Φ_s): Change From Baseline

The LS mean increases from baseline in Φ_s at week 26 in the E5/S100 and E15/S100 groups were not statistically different in any of the comparisons with the individual component treatment groups at corresponding dose strengths.

CDR Reviewer
The proportion of patients who required glycemic rescue therapy was as follows: ertugliflozin 5 mg: [redacted]; ertugliflozin 15 mg: [redacted]; sitagliptin: [redacted]; ertugliflozin 5 mg plus sitagliptin: [redacted]; ertugliflozin 15 mg plus sitagliptin: 0%.[32]

The trial also reported data for the change from baseline in DBP; however, this outcome was outside the ordered statistical testing procedure. The LS mean difference for ertugliflozin 5 mg plus sitagliptin versus sitagliptin was −0.3 mm Hg (95% CI, −1.5 to 0.9) and for ertugliflozin 15 mg plus sitagliptin versus sitagliptin was −1.0 mm Hg (95% CI, −2.2 to 0.2).[32]

2.1.3 VERTIS SITA2 (P006)

The text describing the SITA2 study was added by the CDR clinical reviewer based on data from the Clinical Study Report.[24]

A. Study Characteristics

Table 15: Summary of SITA2 Study

		VERTIS SITA2
Designs and Populations	**Study Design**	DB RCT
	Locations	US, South America, Europe, Asia, Israel
	Randomized (N)	463
	Inclusion Criteria	Patients ≥ 18 years of age with type 2 diabetes mellitus who had inadequate glycemic (A1C 7% to 10.5%) on metformin ≥ 1,500 mg per day plus sitagliptin 100 mg daily for ≥ 8 weeks and BMI ≥ 18.0 kg/m^2 Patients on the following regimens were also eligible: • 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 other DPP-4 inhibitor and A1C 7.0% to 10.5% • metformin ≥ 1,500 mg/day plus sulfonylurea and A1C 7.0% to 10.5% • metformin < 1,500 mg/day plus any DPP-4 inhibitor and A1C 7.5% to 11.0% Patients who underwent up to 8 weeks of washout of DPP-4 inhibitor or sulfonylurea medications and/or metformin dose titration and those with A1C 7% to 10.5% after at least 8 weeks of metformin ≥ 1,500 mg per day plus sitagliptin 100 mg daily were included.
	Exclusion Criteria	• < 80% adherent during placebo run-in period (pill counts) • History of ketoacidosis, type 1 diabetes mellitus, 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 whose weight was not stable due to weight-loss program, bariatric surgery, or medications • Abnormal laboratory 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 [redacted]

		VERTIS SITA2
		[redacted]; obstructive uropathy or indwelling catheter; [redacted]
DRUGS	**Intervention**	Ertugliflozin 5 mg daily Ertugliflozin 15 mg daily
	Comparator(s)	Placebo
DURATION	**Phase**	
	Washout / dose stabilization	Up to 12 weeks
	Placebo run-in	2 weeks
	Treatment	26 weeks (phase A)
	Follow-up	2 weeks
OUTCOMES	**Primary End Point**	Change from baseline to week 26 in A1C for: • ertugliflozin 15 mg versus placebo • ertugliflozin 5 mg versus placebo

	Other End Points	• Change from baseline in:
		  ○ FPG
		  ○ body weight
		  ○ SBP
		  ○ DBP
		  ○ EQ-5D-3L
		• Proportion of patients with A1C < 7.0%
		• Proportion of patients who received rescue therapy
		• Time to rescue therapy
		• Harms

NOTES	**Publications**	Dagogo-Jack et al.[33]

A1C = glycated hemoglobin; BMI = body mass index; DB = double-blind; DBP = diastolic blood pressure; DPP-4 = dipeptidyl peptidase-4; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; FPG = fasting plasma glucose; MI = myocardial infarction; NYHA = New York Heart Association; RCT = randomized controlled trial; SBP = systolic blood pressure; TIA = transient ischemic attack.

Source: Clinical Study Report.[24]

The SITA2 study was a double-blind 26-week randomized controlled trial (RCT) that evaluated the efficacy and safety of ertugliflozin in adults with type 2 diabetes and inadequate glycemic control (A1C 7% to 10.5%) on metformin ≥ 1,500 mg per day plus sitagliptin 100 mg daily for ≥ 8 weeks. Eligible patients underwent a two-week single-blind placebo run-in period and those who were ≥ 80% adherent were randomized. Exclusion criteria were similar to other ertugliflozin trials and those with recent cardiovascular events, history of ketoacidosis, significant alcohol use, or specific laboratory values outside a specified range were not eligible for enrolment.

Patients who met the inclusion criteria were randomized 1:1:1 via an interactive voice or Web response system to ertugliflozin 5 mg daily, ertugliflozin 15 mg daily, or placebo, and randomization was stratified by use of sulfonylurea at screening. The trial used a double-dummy design to maintain blinding, and all patients continued on open-label metformin and sitagliptin during the trial.

Patients who met the glycemic rescue criteria were administered open-label rescue therapy of glimepiride or insulin if glimepiride was not a suitable treatment in the investigator's

opinion. 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 and any background AHA therapies.

The primary outcome was the change from baseline in A1C to week 26. Other outcomes tested included the change from baseline in FPG, body weight, and SBP (sitting), and the proportion of patients who met glycemic targets (A1C < 7%) or who required rescue glycemic therapy. The SITA2 study reported health-related quality of life data using the EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L).

Table 16: Summary of Baseline Characteristics (SITA2 Study)

Characteristics	SITA2		
	Placebo N = 153	**Ertugliflozin 5 mg N = 156**	**Ertugliflozin 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	[redacted]	[redacted]	[redacted]
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 (%)	[redacted]	[redacted]	[redacted]
8.0 to < 9.0, n (%)	[redacted]	[redacted]	[redacted]
≥ 9.0, n (%)	[redacted]	[redacted]	[redacted]
Mean FPG, mg/dL (SD)	169.6 (37.8)	167.7 (37.7)	171.7 (39.1)
Mean eGFR, mL/min/1.73 m^2 (SD)	[redacted]	[redacted]	[redacted]
30 to < 60	[redacted]	[redacted]	[redacted]
60 to < 90	[redacted]	[redacted]	[redacted]
≥ 90	[redacted]	[redacted]	[redacted]
Background AHA therapy at screening, n (%)			
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)
Metformin daily dose, median mg (range)	[redacted]	[redacted]	[redacted]
Medical History			
Cardiac disorders (SOC)	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Metabolism and nutritional disorders (SOC)[a]	[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; FPG = fasting plasma glucose; SD = standard deviation; SOC = system organ class.

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

Source: Clinical Study Report.[24]

B. Results

The change from baseline in A1C, FPG, body weight, and blood pressure were analyzed using a cLDA model that included treatment, time (categorical), treatment by time interaction, baseline eGFR (continuous), and study-specific stratification factors. 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 proportion of patients with A1C < 7% was analyzed using a logistic regression model with treatment and baseline A1C (continuous) as variables. Missing data were imputed using multiple imputation methods or with missing data, assuming that the patient did not achieve the glycemic target.

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

The SITA2 trials used an ordered statistical testing procedure to control the family-wise type I error. 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. Outcomes were testing for ertugliflozin 15 mg versus placebo first, then ertugliflozin 5 mg versus placebo second for outcomes in the following order:

1. Change from baseline to week 26 A1C
2. Change from baseline to week 26 FPG
3. Change from baseline to week 26 body weight
4. Proportion of patients with A1C < 7.0%
5. Change from baseline to week 26 SBP.

The trial planned to enroll 405 patients (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 ertugliflozin versus placebo (two-sided test, alpha = 0.05).

The efficacy analyses were conducted based on the FAS, which was defined as all randomized patients who took at least one dose of the 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 the study drug (based on treatment received).

Table 17: Patient Disposition (SITA2 Study)

	SITA2		
	Placebo	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Screened, N			
Randomized, N (%)			
Not treated			
Discontinued study drug, n (%)			
Adverse event			
Withdrawal by patient			
Lost to follow-up			
Other reason			
FAS, N			
Safety, N			

A1C = glycated hemoglobin; FAS = full analysis set.

Source: Clinical Study Report.[24]

The mean duration of treatment (excluding rescue) was 163.2, 172.1, and 172.5 days in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg group, respectively. The median dose of metformin background therapy was 2,000 mg per day.

