Ertugliflozin in monotherapy and dual therapy: NICE appraisal ID1158

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Abbreviations

AE	Adverse event
AHA	Anti-hyperglycaemic agents
ANCOVA	Analysis of covariance
BMD	Bone mineral density
BMI	Body mass index
CANA	Canagliflozin
CANTATA	CANagliflozin Treatment and Trial Analysis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CrI	Credible interval
CV	Cardiovascular
DAPA	Dapagliflozin
DBP	Diastolic blood pressure
DiRECT	Diabetes Remission Clinical Trial
DPP-4i	Dipeptidyl peptidase 4 inhibitor
eGFR	Estimated glomerular filtration rate
EMA	European Medicine Agency
EMPA	Empagliflozin
EPAR	European assessment report
ERG	Evidence review group
ERG	Evidence review group
ERTU	Ertugliflozin
FAS	Full analysis set
FDA	Food and Drug Administration
FTA	Fast track appraisal
GTI	Genital tract infection

HbA1c	Haemoglobin A1 c
HCHS	Health Care and Hospital Services
HDL	High-density lipoprotein
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat population
IVRS	Interactive voice response system
J2R	Jump to reference analysis
LDL-C	Low-density lipoprotein
LS	Least square
MET	Metformin
Mg	Milligram
MSD	Merck Sharp & Dohme Ltd
MTA	Multiple technology appraisal
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PBO	Placebo
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
R	Randomisation
RCT	Randomised controlled trial
RTB	Return To Baseline
SA	Sensitivity analysis
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT-1	Sodium-glucose cotransporter-1
SGLT-2i	Sodium-glucose cotransporter-2 inhibitor
SITA	Sitagliptin

SU	Sulphonylurea
T2DM	Type 2 Diabetes Mellitus
TA	Technology appraisal
TC	Total cholesterol
UGE	Urinary glucose excretion
UKPDS	United Kingdom prospective diabetes study
UTI	Urinary tract infections

1. Summary

Summary of ERG's view of the case for a cost-comparison FTA

Some of the key decisions are made by the NICE technical team, but the ERG view is that a cost-comparison FTA is appropriate because;

- Ertugliflozin is pharmacologically similar to previously approved drugs from this class, the SGLT-2 inhibitors canagliflozin, dapagliflozin and empagliflozin
- The MSD submission covers the same marketing authorisation and population as the previously approved drugs
- The MSD submission uses comparators already approved by NICE
- MSD has presented evidence using the same outcome measures as those used in the cost-effectiveness models for the previously approved flozins. The primary outcome was HbA1c. Trials were too short to measure long-term complications, but this also applied to trials of the other flozins.
- Ertugliflozin appears to have similar efficacy to the comparators. Good quality RCTs of ertugliflozin in monotherapy and dual therapy have been provided.
- No direct head-to-head trials have been carried out, but MSD have provided an NMA (about which the ERG has some concerns).
- The ERG has examined trials of approved comparators and identified those most useful for comparing ertugliflozin with previously approved drugs, based on design, characteristics of patients included and outcomes. We conclude that ertugliflozin is as effective in monotherapy as canagliflozin, and as effective in dual therapy as dapagliflozin.
- Adverse effects appear similar to other flozins
- No differences on effects on later treatment pathways are expected
- To qualify for a cost-comparison appraisal, the acquisition price of the new drug must be similar to, or lower than, previously approved drugs, and overall costs to NHS should also be similar or lower. This criterion is met.

Follow-up in the studies is up to 52 weeks, so uncertainties remain about any occurrence of infrequent longer-term adverse effects, possibly specific to ertugliflozin.

1.1 Critique of the decision problem in the MSD submission.

No problems. The MSD submission matches the NICE scope, as summarised in Table 1 of the MSD submission. Ertugliflozin is a recent addition to the class of drugs known as the SGLT2 inhibitors, three of which have already been approved by NICE, for use in type 2 diabetes;

- in monotherapy for people who cannot take metformin and in whom neither a sulphonylurea nor pioglitazone are considered appropriate
- in dual therapy in addition to metformin when a sulfonylurea is contraindicated or not tolerated or the person is at significant risk of hypoglycaemia or its consequences

1.2 Summary of the ERG's critique of the clinical effectiveness evidence submitted

The MSD submission has two sections on clinical effectiveness. The first is an account of the relevant trials, and the second is an NMA. We have some reservations about the statistical analysis of the VERTIS MONO trial, which may have over-estimated the reduction in HbA1c compared to placebo, though not enough to affect the final conclusion. We also have reservations about the NMA, but since we do not think an NMA was necessary (because equivalence of clinical effectiveness could be demonstrated more simply and transparently), these reservations are inconsequential.

1.3 Summary of ERG critique of cost evidence submitted by MSD.

No problems. [redacted]. To qualify for a cost-comparison appraisal, the price of the new drug must be similar or lower than previously approved drugs. This criterion is met, [redacted]).

1.4 ERG commentary on robustness of evidence submitted by MSD

Despite our reservations above, explained in detail below, we think the evidence, partly from the MSD submission and the published papers from the VERTIS trials, and partly from additional work by the ERG, is sufficient to show equivalent clinical effectiveness to other flozins already approved by NICE.

2. ERG report: Introduction

2.1 NICE has previously approved three drugs in this class, the sodium-glucose transport protein 2 (SGLT2) inhibitors (in short, the flozins), in monotherapy and dual therapy. These drugs reduce conservation of glucose by the kidneys, leading to loss of glucose in the urine (about 80g/day). The guidances are reproduced in Appendix 1, for reference if required. The combinations approved in dual therapy included only metformin.

The scope for the present appraisal (ID1158) did not limit dual therapy to a combination with metformin but since MSD are seeking approval of ertugliflozin through the FTA cost-comparison system, the restrictions applied by the guidance to the comparator drugs, will also apply to ertugliflozin.

2.2 Background

The MSD positioning of ertugliflozin in the clinical pathway matches approvals of previous drugs in this class, and the NICE guideline for type 2 diabetes, NG28.

MSD reproduce the algorithm from NG28, last updated May 2017.[1] Since then, new evidence on non-pharmacological management has emerged from the DiRECT trial (published March 2018[2]), in which a weight management programme led to remission (i.e. cure, not just improved control) of diabetes in 46%. Details in Discussion section.

2.3 MSD definition of decision problem.

No problems. The MSD submission matches the NICE scope, as summarised in Table 1 of the MSD submission.

3. Clinical effectiveness

3.1 Literature searches. The ERG view is that the MSD submission included all trials relevant to monotherapy and dual therapy. All the VERTIS trials were sponsored by the manufacturers (and most authors are from the manufacturers), so none would be missed. However the ERG has used data from trials of ertugliflozin in other situations for data on genital tract infections.

3.2 Trials

The MSD submission includes very full details of the VERTIS MONO trial[3], which compared ertugliflozin monotherapy with placebo in patients with poor control after standard lifestyle advice, and of two dual therapy trials, VERTIS MET[4] which compared adding ertugliflozin or placebo in patients inadequately controlled on metformin monotherapy, and VERTIS Factorial[5] in which three of five arms were in dual therapy, comparing ertugliflozin 5 mg/daily and 15 mg/daily with sitagliptin 100 daily, added to metformin. The other two arms were of triple therapy, not relevant to this FTA.

One weakness of the VERTIS trials is that patients were randomised to 5 mg/day or 15 mg/day from the start, whereas in practice, patients would start on 5 mg and increase to 15 mg if there was not a sufficient improvement in control. Those who do not respond well to 5 mg might do less well on 15 mg than the patients in the trial who went straight on to 15 mg. (This problem also applies to the canagliflozin and empagliflozin trials).

VERTIS MONO

The key results of VERTIS MONO[3] were reported to be;

- HbA1c was reduced by 0.85% (from Terra 2017[3]) on ertugliflozin 5 mg with values at 26 weeks (86% of cohort) but, according to the submission, rose about 0.2% on placebo. The reported difference was 0.99%. However the reported rise on placebo requires some clarification. It is based on the FAS population. 89 patients were reported to be still on placebo at 26 weeks with mean reduction in HbA1c of 0.35%, but details are lacking of the other 64 and when, or if, their HbA1c was measured. Note that the placebo group lost weight and so we would expect some reduction in HbA1c also.
- For the 15 mg day dose, the reduction in those (82% of original cohort) with HbA1c with results at 26 weeks was 1.07%. This suggests that the 15 mg dose lowers HbA1c by 0.22% more than the 5 mg dose, but see caveat above about trial design. The marginal effect may be less in those who respond less well to the 5 mg dose.
- The proportions of patients achieving a target of HbA1c <7.0% at week 26 were 28% on ertugliflozin 5 mg, 36% on ertugliflozin 15 mg, and 13% on placebo. So on ertugliflozin 5 mg, 72% failed to reach target, and on 15 mg 64% failed to reach target. There was little change in the proportions at 52 weeks in the extension study by Aronson et al[6] – most of those who achieved target at 26 weeks maintained it.
- Weight fell by (from Terra et al 2017[3]– the main MSD submission gives only graphs) 1.3kg on placebo, 3kg on ertugliflozin 5 mg and 3.5kg on ertugliflozin 15 mg, giving weight loss differences between ertugliflozin and placebo of 1.76kg on 5 mg and 2.16kg on 15 mg. Weight loss at 26 weeks was maintained to 52 weeks.
- SBP fell more on ertugliflozin than placebo, with differences at 26 week of 3.3mmHg on 5 mg ($p = 0.015$) and 1.7mmHg on 15 mg (NS, $p = 0.213$) (Terra et al 2017[3]). Curiously, SBP fell by similar amounts on 5mg and 15 mg at 6 and 12 weeks, but rose again on 15 mg by 18 weeks, but did not rise on 5 mg.

- DBP showed a similar picture, with a difference from placebo of 1.8 mmHg on 5 mg at 26 weeks (P= 0.039) but little difference on 15 mg (difference of 0.37 mmHg at 26 weeks, p = 0.66).

The MSD submission notes (page 12, section B.2.1) that in previous appraisals, the NICE Appraisal Committee had preferred a BMI scenario wherein weight losses on flozins were assumed to be temporary with regain after one year. With longer follow-up, this assumption looks too pessimistic. Bailey et al[7] reported that weight loss on dapagliflozin was maintained at 102 weeks.

Thomas and Cherney (2018)[8] reviewed the actions of the flozins on weight, noting that weight loss occurs within the first six months, after which a plateau occurs, despite ongoing loss of glucose (and hence calories) in the urine. A loss of 60-80 g glucose a day equates to 230-310 calories. Most studies report weight loss of 2-3kg[8] which according to Franz and colleagues[9] would be insufficient to have much effect on HbA1c, lipids or blood pressure. They estimate that weight loss of 2-5% baseline body weight would result in a reduction in HbA1c of 0.2-0.3%. However that may be a useful contribution to the overall effects of the flozins. Another likely effect of all the flozins is a reduction in post-prandial glucose peaks, which has been reported with dapagliflozin.[10]

ERG commentary.

We find the HbA1c in VERTIS MONO puzzling. Table 2 of the Terra paper[3] shows that in the placebo group, 89 patients (58% of baseline 153) had a mean reduction of 0.35% in HbA1c at week 26. Yet the table also reports a mean reduction for the whole group at week 26 of 0.09%, converted after least square analysis to an increase of 0.2%. It is not clear where the HbA1c values for the 64 missing at week 26 came from, particularly as the approach used did not obtain HbA1c results from patients who dropped out.

However, if for illustration, we were to assume that all patients had an HbA1c measure included, we can calculate that;

- The 153 with a mean reduction of 0.09% would have a total reduction of 13.77%
- The 89 with results at week 26 would have a total reduction of 31.15%
- So the mean increase in the 64 would have been 0.51%, which seems rather high given that the whole group lost weight.
- If we then take the reported LS increase of 0.2%, that would equate to a total group increase of 30.6%, which implies that the mean increase in the 64 was 0.96%, which does not seem credible.

We submitted a clarification question to MSD. The question and answer are shown below.

Question A4. Table 2 of Terra 2016 reports that the change from baseline analysis included 153 patients randomised to placebo. Please provide a breakdown of this group;

- The table says 89 were on placebo at 26 weeks. Their HbA1c at 26 weeks shows a mean reduction of 0.35%. Yet Table 2 first reports a reduction (in the whole group) of 0.09% then after least squares analysis, a rise of 0.2%.
- When was HbA1c measured in the other 64 patients? If not measured at week 26, please explain where the assumptions on the HbA1c for the 64 patients came from. How many had last observation carried forward from baseline?
- In summary, please explain how the observed improvement in HbA1c of 0.35% on placebo turns into a deterioration of 0.2% in your analysis.

Response

Table 2 of Terra et al., 2017[11] displays results for both observed mean values and model-based estimated values. The observed results are based on the 89 patients with non-missing data at week 26 (mean HbA1c of 7.76% and mean HbA1c change from baseline of -0.09%). The LS mean value for change from baseline is derived from a statistical model that used all available data from 153 patients and therefore can differ from the observed mean value.

We do not find this response to be informative, so we recommend that the Appraisal Committee ignores the deterioration of 0.2% in the least squares analysis. The 89 patients with data at 26 weeks had HbA1c of 7.76%. The baseline HbA1c in the whole group was 8.11%. We are not provided with the baseline HbA1c of the 89, but if they had the same baseline as the whole group, their reduction at 26 weeks was 0.35%, not 0.09%. According to Table 2 of Terra et al[3], the 0.09% reduction applies to the whole 153 patients in the placebo arm.

We note that the US FDA Stats report[12] expresses reservations about the analysis of VERTTIS MONO, including;

- Analysis was not by ITT. Efficacy data were not collected if patients stopped treatment early. Sensitivity analyses to estimate ITT results were based on untestable assumptions. The cLDA (constrained Longitudinal Data Analysis) approach does not address missing data.
- Therefore HbA1c after rescue therapy was classed as missing
- Sensitivity analysis by the manufacturers used jump-to-reference (JTR) and tipping point approaches. The JTR technique assumed that subjects in the drug arm who discontinue have the same HbA1c as completers in the placebo arm, which the FDA considered questionable.
- The FDA preferred a return to baseline (RTB) approach. Compared to the manufacturer's cLDA approach, this gave smaller difference in HbA1c from placebo – for ertugliflozin 5 mg, 0.60% (95% CI 0.35-0.84) with RTB versus 0.99% with cLDA, and for 15 mg, 0.78% (0.53-1.03) and 1.16% (FDA Table 12).

- Considering proportions achieving HbA1c under 7%, for ertugliflozin 5 mg and 15 mg, and placebo, the manufacturer's cLDA analysis gave 28%, 36% and 3%, whereas the FDA analysis gave 30.1%, 38.8% and 16.9% (FDA Table 14).

Another FDA document[13] summarises changes in HbA1c as reductions of 0.2% on placebo, 0.7% on ertugliflozin 5 mg and 0.7% on 15 mg. An ITT analysis adjusting for various baseline values give differences from placebo of 0.6% for 5 mg/day and 0.7% for 15 mg/day. This independent analysis appears more plausible.

Conclusion: the MSD analysis is not transparent, and the ERG thinks it over-estimates the reductions in HbA1c. However the independent FDA analysis reports that both doses of ertugliflozin are clinically effective, with improvements in HbA1c that are similar to those seen with other flozins.

Results by baseline HbA1c.

If the reductions in HbA1c are of the order of 0.6% and 0.7% (based on the FDA analysis), and the target is 7.0%, one question is whether it is worth trying ertugliflozin if baseline HbA1c is over, say 8.0%. However the usual finding with glucose lowering drugs is that the higher the baseline HbA1c, the higher the reduction on treatment. This is shown in VERTIS MONO, where mean reductions in HbA1c with placebo, 5 mg and 15 mg were 0.03%, 0.5% and 0.6% for patients with baseline HbA1c < 8.0%; and 0.5%, 1.14% and 2.5% for patients with baseline HbA1c of 8.0% or over.

VERTIS MET

The key results of VERTIS MET[4] were;

- In those still on treatments to which they were randomised at 26 weeks, HbA1c fell by 0.4% on placebo, and by 0.8% on 5 mg and by 0.9% on ertugliflozin 15 mg. (From Rosenstock et al[4]– the MSD submission provides only a graph). However only 73% of the placebo group were still on that, compared to 93% of the people on ertugliflozin.
- The least squares (LS) analysis from MSD (page 54) reported no reduction on placebo, 0.7% on 5 mg and 0.9% on 15 mg.
- The proportions achieving HbA1c <7% were 16% on placebo, 35% on ertugliflozin 5 mg and 40% on ertugliflozin 15 mg (rounded to whole numbers). So most patients did not reach target, and would require to intensify to triple therapy.
- Weight fell by 1.3kg on placebo, by 3kg on ertugliflozin 5 mg and by 2.9kg on 15 mg.[4] In the submission, the absolute differences from placebo were reported to be 1.67kg on 5 mg and 1.60 on 15 mg.

- SBP changed little on placebo but fell on ertugliflozin, by 4.4mmHg on 5 mg and 5.2mmHg on 15 mg
- DBP showed little change on placebo but there were reductions of 1.6mmHg on 5 mg and 2.2mmHg on 15 mg ertugliflozin.
- Reductions in HbA1c on placebo, 5 mg and 15 mg for patients with baseline HbA1c < 8% were 0.01%, 0.42% and 0.5%; for baseline HbA1c 8% to <9%, 0.38%, 0.75% and 1.15%; and for baseline HbA1c of 9% or over, 0.66%, 1.75% and 1.76%.

ERG Commentary

The FDA analysis using the RTB method, gave slightly different results, with reductions in HbA1c of 0.72% with ertugliflozin 5 mg, 0.86% with 15 mg, and 0.17% with placebo, giving ertugliflozin versus placebo differences of 0.55% and 0.69%. Proportions achieving <7.0% were 36.3%, 43.3% and 18.4%.

VERTIS FACTORIAL

The key results of the dual therapy arms of VERTIS FACTORIAL[5] were;

- HbA1c was reduced by 1.0 % on ertugliflozin 5 mg, by 1.1% on ertugliflozin 15 mg and by 1.1% on sitagliptin 100 mg, all taken once daily.
- By week 26, the target of HbA1c <7.0% was achieved by 26% on ertugliflozin 5 mg, 32% on ertugliflozin 15 mg, and 33% on sitagliptin 100 mg.
- Weight losses were 2.7kg and 3.7kg on ertugliflozin 5 mg and 15 mg, and 0.7kg on sitagliptin
- SBP fell by 3.9 and 3.7mmHg on ertugliflozin 5 mg and 10 mg respectively and by 0.7mmHg on sitagliptin.
- UTIs were seen in 5.2% and 5.6% on ertugliflozin and 3.2% on sitagliptin
- In women, genital tract infections were seen in 4.9% and 7.0% on ertugliflozin and 1% on sitagliptin. In men, 4.7% and 3.7% on ertugliflozin and none on sitagliptin.

Compared to sitagliptin, there is no difference in glycaemia control, but BP and weight are reduced more by ertugliflozin. Infections are more common with ertugliflozin.

In this FTA, what matters is clinical effectiveness relative to one or more of the previously approved flozins, dapagliflozin, canagliflozin or empagliflozin, not sitagliptin. However the VERTIS Factorial trial can be used to assess ertugliflozin compared to canagliflozin, as reported below.

3.3 Relative effectiveness: the NMA.

In a cost-comparison FTA, MSD could have compared ertugliflozin against only one of the previously approved flozins. The comparator need not be the same for monotherapy and dual therapy. The company could have identified the comparator trials with the most similar populations, baseline characteristics, outcomes and results.

However they chose to provide an NMA. Unfortunately the NMA has a number of flaws, including;

- The base case NMA included dapagliflozin 5 mg, which is not a relevant dose. The dose approved by NICE (NICE TA 390) was 10mg. In a number of places, the MSD submission notes that ertugliflozin was statistically significantly superior to dapagliflozin 5mg daily. This is irrelevant.
- However, MSD carried out a sensitivity analysis, excluding dapagliflozin 5 mg, which should have been the base case. The results were very similar. (See tables 29 and 41 of MSD submission)
- The Kaku 2014 monotherapy trial[14] was correctly excluded because it had a lower baseline HbA1c of 7.5% but it was introduced in another sensitivity analysis – this seems unnecessary. As would be expected, it lowered the potency of dapagliflozin compared to placebo, and hence to ertugliflozin.
- Similarly in dual therapy, the Bolinder 2012 trial[15] was correctly excluded because it had a lower baseline HbA1c , but it was included in another sensitivity analysis, which seems unnecessary
- Other trials included were carried out in East Asian (Japanese and Chinese) populations that have lower baseline BMIs. It would have been better to include only trials with similar characteristics to the VERTIS MONO and MET trials
- The higher doses of several drugs are included. The results may not reflect effectiveness as used in routine care, when the dose is increased only in those who do not respond adequately to the lower dose.