Table 18: Summary of Efficacy Results in SITA2 Study

Outcome/Study	Treatment	N	Baseline Mean (SD)	Change From Baseline LS Mean (95% CI)[a]	Difference in LS Mean (95% CI)[a]	*P* Value
Change From Baseline in A1C						
SITA2	Placebo	153	8.0 (0.9)	−0.09 (−0.23 to 0.04)		
	Ertugliflozin 5 mg	156	8.1 (0.9)	−0.78 (−0.91 to −0.65)	−0.69 (−0.87 to −0.50)	< 0.001
	Ertugliflozin 15 mg	153	8.0 (0.8)	−0.86 (−0.99 to −0.72)	−0.76 (−0.95 to −0.58)	< 0.001
Change From Baseline in FPG (mg/dL)						
SITA2	Placebo	153	169.6 (37.8)	−1.8 (−7.7 to 4.2)		
	Ertugliflozin 5 mg	156	167.7 (37.7)	−26.9 (−32.6 to −21.2)	−25.2 (−32.8 to −17.5)	< 0.001
	Ertugliflozin 15 mg	153	171.7 (39.1)	−33.0 (−38.7 to −27.4)	−31.3 (−38.9 to −23.7)	< 0.001
Change From Baseline in Body Weight (kg)						
SITA2	Placebo	153	86.5 (20.8)	−1.3 (−1.8 to −0.9)		
	Ertugliflozin 5 mg	156	87.6 (18.6)	−3.4 (−3.8 to −2.9)	−2.0 (−2.7 to −1.4)	< 0.001
	Ertugliflozin 15 mg	153	86.6 (19.5)	−3.0 (−3.5 to −2.6)	−1.7 (−2.4 to −1.1)	< 0.001
Change From Baseline in SBP (mm Hg)						
SITA2	Placebo					
	Ertugliflozin 5 mg					
	Ertugliflozin 15 mg					

Outcome/Study	Treatment	N	Baseline Mean (SD)	Change From Baseline LS Mean (95% CI)[a]	Difference in LS Mean (95% CI)[a]	*P* Value
Change From Baseline in DBP (mm Hg)						
SITA2	Placebo	[redacted]	[redacted]	[redacted]		
	Ertugliflozin 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Ertugliflozin 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; CI = confidence interval; DBP = diastolic blood pressure; FPG = fasting plasma glucose; LS = least squares; SBP = systolic blood pressure; SD = standard deviation.

[a] Excludes any data after the initiation of rescue glycemic therapy.

[redacted]

Source: Clinical Study Report.[24]

Table 19: Proportion of Patients at Glycemic Target or Who Required Rescue Therapy (SITA2 Study)

Study	Treatment	N	Number (%) With Event at Week 26[a]	Ertugliflozin Versus Placebo, Adjusted OR (95% CI)[a]	*P* Value
Proportion of Patients With A1C < 7%					
SITA2	Placebo	153	[redacted] (17)		
	Ertugliflozin 5 mg	156	[redacted] (32)	3.16 (1.74 to 5.72)	< 0.001
	Ertugliflozin 15 mg	153	[redacted] (40)	4.43 (2.44 to 8.02)	< 0.001
Proportion of Patients Who Received Glycemic Rescue					
	Treatment	**N**	**Number (%) With Event at Week 26[a]**	**Ertugliflozin Versus Placebo, Difference in % (95% CI)**	
SITA2	Placebo	[redacted]	[redacted]		
	Ertugliflozin 5 mg	[redacted]	[redacted]	[redacted]	[redacted]
	Ertugliflozin 15 mg	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; CI = confidence interval; LS = least squares; OR = odds ratio.

[a] Excludes any data after the initiation of rescue glycemic therapy.

[redacted]

Source: Clinical Study Report.[24]

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 the treatment groups reported an LS mean change from baseline of 0.0 to 0.02 points. 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, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively.

Table 20: 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 MET + SIT				**Change From Baseline to Week 26**	**Ertugliflozin Versus Placebo at Week 26**	
SITA2	Placebo	153	[redacted]	0.01 (−0.01 to 0.04)		
	Ertugliflozin 5 mg	155	[redacted]	0.0 (−0.02 to 0.03)	−0.01 (−0.04 to 0.02)	[redacted]
	Ertugliflozin 15 mg	151	[redacted]	0.02 (−0.0 to 0.04)	0.01 (−0.02 to 0.04)	[redacted]

CI = confidence interval; EQ-5L-3L = EuroQol 5-Dimensions 3-Levels questionnaire; LS = least squares; MET = metformin, SD = standard deviation; SIT = sitagliptin.

[a] Excludes any data after the initiation of rescue glycemic therapy.

[redacted]

Source: Clinical Study Report.[24]

2.2 Critical Appraisal of Pivotal Clinical Studies

The critical appraisal was completed by the CDR reviewer.

2.2.1 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 using an interactive voice or Web response system. 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 FACTORIAL study. The trials used an enrichment design, where only those patients who were > 80% adherent to placebo during a two-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 to maintain blinding. Although the overall frequency of AEs was similar between ertugliflozin and control groups, it is possible that some unblinding may have occurred due to the increased frequency of specific AEs 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 ertugliflozin.

Three 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.[34] 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 cardiovascular safety trial underway for ertugliflozin (VERTIS CV). Although all the included studies used an independent adjudication committee to evaluate deaths and cardiovascular 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, as an exploratory outcome. The MET trial reported data on bone mineral density, 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 bone mineral density 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 (e.g., A1C, FPG, weight, and blood pressure). Health-related quality of life, the proportion of patients who required rescue therapy and bone–mineral density outcomes, however, were outside the statistical testing procedure.

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

In all trials, the change from baseline in A1C, weight, and blood pressure were analyzed using a cLDA model with no imputation for missing data. Efficacy analyses were based on a modified intention-to-treat (mITT) rather than a full intention-to-treat (ITT) population, and included all patients who received at least one dose of the study drug and had one or more baseline or post-baseline outcome measures. However, the mITT 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 the study drug treatment early, there was no efficacy outcome data collected after treatment was stopped. These patients were followed by telephone for AEs. 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 the potential confounding effects of rescue therapy, the FDA expressed concerns with this method.[2,34] [redacted]. 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 ertugliflozin. The FDA Statistical Review stated that the preferred analysis would follow an ITT approach and include the outcome data collected, regardless of treatment adherence or need for rescue therapy.[34] 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 sensitivity analyses data showed similar results to the primary findings, 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.[34]

2.2.2 External Validity

External Validity

The population enrolled in the studies was middle-aged and predominantly white, had had diabetes for an average of 4.6 to 9.9 years, and had a low rate of cardiac disorders (≤ 25%). All trials were multinational; however, few Canadians were enrolled (0% to 8%). A substantial proportion of the 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 that of the Canadian diabetes population but, otherwise, the patient characteristics were similar to those seen in clinical practice.

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 cardiovascular safety study is underway and is expected to be completed in 2019.

2.3 Summary of Safety

2.3.1 Safety Evaluation Plan[28]

No phase III studies of the ertugliflozin/metformin FDC tablet have been performed with the ertugliflozin/metformin FDC tablet; however, data obtained from the four phase III studies that assessed the use of ertugliflozin on a background of metformin (≥ 1,500 mg/day) can be bridged to the FDC tablet based on established bioequivalence.[23] The ertugliflozin development program included four studies of ertugliflozin in combination with metformin. Two of the studies, the Add-on to Metformin and Sitagliptin Study (SITA2, P006/1015) and the Placebo-Controlled Add-On to Metformin Study (MET, P007/1017) were placebo-controlled and had a common study design that allowed the data to be pooled (ertugliflozin/metformin [Ertu/Met] Pool) for review of safety.[28]

2.3.2 Safety Populations Evaluated[28]

The Ertu/Met Pool includes 1,083 patients who were randomized and received at least one dose of study medication; 363 were randomized to the ertugliflozin 5 mg group, 358 to the ertugliflozin 15 mg group, and 362 to the placebo group. The mean observation period of patients on study medication was similar in the ertugliflozin 5 mg and 15 mg groups (177.7 days and 174.2 days, respectively) and the placebo group (174.4 days). Demographic and baseline characteristics were generally similar across groups. In the Ertu/Met Pool, 50.9% of patients were male, the mean body mass index (BMI) was 30.8 kg/m^2, and the mean age was 57.7 years. Most of the patients were white (69.1%); 17.9% were Asian, and 6.7% were black. The mean baseline eGFR was 89.4 mL/min/1.73 m^2; the mean duration of diabetes was 8.6 years and the baseline A1C was 8.1% (64.8 mmol/mol).

2.3.3 Overview of Safety[28]

In the Ertu/Met Pool, the incidence of patients with one or more AEs was not notably different in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group. Vulvovaginal mycotic infection was the only AE occurring at ≥ 2% and at a higher incidence (i.e., the 95% CI for the difference excluded 0) in an ertugliflozin group (1.9% and 2.2%, respectively, in the ertugliflozin 5 mg and 15 mg groups) compared with the placebo group (0.3%). Additional terms related to genital mycotic infections were further examined and are discussed in the Special Safety Topics section that follows.

There were no deaths in the 26-week Ertu/Met Pool, and the incidence of non-fatal serious AEs was low and not notably different in the ertugliflozin 5 mg and 15 mg groups (2.8% in both groups) and non-ertugliflozin group (3.6%). Only one specific non-fatal serious AE (acute myocardial infarction in the placebo group) occurred in more than one patient. The incidence of AEs resulting in discontinuation from study medication in the Ertu/Met Pool was low overall and not notably different in the ertugliflozin 5 mg and 15 mg groups (2.2% and 1.1%, respectively) and the placebo group (1.1%) (See Common Technical Document 2.7.4 Summary of Clinical Safety Ertugliflozin/Metformin Fixed-Dose Combination). For a listing of AEs and patients with AEs (incidence ≥ 2%), see Appendix 3.

The CDR reviewer added two summary tables with harms data for the four included studies (Table 21 and Table 22). The AE profile of ertugliflozin 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.

Special Safety Topics for the Ertugliflozin/Metformin Fixed-Dose Combination[28]

Based on the mechanisms of action of ertugliflozin and metformin, the combination of the two drugs does not suggest additional safety or tolerability risks beyond those of the individual drugs. Special safety topics identified for review in the ertugliflozin program are included in the ertugliflozin Summary of Clinical Safety (SCS). Changes in renal function and ketoacidosis are special safety topics for ertugliflozin. Metformin has dosing considerations depending on renal function and carries a risk for lactic acidosis, particularly in patients with significant renal impairment. As such, changes in renal function and metabolic acidosis, along with hypoglycemia, an important safety concern for all AHAs, were designated as special safety topics for the ertugliflozin/metformin FDC.

Changes in Renal Function[28]

In the Ertu/Met Pool, the incidence of renal-related events was low (< 1%) and not notably higher in the ertugliflozin groups relative to the placebo group. None of the events was serious or led to discontinuation. Similarly, in the phase III ertugliflozin development program, there was no increase in renal-related events with ertugliflozin treatment, except in those with moderate renal impairment. In patients with renal impairment, the incidence of renal-related events was low; the incidence was higher in the ertugliflozin groups relative to comparator groups.

Metabolic Acidosis[28]

In a broader pool of patients (all patients on metformin to receive ertugliflozin) 3 of 3,409 (0.1%) ertugliflozin-treated patients were assessed to have met the case definition of ketoacidosis with either "certain" or "possible" likelihood compared with no cases in the non-ertugliflozin group (0 of 1,450 patients).

Although the three cases assessed as certain or possible ketoacidosis were in patients on background metformin enrolled in studies included in this SCS, approximately 75% of the studies in the ertugliflozin phase III program evaluated patients on background metformin and, therefore, this result is not considered to reflect an increased risk of metabolic acidosis with ertugliflozin and metformin combination therapy relative to that of the individual drugs.

Hypoglycemia[28]

When the Ertu/Met Pool data from the studies were examined, the incidence of documented hypoglycemia (≤ 70 mg/dL [3.1mmol/L]) was not notably different across the ertugliflozin 5 mg and 15 mg dose groups (6.1% and 5.3%, respectively) and placebo group (3.9%).

Ertugliflozin was compared with glimepiride (a sulfonylurea drug associated with hypoglycemia) in a study with metformin as background therapy; in that study, the incidence of documented hypoglycemia was lower in the ertugliflozin 5 mg and 15 mg groups (5.6% and 8.2%, respectively) relative to the glimepiride group (27.2%). Severe hypoglycemia was also lower in the ertugliflozin 5 mg and 15 mg groups (0.2% in both groups) compared with the glimepiride group (2.3%).

CDR reviewer: 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, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively (Table 22). The absolute difference between the ertugliflozin 15 mg and glimepiride groups was −14% (95% CI, −18% to −10% ([P < 0.001]). For ertugliflozin 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 the failure of a previous outcome in the testing sequence.

Table 21: Summary of Adverse Events

Adverse Events	MET Study			SU Study		
	Placebo N = 209	Ertugliflozin 5 mg N = 207	Ertugliflozin 15 mg N = 205	Glimepiride N = 437	Ertugliflozin 5 mg N = 448	Ertugliflozin 15 mg N = 440
Patients with ≥ 1 AEs, n (%)[a]	94 (45)	88 (43)	103 (50)	269 (62)	263 (59)	262 (60)
Most common AEs[b]						
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vulvovaginal mycotic infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse Events	MET Study			SU Study		
	Placebo N = 209	Ertugliflozin 5 mg N = 207	Ertugliflozin 15 mg N = 205	Glimepiride N = 437	Ertugliflozin 5 mg N = 448	Ertugliflozin 15 mg N = 440
Patients with ≥ 1 SAEs, n (%)	[redacted]					
Stopped treatment due to AEs, n (%)	[redacted]					
Number of deaths, n (%)	[redacted]					
Including Rescue						
Patients with ≥ 1 SAEs, n (%)	8 (4)	3 (1)	7 (3)	12 (3)	28 (6)	17 (4)
Stopped treatment due to AEs, n (%)	3 (1)	3 (1)	3 (1)	17 (4)	18 (4)	25 (6)
Number of deaths, n (%)	0	0	0	0	5 (1)	1 (< 1)

AE = adverse event; SAE = serious adverse event.

[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.[24,27,30,32]

Table 21: Summary of Adverse Events (Continued)

Adverse Events	FACTORIAL					SITA2		
	Ertugliflozin 5 mg N = 250	Ertugliflozin 15 mg N = 248	SIT N = 247	Ertugliflozin 5 mg + SIT N = 243	Ertugliflozin 15 mg + SIT N = 244	Placebo N = 153	Ertugliflozin 5 mg N = 156	Ertugliflozin 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	[redacted]							
Urinary tract infection								
Hypoglycemia								
Upper respiratory tract infection								
Vulvovaginal mycotic infection								
Constipation								
Headache								
Back pain								
Patients with ≥ 1 SAEs, n (%)								
Stopped treatment due to AEs, n (%)								
Number of deaths, n (%)								
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; SAE = serious adverse event; SIT = sitagliptin.

Table 22: Summary of Notable Harms

Adverse Events	MET Study			SU Study		
	Placebo N = 209	Ertugliflozin 5 mg N = 207	Ertugliflozin 15 mg N = 205	Glimepiride N = 437	Ertugliflozin 5 mg N = 448	Ertugliflozin 15 mg N = 440
Notable Harms, n (%)[a]						
Documented hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic hypoglycemia	4 (2)	7 (3)	7 (3)	84 (19)	14 (3)[b]	23 (5)[c]
Severe hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypovolemia (CMQ)[d]	1 (< 1)	1 (< 1)	2 (1)	3 (1)	6 (1)	3 (1)
Genital mycotic infection (CMQ)[d]						
Males	0	3 (3)	3 (3)	0	10 (4)	4 (2)
Females	1 (1)	6 (6)	7 (6)	3 (1)	17 (8)	25 (10)
Urinary tract infection (CMQ)[d]	2 (1)	6 (3)	7 (3)	30 (7)	30 (7)	28 (6)
Fractures (adjudicated)[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low-trauma fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders (SOC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated renal events[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ketoacidosis or metabolic acidosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower-limb amputation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CMQ = custom MedDRA query; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.

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

[b] Absolute difference between ertugliflozin 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 ertugliflozin 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.[24,27,30,32]

Table 22: Summary of Notable Harms (Continued)

Adverse Events	FACTORIAL					SITA2		
	Ertugliflozin 5 mg N = 250	Ertugliflozin 15 mg N = 248	SIT N = 247	Ertugliflozin 5 mg + SIT N = 243	Ertugliflozin 15 mg + SIT N = 244	Placebo N = 153	Ertugliflozin 5 mg N = 156	Ertugliflozin 15 mg N = 153
Notable Harms, n (%)[a]								
Documented hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic hypoglycemia	6 (2)	6 (2)	6 (2)	6 (2)	12 (5)	4 (3)	6 (4)	1 (1)
Severe hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypovolemia (CMQ)[b]	4 (2)	2 (1)	0	0	0	1 (1)	1 (1)	0
Genital mycotic infection (CMQ)[b]								
Males	6 (5)	5 (4)	0	5 (4)	3 (2)	0	4 (5)	3 (4)

Adverse Events	FACTORIAL					SITA2		
	Ertugliflozin 5 mg N = 250	Ertugliflozin 15 mg N = 248	SIT N = 247	Ertugliflozin 5 mg + SIT N = 243	Ertugliflozin 15 mg + SIT N = 244	Placebo N = 153	Ertugliflozin 5 mg N = 156	Ertugliflozin 15 mg N = 153
Females	6 (5)	8 (7)	1 (1)	6 (5)	9 (8)	1 (2)	6 (8)	9 (13)
Urinary tract infection (CMQ)[b]	13 (5)	14 (6)	8 (3)	8 (3)	9 (4)	3 (2)	4 (3)	7 (5)
Fractures (adjudicated)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low-trauma fracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders (SOC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated renal events[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ketoacidosis or metabolic acidosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower-limb amputation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CMQ = custom MedDRA query; MedDRA = Medical Dictionary for Regulatory Activities; SIT = sitagliptin; SOC = system organ class.