The reported results from the NMA include in monotherapy;

- Ertugliflozin 5 mg daily has similar effects on HbA1c, weight loss, SBP and proportion achieving target as the other flozins.
- Ertugliflozin 15 mg was reported as having more effect on HbA1c than dapagliflozin and both doses of empagliflozin. It was reported to have more effect on SBP than canagliflozin 300, but not than canagliflozin 100 mg.
- Other outcomes are similar.

Overall, ertugliflozin appears as effective as the other drugs.

In dual therapy with metformin, ertugliflozin 5 mg had a similar effect on HbA1c, weight, SBP and proportion reaching target HbA1c as the other flozins.

The results of NMAs vary according to which trials are included partly because of differing baseline characteristics. This was noted in the assessment report for the NICE MTA of the flozins on monotherapy. The East Asian groups start with much lower BMIs – see Ji[16], Kaku[14] and Inagaki[17] trials below in Table 1. There were also differences in the HbA1c changes in the placebo groups, with improvements in the dapagliflozin trials but deterioration in the canagliflozin trials. Such heterogeneity can lead to NMAs producing misleading results.

Table 1 ERG comparison of monotherapy trials

RCT	Baseline A1c	Change on Placebo	Base BMI (kg/m^2)
Dapagliflozin			
Ferrannini 2010[18]	8.0%	-0.23%	33.6
Ji 2014[16]	8.3%	-0.27%	25.8
Kaku 2014[14]	7.5%	-0.06%	25.2
Canagliflozin			
CANTATA-M 2013[19]	8.1%	0.14%	31.3
Inagaki 2014[17]	8.0%	0.29%	25.6
Ertugliflozin			
VERTIS Mono 2017[3]	8.1%	-0.09%?	33

3.4 Relative effectiveness: additional work by ERG

The ERG has considered trials of other flozins approved by NICE, for both mono and dual therapy, to identify suitable comparators for the ertugliflozin trials. The detailed tables are attached in appendix 1, for reference if required, but we do not expect members of the Committee to read these. The key points are summarised below.

Monotherapy

In monotherapy, the designs are similar, but we thought that the Roden 2013 trial[20] trial of empagliflozin was not a good comparator for VERTIS MONO because it was done mainly in Asians,

with a lower baseline BMI (28kg/m^2). The Ferrannini[18] trial of dapagliflozin recruited a slightly younger population (mean age 50.6 years on dapagliflozin 10 mg/day versus 56.8 years on ertugliflozin 5 mg/day) and shorter duration of diabetes (about 6 months versus over 5 years in VERTIS MONO), and there was a larger drop in HbA1c on placebo (reduction 0.25%). So taking ethnicity, baseline BMI and HbA1c change on placebo into account, the best comparison for VERTIS MONO seemed to be the CANTATA-M trial of canagliflozin by Stenlof et al[19], as shown in Table 2 (fuller details are in Appendix Table A2).

Table 2 Monotherapy comparison: ertugliflozin 5 mg versus canagliflozin 100 mg

	VERTIS MONO Terra 2017	CANTATA Stenlof 2013
Baseline (all ertugliflozin 5mg vs canagliflozin 100mg)		
Mean age	57	55
Mean BMI	33	31
Ethnicities	86% white	64% white
Proportion that had previous treatment with glucose lowering drugs	65%	48%
Mean duration of diabetes	5.1 years	4.5 years
Mean SBP mmHg	130.5	126.7
Mean DBP mmHg	78.5	77.7
Mean HbA1c	8.16%	8.1%
Inclusion range of HbA1c	7.0 to 10.5%	7.0 to 10.0%
Results at 24- 26 weeks		
Mean HbA1c changes 26 weeks (LS means)	Ert5 - 0.79% Ert15 -0.96% Pbo + 0.20%	Cana100 - 0.77% Cana300 -`1.03% Pbo + 0.14%
Mean HbA1c change vs PBO (LS means)	Ert5 0.99% Ert15 1.16	Cana100 0.91% Cana300 1.16%
Mean change in weight vs PBO	Ert5 1.76kg	1.9kg
Mean change SBP vs PBO mmHg	Ert5 -3.3	Cana100-3.7
Mean change DBP vs PBO mmHg	Ert5 -1.8	Cana100 -1.6
Urinary tract infections, both sexes, % at 26 wks	Ert5 7.1% PBO 8.5%	Cana100 7.2% Pbo 4.2%
Genital tract infection, women, 26 weeks	Ert5 16.4% Pbo 5.6%	Cana100 8.8% Pbo 3.8%
Results at 52 weeks		
Mean change HbA1c	Ert5 - 0.9%	Cana100 -0.8%
Mean change weight	Ert5 3.6kg	Cana100 kg 2.8kg
GTI women by 52 weeks	Ert5 26.9% Pbo 9.9%	Cana100 11.4% Pbo/sita 4.8%

*Calculated by ERG

Note. The frequency of GTI was much higher in VERTIS MONO than in other ertugliflozin trials.

We conclude that ertugliflozin and canagliflozin have similar effectiveness in monotherapy.

Dual therapy comparison

We first compare two trials, VERTIS MET of ertugliflozin + metformin[4] versus the Bailey et al 2010[21] trial of dapagliflozin (10 mg arm only). We preferred Bailey et al to the Haring 2013[22] empagliflozin trial because the ethnic mix in Bailey was much more comparable.

Details are in Table 3, but in summary, design and inclusions were similar (using the first 26 weeks of VERTIS MET). The dapagliflozin patients were about 3 years younger on average, had slightly shorter duration (by about 2 years, but duration is less important with flozins than with some other drugs due to their insulin-independent mode of action) and slightly lower baseline SBP (by about 3 mmHg).

The results were comparable, with the dapagliflozin results often coming in between those with the two ertugliflozin doses.

Table 3 Ertugliflozin + metformin versus dapagliflozin + metformin

	Ertugliflozin VERTIS MET	**Dapagliflozin (10mg arm only)**
Trial first author and year	Rosenstock 2017[4]	Bailey 2010[21]
Inclusion criteria similar?	Aged ≥18 years with T2DM inadequately controlled (HbA1c, 7.0%-10.5% on metformin monotherapy (≥1500 mg/for ≥8 weeks). BMI 18.0 to 40.0 kg/m^2.	T2DM inadequately controlled (HbA1c 7% to 10%) on metformin (≥1500mg per day) for at least 8 weeks. Aged 18-77 years BMI <45 kg/m^2
Duration	26-week, then 78-week extension	24 weeks
Number of patients	Placebo (n=209) Ertug 15 mg (n=205) Ertug 5 mg (n=207)	Dapa n=135; placebo n=137

Number of centres and countries	Multi-centre: North America (27.2%), Europe (36.1%), South America (3.4%), Asia (13.7%), South Africa (17.9%) and Australia/New Zealand (1.8%).	80 sites (30 in the USA, 21 in Canada, 11 in Argentina, ten in Mexico, and eight in Brazil).
Baseline characteristics		
Mean age	Ertug 5 mg: 56.6 Ertug 15 mg: 56.9 Placebo: 56.5	Dapa: 52.7 Placebo: 53.7
Mean duration of diabetes (years)	Ertug. 5 mg: 7.9 Ertug 15 mg: 8.1 Placebo: 8.0	Dapa 6.1 Placebo: 5.8
Ethnicity	White: 64.7%, 64.9% and 68.9%	Mainly white. (No % given)
Mean BMI (kg/m^2)	Ertug. 5 mg: 30.8 Ertug 15 mg: 31.1 Placebo: 30.7	Dapa: 31.2 Placebo: 31.8
SBP, mean ± SD mmHg	Ertug. 5 mg: 130.5 Ertug. 15 mg: 130.2 placebo: 129.3	Dapa 126.0 Placebo: 127.7
Mean HbA1c *Note 1.*	Ertug. 5 mg: 8.1% Ertug. 15 mg: 8.1% placebo: 8.2	Dapa: 7.92 % placebo 8.11%
Results at 26 weeks		
HbA1c week 26	Ertug. 5 mg: 7.3% Ertug 15 mg: 7.2% Placebo: 7.8%	Dapa: 7.13 % Placebo: 7.79%
HbA1c Change from baseline:	Ertug. 5 mg: -0.70% Ertug. 15 mg: -1.0% placebo: -0.2%	Dapa: -0.84% placebo -0.30%
Proportion of patients achieving HbA1c target of ≤7.0%	Ertug. 5 mg: 35.3% Ertug. 15 mg: 40.0% placebo: 15.8%	Dapa: 40.6% Placebo: 25.9%

Mean SBP change from baseline (mmHg)	Ertug. 5 mg: -4.38 Ertug. 15 mg: -5.20 placebo: -0.70	Dapa: -5.1 placebo -0.2
Mean DBP change from baseline (mmHg)	Ertug. 5 mg: -1.59 Ertug. 15 mg: -2.19 placebo: 0.23	Dapa: -1.8 Placebo: -0.1
Mean weight change from baseline (kg)	Ertug. 5 mg: -3.01 Ertug. 15 mg: -2.93 placebo: -1.33	dapa. -2.9 placebo -0.9
Proportions with urinary tract infections	Ertug. 5 mg: 2.9% Ertug. 15 mg: 3.4% placebo: 1.9%	Dapagliflozin: 7% Placebo: 5%
Proportions with genital tract infections	Genital mycotic infection (men): Ertug. 5 mg: 3.1% Ertug. 15 mg: 3.2% placebo: 0% Genital mycotic infection (women): Ertug. 5 mg: 5.5% Ertug. 15 mg: 6.3% placebo: 0.9%	Male + female: Dapa: 9% Placebo: 5%
% discontinuation due to adverse effects	Ertug. 5 mg: 1.4% Ertug. 15 mg: 1.5% placebo: 1.4%	Dapa: 3% Placebo: 4%
Trial quality	Good	Good

Note 1. There are minor differences in some figures between the published paper and the MSD submission due to rounding. The MS has 8.06% for ertugliflozin 5mg, 8.13% for ertugliflozin 15mg and 8.17 for placebo.

We conclude that ertugliflozin and dapagliflozin have similar effectiveness in dual therapy.

In Table 4 we compare the three dual therapy arms of the VERTIS Factorial trial[5] with the canagliflozin versus sitagliptin trial by Lavalle-Gonzalles and colleagues.[23] There were few baseline differences, though HbA1c was about 0.7% higher in the ertugliflozin trial, which may explain why the reduction in HbA1c was slightly higher with ertugliflozin (0.95% versus about 0.8%) but the

proportions achieving <7% were lower. Systolic blood pressure and weight reductions were slightly higher with canagliflozin.

So on balance, there appears little to choose between ertugliflozin and canagliflozin in dual therapy. Note however that canagliflozin has not been approved by NICE for dual therapy with a DPP-4 inhibitor, so this table is simply to show that ertugliflozin and canagliflozin appear to have similar effectiveness.

Table 4 Comparison of dual therapy with sitagliptin

	Ertugliflozin	**Canagliflozin**
Trial first author and year	VERTIS Factorial[5]	Lavalle-Gonzalez 2013[23]
Inclusion criteria similar?	People ≥18 years of age Inadequate glycaemic control (HbA1c ≥7.5% and ≤11% on a stable dose of metformin monotherapy for at least 8 weeks BMI ≥ 18.0 kg/m^2	People aged ≥18 and ≤80 years Type 2 diabetes Inadequate glycaemic control (HbA1c ≥7.0% and ≤10.5% on stable metformin therapy for ≥8 weeks
Duration of trial	52 weeks: phase A, a 26-week, double-blind, placebo–controlled treatment period; and phase B, a 26-week extension	26-wk placebo- and active-controlled, double-blind treatment period (period I), 26-wk active-controlled, double-blind treatment period (period II) and 4-wk follow-up.
Number of patients, centres and countries	1232 patients 242 centres in 21 countries	918 patients 169 centres in 22 countries
Baseline characteristics		
Mean age (years)	55.1	55.4
Mean duration of diabetes (years)	Ertug 5 mg: 7.1 Ertug 15 mg: 7.3	Cana 100 mg: 6.7 Cana 300 mg: 7.1

	Sita 100 mg: 6.2	sitagliptin: 6.8
Ethnic groups - % white.	81%	70.2%
Mean BMI (kg/m^2)	Ertug 5 mg: 31.8 Ertug 15 mg: 31.5 Sita 100 mg: 31.7	Cana 100 mg: 32.4 Cana 300 mg: 31.4 sitagliptin: 32.0
SBP mean ± SD mmHg	Ertug. 5 mg: 129.7 Ertug. 15 mg: 128.9 Sita. 100 mg: 128.3	Cana. 100 mg: 128.0 Cana. 300 mg: 128.7 sitagliptin: 128.0
DBP mean ± SD mmHg	Ertug. 5 mg: 77.9 Ertug. 15 mg: 77.5 Sita. 100 mg: 77.3	Cana. 100 mg: 77.7 Cana. 300 mg: 77.9 sitagliptin: 77.5
Mean HbA1c	Ertug. 5 mg: 8.6% Ertug. 15 mg: 8.6% Sita. 100 mg: 8.5%	Cana. 100 mg: 7.9 Cana. 300 mg: 7.9 sitagliptin: 7.9
Results		
HbA1c change from baseline	Wk 52: Ertug 5 mg: -1.0% Ertug 15 mg: -0.9% Sita 100 mg: -0.8%	Wk 52: Cana 100 mg: -0.73% Cana 300 mg: -0.88% sitagliptin: -0.73%
Proportion of patients achieving HbA1c target of ≤7.0%	Wk 52: Ertug 5 mg: 25.6% Ertug 15 mg: 22.6% Sita 100 mg: 26.7%	Wk 52: Cana 100 mg: 41.4% Cana 300 mg: 54.7% Sita: 50.6%
Proportion requiring rescue therapy	Wk 52: Ertug. 5 mg: 18.4% Ertug. 15 mg: 21.0% Sita. 100 mg: 27.9%	Wk 52: Cana. 100 mg: 14.7% Cana. 300 mg: 9.3% sitagliptin: 18.0%
SBP Change from baseline LS Mean mmHg	Wk 52: Ertug. 5 mg: -2.7 Ertug. 15 mg: -1.6 Sita. 100 mg: -0.2	Wk 52: Cana. 100 mg: −3.5 Cana. 300 mg: −4.7 sitagliptin: −0.7
DBP Change from baseline LS Mean (SE) mmHg	Wk 52: Ertug. 5 mg: -1.7	Wk 52: Cana. 100 mg: −1.8

	Ertug. 15 mg: -0.7 Sita. 100 mg: 0.8	cana. 300 mg: −1.8 sitagliptin: −0.3
Weight (kg) Mean change from baseline LS Mean (SE or 95% CI)	Wk 52: Ertug. 5 mg: -2.4 Ertug. 15 mg: -3.2 Sita. 100 mg: -0.1	Wk 52: Cana. 100 mg: −3.3 Cana. 300 mg: −3.7 sitagliptin: −1.2)
Adverse effects		
Proportions with urinary tract infection	Wk 52: Ertug. 5 mg: 8.8% Ertug. 15 mg: 8.5% Sita. 100 mg: 5.3%	52 wk: Cana. 100 mg: 7.9% Cana. 300 mg: 4.9% sitagliptin: 6.3%
Proportions with genital tract infection	Wk 52: Genital mycotic infection (men): Ertug. 5 mg: 6.3% Ertug. 15 mg: 5.2% Sita. 100 mg: 0% Genital mycotic infection (women): Ertug. 5 mg: 4.9% Ertug. 15 mg: 7.0% Sita. 100 mg: 2.2%	52 wk: Men: Candida balanitis Cana. 100 mg: 5.2% Cana. 300 mg: 2.4% sitagliptin: 1.2% Women: vulvovaginal candidiasis (VVC): Cana. 100 mg: 11.3% Cana. 300 mg: 9.9% sitagliptin: 2.6%
Discontinuation due to AE by week 52	Ertug. 5 mg: 3.2% Ertug. 15 mg: 3.2% Sita. 100 mg: 2.8%	Cana. 100 mg: 5.2% Cana. 300 mg: 3.3% sitagliptin: 4.4%
Trial quality	Good	Good

4. Cost issues

Costs are dealt with in pages 14 to 19 of the MSD submission. The other flozins are assumed to all cost £477 per annum.

Other costs provided in the MSD submission include costs of other drugs (Table 4), costs of treatment sequences (Table 5), and cost of complications (Tables 5 and 9), none of which are

required for a cost-comparison FTA. Some costs differ between monotherapy and dual therapy. For example the cost of a fatal MI was £1564 in monotherapy and £1765 in dual therapy. This just reflects sources and dates thereof, and anyway these costs are not needed for the FTA.

The MSD submission reports costs associated with monotherapy and dual therapy.

Table 5 reports the annual direct drug costs, which were mainly obtained from the National Health Service (NHS) drug tariff 2015.[24]

Table 5 Annual direct drug costs

Treatment	**Share**	**Annual costs**
DAPA10	--	£477
CANA100	--	£477
CANA300	--	£477
EMPA10	--	£477
EMPA25	--	£477
SITA100	71%	£434
Saxagliptin 5 mg	10%	£412
Vildagliptin 100 mg	3%	£435
Linagliptin 5 mg	12%	£434
Alogliptin 25 mg	3%	£347
Metformin	--	£25.29
Sulphonylureas	--	£29.46
DPP-4i (average)	--	£424.50
Insulin	£0.0055kg-1 per day for 90kg patient	£181
Intensified insulin	£0.0082kg-1 per day for 90kg patient	£269
DAPA10, dapagliflozin 10 mg; CANA100, canagliflozin 100 mg; CANA300, canagliflozin 300 mg; EMPA10, empagliflozin 10 mg; EMPA25, empagliflozin 25 mg; SITA100, sitagliptin 100 mg; MET, metformin; SU, sulphonylureas; DPP-4i, dipeptidyl peptidase 4 inhibitor		

Costs for the treatment of diabetes and its complications are presented in table 6 of the MSD submission. However, these are not relevant if clinical effectiveness of ertugliflozin is similar to the other flozins, because complication rates would not differ.

Four adverse events were considered, urinary tract infections (UTIs), genital mycotic infections, severe hypoglycaemic events and non-serious hypoglycaemic events. The company presented the resource use and costs associated with the treatment of these adverse events. For the treatment of UTIs, it was assumed that males and females would require trimethoprim 200mg twice daily for seven days, with one general practitioner (GP) visit for males and two for females, totalling £73. For the treatment of genetic mycotic infections, it was assumed that males would require one week of fluconazole 200mg, and females three pessaries of clotrimazole 200mg, totalling £51. Treatment of severe hypoglycaemic events were based on the proportion of caregivers: family members, medical practitioners in the community and in the hospital. Costs were obtained from National Institute for Health and Care Excellence (NICE) guideline NG28[1], and uprated to 2014 prices using HCHS pay and price indices. The company reported a cost of £411 to treat a severe hypoglycaemia event. It was assumed that no costs are associated with the treatment of non-severe hypoglycaemic events.

Dual therapy

Resource use and unit costs for dual therapy were obtained from TA418.[25] TA418 reports resource use that is based on triple therapy, but it is assumed that the resource use is applicable to dual therapy. Costs are provided for direct drug costs, treatment of diabetes complications, and treatment of adverse events, and are reported in 2014 prices.
Resource use and costs for the treatment of diabetes complications while on dual therapy were obtained from UKPDS 84 study[26], and uprated to 2014 prices. However, as above, these costs are not relevant if clinical effectiveness is similar to the other flozins.

Table 6 presents the costs associated with the treatment of adverse events. For the treatment of UTIs and genetic mycotic infections, it was assumed that treatment of these events would require a GP visit costing £45 and £51, respectively. A cost of £380 for the treatment of severe hypoglycaemic events was obtained from the NICE diabetes clinical guideline.[1] It was assumed that there are no costs for treating non-severe hypoglycaemic events.