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

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

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

Source: Clinical Study Reports.[24,27,30,32]

2.4 Bioequivalence

In the phase III studies, ertugliflozin and metformin were administered as separate tablets. No phase III studies of the ertugliflozin/metformin FDC tablet have been performed. However, data obtained from the phase III studies that assessed combination treatment with ertugliflozin and metformin can be bridged to the FDC tablet based on the established bioequivalence of the FDC to the individual components and the equivalence of once-daily and twice-daily dosing of ertugliflozin.[23] Additionally, a phase I drug–drug interaction study demonstrated no pharmacokinetic interaction between ertugliflozin and metformin. Thus, data from studies utilizing combination treatment with ertugliflozin and metformin extrapolate directly to the to-be-marketed combination tablet at corresponding doses.

The oral absorption of ertugliflozin is rapid, with median T_{max} occurring at approximately one hour post-dose in the fasted state, and at approximately two hours post-dose in the fed state. Following oral administration of a single 15 mg dose of ertugliflozin as tablets in healthy volunteers, oral bioavailability was determined to be approximately 100%. The pharmacokinetics of ertugliflozin is linear and uncomplicated. The absolute bioavailability of a metformin 500 mg tablet given under fasting conditions is approximately 50% to 60%. The pharmacokinetics of metformin exhibit saturable absorption at higher doses. Because the individual components of the FDC are bioequivalent to the respective comparators, the pharmacokinetics of the combination are deemed to be similar to those of the individual components.

The following four studies were considered pivotal bioequivalence studies for registration in Canada:

- P046/1054 (Comprehensive Summary: Bioequivalence [CSBE] reports the ertugliflozin 7.5 mg component)
- P050/1058 (CSBE reports the ertugliflozin 2.5 mg component)
- P052/1060 (CSBE reports the metformin 500 mg component)
- P053/1061 (CSBE reports the metformin 850 mg component).

Important notice regarding the bioequivalence data pertaining to ertugliflozin/metformin 2.5 mg/1,000 mg and 7.5 mg/1,000 mg:

The bioequivalence of the metformin component of the FDCs was assessed versus both doses of registered Canada-sourced Glucophage. A waiver was sought for not analyzing ertugliflozin in the two bioequivalence studies in which Canada-sourced Glucophage was used. Since a 1,000 mg strength of the innovator reference Glucophage product is not available in Canada, a bioequivalence study for the 1,000 mg metformin containing FDC was not conducted.

Table 23: Bioequivalence Profile for Ertugliflozin/Metformin 7.5 mg/850 mg Combination Product[a]

Parameter	Ertugliflozin as Ertugliflozin/Metformin FDC	Ertugliflozin as Ertugliflozin + Metformin[b]	Metformin as Ertugliflozin/Metformin FDC	Metformin as Ertugliflozin + Metformin[b]
AUC_{0-t} • Mean • Standard deviation[c] • Coefficient of variance • Ratio of least squares geometric mean • 90% confidence interval	 644.5 ng•hr/mL 134.67 ng•hr/mL 21% 100.35% 97.38% to 103.42%	 642.1 ng•hr/mL 146.93 ng•hr/mL 23% NA NA	 11,960 ng•hr/mL 3,150.8 ng•hr/mL 26% 102.37% 98.48% to 106.42%	 11,550 ng•hr/mL 2,973.8 ng•hr/mL 26% NA NA
C_{max} • Mean • Standard deviation[c] • Coefficient of variance • Ratio of least squares geometric mean • 90% confidence interval	 122.8 ng/mL 29.010 ng/mL 24% 97.21% 92.98% to 101.64%	 126.3 ng/mL 30.060 ng/mL 24% NA NA	 1,872 ng/mL 519.50 ng/mL 28% 98.30% 93.04% to 103.87%	 1,891 ng/mL 525.41 ng/mL 28% NA NA
T_{max} • Median • Range	 1.50 hr 1.00 hr to 2.03 hr	 1.00 hr 0.500 hr to 2.00 hr	 2.00 hr 0.500 hr to 4.00 hr	 3.00 hr 1.50 hr to 4.00 hr

AUC = area under the curve; C_{max} = peak concentration; FDC = fixed-dose combination; hr = hour; NA = not applicable; T_{max} = time to peak concentration.

[a] In accordance with current Health Canada bioequivalence standards and data requirements.

[b] Ertugliflozin and EU-sourced metformin, given concurrently.

[c] From tables 14.4.3.1.1, 14.4.3.1.2 P046/1054 Clinical Study Report.

Table 24: Bioequivalence Profile for Ertugliflozin/Metformin 2.5 mg/500 mg Combination Product[a]

Parameter	Ertugliflozin as Ertugliflozin/Metformin FDC	Ertugliflozin as Ertugliflozin + Metformin[b]	Metformin as Ertugliflozin/Metformin FDC	Metformin as Ertugliflozin + Metformin[b]
AUC_{0-t} • Mean • Standard deviation[c] • Coefficient of variance • Ratio of least squares geometric mean • 90% confidence interval	169.7 ng•hr/mL 40.378 ng•hr/mL 24% 98.62% 96.82% to 100.44%	172.9 ng•hr/mL 44.216 ng•hr/mL 26% NA NA	7,050 ng•hr/mL 1,804.7 ng•hr/mL 26% 100.36% 93.28% to 107.98%	6,918 ng•hr/mL 1,293.3 ng•hr/mL 19% NA NA
C_{max} • Mean • Standard deviation[c] • Coefficient of variance • Ratio of least squares geometric mean • 90% confidence interval	35.83 ng/mL 8.3819 ng/mL 23% 100.22% 94.76% to 106.00%	35.84 ng/mL 8.5680 ng/mL 24% NA NA	1,070 ng/mL 287.35 ng/mL 27% 101.49% 93.83% to 109.76%	1,035 ng/mL 208.26 ng/mL 20% NA NA
T_{max} • Median • Range	1.00 hr 1.00 to 2.00 hr	1.00 hr 0.500 to 3.00 hr	2.00 hr 1.00 to 4.02 hr	1.98 hr 0.483 to 4.10 hr

AUC = area under the curve; C_{max} = peak concentration; FDC = fixed-dose combination; hr = hour; NA = not applicable; T_{max} = time to peak concentration.

[a] In accordance with current Health Canada bioequivalence standards and data requirements.

[b] Ertugliflozin and US-sourced metformin, given concurrently.

[c] From tables 14.4.3.1.1, 14.4.3.1.2 P050/1058 Clinical Study Report.

Table 25: Bioequivalence Profile for Ertugliflozin/Metformin 2.5 mg/500 mg Combination Product[a]

Parameter	Metformin as Ertugliflozin/Metformin FDC Fasted	Metformin as Ertugliflozin + Metformin[b] Fasted	Metformin as Ertugliflozin/Metformin FDC Fed	Metformin as Ertugliflozin + Metformin[b] Fed
AUC_{0-t} • Mean • Standard deviation[c] • Coefficient of variance • Ratio of least squares geometric mean • 90% confidence interval	6,993 ng•hr/mL 2,059.9 ng•hr/mL 29% 106.80% 96.17% to 118.61%	6,653 ng•hr/mL 2,222.0 ng•hr/mL 33% NA NA	5,284 ng•hr/mL 1,192.5 ng•hr/mL 23% 98.65% 92.79% to 104.87%	5,409 ng•hr/mL 1,434.5 ng•hr/mL 27% NA NA
C_{max} • Mean • Standard deviation[c] • Coefficient of variance • Ratio of least squares geometric mean • 90% confidence interval	1,144 ng/mL 364.33 ng/mL 32% 108.27% 95.69% to 122.50%	1,067 ng/mL 376.06 ng/mL 35% NA NA	652.6 ng/mL 121.27 ng/mL 19% 101.46 % 97.54 to 105.52%	642.5 ng/mL 118.21 ng/mL 18% NA NA

Parameter	Metformin as Ertugliflozin/Metformin FDC Fasted	Metformin as Ertugliflozin + Metformin[b] Fasted	Metformin as Ertugliflozin/Metformin FDC Fed	Metformin as Ertugliflozin + Metformin[b] Fed
T_{max}				
• Median	2.00 hr	2.00 hr	3.00 hr	4.00 hr
• Range	1.00 to 3.02 hr	0.500 to 4.07 hr	1.00 to 6.00 hr	1.00 to 6.02 hr

AUC = area under the curve; C_{max} = peak concentration; FDC = fixed-dose combination; hr = hour; NA = not applicable; T_{max} = time to peak concentration.

[a] In accordance with current Health Canada bioequivalence standards and data requirements.

[b] Ertugliflozin and Canadian metformin, given concurrently.

[c] From tables 14.4.3.1.1, 14.4.3.1.2 P052/1060 Clinical Study Report.

Table 26: Bioequivalence Profile for Ertugliflozin/Metformin 7.5 mg/850 mg Combination Product[a]

Parameter	Metformin as Ertugliflozin/Metformin FDC Fasted	Metformin as Ertugliflozin+ Metformin[b] Fasted	Metformin as Ertugliflozin/Metformin FDC Fed	Metformin as Ertugliflozin+ Metformin[b] Fed
AUC_{0-t}				
• Mean	9,641 ng•hr/mL	9,590 ng•hr/mL	8,525 ng•hr/mL	8,096 ng•hr/mL
• Standard deviation[c]	2,516.2 ng•hr/mL	1,731.8 ng•hr/mL	1,797.9 ng•hr/mL	1,875.0 ng•hr/mL
• Coefficient of variance	26%	18%	21%	23%
• Ratio of least squares geometric mean	98.87%	NA	105.80%	NA
• 90% confidence interval	91.88% to 106.40%	NA	95.99% to 116.62%	NA
C_{max}				
• Mean	1,506 ng/mL	1,455 ng/mL	1,099 ng/mL	1,117 ng/mL
• Standard deviation[c]	425.04 ng/mL	244.93 ng/mL	253.14 ng/mL	262.73 ng/mL
• Coefficient of variance	28%	17%	23%	24%
• Ratio of least squares geometric mean	101.13%	NA	98.67%	NA
• 90% confidence interval	90.58% to 112.92%	NA	91.50% to 106.40%	NA
T_{max}				
• Median	2.00 hr	2.01 hr	3.53 hr	2.52 hr
• Range	1.00 to 3.02 hr	1.00 to 4.00 hr	1.03 to 4.10 hr	1.02 to 4.03 hr

AUC = area under the curve; C_{max} = peak concentration; FDC = fixed-dose combination; hr = hour; NA = not applicable; T_{max} = time to peak concentration.

[a] In accordance with current Health Canada bioequivalence standards and data requirements.

[b] Ertugliflozin and Canadian metformin, given concurrently.

[c] From tables 14.4.3.1.1.1, 14.4.3.1.1.2 P053/1061 Clinical Study Report.

3. Pharmacoeconomic Evaluation

Information and data in this section were provided by the manufacturer of ertugliflozin/metformin while completing the FDC review template. Additional information and/or data have been included by CDR reviewers.

3.1 Manufacturer-Submitted Cost Information

Table 27: Cost Comparison of New Combination Product and Individual Components[a]

Drug	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)
Ertugliflozin and metformin hydrochloride	2.5 mg/500 mg	Tablets	$1.2250	2 units	$2.4500
Ertugliflozin and metformin hydrochloride	2.5 mg/1,000 mg	Tablets	$1.2250	2 units	$2.4500
Ertugliflozin and metformin hydrochloride	7.5 mg/500 mg	Tablets	$1.2250	2 units	$2.4500
Ertugliflozin and metformin hydrochloride	7.5 mg/1,000 mg	Tablets	$1.2250	2 units	$2.4500
Ertugliflozin	5 mg	Tablets	$2.4500	1 unit	$2.4500
Ertugliflozin	15 mg	Tablets	$2.4500	1 unit	$2.4500
Metformin hydrochloride	500 mg	Tablets	$0.0444 to $0.6068	Up to 4 units	$0.0444 to $0.1078
Metformin hydrochloride	1,000 mg	Tablets	$1.0153 to $1,2196	Up to 2 units	$1.0153 to $2.4392
TOTAL					
Ertugliflozin + metformin hydrochloride	5 mg +1,000 mg				$2.5388 to $3.6696
Ertugliflozin + metformin hydrochloride	5 mg + 2,000 mg				$2.6276 to $4.8892
Ertugliflozin + metformin hydrochloride	15 mg + 1,000 mg				$2.5388 to $3.6696
Ertugliflozin + metformin hydrochloride	15 mg + 2,000 mg				$2.6276 to $4.8892

FDC = fixed-dose combination.

Note: Exclusivity for both ertugliflozin-related products (ertugliflozin [single component] and ertugliflozin/metformin FDC) are based on the ertugliflozin compound patent, CA 2733795, which expires in August 2029. The metformin formulation used is generic.

[a] Source: IQVIA Delta PA (April 2018).

3.1.1 Summary of Potential Cost Savings

The ertugliflozin plus metformin hydrochloride FDC is priced at parity with its parent molecule, ertugliflozin, and allows drug plans to benefit from the optimal daily dose of metformin at no additional cost. Metformin costs associated with daily doses provided as part of the ertugliflozin plus metformin hydrochloride FDC tablets range from $0.0888 per day to $2.4392 per day. Furthermore, drug plans can benefit from savings due to reduced dispensing fees.

In accordance with the CDR submission guidelines for manufacturers, the manufacturer developed a cost-minimization analysis (CMA), as the available clinical evidence demonstrates that treatment outcomes for the ertugliflozin plus metformin hydrochloride FDC tablets and its appropriate comparators are equivalent.

Results from the CMA demonstrate that ertugliflozin plus metformin hydrochloride FDC tablets represent the lowest cost option for payers in comparison with the closest comparators. The use of the ertugliflozin plus metformin hydrochloride FDC is cost-effective compared with each of SGLT2/metformin FDC drugs available in Canada. Ertugliflozin plus metformin hydrochloride FDC tablets also offer cost savings compared with co-administered SGLT2 and metformin. The ertugliflozin plus metformin hydrochloride FDC generates savings of up to $0.68 per day compared with SGLT2/metformin FDCs, while generating savings of $0.38 to $2.90 per day compared with co-administered SGLT2 and metformin.

Based on the prior, ertugliflozin plus metformin hydrochloride tablets represent a cost-effective option for plans. Furthermore, the budget impact analyses demonstrate that the requested reimbursement of ertugliflozin plus metformin hydrochloride tablets would be cost-neutral to cost savings for drug plans and would not result in a greater number of claims or patients treated.

3.2 Cost Comparison Table

Table 28: Cost Comparison Table[a]

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
Canagliflozin/metformin FDC	50 mg/500 mg	Tablets	1.5660	2 units	1.5660
Canagliflozin/metformin FDC	50 mg/850 mg	Tablets	1.5660	2 units	1.5660
Canagliflozin/metformin FDC	50 mg/1,000 mg	Tablets	1.5660	2 units	1.5660
Canagliflozin/metformin FDC	150 mg/500 mg	Tablets	1.5660	2 units	1.5660
Canagliflozin/metformin FDC	150 mg/850 mg	Tablets	1.5660	2 units	1.5660
Canagliflozin/metformin FDC	150 mg/1,000 mg	Tablets	1.5660	2 units	1.5660
Dapagliflozin/metformin FDC	5 mg/850 mg	Tablets	1.2250	2 units	2.4500
Dapagliflozin/metformin FDC	5 mg/1,000 mg	Tablets	1.2250	2 units	2.4500
Empagliflozin/metformin FDC	5 mg/500 mg	Tablets	1.3783	2 units	2.7566
Empagliflozin/metformin FDC	5 mg/850 mg	Tablets	1.3783	2 units	2.7566
Empagliflozin/metformin FDC	5 mg/1,000 mg	Tablets	1.3783	2 units	2.7566
Empagliflozin/metformin FDC	12.5 mg/500 mg	Tablets	1.3783	2 units	2.7566
Empagliflozin/metformin FDC	12.5 mg/850 mg	Tablets	1.3783	2 units	2.7566
Empagliflozin/metformin FDC	12.5 mg/1,000 mg	Tablets	1.3783	2 units	2.7566

FDC = fixed-dose combination.

[a] Source: IQVIA Delta PA (April 2018).

3.3 Manufacturer-Submitted Information Regarding Current Patent Status

Exclusivity for both products (ertugliflozin [single component] and ertugliflozin/metformin FDC) are based on the ertugliflozin compound patent, CA 2733795, which expires in August 2029.

3.4 Critical Appraisal of Cost Information

The manufacturer presented two cost comparisons: one compared the price of ertugliflozin/metformin FDC with the prices of currently available SGLT2 drugs and

metformin products, while the other compared the price of ertugliflozin/metformin FDC with the individual components.