Table 6 Treatment of adverse events, MSD submission

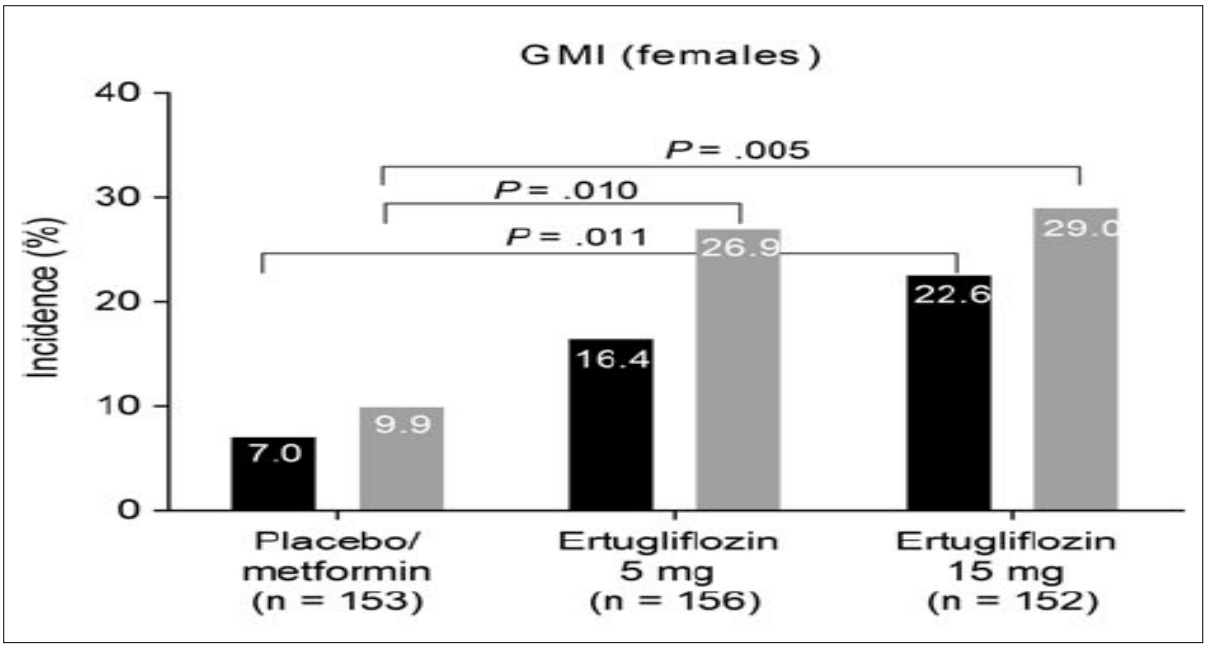
Adverse event	**Monotherapy**	**Dual therapy**	**Comparison**
Urinary tract infections	£73	£45	It was assumed that in monotherapy males

			would require two GP visits compared to one visit for dual therapy.
Genital mycotic infections	£51	£45	Slight differences in treatment costs. The company have not elaborated on the resource use required for treatment of genital mycotic infections in people undergoing second intensification.
Severe hypoglycaemic events	£411	£380	Slight differences between treatment costs.
Non-severe hypoglycaemic events	£0	£0	-

It is not clear why the costs of treating AEs should vary between monotherapy and dual therapy.

GTI events and costs

The incidence of GTI events was higher in the VERTIS MONO trial for ertugliflozin 5mg and 15mg compared to frequency reported in the CANTATA-M trial of canagliflozin 100mg and 300mg. Figure 1 reports the incidence of GTIs in females at week 26 and week 52 for ertugliflozin.



(GMI = genital mycotic infections)

Figure 1 Incidence of GMI in females at week 26 and week 52 (obtained from Aronson et al., 2018)

If this frequency of mycotic infections in women was accepted, if we treat 100 women annually with ertugliflozin and canagliflozin we would expect 26.9% of GTI events with ertugliflozin 5mg, 29.0% with ertugliflozin 15mg, and 11.4% and 9.35% for canagliflozin 100mg and canagliflozin 300mg, respectively. Annual costs for treating these events are shown in Table 7

Table 7 Annual cost of treating GTI events, by treatment regimen

Treatment	**Annual incidence of GTIs in women, %**	**Unit cost of treating GTI (£, 2014)**	**Annual cost of treating GTIs**
Ertugliflozin 5mg	26.9%	£51	£1,371.90
Ertugliflozin 15mg	29.0%		£1,479.00
Canagliflozin 100mg	11.4%		£581.40
Canagliflozin 300mg	9.3%		£474.30

To put this in context, for every 100 women annually treated with ertugliflozin 5mg compared to canagliflozin 100mg, there would be an additional 15.5 GTIs, which would result in a difference in annual treatment costs of approximately £791. Similarly, for every 100 women treated with ertugliflozin 15mg compared to canagliflozin 300mg, there would be in an additional 19.7 GTIs,

which would result in a difference in an annual treatment cost of approximately £1005. [redacted]

However the very high rate of GTI seen in VERTIS MONO, was not seen in other trials of ertugliflozin as shown in Table 8 below.

Table 8 GTI rates in other VERTIS trials

	Placebo	Ertugliflozin 5mg	Ertugliflozin 15mg
% of GTIs in women			
VERTIS SITA 2[27]			
26 weeks	1.9%	8.0%	12.0%
52 weeks	1.9%	3.7%	14.1%
VERTIS Renal[28]			
26 weeks	0%	4.1%	1.3%
52 weeks	2.4%	5.4%	3.8%
VERTIS SU[29]	-	7.7%	10.0%
VERTIS SITA[30]	5.0%	4.9%	10%
VERTIS Factorial[5]			
26 weeks	-	4.9%	7.0%
52 weeks	-	4.9%	7.0%
VERTIS MET[4]	0.9%	5.5%	6.3%

So the high rate seen in VERTIS MONO is an outlier, and overall the frequency of GTIs appears similar with ertugliflozin and canagliflozin.

Only one ertugliflozin trial gave details of how GTI was diagnosed. This was VERTIS Factorial, where the report states: “Diagnosis is made through a genital swab collected, and an analysis is done by the central laboratory”.

In Table 51 of the submission, the company provided drug acquisition costs for the intervention and its comparators. Table 9 shows drug acquisition costs, with costs other than ertugliflozin taken from the national drug tariff.

Table 9 Drug acquisition costs of the intervention and comparators

Drug	Dose regimen	Price per pack (list price)	Acquisition costs per annum
Ertugliflozin	5 mg or 15 mg once daily	[redacted] per 28 pack	[redacted]
Dapagliflozin	5 mg or 10mg once daily	£36.59 per 28 pack	£477.30
Canagliflozin	100 mg or 300 mg once daily	£39.20 per 30 pack	£477.26
Empagliflozin	10mg or 25 mg once daily	£36.59 per 28 pack	£477.30

Results

Base-case results showed that there is an annual cost saving to the NHS of approximately [redacted] per patient. No sensitivity or scenario analyses were undertaken by the company.

Summary

In general, the company provided details on the resource use and costs associated with direct drug costs, treatment of diabetes complications, and treatment of adverse events for monotherapy and dual therapy. Despite there being slight discrepancies between the company's and the ERG's annual drug acquisition costs, we have no concerns relating to the assumptions made and unit costs.

Minor points.

Table 48 of the MSD submission reports that only one adverse effect reached statistical significance in VERTIS MET, genital infections in women, 6.3% on ertugliflozin 15 mg versus 0.9% in PBO. Further down that table, we note cardiac disorders 0.5% PBO, 1.4% ertugliflozin 5mg and 3.4% ertugliflozin 15mg. The ERG calculation around the 3.4% shows the 95% CI overlapping with the PBO CI, but this might need to be watched. The cardiovascular safety trial of ertugliflozin, VERTIS-CV, is underway.[31] Previous cardiovascular safety trials have shown a reduction in CVD events in very high risk people with empagliflozin, though mainly due to an unexplained group of deaths presumed to be

cardiovascular[32, 33], and with canagliflozin in the CANVAS trial[34] where there was a reduction in the composite outcome (OR 0.86, 95% CI 0.75 to 0.97) due to an effect in those with pre-existing CVD.

More impressive is the effect on heart failure admissions, which seem to be reduced by about a third, and to be a class effect [35]. This has been shown in both trials and observational studies such as the CVD-REAL study [36].

Table 14 reports that the VERTIS SU trial is not included "because all VERTIS SU endpoints were collected at 52 weeks" whereas all the other flozin trials reported data at 26 weeks. However, the published VERTIS SU paper[29] provides 26-week data for the main outcomes at week 26 in graphs. On ertugliflozin there is little change between 26 and 52 weeks in HbA1c weight and SBP.

5. Discussion

Outcomes

The outcomes that matter are the adverse effects of type 2 diabetes, which include;

- Macrovascular disease - Ischaemic heart disease, heart failure, stroke and peripheral vascular disease (which can lead to amputations)
- Microvascular disease – retinopathy which can lead to visual loss, and nephropathy which can lead to renal failure
- Short term disturbances of glucose regulation, which include hypoglycaemia (low blood glucose, leading to interruption of normal activities, and, at worst, loss of consciousness) and ketosis related to high blood glucose, leading to at worst unconsciousness and death.

The primary outcome in trials is usually HbA1c, a 3 month indicator of average blood glucose. The minimum clinically meaningful change in HbA1c is usually taken to be 0.5%. Reductions of that or more are taken to be useful in reducing the microvascular complication rates.

However a more important outcome is whether patients reach the glycaemic targets proposed by NICE and other organisations. The evidence from the VERTIS trials is that only a minority of patients reach targets such as HbA1c 7.0%. The NICE guideline in Box 1 proposes a target of 6.5% for most people, though targets should be decided for each individual.

For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, support the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, support the person to aim for an HbA1c level of 53 mmol/mol (7.0%).

In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher:

- reinforce advice about diet, lifestyle and adherence to drug treatment **and**
- support the person to aim for an HbA1c level of 53 mmol/mol (7.0%) **and**
- intensify drug treatment.

Box 1: Management of type 2 diabetes in adults (aged 18 and over)

So for most people similar to those in the VERTIS dual therapy trials, dual therapy is a stage they will pass through to further intensification of treatment. Unless they lose a clinically meaningful amount of weight. Many people with type 2 diabetes do not reach targets. The National Audit for England [37] reported that only about two thirds of patients reached a target of 7.5% or less, with little change in recent years. Similar findings have been reported from the USA by Edelman and Polonsky [38] who also note that results seen in trials are not usually matched in routine care, partly because of poor adherence to medication, as well as lifestyle change.

Other comparators

There are two developments in the management of type 2 diabetes which merit attention.

The DiRECT trial

The first is the DiRECT trial.[2] This trial, carried out in primary care, randomised overweight and obese people (BMI 27- 45 kg/m^2) with type 2 diabetes, with duration of diabetes up to 6 years, to a 3-stage weight management programme;

- Low calorie diet replacement (825-853 kcal/day) for 3-5 months
- Stepped food re-introduction for 2-8 weeks
- Structured support for long-term weight loss maintenance

All diabetes drugs were stopped. The key outcome was diabetes remission, defined as HbA1c <6.5% (<48 mmol/mol) after at least 2 months off all diabetes medications. Diabetes remission was achieved in 46% in the intervention group and 4% in the standard care group. Mean body weight fell by 10kg in the intervention group and by 1kg in the control group. The greater the weight loss, the greater the chance of remission, with 86% remission in those who lost 15kg or more, who comprised 24% of the intervention group. At baseline, 75% of recruits were on one or more glucose-lowering drugs. At 12 months, 74% were taking no glucose lowering drugs, with mean HbA1c 6.4% (46.8 mmol/mol). Remission was less frequent in those with baseline HbA1c >8.0%, but 27.5% achieved

remission. The overall mean reduction in HbA1c was 0.9% but the published paper does not give HbA1c results in those who lost weight but did not achieve remission.

Mean blood pressure was similar at 12 months, but 48% of the intervention group who had been taking antihypertensive drugs at baseline, had not re-started them, compared to none of the control group. Antihypertensive drugs were re-started if SBP exceeded 140 mmHg.

A key feature of the trial was that the intervention was delivered in primary care by local nurses or dietitians, rather than in specialist centres by specialist staff. The drop-out rate in the intervention group was 25%, so the intervention was acceptable to the majority.

The study will continue to 4 years of follow-up. However the results are striking and we think that NICE should update the type 2 diabetes guideline to take account of them.

Treatment at diagnosis of type 2 diabetes

The second development has been intensive treatment at diagnosis of type 2 diabetes, where intensive included intensive insulin therapy for 2 weeks. In many patients, this led to remission of diabetes, on no treatment, for 12 months. Most such work comes from China, with only two small studies[39, 40] in the West. Further research in European populations is desirable.

Relative potencies of the flozins

A number of articles (such as Thomas and Cherney 2018 [8]) report that canagliflozin 300 mg reduces HbA1c by more than other flozins. This is based on meta-analyses such as that by Zaccardi et al. [41] However there was considerable baseline heterogeneity amongst the 38 trials of dapagliflozin, canagliflozin and empagliflozin included by Zaccardi and colleagues, with differences in baseline HbA1c and BMI, and as noted earlier (Table 1), HbA1c in the placebo groups improved in some dapagliflozin trials but worsened in some canagliflozin trials, making the placebo-adjusted HbA1c effect smaller for dapagliflozin. So we do not regard the superiority of canagliflozin 300mg as soundly proven.

The ERG concludes that ertugliflozin is as effective in monotherapy and dual therapy as the flozins previous approved by NICE.

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Appendix 1. Previous NICE guidance on the SGLT2 inhibitors in type 2 diabetes

Monotherapy

TA390

Canagliflozin, dapagliflozin and empagliflozin as monotherapies are recommended as options for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:

- a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and
- a sulfonylurea or pioglitazone is not appropriate

Dual therapy

TA288. Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated **or**
- the person is at significant risk of hypoglycaemia or its consequences.

TA135. Canagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated **or**
- the person is at significant risk of hypoglycaemia or its consequences

TA336. Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated, or
- the person is at significant risk of hypoglycaemia or its consequences

Appendix 2. Comparator trials

Table A1. Monotherapy trials – summary of comparison.

	Ertugliflozin	**Dapagliflozin**	**Canagliflozin**	**Empagliflozin**
Trial first author and year	Terra 2017 / Aronson 2018 (NCT01958671)	Ferrannini 2010 / Bailey 2015 (NCT 00528372)	CANTATA-M (Stenlöf 2013 / Stenlöf 2014) (NCT01081834)	Roden 2013/14 (NCT01177813)
Design	Similar	Similar	Similar	Similar
Duration	Similar – main study period 24-26 weeks	Similar – main study period 24-26 weeks	Similar – main study period 24-26 weeks	Similar – main study period 24-26 weeks
Inclusion criteria similar?	Similar, not all define BMI Diet / exercise (or AHA monotherapy with washout)	Similar, not all define BMI Diet / exercise	Similar, not all define BMI Diet / exercise or AHA	Similar, not all define BMI Diet / exercise
Exclusions similar?	Largely similar	Largely similar	Largely similar	Largely similar
Number of patients	Largely similar	<half the sample size of the others	Largely similar	Largely similar

	Ertugliflozin	**Dapagliflozin**	**Canagliflozin**	**Empagliflozin**
Number of centres and countries	Largely similar – multicentre / worldwide	Largely similar – multicentre / worldwide	Largely similar – multicentre / worldwide	Largely similar – multicentre / worldwide
Sponsor	Similar – sponsored by industry	Similar – sponsored by industry	Similar – sponsored by industry	Similar – sponsored by industry
Interventions				
Run-in	Largely similar	Largely similar	Largely similar	Largely similar
All groups	Largely similar – all define rescue therapy	Largely similar – all define rescue therapy	Largely similar – all define rescue therapy	Largely similar – all define rescue therapy
Extension	Largely similar	Largely similar	Largely similar	Largely similar
Outcomes				
Primary outcomes	Similar – HbA1c after 24-26 weeks	Similar – HbA1c after 24-26 weeks	Similar – HbA1c after 24-26 weeks	Similar – HbA1c after 24-26 weeks
Secondary outcomes	Largely similar	Largely similar	Largely similar	Largely similar
Other outcomes	Largely similar	Largely similar	Largely similar	Largely similar

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Baseline characteristics				
Mean age and range (years)	**ertu5:** 56.8 (SD11.4) **ertu15:** 56.2 (SD10.8) **placebo:** 56.1 (SD10.9)	**dapa10 AM:** 50.6 (SD 10.0) **placebo:** 52.7 (SD 10.3) Slightly younger age	**cana100**: 55.1 (SD 10.8) **cana300:** 55.3 (SD 10.2) **placebo:** 55.7 (SD 10.9)	**empa10:** 56.2 (SD 11.6) **empa25:** 53.8 (SD 11.6) **placebo:** 54.9 (SD 10.9)
Sex (% women)s	**ertu5:** 42.9% **ertu15:** 40.8% **placebo:** 46.4%	**dapa10 AM:** 51.4% **placebo:** 58.7%	**cana100:** 58.5% **cana300:** 54.8% **placebo:** 54.2%	**empa10:** 37% **empa25:** 35% **placebo:** 46%
Duration of diabetes (years)	**ertu5:** 5.11 (SD 5.09) **ertu15:** 5.22 (SD 5.55) **placebo:** 4.63 (SD 4.52)	(median, IQR) **dapa10 AM:** 0.45 (0.1-3.4) **placebo:** 0.5 (0.1-3.4) Shorter duration	**cana100:** 4.5 (SD 4.4) **cana300:** 4.3 (SD 4.7) **placebo:** 4.2 (SD 4.1)	**empa10:** 39% ≤1 year, 41% 1-5 years, 13% 5-10 years, 7% >10 years **empa25:** 41% ≤1 year, 37% 1-5 years, 17% 5-10 years, 6% >10 years **placebo:** 32% ≤1 year, 46% 1-5 years, 15% 5-10 years, 8% >10 years
Comorbidities	NR	**dapa10 AM:** 1.4% diabetic neuropathy, 1.4%	NR	NR

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
		microalbuminuria, 41.4% hypertension **placebo:** 8% diabetic neuropathy, 1.3% diabetic retinopathy, 1.3% microalbuminuria, 52% hypertension		
Ethnic groups - % white. *If Asians, say whether East or South***	>80% White	>80% White	>60% White	>60% Asian
BMI (kg/m^2)	**ertu5:** 33.2 (SD 7.4) **ertu15:** 32.5 (SD 5.7) **placebo:** 33.3 (SD 6.8)	**dapa10 AM:** 33.6 (SD 5.4) **placebo:** 32.3 (SD 5.5)	**cana100:** 31.3 (SD 6.6) **cana300:** 31.7 (SD 6.0) **placebo:** 31.8 (SD 6.2)	**empa10:** 28.3 (SD 5.5) **empa25:** 28.2 (SD 5.5) **placebo:** 28.7 (SD 6.2) Lower BMI, but to be expected in a largely Asian population
Systolic blood pressure (mmHg)	**ertu5:** 130.5 (SD 13.5) **ertu15:** 129.7 (SD 14.2)	NR	**cana100:** 126.7 (SD 12.5) **cana300:** 128.5 (SD 12.7) **placebo:** 127.7 (SD 13.7)	**empa10:** 133.0 (SD 16.6) **empa25:** 129.9 (SD 17.5) **placebo:** 130.4 (SD 16.3)

	Ertugliflozin	**Dapagliflozin**	**Canagliflozin**	**Empagliflozin**
	Similar		Similar	Similar
Diastolic blood pressure (mmHg)	**ertu5:** 78.5 (SD 8.1) **ertu15:** 78.5 (SD 7.7) Similar	NR	**cana100:** 77.7 (SD 6.8)) **cana300:** 79.1 (SD 8.3) **placebo:** 77.4 (SD 8.4) Similar	**empa10:** 79.2 (SD 9.6) **empa25:** 78.3 (SD 9.4) **placebo:** 78.9 (SD 9.6) Similar
HbA1c (%), mean and range	HbA1c >8% (up to 8.3%)	HbA1c 7.8 to 8%	HbA1c >8% (up to 8.1%)	HbA1c <8% (around 7.9%)
Baseline eGFR (mL/min/1.73 m^2)	**ertu5:** 88.5 (SD 18.4) **ertu15:** 88.3 (SD 18.0) **placebo:** 86.2 (SD 19.4) Similar	NR	**cana100:** 88.5 (SD 20.2) **cana300:** 86.6 (SD 19.1) **placebo:** 86.0 (SD 21.5) Similar	**empa10:** 87.7 (SD 19.2) **empa25:** 87.6 (SD 18.3) **placebo:** 86.8 (SD 17.9) Similar
Prior treatment with GLD? *% drug naïve* *% previously treated*	50 to 55% on AHA with washout prior to trial	Only diet/exercise	About 48% on AHA	Only diet/exercise

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
% on anti-hypertensives at baseline	NR	**dapa10 AM:** 41.4% on antihypertensives **placebo:** 41.3% on antihypertensives	NR	NR

Table A2. Details of monotherapy trials

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Trial first author and year	Terra 2017 / Aronson 2018 (NCT01958671)	Ferrannini 2010 / Bailey 2015 (NCT 00528372)	CANTATA-M (Stenlöf 2013 / Stenlöf 2014) (NCT01081834)	Roden 2013/14 (NCT01177813)
Design	Phase III RCT, double blind, parallel group, placebo controlled	Phase III RCT, double blind, parallel group, placebo controlled	Phase III RCT, double-blind, placebo controlled	Phase III RCT, placebo controlled, double blind, parallel group
Duration	26 weeks + 26 weeks extension	24 weeks + 78 weeks extension	26 weeks + 26 weeks extension	24 weeks + ≥52 weeks extension
Inclusion criteria similar?	**Condition:** type 2 diabetes mellitus **Age:** ≥18 years	**Condition:** type 2 diabetes mellitus **Age:** 18-77 years	**Condition:** type 2 diabetes mellitus **Age:** 18-80 years **Glycaemic control:** inadequately controlled with diet and exercise or	**Condition:** type 2 diabetes mellitus **Age:** aged ≥18 years (≥20 years in Japan, 18-65 years in India)

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	Glycaemic control: HbA1c of 7.0% to 10.5% (53-91 mol/mol) **Previous treatment:** without treatment with an antihyperglycaemic agent (AHA) for ≥8 weeks prior to screening; people who reported taking a single AHA and had HbA1c levels 6.5% to 9.5% (48-80 mmol/mol) during the screening visit were instructed to discontinue the AHA for at least 8 weeks and return for a second screening visit **BMI:** ≥18.0 kg/m^2	**Glycaemic control:** inadequately controlled with diet and exercise; fasting C-peptide ≥1.0 ng/ml **Previous treatment:** naive to treatment, except diet and exercise **BMI:** ≤45 kg/m^2	on AHAs, who underwent washout of the agent; HbA1c for participants not on AHAs ≥7.0% to ≤10.0%; HbA1c for participants on AHA monotherapy or sulphonylurea plus metformin ≥6.5% and ≤9.5% at screening and ≥7.0% and ≤10% and FPG <15 mmol/L at -2 weeks; substudy conducted for participants with HbA1c >10.0% and ≤12.0% at screening or -1 weeks and FPG ≤19.4 mmol/L at -1 weeks **Previous treatment:** diet and exercise or on antihyperglycaemic agents (AHAs) **BMI:** NR	**Glycaemic control:** insufficient glycaemic control despite diet/exercise regimen [HbA1c 7.0-10.0% (or 7.0-9.0% in Germany)] at screening for patients eligible for randomised treatment, or >10.0% for those eligible for the open-label treatment group (this arm not included in Germany or Ireland) **Previous treatment:** previously untreated, except diet and exercise (no oral or injected anti-diabetes treatment for 12 weeks before randomisation or start of open-label treatment) **BMI:** ≤45 kg/m2
Exclusions similar?	**Diabetes-related:** type 1 diabetes mellitus; history	**Diabetes-related:** type 1 diabetes, symptoms of	**Diabetes-related:** history of type 1 diabetes, repeated FPG repeatedly	**Diabetes-related:** Uncontrolled hyperglycaemia (PG >13.3 mmol/L

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	of ketoacidosis; screening fasting plasma glucose (FPG) or finger-stick glucose >15 mmol/L (270 mg/dL) **Other conditions:** estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2; serum creatinine ≥115 µmol/L (1.3 mg/dL) in men or ≥106 µmol/L (1.2 mg/dL) in women; or history of a cardiovascular event within 3 months of screening **Treatment-related:** known hypersensitivity or intolerance to any sodium-glucose co-	severely uncontrolled diabetes (including marked polyuria and polydipsia with >10% weight loss during last 3 months before enrolment) **Other conditions:** serum creatinine ≥133 µmol/L (men) or ≥124 µmol/L (women), urine albumin/ creatinine ratio >200 mg/mmol, aspartate transaminase and/or alanine transaminase >3 times the upper limits of normal, creatine kinase ≥3 times the upper limit of normal; significant renal, hepatic, haematological, oncological, endocrine, psychiatric, or rheumatic diseases, cardiovascular event within 6	>15.0 mmol/L during pretreatment (or >19.4 mmol/L for the high-glycaemic substudy) **Other conditions:** hereditary glucose/galactose malabsorption, primary renal glucosuria or CVD; eGFR <50 ml/minute/1.73 m^2 at screening **Treatment-related:** treatment with a PPARG-agonist, insulin, another SGLT2 inhibitor or any other AHA except as specified in the inclusion criteria within 12 weeks before screening	after overnight fast during placebo run-in phase and confirmed by second measurement) **Other conditions:** eGFR (estimated using modification of diet in renal disease equation) <50 ml/minute/1.73m^2 (or < 60 ml/minute/1.73 m^2 in China), any uncontrolled endocrine disorder apart from type 2 diabetes **Treatment-related:** any contraindications to sitagliptin according to local label, treatment with anti-obesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in thyroid hormone dose within 6 weeks before informed consent

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	transporter 2 (SGLT2) inhibitor or metformin	months of enrolment, severe uncontrolled BP (systolic ≥180 mmHg and/or diastolic ≥110 mmHg) **Treatment-related:** NR		
Number of patients	461	145 in relevant comparison groups	584 in relevant comparison groups	676 in relevant comparison groups
Number of centres and countries	Multicentre (n = 67); USA, Canada, Israel, Italy, Mexico, South Africa, UK	Multicentre (n = 85); USA, Canada, Mexico and Russia	Multicentre (n = NR) 17 countries (USA, Austria, Colombia, Estonia, Guatemala, Iceland, India, Korea, Republic of, Lithuania, Malaysia, Mexico, Philippines, Poland, Puerto Rico, Romania, South Africa, Spain and Sweden)	Multicentre (n = 124); Nine countries (Belgium, Canada, China, Germany, India, Ireland, Japan, Switzerland and USA)
Sponsor	Merck Sharp & Dohme Corp.; Pfizer Inc	Bristol-Myers Squibb; AstraZeneca	Janssen Research & Development, LLC	Boehringer Ingelheim; Eli Lilly
Interventions				
Comparison groups	**ertu5 (n = 156):** ertugliflozin 5 mg once	**dapa10 AM (n = 70):** 10 mg/day dapagliflozin, administered once daily in	**cana100 (n = 195):** 100 mg/day canagliflozin	**empa10 (n = 224):** empagliflozin 10 mg/day in people with HbA1c 7–10%

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	daily taken in the morning **ertu15 (n = 152):** ertugliflozin 15 mg once daily taken in the morning **placebo (n = 153):** placebo once daily taken in the morning	the morning in people with HbA1c 7-10% **placebo (n = 75):** placebo, once daily in people with HbA1c 7-10% Groups receiving 2.5 or 5 mg/day dapagliflozin or 10 mg/day dapagliflozin in the evening and groups with initial HbA1c >10% not considered here	**cana300 (n = 197):** 300 mg/day canagliflozin **placebo (n = 192):** placebo Groups with initial HbA1c >10% not considered here	**empa25 (n = 224):** empagliflozin 25 mg/day in people with HbA1c 7–10% **placebo (n = 228):** placebo once a day in people with HbA1c 7–10% Group receiving sitagliptin and group with initial HbA1c >10% not considered here

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Run-in	2 week single-blind placebo run-in – patients randomised if compliance ≥80%	2-week diet/exercise placebo lead-in (1 week for patients with HbA1c 10.1–12.0%)	8 weeks and diet and exercise and washout period for participants on AHA, followed by a 2-week single-blind placebo run-in period; participants not on AHA directly entered the 2-week placebo run-in period; participants in the high-glycaemic substudy entered a 1-week, single-blind placebo run-in period	2-week, open-label placebo run-in
All groups	Glycaemic rescue therapy with open-label metformin was prescribed for participants who exceeded the following thresholds: fasting plasma glucose (FPG) values >15.0 mmol/L after randomisation up to week 6; >13.3 mmol/L	If fasting FPG was >270 mg/dl at week 4, >240 mg/dl at week 8 or >200 mg/dl at weeks 12 to 24, patients were eligible for open-label rescue medication (500 mg metformin, titrated as needed up to 2000 mg); patients with HbA1c >8.0% for 12 weeks despite maximum tolerated	Rescue therapy with metformin was initiated if FPG was >15.0 mmol/L after day 1 to week 6, >13.3 mmol/L after week 6 to week 12 and >11.1 mmol/L after week 12 to week 26; HbA1c >8% after week 26	All received diet/exercise counselling according to local recommendations; rescue medication was started at FPG >13.3 mmol/L between weeks 1 and 12 or FPG >11.1 mmol/L between weeks 12 and 24 (drug of choice at the discretion of the investigator, but GLP-1 agonists and DPP-4 inhibitors were not permitted)

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	after week 6 and up to week 12; >11.1 mmol/L after week 12 and up to week 26; diet and exercise counselling / monitoring throughout the study	metformin dose were discontinued; the strategy for rescue medication based on HbA1c was continued during the extension period. Patients received diet/exercise counselling according to ADA recommendations throughout the study		

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Extension	384/461 (83%) participants entered the second 26 weeks. Participants randomised to placebo who did not receive glycaemic rescue in the first 26 weeks were switched to blinded metformin beginning at the Week 26 visit. Participants rescued with open-label metformin during the first 26 weeks continued to receive this during the second 26 weeks in addition to the randomised treatment (titration schedule for metformin described)	After 24 weeks, the placebo group received low-dose metformin (500 mg/day) and the dapa groups received matching placebo (78 weeks, double-blind)	After 26 weeks, the placebo group received double-blind sitagliptin (100 mg/day) for 26 weeks (not considered here)	68.4% of the 899 patients continued in a double-blind extension (numbers in each group not given) for ≥52 weeks (78 week extension)
Outcomes				

	Ertugliflozin	**Dapagliflozin**	**Canagliflozin**	**Empagliflozin**
Primary outcomes	Change from baseline in HbA1c at week 26	Change from baseline in HbA1c at week 24 in the dapa10 AM group	Change in HbA1c from baseline to week 26	Change from baseline HbA1c at week 24
Secondary outcomes	Changes from baseline at week 26 in FPG level, body weight, 2-hour postprandial glucose (PPG) level, SBP, DBP, proportion of participants with HbA1c <7.0% (53 mmol/mol) at week 26	FPG, body weight	Proportion achieving HbA1c <7.0%, FPG, 2-hour postprandial glucose, HOMA, SBP, HDL-C, triglycerides, body weight	Weight, systolic and diastolic blood pressure

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Other outcomes	Safety assessments (adverse events monitoring, physical examination, vital signs, laboratory evaluations, ECG)	Safety assessments and adverse events (including laboratory, vital signs, urinary tract and genital infections, hypoglycaemia)	LDL-C, non-HDL-C, apolipoprotein B, DBP, safety assessments (including laboratory, vital signs, hypoglycaemia)	Percentage achieving HbA1c < 7.0% (of those with HbA1c > 7.0% at baseline), FPG, percentage with > 5.0% reduction in body weight, waist circumference, percentage of patients with previously uncontrolled hypertension who achieved controlled BP (<130 mmHg systolic, <80 mmHg diastolic); use of rescue therapy, safety end points (vital signs, clinical laboratory parameters, adverse events, e.g. hypoglycaemic episodes, urinary tract and genital infections)
Baseline characteristics				
Mean age and range (years)	**ertu5:** 56.8 (SD11.4) **ertu15:** 56.2 (SD10.8) **placebo:** 56.1 (SD10.9)	**dapa10 AM:** 50.6 (SD 10.0) **placebo:** 52.7 (SD 10.3)	**cana100**: 55.1 (SD 10.8) **cana300:** 55.3 (SD 10.2) **placebo:** 55.7 (SD 10.9)	**empa10:** 56.2 (SD 11.6) **empa25:** 53.8 (SD 11.6) **placebo:** 54.9 (SD 10.9)

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Sex (% women)s	**ertu5:** 42.9% **ertu15:** 40.8% **placebo:** 46.4%	**dapa10 AM:** 51.4% **placebo:** 58.7%	**cana100:** 58.5% **cana300:** 54.8% **placebo:** 54.2%	**empa10:** 37% **empa25:** 35% **placebo:** 46%
Duration of diabetes (years)	**ertu5:** 5.11 (SD 5.09) **ertu15:** 5.22 (SD 5.55) **placebo:** 4.63 (SD 4.52)	(median, IQR) **dapa10 AM:** 0.45 (0.1-3.4) **placebo:** 0.5 (0.1-3.4)	**cana100:** 4.5 (SD 4.4) **cana300:** 4.3 (SD 4.7) **placebo:** 4.2 (SD 4.1)	**empa10:** 39% ≤1 year, 41% 1-5 years, 13% 5-10 years, 7% >10 years **empa25:** 41% ≤1 year, 37% 1-5 years, 17% 5-10 years, 6% >10 years **placebo:** 32% ≤1 year, 46% 1-5 years, 15% 5-10 years, 8% >10 years
Comorbidities	NR	**dapa10 AM:** 1.4% diabetic neuropathy, 1.4% microalbuminuria, 41.4% hypertension **placebo:** 8% diabetic neuropathy, 1.3% diabetic retinopathy, 1.3%	NR	NR

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
		microalbuminuria, 52% hypertension		
*Ethnic groups - % white. If Asians, say whether East or South***	**ertu5:** 85.9% White, 6.4% Asian, 6.4% Black / African American, 1.3% Multiple **ertu15:** 82.9% White, 9.2% Asian, 6.6% Black / African American, 1.3% Multiple **placebo:** 82.4% White, 9.8% Asian, 5.9% Black / African American, 1.3% Multiple, 0.7% American Indian / Alaska Native	**dapa10 AM:** 90% White, 2.9% Black, 4.3% Asian, 2.9% other **placebo:** 94.7% White, 2.7% Black, 2.7% Asian	**cana100:** 63.6% White, 9.2% Black, 13.8% Asian, 13.3% other **cana300:** 69.5% White, 7.1% Black, 14.7% Asian, 8.6% other **placebo:** 69.8% White, 4.7% Black, 15.1% Asian, 10.4% other	**empa10:** 64% Asian, 34% White, 1% Black/African American, < 1% Hawaiian/Pacific Islander; **empa25**: 64% Asian, 33% White, 3% Black/African American; **placebo:** 64% Asian, 33% White, 3% Black/African American
BMI (kg/m^2)	**ertu5:** 33.2 (SD 7.4) **ertu15:** 32.5 (SD 5.7) **placebo:** 33.3 (SD 6.8)	**dapa10 AM:** 33.6 (SD 5.4) **placebo:** 32.3 (SD 5.5)	**cana100:** 31.3 (SD 6.6) **cana300:** 31.7 (SD 6.0) **placebo:** 31.8 (SD 6.2)	**empa10:** 28.3 (SD 5.5) **empa25:** 28.2 (SD 5.5) **placebo:** 28.7 (SD 6.2)
Systolic blood pressure (mmHg)	**ertu5:** 130.5 (SD 13.5) **ertu15:** 129.7 (SD 14.2)	NR	**cana100:** 126.7 (SD 12.5) **cana300:** 128.5 (SD 12.7) **placebo:** 127.7 (SD 13.7)	**empa10:** 133.0 (SD 16.6) **empa25:** 129.9 (SD 17.5) **placebo:** 130.4 (SD 16.3)

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Diastolic blood pressure (mmHg)	**ertu5:** 78.5 (SD 8.1) **ertu15:** 78.5 (SD 7.7)	NR	**cana100:** 77.7 (SD 6.8)) **cana300:** 79.1 (SD 8.3) **placebo:** 77.4 (SD 8.4)	**empa10:** 79.2 (SD 9.6) **empa25:** 78.3 (SD 9.4) **placebo:** 78.9 (SD 9.6)
HbA1c (%), mean and range	**ertu5:** 8.16 (SD 0.88) **ertu15:** 8.35 (SD 1.12) **placebo:** 8.11 (SD 0.92)	**dapa10 AM:** 8.01 (SD 0.96) **placebo:** 7.84 (SD 0.87)	**cana100:** 8.1 (SD 1.0) **cana300:** 8.0 (SD 1.0) **placebo:** 8.0 (SD 1.0)	**empa10:** 7.87 (SD 0.88) **empa25:** 7.86 (SD 0.85) **placebo:** 7.91 (SD 0.78)
Baseline eGFR (mL/min/1.73 m^2)	**ertu5:** 88.5 (SD 18.4) **ertu15:** 88.3 (SD 18.0) **placebo:** 86.2 (SD 19.4)	NR	**cana100:** 88.5 (SD 20.2) **cana300:** 86.6 (SD 19.1) **placebo:** 86.0 (SD 21.5)	**empa10:** 87.7 (SD 19.2) **empa25:** 87.6 (SD 18.3) **placebo:** 86.8 (SD 17.9)
Prior treatment with GLD? *% drug naïve* *% previously treated*	**ertu5:**54.5% currently on AHA therapy; 10.9% not currently on AHA therapy, previously treated; 34.6% never treated **ertu15:** 51.3% currently on AHA therapy; 13.8% not currently on AHA therapy, previously treated; 34.9% never treated	Only GLD treatment-naïve participants included	*Patients on AHA at screening:* **cana100:** 48.2% **cana300:** 48.2% **placebo:** 47.9%	No oral/injectable anti-diabetic drug

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	placebo: 50.3% currently on AHA therapy; 8.5% not currently on AHA therapy, previously treated; 41.2% never treated			
% on anti-hypertensives at baseline	NR	**dapa10 AM:** 41.4% on antihypertensives **placebo:** 41.3% on antihypertensives	NR	NR
Results				
Study flow / discontinuation	***Discontinuations:*** ***Main study:*** **ertu5:** 22/156 (14%) **ertu15:** 21/152 (14%) **placebo:** 34/153 (22%) ***Extension:*** **ertu5:** 20/134 (15%) **ertu15:** 13/131 (10%) **placebo:** 17/119 (14%)	***Discontinuations:*** ***Main study:*** **dapa10:** 13/70 (19%) **placebo:** 12/75 (16%) ***Extension:*** **dapa10 AM:** 14/56 (25%) **placebo:** 20/62 (32%)	***Discontinuations:*** ***Main study:*** **cana10:** 23/195 (12%) **cana300:** 22/197 (12%) **placebo:** 32/192 (17%) ***Extension:*** **cana100:** 18/170 (11%) **cana300:** 5/170 (3%) **placebo:** 20/155 (13%)	***Discontinuations:*** ***Main study:*** **empa10:** 18/224 (8.0%) **empa25:** 20/224 (8.9%) **placebo:** 41/228 (18%) ***Extension:*** **empa10:** 18/165 (10.9%) **empa25:** 16/159 (10.1%) **placebo:** 17/136 (12.5%)

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
HbA1c (final level, change from baseline) (%)	***Final HbA1c level*** **26 weeks:** **ertu5:** 7.31 (SD 0.86), p<0.001 vs placebo **ertu15:** 7.28 (SD 1.01), p<0.001 vs placebo **placebo:** 7.76 (SD 1.02) **52 weeks:** **ertu5:** 7.0 (SD 0.7) **ertu15:** 7.0 (SD 0.6) ***Change from baseline*** **26 weeks:** **ertu5:** -0.80 (SD 0.83), p<0.001 vs placebo **ertu15:** -1.04 (SD 1.04), p<0.001 vs placebo **placebo:** -0.09 (SD 0.90) **52 weeks:**	***Final HbA1c level NR*** ***Change from baseline*** **24 weeks:** **dapa10 AM:** -0.89 (SD 0.92), p<0.0001 vs placebo **placebo:** -0.23 (SD 0.87) **102 weeks:** **dapa10 AM:** -0.61 (SD 0.70) , p=0.048 vs placebo **placebo/metformin:** -0.17, (SD 0.67)	***Final HbA1c level NR*** **26 weeks:** **cana100:** -0.77 (SD 0.7), p<0.001 vs placebo **cana300:** -1.03 (SD 0.7), p<0.001 vs placebo **placebo:** 0.14 (SD 0.7) **52 weeks:** **cana100:** -0.81 (95% CI: -0.94, -0.68) **cana300:** -1.11% (95% CI: -1.24, -0.98)	***Final HbA1c level*** **24 weeks:** **empa10:** 7.21 (95% CI: 7.10, 7.32), p<0.0001 vs placebo **empa25:** 7.09 (95% CI: 6.98, 7.21), p<0.0001 vs placebo **placebo:** 7.55 (95% CI: 7.24, 7.86) **76 weeks:** **empa10:** 7.22 (SE 0.06), p<0.001 vs placebo **empa25:** 7.12(SE 0.06), p<0.001 vs placebo **placebo:** 8.01 (SE 0.06) ***Change from baseline*** **24 weeks:** **empa10:** -0.66 (SD 0.76), p<0.0001 vs placebo **empa25:** -0.78 (SD 0.80), p<0.0001 vs placebo

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	ertu5: -0.9 (SD 0.9) **ertu15:** -1.0 (SD 1.0) **placebo/metformin:** -1.0 (SE 0.1)			**placebo:** 0.08 (SD 0.81) **76 weeks:** **empa10:** -0.65 (SE 0.06), p<0.001 vs placebo **empa25:** -0.76(SE 0.06), p<0.001 vs placebo **placebo:** 0.13 (SE 0.06)
HbA1c % achieving target	***% achieving HbA1c <7.0%*** **26 weeks:** **ertu5:** 28.2%, p<0.001 vs placebo **ertu15:** 35.8%, p<0.001 vs placebo **placebo:** 13.1% **52 weeks:** **ertu5:** 25.6% **ertu15:** 28.5%	***% achieving HbA1c <7.0%*** **24 weeks:** **dapa10 AM:** 51% **placebo:** 32%	***% achieving HbA1c <7.0%*** **26 weeks:** **cana100:** 44.5%, p<0.001 vs placebo **cana300:** 62.4%, p<0.001 vs placebo **placebo:** 20.6% **52 weeks:** **cana100:** 52.4% **cana300:** 64.5%	***Patients with HbA1c ≥7.0% at baseline who reached HbA1c <7.0%*** **24 weeks:** **empa10:** 72/204 (35%), p<0.0001 vs placebo **empa25:** 88/202 (44%), p<0.0001 vs placebo **placebo:** 25/208 (12%) **76 weeks:** **empa10:** 46.6%, p<0.001 vs placebo