The manufacturer reported the daily cost of ertugliflozin/metformin is $2.45, which, when compared with the daily costs of ertugliflozin and metformin used as individual products, resulted in cost savings of $0.09 to $2.44 per day. In its comparison of ertugliflozin/metformin FDC with other available SGLT2/metformin FDC drugs and the individual components, the manufacturer reported that ertugliflozin/metformin FDC would generate a cost savings of up to $0.68 per day compared with SGLT2 FDCs, and between $0.38 and $2.90 per day when compared with the individual components.

CDR identified the following limitations with the manufacturer's cost comparison tables:

- There was an error in the manufacturer's Table 28: the daily cost of the canagliflozin/metformin FDC was $3.13 as opposed to the reported $1.57.
- Alternate publicly available prices for metformin were identified. The public prices identified by CDR were slightly lower than those listed by the manufacturer, which reduced the reported cost savings compared with the individual components at the low end ($0.05 to $0.10 per day, Table 29).
- CDR also noted that an 850 mg strength of metformin was available. The impact of changing the metformin dose on patients receiving the 850 mg tablet is uncertain.

Table 29: CDR Reanalysis of Manufacturer's Cost Comparison of Individual and New Combination Ertugliflozin/Metformin

Drug	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)
Metformin	500 mg	Tablet	0.0247	Two to four times daily	0.05 to 0.10
Metformin	850 mg	Tablet	0.0339[a]	Two to three times daily	0.07 to 0.10
Metformin	500 mg	ER tablet	0.6068[b]	1,000 mg to 2,000 mg daily	1.22
Metformin	1,000 mg	ER tablet	1.2196[b]	1,000 mg to 2,000 mg daily	2.44
Ertugliflozin	5 mg 15 mg	Tablet	2.45[c]	Once daily	2.45
TOTAL					
Ertugliflozin + metformin	5 mg + 1,000 mg 15 mg + 1,000 mg				2.50 to 3.67
Ertugliflozin + metformin	5 mg + 2,000 mg 15 mg + 2,000 mg				2.55 to 4.89

CDR = CADTH Common Drug Review; ER = extended release.

[a] Saskatchewan Drug Formulary (July 2018).[35]

[b] IMS Delta PA. IMS Brogan (July 2018).[36]

[c] Manufacturer-submitted price.[37]

The CDR clinical review identified uncertainty regarding the comparative efficacy of ertugliflozin/metformin FDC, given the lack of randomized controlled studies using the FDC product. The CDR clinical review notes that ertugliflozin, in combination with metformin or metformin plus sitagliptin, is more effective than placebo (at least in the short term), and may have efficacy similar to other SGLT2 inhibitors, as per the review of the network meta-analysis (NMA) reported in the ertugliflozin review (although caution should be used when

interpreting the results due to limited evidence and the limited robustness of results with the NMA).

Due to the uncertainty of the effectiveness of ertugliflozin/metformin FDC compared with other treatments for type 2 diabetes mellitus, CDR presents a cost table noting the daily drug cost of ertugliflozin/metformin and other antidiabetic drugs, including FDC metformin products (Table 30).

Table 30: Cost Comparison Table

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
Ertugliflozin/ metformin (Segluromet)	2.5 mg/500 mg 2.5 mg/1,000 mg 7.5 mg/500 mg 7.5 mg/1,000 mg	Tablet	1.2250	One tablet, twice daily	2.45
Sodium-Glucose Transport Protein Inhibitors					
Ertugliflozin (Steglatro)	5 mg 15 mg	Tablet	2.4500	5 mg or 15 mg daily	2.45
Empagliflozin (Jardiance)	10 mg 25 mg	Tablet	2.6177	10 mg or 25 mg daily	2.62
Canagliflozin (Invokana)	100 mg 300 mg	Tablet	2.7627	100 mg or 300 mg daily	2.76
Dapagliflozin (Forxiga)	5 mg 10 mg	Tablet	2.6750	5 mg or 10 mg daily	2.68
Sodium-Glucose Transport Protein Inhibitors Plus Metformin Fixed-Dose Combinations					
Dapagliflozin/ metformin (Xigduo)	5 mg/850 mg 5 mg/1,000 mg	Tablet	1.2250	Two tablets daily	2.45
Empagliflozin/ metformin (Synjardy)	5 mg/500 mg 5 mg/850 mg 5 mg/1,000 mg 12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	Tablet	1.3783	Two tablets daily	2.76
Canagliflozin/ metformin (Invokamet)	50 mg /500 mg 50 mg/850 mg 50 mg/1,000 mg 150 mg /500 mg 150 mg/850 mg 150 mg/1,000 mg	Tablet	1.5660	Two tablets daily	3.13
Dipeptidyl Peptidase-4 Inhibitors					
Sitagliptin (Januvia)	25 mg 50 mg 100 mg	Tablet	3.0932	100 mg daily	3.09
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	Tablet	2.4760 2.9680	5 mg daily	2.48 2.97
Linagliptin (Trajenta)	5 mg	Tablet	2.5500	5 mg daily	2.55
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	Tablet	2.2,000[a]	25 mg daily	2.20

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
Dipeptidyl Peptidase-4 Inhibitors / Metformin Fixed-Dose Combinations					
Sitagliptin/metformin (Janumet)	50 mg/500 mg 50 mg/1,000 mg	ER tablet	1.6779	Once daily: 100 mg sitagliptin and 2,000 mg metformin	3.36
	100 mg/1,000 mg		3.3557		3.36
Sitagliptin/metformin (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	Tablet	1.6779	Two tablets daily: 100 mg sitagliptin and 2,000 mg metformin	3.36
Saxagliptin/ metformin (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tablet	1.2700	Two tablets daily	2.54
Linagliptin/metformin (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tablet	1.3337	Two tablets daily	2.67
Alogliptin/metformin (Kazano)	12.5 mg/500 mg 12.5 mg/ 850 mg 12.5 mg/1,000 mg	Tablet	1.1950[a]	Two tablets daily	2.39
Glucagon-Like Peptide-1 Receptor Agonist					
Lixisenatide (Adlyxine)	10 mcg 20 mcg	14-dose pre-filled pen (3 mL)	56.9800[a]	Starting dose of 10 mcg once daily for 14 days, after which the dose should be increased to 20 mcg once daily	4.07
Dulaglutide (Trulicity)	0.75 mg/0.5 mL 1.5 mg/0.5 mL	4 × 0.5 mL pre-filled pen	49.7900[a]	0.75 mg to 1.5 mg once weekly	7.11
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/mL)	119.7250[a] per mL 59.8625[a] per mL	5 mg to 10 mcg twice daily	4.79
Exenatide (Bydureon)	2 mg	2 mg pre-filled pen	49.4850[a]	2 mg once weekly	7.07
Liraglutide (Victoza)	2 × 3 mL 3 × 3 mL	Pre-filled pen (6 mg/mL)	29.0133[a] per mL	1.2 mg to 1.8 mg daily	5.80 to 8.70
Biguanides					
Metformin (generics)	500 mg 850 mg	Tablet	0.0247 0.0339[b]	500 mg three to four times daily 850 mg two to three times daily	0.07 to 0.10
	500 mg 1,000 mg	ER tablet	0.6068[a] 1.2196[a]	1,000 mg to 2,000 mg daily	1.22 to 2.44
Sulfonylureas					
Gliclazide	80 mg	Tablet	0.0931	80 mg to 320 mg daily (in divided doses if > 160 mg daily)	0.09 to 0.37
Gliclazide long acting (Diamicron MR)	30 mg 60 mg	SR tablet ER tablet	0.0931 0.0632	30 mg to 120 mg daily	0.03 to 0.13
Glimepiride (generics)	1 mg 2 mg 4 mg	Tablet	0.4900	1 mg to 4 mg daily	0.49
Glyburide (generics)	2.5 mg 5.0 mg	Tablet	0.0321 0.0574	2.5 mg to 20 mg daily (in divided doses if > 10 mg daily)	0.03 to 0.23
Thiazolidinediones					
Pioglitazone (generics)	15 mg 30 mg	Tablet	1.2250[c] 1.5716[c]	15 mg to 45 mg daily	1.23 to 3.31

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
	45 mg		3.3105[c]		
Rosiglitazone (generics)	2 mg 4 mg 8 mg	Tablet	1.1692[c] 1.8346[c] 2.6235[c]	4 mg to 8 mg daily	1.17 to 2.62
Meglitinides					
Repaglinide	0.5 mg 1 mg 2 mg	Tablet	0.2083 0.2165 0.2441	0.5 mg to 2 mg daily	0.21 to 0.24
Alpha-Glucosidase Inhibitors					
Acarbose (Glucobay)	50 mg 100 mg	Tablet	0.2695 0.3732	50 to 100 mg 3 times daily	0.81 to 1.12

ER = extended release; SR = sustained release.