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	placebo/metformin: 27.5%			**empa25:** 46.5%, p<0.001 vs placebo **placebo:** 17.9%
Systolic blood pressure (mmHg) (change from baseline), % achieving <130/90, etc.	**26 weeks (vs placebo):** **ertu5:** -3.31 (95% CI -5.98, -0.65) **ertu15:** -1.71 (95% CI -4.40, 0.98), p=0.21 vs placebo **52 weeks :** **ertu5:** -3.7 (SD 11.8) **ertu15:** -1.8 (SD 12.2)	**24 weeks:** **dapa10 AM:** -3.6 (SD 15.9) **placebo:** -0.9 (SD 15.6) **102 weeks:** **dapa10 AM:** 3.9 (SD 14.7) **placebo/metformin:** 2.1 (SD 18.6)	**26 weeks:** **cana100:** -3.3 (SD 11.1), p<0.001 vs placebo **cana300:** -5.0 (SD 11.2), p<0.001 vs placebo **placebo:** 0.4 (SD 11.0) **52 weeks.** **cana100:** -1.4 (95% CI: -3.0, 0.2) **cana300:** -3.9 (95% CI: -5.5, -2.3)	**24 weeks:** **empa10:** -2.9 (SD 12.2), p=0.02 vs placebo **empa25:** -3.7 (SD 12.2), p=0.003 vs placebo **placebo:** -0.3 (SD 12.3) **76 weeks:** **empa10:** -4.1 (SE 0.8), p=0.003 vs placebo **empa25:** -4.2 (SE 0.8), p=0.002 vs placebo **placebo:** -0.7 (SE 0.8)
Diastolic blood pressure (mmHg) (change from baseline)	**26 weeks (vs placebo):** **ertu5:** -1.80 (95% CI -3.51, -0.09) **ertu15:** -0.37 (95% CI -2.09, 1.35)	**24 weeks:** **dapa10 AM:** -2.0 (SE 1.1) **placebo:** -0.7 (SE 1.0) **102 weeks:**	**26 weeks:** **cana100:** -1.7 (SE 0.5) **cana300:** -2.1 (SE 0.5) **placebo:** -0.1 (SE 0.5)	**24 weeks:** **empa10:** -1.0 (95% CI: -2-0, -0.1), p=0.4 vs placebo **empa25:** -1.9 (95% CI: -2.9, -1.0), p=0.03 vs placebo

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	52 weeks : **ertu5:** -0.8 (SD 6.9) **ertu15:** 0.4 (SD 7.2)	**dapa10 AM:** 1.7 (95% CI: -0.8, 4.2) **placebo/metformin:** 0.5 (95% CI: -2.0, 3.0)	**52 weeks.** **cana100:** -0.6 (SE 0.5) **cana300:** -0.9 (SE 0.5)	**placebo:** -0.5 (95% CI: -1.4, 0.5) **76 weeks:** **empa10:** -1.6 (SE 0.5), p=0.13 vs placebo **empa25:** -1.6 (SE 0.5), p=0.16 vs placebo **placebo:** -0.6 (SE 0.5)
BMI	NR			
Weight loss (kg)	**26 weeks (vs placebo):** **ertu5:** -1.76 (95% CI -2.57, -0.95), p<0.001 vs placebo **ertu15:** -2.16 (95% CI -2.98, -1.34), p<0.001 vs placebo **52 weeks :** **ertu5:** -3.6 (SD 4.0) **ertu15:** -3.7 (SD 3.5)	**24 weeks:** **dapa10 AM:** -3.20 (SD 4.18), p=NS vs placebo **placebo:** -2.20 (SD 3.46) **102 weeks:** **dapa10 AM:** -3.94 (SD 3.52), p=0.016 vs placebo **placebo/metformin:** -1.34 (SD 3.34)	**26 weeks:** **cana100:** -2.5 (SD 2.4), p<0.001 vs placebo **cana300:** -3.4 (SD 2.4), p<0.001 vs placebo **placebo:** -0.5 (SD 2.4) **52 weeks:** **cana100:** -2.8 (95% CI: -3.4, -2.1) **cana300:** -3.9 (95% CI: -4.6, -3.3)	**24 weeks:** **empa10:** -2.3 (SD 2.6), p<0.0001 vs placebo **empa25:** -2.5 (SD 2.6), p<0.0001 vs placebo **placebo:** -0.3 (SD 2.6) **76 weeks:** **empa10:** -2.2 (SE 0.2), p<0.001 vs placebo **empa25:** -2.5 (SE 0.2), p<0.001 vs placebo

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
				placebo: -0.4 (SE 0.2)
Adverse effects				
Discontinuation due to AE (%)	**26 weeks:** **ertu5:** 4/156 (2.6%) **ertu15:** 3/152 (2.0%) **placebo:** 5/153 (3.3%) **52 weeks:** **ertu5:** 7/156 (4.5%) **ertu15:** 6/152 (3.9%) **placebo/metformin:** 10/153 (6.5%)	**24 weeks:** **dapa10 AM:** 5/70 (7.1%) **placebo:** 1/75 (1.3%) **102 weeks:** **dapa10 AM:** 5/70 (7.1%) **placebo/metformin:** 4/75 (5.3%)	**26 weeks:** **cana100:** 5/195 (2.6%) **cana300:** 3/197 (1.5%) **placebo:** 2/192 (1.0%) **52 weeks:** **cana100:** 0/170 **cana300:** 0/170	**24 weeks:** **empa10:** 2/224 (0.9%) **empa25:** 4/224 (1.8%) **placebo:** 8/228 (3.5%) **76 weeks:** **empa10:** 11/224 (4.9%) **empa25:** 9/224 (4.0%) **placebo:** 15/229 (6.6%)
Hypoglycaemia; Severe Non-severe How defined?	**26 weeks:** **ertu5:** 1.3% symptomatic hypoglycaemia, 2.6% documented hypoglycaemia (symptomatic and nonsymptomatic) **ertu15:** 2.6% symptomatic	**24 weeks:** **dapa10 AM:** 2.9% (none requiring third party assistance) **placebo:** 2.7% (none requiring third party assistance) **102 weeks:**	**26 weeks:** **cana100:** documented hypoglycaemia 3.6%, no severe hypoglycaemia **cana300:** documented hypoglycaemia 3.0%, no severe hypoglycaemia	**24 weeks:** **empa10:** 0.4% confirmed hypoglycaemia, none requiring assistance **empa25:** 0.4% confirmed hypoglycaemia, none requiring assistance

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	hypoglycaemia, 2.6% documented hypoglycaemia, 1.3% severe hypoglycaemia (requiring assistance) **placebo:** 1.3% symptomatic hypoglycaemia, 0.7% documented hypoglycaemia **52 weeks:** **ertu5:** 1.3% symptomatic hypoglycaemia, 3.8% documented hypoglycaemia (symptomatic and nonsymptomatic) **ertu15:** 2.6% symptomatic hypoglycaemia, 5.3%	**dapa10 AM:** 4.3% (none requiring third party assistance) **placebo/metformin: 5**.3% (none requiring third party assistance)	**placebo:** documented hypoglycaemia 2.6%, no severe hypoglycaemia **52 weeks:** **cana100:** documented hypoglycaemia 5.1%, none leading to discontinuation **cana300:** documented hypoglycaemia 3.6%, none leading to discontinuation	**placebo:** 0.4% confirmed hypoglycaemia, none requiring assistance **76 weeks:** **empa10:** 0.9% confirmed hypoglycaemia, n=1 requiring assistance **empa25:** 0.9% confirmed hypoglycaemia, none requiring assistance **placebo:** 0.9% confirmed hypoglycaemia, none requiring assistance

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	documented hypoglycaemia, 1.3% severe hypoglycaemia (requiring assistance) **placebo/metformin:** 4.6% symptomatic hypoglycaemia, 5.2% documented hypoglycaemia, 0.7% severe hypoglycaemia (requiring assistance)			
Urinary tract infections	**26 weeks:** **ertu5:** 11/156 (7.1%) **ertu15:** 6/152 (3.9%) **placebo:** 13/153 (8.5%) **52 weeks:** **ertu5:** 10.9% **ertu15:** 6.6% **placebo/metformin:** 13.7%	**24 weeks:** **dapa10 AM:** 4/70 (5.7%) **placebo:** 3/75 (4.0%) **102 weeks:** **dapa10 AM:** 6/70 (8.6%) [men: 2/34 (5.9%); women: 4/36 (11.1%)]	**26 weeks:** **cana100:** 14/195 (7.2%) **cana300:** 10/197 (5.1%) **placebo:** 8/192 (4.2%) **52 weeks** **cana100:** 16/195 (8.2%) **cana300:** 14/197 (7.1%)	**24 weeks:** **empa10:** 15/224 (6.7%) [men: 3/142 (2.1%); women: 12/82 (14.6%)] **empa25:** 12/223 (5.4%) [men: 2/144 (1.4%); women: 10/79 (12.7%)] **placebo:** 12/229 (5.2%) [men: 3/124 (2.4%); women: 9/105 (8.6%)]

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
		placebo/metformin: 3/75 (4.0%) [men: 0/31 (0.0%); women: 3/44 (6.8%)]		**≥76 weeks:** **empa10:** 21/224 (9.4%) **empa25:** 20/224 (8.9%) **placebo:** 25/228 (11.0%)
Genital tract infections (by gender)	**Genital mycotic infection** **26 weeks:** **ertu5:** women: 11 (16.4%), men: 3 (3.4%) **ertu15:** women: 14 (22.6%), men: 5 (5.6%) **placebo:** women: 4 (5.6%), men: 1 (1.2%) p<0.05 for women in the ertugliflozin groups vs placebo **52 weeks:** **ertu5:** women: 26.9%, men: 3.4%	**24 weeks:** **dapa10 AM:** 9/70 (12.9%) [NR by gender] **placebo:** 1/75 (1.3%) [NR by gender] **102 weeks:** **dapa10 AM:** 11/70 (15.7%) [men: 2/34 (5.9%); women: 9/36 (25.0%)] **placebo/metformin:** 1/75 (1.3%)) [men: 0/31 (0.0%); women: 1/44 (2.3%)]	**26 weeks:** **cana100:** 12/195 (6.2%) [men: 2/195 (2.5%); women: 10/195 (8.8%)] **cana300:** 13/197 (6.6%) [men: 5/197 (5.6%); women: 8/197 (7.4%)] **placebo:** 4/192 (2.1%) [men: 0/192 (0.0%); women: 4/192 (3.8%)] **52 weeks** **cana100:** 18/195 (9.2%) [men: 5/195 (6.2%); women: 13/195 (11.4%)]	**24 weeks:** **empa10:** 7/224 (3.1%) [men: 4/142 (2.8%); women: 3/82 (3.7%)] **empa25:** 9/223 (4.0%) [men: 2/144 (1.4%); women: 10/79 (12.7%)] **placebo:** 0/229 (0.0%) [men: 0/124 (0.0%); women: 0/105 (0.0%)] **≥76 weeks:** **empa10:** women: 9 (11.0%), men: 4 (2.8%) **empa25:** women: 10 (12.6%), men: 4 (2.8%) **placebo:** women: 1 (1.9%), men: 2 (1.6%)

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	ertu15: women: 29.0%, men: 7.8% **placebo/metformin:** women: 9.9%, men: 1.2%		**cana300:** 18/197 (9.1%) [men: 8/197 (9.0%); women: 10/197 (9.3%)]	
*Any DKA, amputations, fractures**	NR	NR	NR	NR
Other if common (>5%)	***AEs related to study drug*** **26 weeks:** **ertu5:** 32/156 (20.5%) **ertu15:** 28/152 (18.4%) **placebo/metformin:** 19/153 (12.4%) **52 weeks:** **ertu5:** 42/156 (26.9%) **ertu15:** 37/152 (24.3%) **placebo:** 45/153 (29.4%)	***AEs related to study drug*** **24 weeks:** NR **102 weeks:** **dapa10 AM:** 17/70 (24.3%) **placebo/metformin:** 15/75 (20%)	***AEs related to study drug*** **26 weeks:** **cana100:** 34/195 (17.4%) **cana300:** 50/197 (25.4%) **placebo:** 18/192 (9.4%) **52 weeks** **cana100:** 44/195 (22.6%) **cana300:** 53/197 (26.9%)	***AEs related to study drug*** **24 weeks:** **empa10:** 27/224 (12%) **empa25:** 39/223 (17%) **placebo:** 17/229 (7%) **76 weeks:** **empa10:** 49/224 (21.9%) **empa25:** 52/223 (23.3%) **placebo:** 36/229 (15.7%)

AHA=antihyperglycaemic agent; IQR=interquartile range

*Adverse effects. These may not appear in the trials because of numbers and duration, but please check FDA and EMA websites for any warnings. Fractures have been reported with canagliflozin but not (so far) with any others. Toe amputations also reported with canagliflozin. DKA (diabetic ketoacidosis) has been reported with all the flozins, but some of the cases may have been mis-reported as type 2 when they were really type 1. Curiously, some of the DKA cases seen with flozins in type have had relatively low blood glucose levels. BG is usually high in DKA.

Severe hypoglycaemia includes loss of consciousness, but is usually defined as requiring assistance

**Asians. East Asians such as Chinese or Japanese tend to have lower BMIs than South Asians (India etc). Chinese people with T2 diabetes have lower BMIs and a more insulin-deficient pattern than the overweight insulin-resistant Indians. In studies in the USA, “Asian” may mean of Chinese or Korean descent.

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	ITT analysis	Selective reporting	Similarity at baseline	Other (e.g. power anylsis)	Overall
Ertugliflozin										
Terra 2017[42] / Aronson 2018[6]	*Low risk* Random assignment via an interactive automated system, based on a computer-generated randomisation code using the method of random permuted blocks	*Low risk* Interactive automated system	*Low risk* Double-blind	*Unclear risk* NR	*Unclear risk* Discontinuation 26 weeks: **ertu5:** 14.1% **ertu 15:** 13.8% **placebo:** 22.2% *Extension:* **ertu5:** 14.9% **ertu 15:** 9.9% **placebo:** 14.4% Reasons given	*Low risk* Efficacy analyses consisted of all randomised participants who received at least one dose of study medication and had at least one measurement of the analysis endpoint (baseline or post-baseline)	*Low risk* Outcomes reported as specified on clinicaltrials.gov	*Low risk* Demographics and baseline characteristics were similar across the treatment groups	*Low risk* >99% power to detect a difference of 0.6% in the change from baseline at week 26 in HbA1c with 450 participants	**7/9 low risk**

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	ITT analysis	Selective reporting	Similarity at baseline	Other (e.g. power anylsis)	Overall
Dapagliflozin										
Ferrannini 2010[43]/Bailey 2012[7]	*Low risk* 'Computer-generated randomisation by an interactive voice response system, stratified by site in blocks of 7'	*Low risk* 'Randomisation codes kept centrally at Bristol-Myers Squibb'	*Low risk* 'Investigators, other clinical staff and participants blinded to treatment allocation during the 24-week initial and 78-week extension periods'	*Low risk* See previous	*Low risk* Discontinuation 24 weeks: **dapa10:** 15.7% **placebo:** 16% *Extension:* **dapa10AM:** 40% **placebo:** 44% Reasons given	*Unclear risk* States that analyses were based on all participants taking at least one dose of medication, but main follow-up data appear to be based on fewer participants?	*Low risk* All outcomes reported as indicated in the methods section	*Low risk* Between dapa10 AM/PM groups and placebo, the dapa10 high HbA1c group had a longer diabetes duration (other than a higher HbA1c)	*Low risk* 90% power to detect a difference in HbA1c with 67 participants per group (primary end point)	**8/9 low risk (main analysis)**
Canagliflozin										

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	ITT analysis	Selective reporting	Similarity at baseline	Other (e.g. power anylsis)	Overall
CANTATA-M (Stenlöf 2013)[19]	*Unclear risk* Method not reported; Randomisation stratified by previous AHA use	*Unclear risk* NR	*Low risk* Double-blind	*Unclear risk* NR	*Low risk* Discontinuation 26 weeks: **cana100:** 11.8% **cana300:** 11.2% **placebo:** 16.7% Reasons given	*Low risk* ITT for all patients receiving at least one dose of study drug; LOCF for missing data	*Low risk* But some data shown only in graphs with no numeric values given	*Low risk*	*Low risk* 90% power to detect a difference in HbA1c with 85 participants per group	**6/9 low risk**

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	ITT analysis	Selective reporting	Similarity at baseline	Other (e.g. power anylsis)	Overall
Empagliflozin										
Roden 2013[44]	*Low risk* Computer-generated random sequence in block sizes of four, stratified by region (Asia, Europe, North America), HbA1c at screening (< 8.5%, ≥ 8.5%) and eGFR (≥ 90, 60–89, 50–59ml/ minute)	*Low risk* Study sponsor allocated participants using an interactive voice and internet-based response system	*Low risk* 'Patients, investigator and individuals involved in the analysis of trial data were masked to treatment assignment'	*Low risk* See previous	*Low risk* Discontinuation 24 weeks: **placebo:**: 18% **empa10:** 8% **empa25:** 9% **empa25open**: 10% Reasons given	*Low risk* Efficacy data were analysed with a full analysis set of individuals who took at least one dose of study medication; missing values imputed using LOCF	*Low risk* All outcomes reported as indicated in the methods section	*Low risk* Between empa10, empa25, sita100 and control groups; empa25open had greater proportion of participants at ≤ 1 year	*Low risk* 95% power to detect a difference in HbA1c with 180 participants per group (primary end point)	**9/9 low risk**

AHA=antihyperglycaemic agent; IQR=interquartile range

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	ITT analysis	Selective reporting	Similarity at baseline	Other (e.g. power anylsis)	Overall
Ertugliflozin										
Terra 2017[42] / Aronson 2018[6]	*Low risk* Random assignment via an interactive automated system, based on a computer-generated randomisation code using the method of random permuted blocks	*Low risk* Interactive automated system	*Low risk* Double-blind	*Unclear risk* NR	*Unclear risk* Discontinuation 26 weeks: **ertu5:** 14.1% **ertu 15:** 13.8% **placebo:** 22.2% *Extension:* **ertu5:** 14.9% **ertu 15:** 9.9% **placebo:** 14.4% Reasons given	*Low risk* Efficacy analyses consisted of all randomised participants who received at least one dose of study medication and had at least one measurement of the analysis endpoint (baseline or post-baseline)	*Low risk* Outcomes reported as specified on clinicaltrials.gov	*Low risk* Demographics and baseline characteristics were similar across the treatment groups	*Low risk* >99% power to detect a difference of 0.6% in the change from baseline at week 26 in HbA1c with 450 participants	**7/9 low risk**

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	ITT analysis	Selective reporting	Similarity at baseline	Other (e.g. power anylsis)	Overall
Dapagliflozin										
Ferrannini 2010[43]/Bailey 2012[7]	*Low risk* 'Computer-generated randomisation by an interactive voice response system, stratified by site in blocks of 7'	*Low risk* 'Randomisation codes kept centrally at Bristol-Myers Squibb'	*Low risk* 'Investigators, other clinical staff and participants blinded to treatment allocation during the 24-week initial and 78-week extension periods'	*Low risk* See previous	*Low risk* Discontinuation 24 weeks: **dapa10:** 15.7% **placebo:** 16% *Extension:* **dapa10AM:** 40% **placebo:** 44% Reasons given	*Unclear risk* States that analyses were based on all participants taking at least one dose of medication, but main follow-up data appear to be based on fewer participants?	*Low risk* All outcomes reported as indicated in the methods section	*Low risk* Between dapa10 AM/PM groups and placebo, the dapa10 high HbA1c group had a longer diabetes duration (other than a higher HbA1c)	*Low risk* 90% power to detect a difference in HbA1c with 67 participants per group (primary end point)	**8/9 low risk (main analysis)**
Canagliflozin										

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	ITT analysis	Selective reporting	Similarity at baseline	Other (e.g. power anylsis)	Overall
CANTATA-M (Stenlöf 2013)[19]	*Unclear risk* Method not reported; Randomisation stratified by previous AHA use	*Unclear risk* NR	*Low risk* Double-blind	*Unclear risk* NR	*Low risk* Discontinuation 26 weeks: **cana100:** 11.8% **cana300:** 11.2% **placebo:** 16.7% Reasons given	*Low risk* ITT for all patients receiving at least one dose of study drug; LOCF for missing data	*Low risk* But some data shown only in graphs with no numeric values given	*Low risk*	*Low risk* 90% power to detect a difference in HbA1c with 85 participants per group	**6/9 low risk**

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	ITT analysis	Selective reporting	Similarity at baseline	Other (e.g. power anylsis)	Overall
Empagliflozin										
Roden 2013[44]	*Low risk* Computer-generated random sequence in block sizes of four, stratified by region (Asia, Europe, North America), HbA1c at screening (< 8.5%, ≥ 8.5%) and eGFR (≥ 90, 60–89, 50–59ml/ minute)	*Low risk* Study sponsor allocated participants using an interactive voice and internet-based response system	*Low risk* 'Patients, investigator and individuals involved in the analysis of trial data were masked to treatment assignment'	*Low risk* See previous	*Low risk* Discontinuation 24 weeks: **placebo:**: 18% **empa10:** 8% **empa25:** 9% **empa25open**: 10% Reasons given	*Low risk* Efficacy data were analysed with a full analysis set of individuals who took at least one dose of study medication; missing values imputed using LOCF	*Low risk* All outcomes reported as indicated in the methods section	*Low risk* Between empa10, empa25, sita100 and control groups; empa25open had greater proportion of participants at ≤ 1 year	*Low risk* 95% power to detect a difference in HbA1c with 180 participants per group (primary end point)	**9/9 low risk**

NR=not reported, LOCF=last observation carried forward

Dual therapy – ertugliflozin versus placebo

	Ertugliflozin	**Dapagliflozin**	**Canagliflozin**	**Empagliflozin**
Trial first author and year	VERTIS MET (Rosenstock 2018)[4](NCT02033889)	Bailey 2010[21]/2013[45](NCT02033889)	CANTATA-D (Lavalle-González 2013)[23] (NCT01106677)	EMPA-REG MET (Häring 2014) [22](NCT01159600)
Design	Phase III RCT, double blind, parallel group, placebo controlled	Phase III RCT, double blind, parallel group, placebo controlled	Phase III RCT, double blind, parallel group, placebo controlled	Phase III RCT, double blind, parallel group, placebo controlled
Duration	26 weeks + 78 weeks extension (ongoing)	24 weeks + 78 weeks extension	26 weeks placebo- and active-controlled + 26 weeks active-controlled only	24 weeks
Inclusion criteria similar?	**Condition:** type 2 diabetes mellitus (according to American Diabetes Association guidelines) **Age:** ≥18 years **Glycaemic control:** inadequately controlled with metformin monotherapy: HbA1c 7.0% to 10.5% (53-91 mmol/mol) inclusive **Previous treatment:** metformin monotherapy (≥1500 mg/day for ≥8 weeks) **BMI:** 18.0 to 40.0 kg/m^2 **Other:** receiving stable doses of blood pressure and/or lipid-altering medications for ≥4 weeks prior to randomization	**Condition:** type 2 diabetes mellitus **Age:** 18-77 years **Glycaemic control:** inadequately controlled with metformin monotherapy: HbA1c 7% to 10% **Previous treatment:** taking a stable dose of metformin (≥1500 mg/day) for ≥8 weeks **BMI:** <45 kg/m^2	**Condition:** type 2 diabetes mellitus **Age:** ≥18 - ≤80 years **Glycaemic control:** inadequately controlled with metformin monotherapy: HbA1c 7.0% to 10.5% (53 mmol/mol to 91 mmol/mol); fasting plasma glucose (FPG) <15 mmol/L at week -2 and fasting fingerstick glucose ≥6.1 mmol/L and <15 mmol/L on day 1 **Previous treatment:** stable metformin therapy (≥2000 mg/day [or ≥1500 mg/day if unable to tolerate higher dose]) for ≥8 weeks	**Condition:** type 2 diabetes mellitus **Age:** ≥18 years **Glycaemic control:** inadequately controlled on diet and exercise and metformin: HbA1c ≥7% to ≤10% (patients with HbA1c >10% were eligible to participate in an open-label treatment arm) **Previous treatment:** diet and exercise and a stable regimen (unchanged for ≥12 weeks prior to randomisation) of metformin immediate release **BMI:** ≤45kg/m^2

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
			BMI: NR	
Exclusions similar?	**Diabetes-related:** type 1 diabetes mellitus, history of ketoacidosis **Renal:** estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2 according to the 4-variable modification of diet in renal disease equation at screening **Other conditions:** documented history of osteoporosis or gender-specific bone mineral density (BMD) T-score of <-2.5 at any skeletal site assessed at screening, or any illness that could impact BMD assessment **Treatment-related:** <80% compliance (based on pill count) with the placebo run-in medication; had received prior therapeutic agents that could confound BMD assessment or affect bone turnover; bariatric surgery; use of anti-hyperglycaemic agent (AHAs) other than those approved by the study protocol and use of bone- active therapeutic agents (e.g.	**Diabetes-related:** symptoms of poorly controlled diabetes **Renal:** serum creatinine >133 µmol/L for men and >124 µmol/L for women; urine albumin/creatinine ratio >203.4 mg/mmol; significant renal disease **Other conditions:** AST or ALT >3 times upper limit of normal; clinically significant hepatic, haematological, oncological, endocrine, psychiatric or rheumatic disease; cardiovascular event within 6 months; New York Heart Association class III or IV congestive heart failure; systolic blood pressure ≥180 mmHg, diastolic blood pressure ≥110 mmHg **Treatment-related:** NR	**Diabetes-related:** repeated fasting plasma glucose and/or fasting self-monitored blood glucose ≥15.0 mmol/L during the pretreatment phase; history of type 1 diabetes **Renal:** estimated glomerular filtration rate (eGFR) <55 ml/min/1.73 m^2 (or <60 ml/min/1.73 m^2 if based upon restriction in local label) or serum creatinine ≥124 µmol/L (men) or ≥115 µmol/L (women) **Other conditions:** cardiovascular disease (including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening; uncontrolled hypertension **Treatment-related:** treatment with a peroxisome proliferator-activated receptor gamma agonist, insulin, another sodium	**Diabetes-related:** uncontrolled hyperglycaemia (glucose level >13.3 mmol/L) after an overnight fast confirmed by a second measurement; **Renal:** impaired kidney function (eGFR <30 mL/min/1.73 m^2) during screening or run-in **Other conditions:** acute coronary syndrome, stroke, or transient ischaemic attack within 3 months prior to informed consent; indication of liver disease (alanine aminotransferase, alkaline aminotransferase, or alkaline phosphatase levels >3 times upper limit of normal); history of cancer (except basal cell carcinoma) or treatment for cancer within the last 5 yr; blood dyscrasias or any disorders causing haemolysis or unstable erythrocytes **Treatment-related:** contra-indications to metformin according to the local label; bariatric surgery or other gastrointestinal surgeries that induce chronic malabsorption; treatment with

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	bisphosphonates) prohibited for the entire duration of the trial		glucose co-transporter 2 (SGLT2) inhibitor or any other anti-hyperglycaemic agent (AHA) (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 weeks before screening	antiobesity drugs 3 months prior to consent; use of any treatment at screening leading to unstable body weight; treatment with systemic steroids at time of consent; change in dosage of thyroid hormones within 6 wk prior to consent; alcohol or drug abuse within 3 months of consent; investigational drug intake in another trial within 30 days prior to the current trial
Number of patients	621 Placebo 209, ert 5 207, ert 15 205	272 Dapa 10mg 135, placebo 137	918 Cana 100mg 368 300mg 367 Sita 100mg 366 Placebo/sita 183	638 Empa 10mg 217 25mg 214 Placebo 207
Number of centres and countries	Multicentre North America (27.2%), Europe (36.1%), South America (3.4%), Asia (13.7%), South Africa (17.9%), Australia/New Zealand (1.8%)	Multicentre (n = 80) USA (n = 30), Canada (n = 21), Argentina (n = 11), Mexico (n = 10), Brazil (n = 8)	Multicentre 169 centres in 22 countries (Argentina, Bulgaria, Colombia, Czech Republic, Estonia, Greece, India, Latvia, Malaysia, Mexico, Peru, Poland, Portugal, Puerto Rico, Russian Federation, Singapore, Slovakia, Sweden, Thailand, Turkey, Ukraine, USA)	Multicentre 148 centers in 12 countries (Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, and the USA)

	Ertugliflozin	**Dapagliflozin**	**Canagliflozin**	**Empagliflozin**
Sponsor	Pfizer Inc; Merck & Co Inc	Bristol-Myers Squibb; AstraZeneca	Janssen Research & Development, LLC	Boehringer Ingelheim; Eli Lilly
Interventions				
Comparison groups	ertu5 (n = 207): ertugliflozin 5 mg once daily ertu15 (n = 205) once daily **placebo (n = 209):** placebo once daily	**dapa10 (n = 135)** **placebo (n = 137)** Groups receiving 2.5 or 5 mg/day dapagliflozin not considered here	**cana100 (n = 368):** canagliflozin 100 mg once daily **cana300 (n = 367):** canagliflozin 300 mg once daily; sitagliptin 100 mg: n=366; **placebo (n=183):** placebo once daily Group receiving sitagliptin – see table below	**empa10 (n = 217):** empagliflozin 10 mg once daily **empa25 (n = 214):** empagliflozin 25 mg once daily **placebo (n=207)**once daily
Run-in	Screening period (during which, if needed, background diabetes medication was adjusted to achieve a minimum 8-week metformin monotherapy stable dose [≥1500 mg/day]); 2-week single-blind placebo run-in period	2-week single-blind placebo run-in period	2-week single-blind placebo run-in period; those on metformin extended release (XR), metformin immediate release (IR) or XR at below protocol-specified doses or metformin plus sulfonylurea underwent a metformin IR dose titration/dose stablisation and, if applicable, a sulfonylurea washout period of up to 10 weeks, followed by the placebo run-in period	2-week open-label placebo run-in period

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
All groups	Stable metformin monotherapy (median baseline dose 2000 mg/day); dietary and lifestyle counselling	Stable metformin monotherapy (median baseline dose 1500 mg/day); diet and exercise counselling	Stable metformin immediate release monotherapy (≥2000 mg/day [or ≥1500 mg/day if unable to tolerate higher dose])	Metformin (≥1500 mg/day or maximum tolerated dose or maximum dose according to local label)
Rescue therapy	In phase A, participants received glycaemic rescue therapy with open-label glimepiride if they exceeded the following fasting plasma glucose (FPG) thresholds: >15.0 mmol/L after randomization through week 6, >13.3 mmol/L after week 6 through week 12, and >11.1 mmol/L after week 12 through week 26. Bone rescue therapy was to be administered to participants with a confirmed reduction from baseline in BMD of >7% at any anatomical site, together with a T-score of <-2.5. Participants receiving glycaemic or bone rescue therapy continued to receive ertugliflozin or matching placebo.	Glycaemic measurements were assessed from week 4 to week 24 to determine the need for open-label pioglitazone or acarbose as a rescue medication for fasting plasma glucose concentrations more than 15.0 mmol/L (week 4‑8), 13.3 mmol/L (week 8‑12), or 11.1 mmol/L (week 12‑24).	During the double-blind treatment period, glycaemic rescue therapy with glimepiride (added to study drug and background metformin) was initiated if FPG >15.0 mmol/L after day 1 to week 6, >13.3 mmol/L after week 6 to week 12, and >11.1 mmol/L after week 12 to week 26. Glimepiride therapy was also started if HbA1c >8.0% (64 mmol/mol) after week 26.	Rescue medication treatment was initiated during the treatment period if, between weeks 1 and 12, a patient had a glucose level >13.3 mmol/L after an overnight fast; between weeks 12 and 24 a patient had a glucose level >11.1 mmol/L after an overnight fast; or an HbA1c level >8.5% (>69 mmol/mol). The initiation, choice, and dosage of rescue medication used were at the discretion of the investigator, according to local prescribing information. In cases of hypoglycemia, rescue medication was to be reduced or discontinued. Where hyperglycemia or hypoglycaemia could not be controlled, the patient was discontinued from the trial.
Extension	Phase B: double-blind 78-week treatment extension period, participants randomized to ertugliflozin continued to receive ertugliflozin; those randomized to	Patients who completed 24 weeks of study were eligible for continuation into a long-term study for a total of 102 weeks (same interventions as before. Patients receiving rescue therapy (primarily	Participants who completed the first 26 weeks then entered period II (26 weeks), during which those randomised to canagliflozin (100 or 300 mg) or sitagliptin 100	No extension

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	placebo received blinded glimepiride (if not rescued during phase A); posttreatment telephone contact 14 days after the last dose of blinded study medication. [Extension not considered here, as not placebo-controlled.]	pioglitazone, or acarbose) during thefirst 24 weeks continued to receive rescue therapy to 102 weeks.	mg continued on those treatments while those randomised to placebo switched to sitagliptin 100 mg/day in a blinded fashion. 4 weeks follow-up. [Extension not considered here, as not placebo-controlled.]	
Outcomes				
Primary outcomes	Change from baseline in HbA1c at week 26	Change from baseline in HbA1c at week 24	Change from baseline in HbA1c at week 26	Change from baseline HbA1c at week 24
Secondary outcomes	Changes from baseline at week 26 in FPG, body weight, systolic and diastolic blood pressure, proportion with HbA1c <7.0% (53 mmol/mol) at week 26 and proportions receiving glycaemic rescue therapy	FPG and total body weight at week 24, change in FPG at week 1, proportion of patients with HbA1c <7% at week 24), change in HbA1c in patients with HbA1c at baseline of 9% or more	Change from baseline in HbA1c at week 52; changes at week 26 of were proportion of participants reaching HbA1c <7.0% (53 mmol/mol), change in FPG, 2 h postprandial glucose (PPG), systolic blood pressure, percent change in body weight, triacylglycerol (i.e. triglycerides), HDL-cholesterol	Change from baseline to week 24 in body weight and mean daily glucose using an 8-point blood glucose profile
Other outcomes	Safety assessments (adverse event monitoring, bone mineral density and biomarkers of bone turnover, physical examination, evaluation of vital signs (including sitting measurements and postural changes in blood pressure	Percentage change from baseline in body weight; decreases in bodyweight of 5% or more; urinary and genital tract infections; other safety and tolerability measures, including change in blood pressure	Safety and tolerability (adverse event reports, safety laboratory tests, vital sign measurements, physical examinations, SMBG and 12-lead electrocardiograms, urinary tract infections and	Percentage of patients with baseline HbA1c ≥7.0% who had HbA1c <7% at week 24; change from baseline in FPG, waist circumference, systolic and diastolic blood pressure at week 24; percentage of patients with >5%

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	and pulse rate) and laboratory evaluations, hypoglycaemia, genital mycotic infection, urinary tract infection, hypovolaemia)		genital mycotic infections, documented episodes of hypoglycaemia)	reduction in body weight at week 24; use of rescue medication; percentage of patients with uncontrolled blood pressure at baseline who had controlled BP (SBP <130 and DBP <80 mmHg) at week 24; change from baseline in 2-h postprandial glucose in a subset of patients; safety end points (vital signs, clinical laboratory parameters, 12-lead electrocardiogram, adverse events, hypoglycaemia, urinary tract infection, genital tract infection)
Baseline characteristics				
Mean age (years)	**ertu5:** 56.6 (SD 8.1) **ertu15:** 56.9 (SD 9.4) **placebo:** 56.5 (SD 8.7)	**dapa10**: 52.7 (SD 9.9) **placebo:** 53.7 (SD 10.3)	**cana100:** 55.5 (SD 9.4) **cana300:** 55.3 (SD 9.2) **placebo:** 55.3 (SD 9.8)	**empa10:** 55.5 (SD 9.9)) **empa25:** 55.6 (SD 10.2) **placebo:** 56.0 (SD 9.7)
Sex (% women)	**ertu5:** 53.1% **ertu15:** 54.6% **placebo:** 53.1%	**dapa10**: 43% **placebo:** 45%	**cana100:** 52.7% **cana300:** 55.0% **placebo:** 48.6%	**empa10:** 42.4% **empa25:** 43.7% **placebo:** 44.0%
Duration of diabetes (years)	**ertu5:** 7.9 (SD 6.1) **ertu15:** 8.1 (SD 5.5) **placebo:** 8.0 (SD 6.3)	**dapa10**: 6.1 (SD 5.4) **placebo:** 5.8 (SD 5.1)	**cana100:** 6.7 (SD 5.4) **cana300:** 7.1 (SD 5.4) **placebo:** 6.8 (SD 5.3) sitagliptin: 6.8 (SD 5.2)	**empa10:** 1% ≤1 yr, 26% >1 to 5 yrs, 33% >5 to 10 yrs, 40% >10 yrs **empa25:** 3% ≤1 yr, 20% >1 to 5 yrs, 37% >5 to 10 yrs, 40% >10 yrs **placebo:** 1% ≤1 yr, 16% >1 to 5 yrs, 42% >5 to 10 yrs, 41% >10 yrs

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Comorbidities	NR	NR	NR	NR
Ethnic groups	**ertu5:** White 64.7%, Black/African-American 10.6%, Asian 16.4%, Multiple 8.2% **ertu15:** White 64.9%, Black/African-American 11.2%, Asian 17.1%, Multiple 6.8% **placebo:** White 68.9%, Black/African-American 9.1%, Asian 14.8%, Multiple 7.2%	Patients of different ethnic origins included but , recruitment occurred only in North and South America, and patients were mainly White [no further details]	**cana100:** White 68.5%, Black/African-American 4.3%, Asian 13.9%, other 13.3% **cana300:** White 69.8%, Black/African-American 3.5%, Asian 16.3%, other 10.4% **placebo:** White 70.5%, Black/African-American 1.6%, Asian 16.4%, other 11.5% "other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander. Asian - not stated whether East or South.	**empa10:** Asian 45.6%, White 51.6%, Black/African American 1.8%, American Indian/Alaska native 0.9% **empa25:** Asian 46.0%, White 53.1%, Black/African American 0%, American Indian/Alaska native 0.9% **placebo:** Asian 44.4%, White 54.6%, Black/African American 1.0%, American Indian/Alaska native 0% Asian will be a mix of ethnicities?
BMI (kg/m^2)	**ertu5:** 30.8 (SD 4.8) **ertu15:** 31.1 (SD 4.5) **placebo:** 30.7 (SD 4.7)	**dapa10**: 31.2 (SD 5.1) **placebo:** 31.8 (SD 5.3)	**cana100:** 32.4 (SD 6.4) **cana300:** 31.4 (SD 6.3) **placebo:** 31.1 (SD 6.1)	**empa10:** 29.1 (SD 5.5) **empa25:** 29.7 (SD 5.7) **placebo:** 28.7 (SD 5.2)
Systolic blood pressure (mmHg)	**ertu5:** 130.5 (SD 13.8) **ertu15:** 130.4 (SD 12.0) **placebo:** 129.3 (SD 15.4)	**dapa10**: 126.0 (SD 15.9) **placebo:** 127.7 (SD 14.6)	**cana100:** 128.0 (SD 12.7) **cana300:** 128.7 (SD 13.0) **placebo:** NR	**empa10:** 129.6 (SD 14.1) **empa25:** 130.0 (SD 15.1) **placebo:** 128.6 (SD 14.7)
Diastolic blood pressure (mmHg)	**ertu5:** 78.5 (SD 8.3) **ertu15:** 78.1 (SD 7.5) **placebo:** 77.5 (SD 7.6)	**dapa10**: 79.0 (SD 10.2) **placebo:** 80.9 (SD 9.0)	**cana100:** 77.7 (SD 8.4) **cana300:** 77.9 (SD 8.3) **placebo:** NR	**empa10:** 79.6 (SD 8.0) **empa25:** 78.4 (SD 8.4) **placebo:** 78.1 (SD 7.9)
HbA1c (%)	**ertu5:** 8.1 (SD 0.9) **ertu15:** 8.1 (SD 0.9) **placebo:** 8.2 (SD 0.9)	**dapa10**: 7.92 (SD 0.82) **placebo:** 8.11 (SD 0.96)	**cana100:** 7.9 (SD 0.9) **cana300:** 7.9 (SD 0.9) **placebo:** 8.0 (SD 0.9)	**empa10:** 7.94 (SD 0.79) **empa25:** 7.86 (SD 0.87) **placebo:** 7.90 (SD 0.88)

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Baseline eGFR (mL/min/1.73 m²)	**ertu5:** 88.9 (SD 17.5) **ertu15:** 91.0 (SD 20.6) **placebo:** 91.6 (SD 19.8)	NR	**cana100:** 89.7 (SD NR) **cana300:** 90.2 (SD NR) **placebo:** 87.7 (SD NR)	**empa10:** 89.5 (SD 19.6) **empa25:** 87.7 (SD 19.3) **placebo:** 89.7 (SD 21.4)
Prior treatment with glucose-lowering drug (GLD)	**ertu5:** metformin 100.0%, DPP-4 inhibitors 2.9%, other GLDs 1.4%, sulphonylureas 27.5%, 1 GLD 68.1%, 2 GLDs 31.9% **ertu15:** metformin 99.5%), DPP-4 inhibitors 3.9%, other GLDs 1.0%, sulphonamides / urea derivatives 22.0%, 1 GLD 73.7%, 2 GLDs 26.3% **placebo:** metformin 100.0%, DPP-4 inhibitors 3.3%, other GLDs 0%, sulphonamides / urea derivatives 29.7%, 1 GLD 67.0%, 2 GLDs 33.0%	On stable dose of metformin	On stable dose of metformin	On stable dose of metformin
% on anti-hypertensives at baseline	Overall: 70% receiving ≥1 anti-hypertensive agent (agents acting on the renin-angiotensin system 60%, beta blockers 22%, calcium channel blockers 21%, diuretics 24%)	NR	NR	NR
LDL cholesterol mean (SD) mmol/L or mg/dL	Ertug. 5 mg: 98.8mg/dL Ertug 15 mg: 93.2mg/dL Placebo: 99.3mg/dL	Dapa. 10mg: 2.7 (0.9) Placebo: 2.6 (0.9)	Cana. 100 mg: 2.8 (0.8) Cana. 300 mg: 2.8 (0.9) sitagliptin: 2.8 (0.9)	Empa. 10mg: 2.40 (0.06) Empa. 25 mg: 2.48 (0.06) Placebo: 2.46 (0.06)
HDL cholesterol mean (SD) mmol/L or mg/dL	Ertug. 5 mg: 48.5 mg/dL Ertug 15 mg: 48.2mg/dL Placebo: 48.6mg/dL	Dapa. 10mg: 1.1 (0.3) Placebo: 1.1 (0.2)	Cana. 100 mg: 1.2 (0.3) Cana. 300 mg: 1.2 (0.3) sitagliptin: 1.2 (0.3)s	Empa. 10mg: 1.28 (0.02) Empa. 25 mg: 1.28 (0.02) Placebo: 1.22 (0.02)