Source: Ontario Drug Benefit (May 2018) prices, unless otherwise indicated.[38]

[a] IMS Delta PA. IMS Brogan (May 2018).[36]

[b] Saskatchewan Drug Formulary (May 2018).[35]

[c] Pioglitazone was listed on other drug formularies at a cheaper price (e.g., on the Saskatchewan Drug Formulary, pioglitazone is listed at $0.38 per 15 mg tablet, $0.54 per 30 mg tablet, and $0.81 per 45 mg tablet).

[d] Rosiglitazone (Avandia) was listed on other drug formularies at higher prices (e.g., on the Saskatchewan and Alberta Drug Formulary, rosiglitazone is listed at $1.03 per 2 mg tablet, $1.62 per 4 mg tablet, and $2.32 per 8 mg tablet.

As can be seen in Table 30, based on the publicly available prices, ertugliflozin/metformin FDC is more costly than one DPP4-inhibitor, alogliptin, and alogliptin/metformin FDC (though neither is currently listed on a CDR-participating public drug plan), but less costly than other DPP-4 inhibitors and all glucagon-like peptide 1 receptor agonists. Ertugliflozin/metformin FDC is also more costly than all other second-line therapies, including sulfonylureas, thiazolidinediones, meglitinides, and alpha-glucosidase inhibitors (when added to the generic metformin).

However, the comparative efficacy and dosing of ertugliflozin/metformin FDC compared with other antidiabetic drugs (both FDC and individual components) is uncertain due to the lack of clinical studies conducted with ertugliflozin/metformin FDC. Thus, it is difficult to draw any definitive conclusions on the costs of ertugliflozin/metformin compared with other antidiabetic FDC drugs.

CDR pharmacoeconomic reviewers identified the following additional issues for consideration regarding the cost comparison:

- There is substantial variation in the listing of second- and third-line therapies for type 2 diabetes mellitus products. Public prices also vary across jurisdiction, with the caveat that there may be confidential prices that have been negotiated.
- The use of ertugliflozin/metformin FDC may lead to savings on dispensing fees per claim when compared with the combination of the individual component medications.

4. Discussion

The Discussion and Conclusions sections of this review were completed by the CDR reviewer. This review was conducted in tandem with the evaluation of ertugliflozin 5 mg and 15 mg tablets (Steglatro), which includes additional study data and an appraisal of the manufacturer-submitted indirect treatment comparison that are not presented in this report.

A total of four double-blind RCTs provided evidence on the efficacy and safety of ertugliflozin in adults with type 2 diabetes and inadequate glycemic control with 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 ertugliflozin 5 mg and 15 mg daily versus placebo (MET, SITA2) or glimepiride (SU). The FACTORIAL trial compared ertugliflozin 5 mg and 15 mg daily plus sitagliptin with ertugliflozin or sitagliptin alone.

4.1 Interpretation of Results

4.1.1 Efficacy

Ertugliflozin 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 −0.9%). Ertugliflozin plus sitagliptin (as add-on to metformin) also showed statistically significant differences in A1C compared with ertugliflozin or sitagliptin (plus metformin) (LS mean difference: −0.4% to −0.5%). More patients on ertugliflozin achieved glycemic targets (A1C < 7%) and fewer required rescue therapy than placebo. In the head-to-head study, ertugliflozin 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 ertugliflozin 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 −2.0 kg for ertugliflozin versus placebo and from −1.9 kg to −2.3 kg for ertugliflozin plus sitagliptin versus sitagliptin after 26 weeks of therapy, which were statistically significant. Somewhat larger mean differences were noted between ertugliflozin 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 ertugliflozin and the 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 to be clinically relevant. SBP data from the SU study was inconclusive due to the failure of a previous outcome in the statistical testing procedure. The differences between the ertugliflozin and control groups for the change from baseline in DBP were not statistically significant or conclusive in three of the four studies (SU, FACTORIAL, 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.

No statistically significant differences were detected between ertugliflozin 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 bone mineral density after 26 weeks of therapy for ertugliflozin versus placebo; however, the duration of follow-up may have

been insufficient to detect meaningful changes. Furthermore, the reporting of bone mineral density as raw scores, rather than T-scores, makes interpretation difficult.

The manufacturer submitted an indirect treatment comparison[10] that compared ertugliflozin, as add-on therapy to metformin, with the three SGLT2 inhibitors approved in Canada (canagliflozin, dapagliflozin, and empagliflozin) (see CDR Clinical Report of Steglatro for details). 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 NMA suggest that ertugliflozin has effects on A1C, weight, and blood pressure that are similar to other SGLT2 inhibitors in the short term. Although it was planned that the NMA would examine hypoglycemia, UTIs, genital infections, and overall AEs, 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 have increased the chances of finding no difference between drugs. Based on the results of the submitted indirect treatment comparison, ertugliflozin in combination with metformin for the treatment of type 2 diabetes mellitus is likely more efficacious than placebo. Little can be elucidated on the comparative efficacy versus other SGLT2 inhibitors or the relative safety of the product. Other than the SU study, direct evidence of the comparative efficacy of ertugliflozin versus other diabetes treatments is lacking.

The available evidence on the efficacy of ertugliflozin was limited by the relatively short duration of the four 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 ertugliflozin groups, the ertugliflozin treatment effects may be overestimated. Although the manufacturer and the 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, changes in A1C have been classified as modest.[2]

4.1.2 Harms

The AE profile of ertugliflozin 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 AEs was generally similar between groups within studies, and the proportion of patients who stopped the study drug due to AEs was low (≤ 5% per group). Serious AEs were reported by [redacted] of patients who received placebo, [redacted] of those who received ertugliflozin (alone or with sitagliptin), [redacted] who received sitagliptin or glimepiride. Genital mycotic infections were reported more frequently among patients who received ertugliflozin than other therapies. Changes in bone mineral density and an increased risk of fractures have been raised as a possible concern with other SGLT2 inhibitors. Few fractures were reported during phase A of the RCTs. Pooled study data from the FDA reported a total of 11 non-traumatic limb amputations among 3,409 patients who received ertugliflozin (0.3%) compared with one out of 1,450 (0.1%) of those who received a control treatment.[34] Additional data on these AEs may be available from the ertugliflozin cardiovascular safety study, as the included trials were of insufficient duration and sample size to detect and quantify rare events. Although

adverse cardiovascular events were captured during the trials, data on these events will not be reported until after the completion of the VERTIS CV study.

4.1.3 Potential Place in Therapy[2]

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%; however, if patients present with A1C > 1.5% above their glycemic target, then the recommended initial therapy is metformin plus a second-line drug.[4] The second-line therapy choice includes a multitude of options; however, in those with known clinical cardiovascular disease, there is a strong recommendation to use a medication that has clinical trial evidence of cardiovascular protection (empagliflozin, canagliflozin, or liraglutide).[5-7] There are a number of studies that suggest combinations of submaximal doses of two drugs produces better glycemic control with fewer adverse effects than monotherapy at maximal doses.[8]

Deciding on the second-line treatment should involve shared decision-making with the 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 glucagon-like peptide 1 [GLP-1] agonists). When patients have insurance coverage for their medications, choosing between these three drugs is based on patients' desire for weight loss and willingness to accept adverse effects. Again, if the patient has clinical cardiovascular disease, then a drug with clinical trial evidence of cardiovascular protection 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 with ertugliflozin 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 VERTIS CV outcome trial due out in 2019 will be important to understand if these unexpected AEs seen with canagliflozin[6] 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 the ertugliflozin renal study showed it to be no different than the other available therapies. In the earlier stages of renal disease, both empagliflozin and canagliflozin have been shown to reduce progression,[6,9] but there is no data to support that yet for ertugliflozin.

Given that ertugliflozin does not yet have evidence of clinical cardiovascular or renal benefit (it has an ongoing trial with results expected in the fall of 2019) and its glucose-lowering potential and adverse-effect profile appear to be similar to the currently available SGLT2 inhibitors, it does not appear to offer any significant benefit over the currently available SGLT2 inhibitors. If ertugliflozin is reimbursed as monotherapy, however, then it would make sense to reimburse

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

the combination product, given that many patients require more than one drug to manage their hyperglycemia, and patients appreciate the reduced pill burden offered by combination products.

4.1.4 Cost

The manufacturer reported a daily cost of $2.45 for all dosing schemes of ertugliflozin/metformin FDC, which is priced similarly to the publicly available prices of other SGLT2/metformin FDC drugs. Ertugliflozin/metformin FDC is more costly than the public price of most older second- and third-line drugs in combination with metformin, but is less costly than the public price of most newer second- and third-line drugs in combination with metformin. However, the CDR clinical review highlighted several sources of uncertainty pertaining to the comparative effectiveness of ertugliflozin/metformin FDC against all relevant comparators.

Therefore, it is difficult to draw any definitive conclusions on the comparative costs given the uncertainty associated with the comparative efficacy data and lack of data on the comparative dosing of the individual components of ertugliflozin and metformin as well as other antidiabetic drugs.

4.1.5 Conclusions

Ertugliflozin as add-on therapy to metformin, or metformin plus sitagliptin, was associated with statistically significant short-term (six-month) reductions in A1C, body weight, and SBP as compared with placebo plus add-on therapies. In addition, ertugliflozin 15 mg daily was noninferior to glimepiride for the change from baseline in A1C after 52 weeks. Noninferiority, however, was not met for ertugliflozin 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 ertugliflozin plus sitagliptin, as add-on therapy to metformin, versus sitagliptin plus metformin.

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

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

The results of the manufacturer-submitted indirect treatment comparisons suggest that ertugliflozin in combination with metformin for the treatment of type 2 diabetes mellitus is likely more efficacious than placebo; however, little can be elucidated on the comparative efficacy of ertugliflozin in combination with metformin versus other SGLT2 inhibitors or the relative safety of the product.

Ertugliflozin/metformin FDC may provide cost savings versus other SGLT2/metformin FDC drugs and newer second- and third-line drugs in combination with metformin, but appears to be more costly than most older second- and third-line drugs in combination with metformin. However, there is uncertainty related to the comparative clinical evidence with ertugliflozin/metformin FDC and other antidiabetic therapies, precluding definitive conclusions on the comparative costs.

Appendix 1: Drug Plan Listing Status for Individual Components

Abbreviation	Description
FB	Full benefit
UR	Under review

Table 31: Reimbursement Status for Individual Components of the New Combination Product

Components	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Ertugliflozin	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR
Metformin	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB

AB = Alberta, BC = British Columbia, CDR = CADTH Common Drug Review; DND = Department of National Defence; FB = full benefit; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; UR = under review; VAC = Veterans Affairs Canada; YK = Yukon.

Appendix 2: Summary of Patient Input

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 has 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 conducted in October 2016 and April/May 2018. The 2018 survey posed a number of questions specifically about the drug under review, ertugliflozin and metformin hydrochloride, as well as ertugliflozin (Steglatro). 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; 60% have lived with diabetes for more than 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 data on age and date of diagnosis: 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% have 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. Over time, high blood glucose 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 to avoid or delay complications.

Most patients surveyed talked about the adverse effect diabetes has had on their lives. Patients describe their diabetic conditions as "manageable but a bother," "a constant battle every day," "terrible," inconvenient, frustrating, and exhausting. Their diabetes affects all aspects of their lives, from eating and exercising to working and socializing. 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.

The following 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, increased 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 they have used (in the past or currently) the following antihyperglycemic drugs: 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, a combination of DPP-4 inhibitors and metformin, sulfonylureas, thiazolidinediones (TZDs), a combination of TZDs, a combination of TZDs and metformin, and glimepiride, meglitinides, acarbose, and insulin. More than 60% of those who responded to the October 2016 survey, and more than 45% of those who responded to the 2018 survey, noted improvements in meeting target blood glucose levels (fasting, post-prandial, upon waking) and glycated hemoglobin (A1C) levels since initiating their current medication regimen compared with before (when they were not on treatment). In the survey administered in October 2016, about 46% of patients said they were "better" or "much better" able to avoid hypoglycemia, and 39% said their current regimen has helped them maintain or lose weight more effectively than in the past. Gastrointestinal side effects were "neither better nor worse" than previously, according to 39% of respondents. About two-thirds indicated they were either "satisfied" or "very satisfied" with the medication or combination of medications they are currently taking to manage their diabetes. Among the respondents to both surveys, the factors that were considered "quite important" or "very important" to choosing diabetes medications were, among others: keeping blood glucose at a satisfactory level, avoiding low blood sugar, avoiding weight gain or facilitating weight loss, reducing risk of heart problems, and avoiding gastrointestinal issues (nausea, vomiting, diarrhea, pain) and urinary tract and/or yeast infections.

4. Expectations About the Drug Being Reviewed

Patients who participated in the survey either reported no experience with using ertugliflozin and metformin 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 A1C without causing weight gain or hypoglycemia. They wish for new treatments that have been proven to be safe, that enhance weight loss and that improve health outcomes. They want affordable drug options; ideally, they would 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. The majority of respondents (56%) thought it would be "extremely beneficial" or "very beneficial" to have combination antihyperglycemic medications like ertugliflozin and metformin hydrochloride available as treatment options for people living with diabetes, while 17% said this would be "not so beneficial" or "not at all beneficial."

Below are a few examples of quotes from patients regarding their hopes and expectations for new treatments:

- *"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 3: Adverse Event Summary

Table 32: All Patients as Treated, Ertugliflozin/Metformin (Ertu/Met) Fixed-Dose Combination Pool

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	%	n	%	n	%	n	%
Patients in population:	362		363		358		721	
With one or more AE	178	49.2	154	42.4	172	48.0	326	45.2
With no AE	184	50.8	209	57.6	186	52.0	395	54.8
With drug-related AE[a]	27	7.5	42	11.6	47	13.1	89	12.3
With serious AEs	13	3.6	10	2.8	10	2.8	20	2.8
With serious drug-related AEs	0	0.0	0	0.0	1	0.3	1	0.1
Who died	0	0.0	0	0.0	0	0.0	0	0.0
Who discontinued[b] due to an AE	4	1.1	8	2.2	4	1.1	12	1.7
Who discontinued due to a drug-related AE	2	0.6	4	1.1	2	0.6	6	0.8
Who discontinued due to a serious AE	2	0.6	0	0.0	0	0.0	0	0.0
Who discontinued due to a serious drug-related AE	0	0.0	0	0.0	0	0.0	0	0.0

AE = adverse event.

Note: One patient in the ertugliflozin 5 mg group with an AE started in phase A and later discontinued the study medication due to the AE after the completion of phase A and during phase B.

[a] Determined by the investigator to be related to the drug.

[b] Study medication withdrawn.

Table 33: Patients With Adverse Events (Incidence ≥ 2% in One or More Treatment Groups) — All Patients as Treated, Ertugliflozin/Metformin (Ertu/Met) Fixed-Dose Combination Pool, Including Rescue Approach

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	362		363		358		721	
with one or more adverse events	178	(49.2)	154	(42.4)	172	(48.0)	326	(45.2)
with no adverse events	184	(50.8)	209	(57.6)	186	(52.0)	395	(54.8)
Cardiac disorders	**3**	**(0.8)**	**5**	**(1.4)**	**7**	**(2.0)**	**12**	**(1.7)**
Gastrointestinal disorders	**26**	**(7.2)**	**29**	**(8.0)**	**24**	**(6.7)**	**53**	**(7.4)**
Diarrhoea	9	(2.5)	4	(1.1)	4	(1.1)	8	(1.1)
General disorders and administration site conditions	**13**	**(3.6)**	**8**	**(2.2)**	**9**	**(2.5)**	**17**	**(2.4)**
Infections and infestations	**76**	**(21.0)**	**62**	**(17.1)**	**72**	**(20.1)**	**134**	**(18.6)**
Influenza	9	(2.5)	4	(1.1)	7	(2.0)	11	(1.5)
Nasopharyngitis	8	(2.2)	7	(1.9)	6	(1.7)	13	(1.8)
Upper respiratory tract infection	20	(5.5)	8	(2.2)	16	(4.5)	24	(3.3)
Urinary tract infection	4	(1.1)	7	(1.9)	7	(2.0)	14	(1.9)
Vulvovaginal mycotic infection	1	(0.3)	7	(1.9)	8	(2.2)	15	(2.1)
Injury, poisoning and procedural complications	**11**	**(3.0)**	**12**	**(3.3)**	**17**	**(4.7)**	**29**	**(4.0)**
Investigations	**15**	**(4.1)**	**14**	**(3.9)**	**16**	**(4.5)**	**30**	**(4.2)**
Weight decreased	5	(1.4)	4	(1.1)	11	(3.1)	15	(2.1)
Metabolism and nutrition disorders	**40**	**(11.0)**	**26**	**(7.2)**	**23**	**(6.4)**	**49**	**(6.8)**
Hypoglycaemia	15	(4.1)	15	(4.1)	12	(3.4)	27	(3.7)
Musculoskeletal and connective tissue disorders	**27**	**(7.5)**	**20**	**(5.5)**	**35**	**(9.8)**	**55**	**(7.6)**
Back pain	8	(2.2)	7	(1.9)	12	(3.4)	19	(2.6)
Nervous system disorders	**19**	**(5.2)**	**24**	**(6.6)**	**23**	**(6.4)**	**47**	**(6.5)**
Headache	5	(1.4)	12	(3.3)	8	(2.2)	20	(2.8)

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