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Results				
Discontinuation	***Discontinuations:*** **26 weeks:** **ertu5:** 2.9% **ertu15:** 7.3% **placebo:** 9.1%	***Discontinuations:*** **24 weeks:** **dapa10:** 14/135 (10.4%) **placebo:** 18/137 (13.1%) **102 weeks:** **dapa10:** 24/119 (20.2%) **placebo:** 42/115 (36.5%)	***Discontinuations:*** **26 weeks:** **cana100:** 12.5% **cana300:** 12.0% **placebo:** 15.3%	***Discontinuations:*** **24 weeks:** **empa10:** 4% **empa25:** 8% **placebo:** 10%
HbA1c (final level, change from baseline, difference to placebo) (%)	**26 weeks:** ***Final HbA1c level*** **ertu5:** 7.3 (SD 0.8) **ertu15:** 7.2 (SD 0.8) **placebo:** 7.8 (SD 1.1) ***Change from baseline*** **ertu5:** -0.7 (SD 0.9) **ertu15:** -1.0 (SD 0.9) **placebo:** -0.2 (SD 0.9) ***Difference to placebo:*** **ertu5:** -0.70 (95% CI: -0.87, -0.53) **ertu15:** -0.88 (95% CI: -1.05, -0.71) Both p<0.001 vs. placebo	**24 weeks:** ***Final HbA1c level*** **dapa10:** 7.13 (SD 0.94) **placebo:** 7.79 (SD 1.18) ***Change from baseline*** **dapa10:** -0.84 (95% CI: -0.98, -0.70), p<0.0001 vs. placebo **placebo:** -0.30 (95% CI: -0.44, -0.16) ***Difference versus placebo*** **dapa10:** -0.51 (95% CI: -0.71, -0.31), p<0.0001 **102 weeks:** ***Change from baseline*** **dapa10:** -0.78 (95% CI: -0.97,	**26 weeks:** ***Final HbA1c level*** **cana100:** 7.13 (SD 0.86) **cana300:** 6.98 (SD 0.82) **placebo:** 7.76 (SD 1.22) ***Change from baseline*** **cana100:** -0.79 (SE 0.04) **cana300:** -0.94 (SE 0.04) **placebo:** -0.17 (SE 0.06) ***Difference versus placebo*** **cana100:** -0.62% (95% CI: -0.76, -0.48), p<0.001 vs. placebo **cana300:** -0.77 (95% CI: -0.91, -0.64), p<0.001 vs. placebo	**24 weeks:** ***Final HbA1c level NR*** **empa10:** 7.22 (SE 0.05) **empa25:** 7.11 (SE 0.06) **placebo:** 7.77% (SE 0.07) ***Change from baseline*** **empa10:** -0.70 (SE 0.05) **empa25:** -0.77 (SE 0.05) **placebo:** -0.13 (SE 0.05) ***Difference versus placebo*** **empa10:** -0.57% (95% CI : -0.70, -0.43), p<0.0001 vs. placebo **empa25:** -0.64% SE 0.07 (95% CI : -0.77, -0.50), p<0.0001 vs. placebo

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
		-0.60), p<0.0001 vs. placebo **placebo:** 0.02 (95% CI: -0.20 to 0.23) ***Difference versus placebo*** **dapa10:** -0.80 (95% CI: -1.08, -0.52), p<0.0001	DPP-4 i (sitagliptin): 7.08 (0.970)	
HbA1c % achieving target	**26 weeks:** ***% achieving HbA1c <7.0%*** **ertu5:** 35.3% **ertu15:** 40.0% **placebo:** 15.8%	**24 weeks:** ***% achieving HbA1c <6.5%*** **dapa10:** 25.2%, p=0.02 vs. placebo **placebo:** 13.8% ***% achieving HbA1c <7.0%*** **dapa10:** 40.6% (14.0% vs. placebo), p=0.0062 vs. placebo **placebo:** 25.9% **102 weeks:** ***% achieving HbA1c <7.0%*** **dapa10:** 31.5% (16.1% vs. placebo), p=0.0011 vs. placebo **placebo:** 15.4%	**26 weeks:** ***% achieving HbA1c <7.0%*** **cana100:** 45.5% **cana300:** 57.8% **placebo:** 29.8% sitagliptin: 54.5% Wk 52: Cana. 100 mg: 41.4% Cana. 300 mg: 54.7% sitagliptin: 50.6%	**24 weeks:** ***% achieving HbA1c <7.0% (in those with HbA1c ≥7.0% at baseline)*** **empa10:** 37.7% **empa25:** 38.7% **placebo:** 12.5%
Systolic blood pressure (mmHg) (change from baseline, difference to placebo), %	**26 weeks:** ***Change from baseline*** **ertu5:** -4.38 (SE 0.83) **ertu15:** -5.20 (SE 0.85) **placebo:** -0.70 (SE 0.90)	**24 weeks:** ***Change from baseline*** **dapa10:** -5.1 (SE 1.3), p vs. placebo NR **placebo:** -0.2 (SE 1.2)	**26 weeks:** ***Change from baseline*** **cana100:** -3.84 (SE 0.60) **cana300:** -5.06 (SE 0.61) **placebo:** +1.52 (SE 0.83)	**24 weeks:** ***Change from baseline*** **empa10:** -4.5 (SE 0.7) **empa25:** -5.2 (SE 0.7) **placebo:** -0.4 (SE 0.7)

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
achieving <130/90, etc.	***Difference to placebo:*** **ertu5:** -3.68 (95% CI: -5.96, -1.39), p=0.002 **ertu15:** -4.50 (95% CI: -6.81, -2.19), p<0.001	***% with previous hypertension achieving <130/80 mmHg:*** **dapa10:** 37.5%, p vs. placebo NR **placebo:** 8.8% **102 weeks:** ***Change from baseline*** **dapa10:** -0.3 (SE 1.54), p vs. placebo NR **placebo:** +1.5 (SE 1.61)	***Difference to placebo:*** **cana100:** -5.36 (95% CI: -7.28, -3.44), p<0.001 vs. placebo **cana300:** -6.58 (95% CI: -8.50, -4.65) , p<0.001 vs. placebo	***Difference to placebo:*** **empa10:** -4.1 (95% CI: -6.2 to -2.1), p<0.0001 vs. placebo **empa25:** -4.8 (95% CI: -6.9 to -2.7), p<0.0001 vs. placebo ***% with previous hypertension achieving <130/80 mmHg:*** **empa10:** 35.9%, p<0.001 vs. placebo **empa25:** 30.4%, p<0.001 vs. placebo **placebo:** 13.2%
Diastolic blood pressure (mmHg) (change from baseline, difference to placebo)	**26 weeks :** ***Change from baseline*** **ertu5:** -1.59 (95% CI: -2.59, -0.59) **ertu15:** -2.19 (95% CI: -3.21, -1.17) **placebo:** 0.23 (95% CI: -0.85, 1.31) ***Difference to placebo:*** **ertu5:** -1.82 (95% CI: -3.24, -0.39), p=0.013 **ertu15:** -2.42 (95% CI: -3.86, -0.98), p=0.001	**24 weeks:** ***Change from baseline*** **dapa10:** -1.8 (SE 0.8), p vs. placebo NR **placebo:** -0.1 (SE 0.7) **102 weeks:** ***Change from baseline*** **dapa10:** -1.2 (SE 1.0), p vs. placebo NR **placebo:** -1.0 (SE 0.9)	**26 weeks:** ***Change from baseline*** **cana100:** -2.2 (SE 0.4) **cana300:** -2.1 (SE 0.4) **placebo:** +0.3 (SE 0.5) ***Difference to placebo:*** **cana100:** -2.5 (95% CI: -3.7, -1.2), p vs. placebo NR **cana300:** -2.4 (95% CI: -3.6, -1.1), p vs. placebo NR	**24 weeks:** ***Change from baseline*** **empa10:** -2.0 (SE 0.5) **empa25:** -1.6 (SE 0.5) **placebo:** 0.0 (SE 0.5) ***Difference to placebo:*** **empa10:** -1.9 (95% CI: -3.3, -0.6), p=0.006 vs. placebo **empa25:** -1.6 (95% CI: -2.9, -0.2), p=0.026 vs. placebo
BMI	NR	NR	NR	NR

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Weight (kg) (change from baseline, difference to placebo)	**26 weeks:** ***Change from baseline*** **ertu5:** -3.01 (SE 0.20) **ertu15:** -2.93 (SE 0.20) **placebo:** -1.33 (SE 0.21) ***Difference to placebo:*** **ertu5:** -1.67 (95% CI: -2.24, -1.11) **ertu15:** -1.60 (95% CI: -2.16, -1.03) Both p<0.001 vs. placebo	**24 weeks:** ***Change from baseline*** **dapa10:** -2.9 (95% CI: -3.3, -2.4), p<0.0001 vs. placebo **placebo:** -0.9 (95% CI: -1.4, -0.4) ***Difference to placebo:*** **dapa10:** -2.24 (95% CI: -2.96, -1.53), p<0.0001 vs. placebo **102 weeks:** ***Change from baseline*** **dapa10:** -1.74 (95% CI: -2.51, -0.96), p<0.0001 vs. placebo **placebo:** +1.36 (95% CI: 0.53, 2.2) ***Difference to placebo:*** **dapa10:** -3.10 (95% CI: -4.24, -1.96), p<0.0001 vs. placebo	**26 weeks:** ***Change from baseline*** **cana100:** -3.3 (SE 0.2) **cana300:** -3.6 (SE 0.2) **placebo:** -1.1 (SE 0.2) ***Difference to placebo:*** **cana100:** -2.5 (95% CI: -3.1, -1.9), p<0.001 vs. placebo **cana300:** -2.9 (95% CI: -3.5, -2.3), p<0.001 vs. placebo	**24 weeks:** ***Change from baseline*** **empa10:** -2.08 (SE 0.17) **empa25:** -2.46 (SE 0.17) **placebo:** -0.45 (SE 0.17) ***Difference to placebo:*** **empa10:** -1.63 (95% CI : -2.11, -1.15), p<0.001 vs. placebo **empa25:** -2.01 (95% CI : -2.49, -1.53), p<0.001 vs. placebo
Lipids				
HDL-cholesterol (change from baseline, difference to placebo)	**26 weeks:** ***Difference to placebo:*** **ertu5:** +4.5% (95% CI: 1.4, 7.6) **ertu15:** +4.4% (95% CI: 1.3, 7.5)	**24 weeks:** ***Change from baseline*** **dapa10:** +4.4% (SD 1.5), p vs. placebo NR **placebo:** +0.4% (SD 1.4)	**26 weeks:** ***Change from baseline*** **cana100:** +10.3% (SE 0.9) **cana300:** +12.1% (SE 1.0) **placebo:** +3.7% (SE 1.3)	**24 weeks:** ***Change from baseline*** **empa10:** +0.08 mmol/L (SD 0.01) **empa25:** +0.06 mmol/L (SD 0.01) **placebo:** +0.00 mmol/L (SD 0.01)

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
			Difference to placebo: **cana100:** 6.6 (95% CI: 3.6, 9.7), p<0.001 vs. placebo **cana300:** 8.4 (95% CI: 5.3, 11.5), p<0.001 vs. placebo	***Difference to placebo:*** **empa10:** 0.08 mmol/L (SD 0.02), p<0.001 vs. placebo **empa25:** 0.06 mmol/L (SD 0.02), p=0.001 vs. placebo
LDL-cholesterol (change from baseline, difference to placebo)	**26 weeks:** ***Difference to placebo:*** **ertu 5:** 2.0% (95% CI: -6.0, 10.0) **ertu15:** 2.6% (95% CI: -5.5, 10.7)	**24 weeks:** ***Change from baseline*** **dapa10:** +9.5% (SD 2.4), p vs. placebo NR **placebo:** +3.5% (SD 2.3)	**26 weeks:** ***Change from baseline*** **cana100:** +6.5% (SE 1.7) **cana300:** +10.7% (SE 1.8) **placebo:** -1.5% (SE 2.4) ***Difference to placebo:*** **cana100:** 7.9 (95% CI: 2.4, 13.5), p vs. placebo NR **cana300:** 12.2 (95% CI: 6.6, 17.8), p vs. placebo NR	**24 weeks:** ***Change from baseline*** **empa10:** +0.15 mmol/L (SD 0.04) **empa25:** +0.15 mmol/L (SD 0.04) **placebo:** +0.03 mmol/L (SD 0.04) ***Difference to placebo:*** **empa10:** 0.12 mmol/L (SD 0.06), p=0.043 vs. placebo **empa25:** 0.12 mmol/L (SD 0.06), p=0.032 vs. placebo
Triglycerides (change from baseline, difference to placebo)	NR	**24 weeks:** ***Change from baseline*** **dapa10:** -6.2% (SD 3.3), p vs. placebo NR **placebo:** +2.1% (SD 3.6)	**26 weeks:** ***Change from baseline*** **cana100:** +1.6% (SE 2.6) **cana300:** -1.4% (SE 2.6) **placebo:** +3.2% (SE 3.6) ***Difference to placebo:*** **cana100:** -1.6 (95% CI: -9.9, 6.7), p=NS vs placebo	**24 weeks:** ***Change from baseline*** **empa10:** 0.00 mmol/L (SD 0.08) **empa25:** -0.04 mmol/L (SD 0.08) **placebo:** +0.11 mmol/L (SD 0.08) ***Difference to placebo:*** **empa10:** -0.11 mmol/L (SD 0.11), p=0.327 vs. placebo

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
			cana300: -4.6 (95% CI: -13.0, 3.7), p=NS vs placebo	**empa25:** -0.14 mmol/L (SD 0.11), p=0.204 vs. placebo
Total cholesterol (change from baseline, difference to placebo)	NR	**24 weeks:** ***Change from baseline*** **dapa10:** +4.2% (SD 1.3), p vs. placebo NR **placebo:** +2.7% (SD 1.3)	NR	**24 weeks:** ***Change from baseline*** **empa10:** +0.23 mmol/L (SD 0.05) **empa25:** +0.21 mmol/L (SD 0.05) **placebo:** +0.09 mmol/L (SD 0.05) ***Difference to placebo:*** **empa10:** 0.14 mmol/L (SD 0.07), p=0.043 vs. placebo **empa25:** 0.13 mmol/L (SD 0.07), p=0.071 vs. placebo
Adverse effects (AE)				
Discontinuation due to AE (%)	**ertu5:** 1.4% **ertu15:** 1.5% **placebo:** 1.4%	**24 weeks:** **dapa10:** 3% **placebo:** 4% **102 weeks:** **dapa10:** 4.4% **placebo:** 6.6%	**26 weeks:** **cana100:** 4.9% **cana300:** 1.6% **placebo:** 3.8%	**24 weeks:** **empa10:** 0.9% **empa25:** 2.3% **placebo:** 3.4%
Hypoglycaemia; *Severe* *Non-severe* *How defined?*	**26 weeks:** **ertu5:** 7.2% documented hypoglycaemia, 3.4% symptomatic	**24 weeks:** **dapa10:** 4% **placebo:** 3%	**52 weeks:** **cana100:** 6.8% documented hypoglycaemia, n=1 severe hypoglycaemia	**24 weeks:** **empa10:** 1.8% hypoglycaemia, no events requiring assistance

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
	hypoglycaemia, n=1 severe hypoglycaemia **ertu15:** 7.8% documented hypoglycaemia, 3.4% symptomatic hypoglycaemia, 0 severe **placebo:** 4.3% documented hypoglycaemia, 1.9% symptomatic hypoglycaemia, n=1 severe Documented hypoglycaemia: episodes with a glucose level ≤3.9 mmol/L (70 mg/dL) with or without symptoms Severe hypoglycaemia: requiring assistance	None led to discontinuation from the study. None was a major event, defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose concentration less than 3 mmol/L, and prompt recovery after glucose or glucagon administration. **102 weeks:** **dapa10:** 5.2% **placebo:** 5.8% None requiring external assistance (and definition above)	**cana300:** 6.8% documented hypoglycaemia, 0 severe hypoglycaemia **placebo:** 2.7% documented hypoglycaemia, 0 severe hypoglycaemia Documented hypoglycaemia: included biochemically confirmed episodes (concurrent fingerstick or plasma glucose ≤3.9 mmol/L) Severe episodes: requiring the assistance of another individual or resulting in seizure or loss of consciousness	**empa25:** 1.4%, no events requiring assistance **placebo:** 0.5%, no events requiring assistance Hypoglycaemia: events consistent with hypoglycaemia and with plasma glucose levels of ≤3.9 mmol/L and/or requiring assistance
Urinary tract infections	**26 weeks:** **ertu5:** 2.9% **ertu15:** 3.4% **placebo:** 1.0%	**24 weeks:** (events suggestive of urinary tract infection) **dapa10: 7**% **placebo:** 5% **102 weeks:** (events suggestive of urinary tract infection) **dapa10:** 13.3% **placebo:** 8.0%	**52 weeks:** **cana100:** 7.9% **cana300:** 4.9% **placebo:** 6.6% DPP-4 i (sitagliptin): 6.3%	Empa. 10mg: Male: 0%; Female: 12.0% Empa. 25 mg: Male: 0.8%; Female: 11.8% Placebo: Male: 2.6%; Female: 7.7% Male + female: Empa. 10mg: 5.1% Empa. 25 mg: 5.6% Placebo: 4.9%

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
Genital tract infections (by gender)	**26 weeks:** ***Genital mycotic infection (men):*** **ertu5:** 3.1% **ertu15:** 3.2% **placebo:** 0% ***Genital mycotic infection (women):*** **ertu5:** 5.5% **ertu15:** 6.3%, p=0.032 vs. placebo **placebo:** 0.9%	**24 weeks:** (events suggestive of genital infection, NR by gender) **dapa10:** 9% **placebo:** 5% **102 weeks:** (events suggestive of genital infection) **dapa10:** 12.6% (20.7% women, 6.5% men) **placebo:** 5.1% (11.5% women, 0% men)	**52 weeks:** **cana100:** 5.2% men, 11.3% women **cana300:** 2.4% men, 9.9% women **placebo:** 1.1% men, 1.1% women	**24 weeks:** **empa10:** 3.7% (0.8% men, 7.6% women) **empa25:** 4.7% (0.8% men, 9.7% women) **placebo:** 0%
Any DKA, amputations, fractures	**26 weeks:** No DKA in any group, no fractures in ertugliflozin groups, no amputations reported	**102 weeks:** 1 fracture in dapa10 group, DKA or amputation not reported	**52 weeks:** 1 fracture in cana100 group, no DKA in any relevant group, amputation not reported	**24 weeks:** 2 fractures in empa10 group, DKA or amputation not reported
Other if common (>5%)	**26 weeks:** ***AEs related to study drug*** **ertu5:** 11.6% **ertu15:** 12.2% **placebo:** 6.2%	**24 weeks:** ***AEs related to study drug*** **dapa10:** 23% **placebo:** 16% Other adverse events occurring in >5% but <10%, no obvious difference between groups: headache, back pain, diarrhoea, influenza, nasopharyngitis, upper respiratory tract infection, cough **102 weeks:**	**52 weeks:** ***AEs related to study drug*** **cana100:** 26.4% **cana300:** 19.9% **placebo:** 12.6% **Other:** **cana100:** 5.7% pollakiuria **cana300:** 3.0% pollakiuria **placebo:** 0.5% pollakiuria	**24 weeks:** ***AEs related to study drug*** **empa10:** 16.1% **empa25:** 12.6% **placebo:** 12.1% **Other:** 5.5 to 7.8% Nasopharyngitis in all groups; 11.2% hyperglycaemia in placebo group, <3% in empa groups

	Ertugliflozin	Dapagliflozin	Canagliflozin	Empagliflozin
		AEs related to study drug **dapa10:** 33.3% **placebo:** 20.4% Other adverse events occurring in >5% but <10%, no obvious difference between groups: headache, back pain, diarrhoea, influenza, nasopharyngitis, upper respiratory tract infection		
Trial quality	Good – no specific quality issues	Good – no specific quality issues	Good – no specific quality issues	Good – no specific quality issues
Rescue therapy	26 wk: **ertu5:** <3% **ertu15:** <3% placebo: 17.7%	Dapa. 2-5 mg: 5/137 (3.6%) Dapa. 5 mg: 5/137 (3.6%) Dapa. 10mg: 5/135 (3.7%) Placebo: 22/137 (16.1%)	Wk 52: Cana. 100 mg: 14.7% Cana. 300 mg: 9.3% sitagliptin: 18.0% placebo/sitagliptin: 24.6% (not shown for placebo only at wk 26)	Empa. 10mg: 5.3% Empa. 25 mg: 3.3% Placebo: 14.0%

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	ITT analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Ertugliflozin										
Rosenstock 2018[4]	*Low risk* Random assignment based on a computer-generated randomisation code using the method of random permuted blocks	*Unclear risk* Not stated	*Low risk* Double-blind (patient, investigator)	*Unclear risk* NR	*Low risk* Discontinuation 26 weeks: **ertu5:** 2.9% **ertu15:** 7.3% **placebo:** 9.1% The most common reason in the placebo and ertugliflozin 15-mg groups was withdrawal by participant; in the ertugliflozin 5-mg group, the most common reasons were withdrawal by participant and AEs	*Low risk* Efficacy analyses comprised all randomized participants who received ≥1 dose of study medication. Efficacy data obtained after initiation of glycaemic rescue therapy were censored (ie, treated as missing) to avoid confounding (termed "excluding glycaemic rescue"). The "excluding glycaemic rescue" approach was also the primary analysis for laboratory parameters and AEs (including hypoglycaemia), with the exception of serious AEs (SAEs), deaths, AEs resulting in discontinuation of study medication, and measurements of postural blood pressure and pulse rate, which were assessed using the "including glycaemic rescue" approach.	*Low risk* Outcomes reported as specified on clinicaltrials.gov except results for HbA1c <7.0% rather than <6.5% specified on clinicaltrials.gov	*Low risk* Demographics and baseline characteristics were similar across the treatment groups	*Low risk* >99% power to detect a difference of 0.5% in the change from baseline at week 26 in HbA1c with 600 participants	**7/9 low risk**

Dual therapy - Ertugliflozin versus sitagliptin

	Ertugliflozin	**Canagliflozin**
Trial first author and year	VERTIS FACTORIAL (Pratley 2018)[5] (NCT02099110)	CANTATA-D (Lavalle-González 2013)[23] (NCT01106677)
Design	Phase III RCT, double blind, parallel group, active controlled	Phase III RCT, double blind, parallel group, active controlled
Duration	26 weeks + 26 weeks extension	26 weeks placebo- and active-controlled + 26 weeks active-controlled only
Inclusion criteria similar?	**Condition:** type 2 diabetes mellitus (according to American Diabetes Association guidelines) **Age:** ≥18 years **Glycaemic control:** inadequate glycaemic control (HbA1c ≥7.5% and ≤11% [≥58 mmol/mol and ≤97 mmol/mol]) on metformin monotherapy **Previous treatment:** stable dose of metformin monotherapy for at least 8 weeks **BMI:** ≥ 18.0 kg/m^2	**Condition:** type 2 diabetes mellitus **Age:** ≥18 - ≤80 years **Glycaemic control:** inadequately controlled with metformin monotherapy: HbA1c 7.0% to 10.5% (53 mmol/mol to 91 mmol/mol); fasting plasma glucose (FPG) <15 mmol/L at week -2 and fasting fingerstick glucose ≥6.1 mmol/L and <15 mmol/L on day 1 **Previous treatment:** stable metformin therapy (≥2000 mg/day [or ≥1500 mg/day if unable to tolerate higher dose]) for ≥8 weeks **BMI:** NR
Exclusions similar?	**Diabetes-related:** diagnosis of type 1 diabetes mellitus, history of ketoacidosis **Renal:** estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, serum creatinine ≥1.3 mg/dL (men) or ≥1.2 mg/dL (women) **Other conditions:** cardiovascular event within 3 months of screening; history of malignancies; HIV; liver disease; hyperthyroidism **Treatment-related:** treated with any anti-hyperglycemic agents (AHA) other than protocol-approved agents within 12 weeks of screening	**Diabetes-related:** repeated fasting plasma glucose and/or fasting self-monitored blood glucose ≥15.0 mmol/L during the pretreatment phase; history of type 1 diabetes **Renal:** estimated glomerular filtration rate (eGFR) <55 ml/min/1.73 m^2 (or <60 ml/min/1.73 m^2 if based upon restriction in local label) or serum creatinine ≥124 µmol/L (men) or ≥115 µmol/L (women) **Other conditions:** cardiovascular disease (including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening; uncontrolled hypertension **Treatment-related:** treatment with a peroxisome proliferator-activated receptor gamma agonist, insulin, another sodium glucose co-transporter 2 (SGLT2) inhibitor or

	Ertugliflozin	**Canagliflozin**
		any other anti-hyperglycaemic agent (AHA) (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 weeks before screening
Number of patients	Ertu 5mg 250 Ertu 15mg 248 Sitagliptin 247	Cana 100 mg 368 Cana 300g 367 Sitagliptin 366
Number of centres and countries	Multicentre (n = 242) 21 countries (Canada, USA, Argentina, Chile, Colombia, Mexico, Bulgaria, Czech Republic, Finland, Hungary, Italy, Poland, Romania, Russia, Slovakia, Ukraine, Israel, Malaysia, Philippines, Thailand, New Zealand)	Multicentre (n = 169) 22 countries (Argentina, Bulgaria, Colombia, Czech Republic, Estonia, Greece, India, Latvia, Malaysia, Mexico, Peru, Poland, Portugal, Puerto Rico, Russian Federation, Singapore, Slovakia, Sweden, Thailand, Turkey, Ukraine, USA)
Sponsor	Pfizer Inc; Merck & Co Inc	Janssen Research & Development, LLC
Interventions		
Comparison groups	**ertu5**: ertugliflozin 5 mg once daily **ertu15:** ertugliflozin 15 mg once daily **sita100:** sitagliptin 100 mg once daily Groups receiving ertugliflozin plus sitagliptin not considered here	**cana100 (n = 368):** canagliflozin 100 mg once daily **cana300 (n = 367):** canagliflozin 300 mg once daily **sita100 (n = 366):** sitagliptin 100 mg once daily Group receiving placebo not considered here – see table above
Run-in	Patients receiving ≥1500 mg/day metformin for <8 weeks or receiving <1500 mg/day at screening entered a titration/stabilisation period and were eligible after completing 8 weeks of metformin monotherapy ≥1500 mg/day	2-week single-blind placebo run-in period; those on metformin extended release (XR), metformin immediate release (IR) or XR at below protocol-specified doses or metformin plus sulfonylurea underwent a metformin IR dose titration/dose stablisation and, if applicable, a sulfonylurea washout period of up to 10 weeks, followed by the placebo run-in period
All groups	Stable metformin monotherapy ≥1500 mg/day	Stable metformin immediate release monotherapy (≥2000 mg/day [or ≥1500 mg/day if unable to tolerate higher dose])

	Ertugliflozin	**Canagliflozin**
Rescue therapy	Patients were prescribed with glycaemic rescue therapy in the form of open-label glimepiride or basal insulin when exceeding the following thresholds: FPG > 270 mg/dL after randomisation through week 6 FPG > 240 mg/dL after week 6 through week 12 FPG > 200 mg/dL after week 12 through week 26 FPG > 200 mg/dL or HbA1c >8% (64 mmol/mol) after week 26	During the double-blind treatment period, glycaemic rescue therapy with glimepiride (added to study drug and background metformin) was initiated if FPG >15.0 mmol/L after day 1 to week 6, >13.3 mmol/L after week 6 to week 12, and >11.1 mmol/L after week 12 to week 26. Glimepiride therapy was also started if HbA1c >8.0% (64 mmol/mol) after week 26.
Extension	26-week extension (phase B) for assessing longer term effects – blinding maintained for whole period	Participants who completed the first 26 weeks then entered period II (26 weeks), during which those randomised to canagliflozin (100 or 300 mg) or sitagliptin 100 mg continued on those treatments while those randomised to placebo switched to sitagliptin 100 mg/day in a blinded fashion. 4 weeks follow-up.
Outcomes		
Primary outcomes	Change from baseline in HbA1c at week 26	Change from baseline in HbA1c at week 26
Secondary outcomes	Change from baseline in FPG, body weight and systolic blood pressure; proportion of patients with HbA1c <7.0% (<53 mmol/mol); in subset with mixed-meal tolerance test: change from baseline in beta-cell responsivity static component	Change from baseline in HbA1c at week 52; changes at week 26 of were proportion of participants reaching HbA1c <7.0% (53 mmol/mol), change in FPG, 2 h postprandial glucose (PPG), systolic blood pressure, percent change in body weight, triacylglycerol (i.e. triglycerides), HDL-cholesterol
Other outcomes	Safety endpoints included the number (adverse events, adverse events of special interest (symptomatic hypoglycaemia, genital mycotic infection (gender-specific), urinary tract infection, hypovolaemia))	Safety and tolerability (adverse event reports, safety laboratory tests, vital sign measurements, physical examinations, SMBG and 12-lead electrocardiograms, urinary tract infections and genital mycotic infections, documented episodes of hypoglycaemia)
Baseline characteristics		
Mean age (years)	**ertu5:** 55.1 (SD 10.1) **ertu15:** 55.3 (SD 9.5) **sita100:** 54.8 (SD 10.7)	**cana100:** 55.5 (SD 9.4) **cana300:** 55.3 (SD 9.2) **sita100:** 55.5 (SD 9.6)
Sex (% women)	**ertu5:** 49.2%	**cana100:** 52.7%

	Ertugliflozin	Canagliflozin
	ertu15: 46.0% **sita100:** 37.7%	**cana300:** 55.0% **sita100:** 53.0%
Duration of diabetes (years)	**ertu5:** 7.1 (SD 5.4) **ertu15:** 7.3 (SD 5.4) **sita100:** 6.2 (SD 5.2)	**cana100:** 6.7 (SD 5.4) **cana300:** 7.1 (SD 5.4) **sita100:** 6.8 (SD 5.2)
Comorbidities	NR	NR
Ethnic groups	**ertu5:** White 82.4%, Asian 8.8%, Multiple 3.2%, Black or African American 2.8%, American Indian or Alaska Native 2.8%, Native Hawaiian or other Pacific Islander 0% **ertu15:** White 82.7%, Asian 8.9%, Multiple 4.4%, Black or African American 2.4%, American Indian or Alaska Native 1.6%, Native Hawaiian or other Pacific Islander 0% **sita100:** White 78.1%, Asian 11.7%, Multiple 3.6%, Black or African American 4.5%, American Indian or Alaska Native 1.6%, Native Hawaiian or other Pacific Islander 0.4%	**cana100:** White 68.5%, Black/African-American 4.3%, Asian 13.9%, other 13.3% **cana300:** White 69.8%, Black/African-American 3.5%, Asian 16.3%, other 10.4% **sita 100:** White 72.1%, Black/African-American 3.6%, Asian 11.2%, other 13.1% "other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple and other
BMI (kg/m^2)	**ertu5:** 31.8 (SD 6.2) **ertu15:** 31.5 (SD 5.8) **sita100:** 31.7 (SD 6.5)	**cana100:** 32.4 (SD 6.4) **cana300:** 31.4 (SD 6.3) **sita100:** 32.0 (SD 6.1)
Systolic blood pressure (mmHg)	**ertu5:** 129.7 (SD 12.5) **ertu15:** 128.9 (SD 12.5) **sita100:** 128.3 (SD 12.2)	**cana100:** 128.0 (SD 12.7) **cana300:** 128.7 (SD 13.0) **sita100:** 128.0 (SD 13.5)
Diastolic blood pressure (mmHg)	**ertu5:** 77.9 (SD NR) **ertu15:** 77.5 (SD NR) **sita100:** 77.3 (SD NR)	**cana100:** 77.7 (SD 8.4) **cana300:** 77.9 (SD 8.3) **sita100:** 77.5 (SD 8.0)
HbA1c (%)	**ertu5:** 8.6% (SD 1.0) **ertu15:** 8.6% (SD 1.0)	**cana100:** 7.9 (SD 0.9) **cana300:** 7.9 (SD 0.9)

	Ertugliflozin	Canagliflozin
	sita100: 8.5 (SD 1.0)	**sita100:** 7.9 (SD 0.9)
Baseline eGFR (mL/min/1.73 m²)	**ertu5:** 91.9 (SD 20.6) **ertu15:** 92.8 (SD 21.4) **sita100:** 92.6 (SD 18.2)	**cana100:** 89.7 (SD NR) **cana300:** 90.2 (SD NR) **sita100:** 89.1 (SD NR)
Prior treatment with glucose-lowering drug (GLD)	Metformin monotherapy at a dose ≥1500 mg/day for at least 8 weeks, no futher details reported **ertu5:** Insulin injection 0.4%, 1 agent 99.6%, 2 agents 0.4% **ertu15:** Insulins and analogs for injection 0%, 1 agent 100.0%, 2 agents 0% **sita100:** NR	On stable metformin therapy, no details reported
% on anti-hypertensives at baseline	NR	NR
Results		
Study flow / discontinuation	***Discontinuations:*** **26 weeks:** **ertu5:** 6.8% **ertu15:** 8.8% **sita100:** 10.5% **52 weeks (total discontinuations):** **ertu5:** 12.8% **ertu15:** 16.1% **sita100:** 16.2%	***Discontinuations:*** **26 weeks:** **cana100:** 12.5% **cana300:** 12.0% **sita100:** 12.8% **52 weeks (total discontinuations):** **cana100:** 19.0% **cana300:** 18.5% **sita100:** 22.1%

	Ertugliflozin	Canagliflozin
HbA1c (final level, change from baseline, difference to sitagliptin) (%)	**26 weeks:** ***Final HbA1c level*** **ertu5:** 7.4 (SD 0.9) **ertu15:** 7.4 (SD 1.0) **sita100:** 7.3 (SD 1.1) ***Change from baseline*** **ertu5:** -1.0 (95% CI: -1.1, -0.9) **ertu15:** -1.1 (95% CI: -1.2, -1.0) **sita100:** -1.1 (95% CI: -1.2, -0.9) ***Difference to sitagliptin NR*** **52 weeks :** ***Change from baseline*** **ertu5:** -1.0 (95% CI: -1.1, -0.8) **ertu15:** -0.9 (95% CI: -1.1, -0.8) **sita100:** -0.8 (95% CI: -1.0, -0.7) ***Difference/p versus sitagliptin NR***	**26 weeks:** ***Final HbA1c level*** **cana100:** 7.13 (SD 0.86) **cana300:** 6.98 (SD 0.82) **sita100:** 7.08 (SD 0.97) ***Change from baseline*** **cana100:** -0.79 (SE 0.04) **cana300:** -0.94 (SE 0.04) **sita100:** -0.82 (SE 0.04) ***Difference to sitagliptin NR*** **52 weeks :** ***Change from baseline*** **cana100:** -0.73 (SE 0.05) **cana300:** -0.88 (SE 0.05) **sita100:** -0.73 (SE 0.05) ***Difference to sitagliptin*** **cana100:** 0.00% (95% CI: -0.12, 0.12), non-inferior to sitagliptin **cana300:** -0.15% (95% CI: -0.27, -0.03), non-inferior to sitagliptin
HbA1c % achieving target	**26 weeks:** ***% achieving HbA1c <7.0%*** **ertu5:** 26.4% **ertu15:** 31.9%	**26 weeks:** ***% achieving HbA1c <7.0%*** **cana100:** 45.5% **cana300:** 57.8%

	Ertugliflozin	Canagliflozin
	sita100: 32.8% **52 weeks:** ***% achieving HbA1c <7.0%*** **ertu5:** 25.6% **ertu15:** 22.6% **sita100:** 26.7% ***Difference/p versus sitagliptin NR***	**sita100:** 54.5% **52 weeks:** ***% achieving HbA1c <6.5%*** **cana100:** 21.9% **cana300:** 26.9% **sita100:** 24.9% ***% achieving HbA1c <7.0%*** **cana100:** 41.4% **cana300:** 54.7% **sita100:** 50.6%
Systolic blood pressure (mmHg) (change from baseline, difference to sitagliptin), % achieving <130/90, etc.	**26 weeks:** ***Change from baseline*** **ertu5:** -3.9 (95% CI: -5.3, -2.5) **ertu15:** -3.7 (95% CI: -5.1, -2.3) **sita100:** -0.7 (95% CI: -2.1, 0.8) **52 weeks:** ***Change from baseline*** **ertu5:** -2.7 (95% CI: -4.2, -1.2) **ertu15:** -1.6 (95% CI: -3.1, 0.0) **sita100:** -0.2 (95% CI: -1.8, 1.5) ***Difference/p versus sitagliptin NR***	**26 weeks:** ***Change from baseline*** **cana100:** -3.84 (SE 0.60) **cana300:** -5.06 (SE 0.61) **sita100:** -1.83 (SE 0.61) **52 weeks:** ***Change from baseline*** **cana100:** -3.5 (SE 0.6) **cana300:** -4.7 (SE 0.6) **sita100:** -0.7 (SE 0.6) ***Difference to sitagliptin*** **cana100:** -2.9 (95% CI: -4.5, -1.3), p<0.001 v. sitagliptin

	Ertugliflozin	Canagliflozin
		cana300: -4.0 (95% CI: -5.6, -2.4), p<0.001 v. sitagliptin
Diastolic blood pressure (mmHg) (change from baseline, difference to sitagliptin)	**26 weeks :** ***Change from baseline*** **ertu5:** -1.1 (95% CI: -2.0, -0.3) **ertu15:** -1.0 (95% CI: -1.8, -0.1) **sita100:** -0.3 (95% CI: -1.2, 0.5) **52 weeks:** ***Change from baseline*** **ertu5:** -1.7 (95% CI: -2.7, -0.7) **ertu15:** -0.7 (95% CI: -1.7, 0.3) **sita100:** 0.8 (95% CI: -0.3, 1.8) ***Difference/p versus sitagliptin NR***	**26 weeks :** ***Change from baseline*** **cana100:** -2.2 (SE 0.4) **cana300:** -2.1 (SE 0.4) **sita100:** -1.1 (SE 0.4) **52 weeks:** ***Change from baseline*** **cana100:** -1.8 (SE 0.4) **cana300:** -1.8 (SE 0.4) **sita100:** -0.3 (SE 0.4) ***Difference to sitagliptin*** **cana100:** -1.4 (95% CI: -2.4, -0.5), p vs. sitagliptin NR **cana300:** -1.5 (95% CI: -2.5, -0.5), p vs. sitagliptin NR
BMI	NR	NR
Weight (kg) (change from baseline, difference to sitagliptin)	**26 weeks:** ***Change from baseline*** **ertu5:** -2.7 (95% CI: -3.1, -2.2) **ertu15:** -3.7 (95% CI: -4.2, -3.3) **sita100:** -0.7 (95% CI: -1.1, -0.2) **52 weeks:** ***Change from baseline*** **ertu5:** -2.4 (95% CI: -2.9, -1.8)	**26 weeks:** ***Change from baseline*** **cana100:** -3.3 (SE 0.2) **cana300:** -3.6 (SE 0.2) **sita100:** -1.1 (SE 0.2) **52 weeks:** ***Change from baseline*** **cana100:** -3.3 (SE 0.2)

	Ertugliflozin	Canagliflozin
	ertu15: -3.2 (95% CI: -3.8, -2.7) **sita100:** -0.1 (95% CI: -0.7, 0.5) ***Difference/p versus sitagliptin NR***	**cana300:** -3.7 (SE 0.2) **sita100:** -1.2 (SE 0.2) ***Difference to sitagliptin*** **cana100:** -2.4 (95% CI: -3.0, -1.8), p<0.001 v. sitagliptin **cana300:** -2.9 (95% CI: -3.4, -2.3), p<0.001 v. sitagliptin
Lipids		
HDL-cholesterol (change from baseline, difference to sitagliptin)	**26 weeks:** ***Change from baseline*** **ertu5:** +6.2% (95% CI: 4.0, 8.5) **ertu15:** +8.2% (95% CI: 5.9, 10.5) **sita100:** +1.8% (95% CI: -0.6, 4.1) **52 weeks:** ***Change from baseline*** **ertu5:** +6.3% (95% CI: 4.1, 8.5) **ertu15:** +7.2% (95% CI: 4.9, 9.4) **sita100:** +0.8% (95% CI: -1.5, 3.1) ***Difference/p versus sitagliptin NR***	**26 weeks:** ***Change from baseline*** **cana100:** +10.3% (SE 0.9), p<0.05 vs. sitagliptin **cana300:** +12.1% (SE 1.0), p<0.05 vs. sitagliptin **sita100:** +5.0% (SE 1.0) **52 weeks:** ***Change from baseline*** **cana100:** +11.2% (SE 1.0) **cana300:** +13.2% (SE 1.1) **sita100:** +6.0% (SE 1.1) ***Difference to sitagliptin*** **cana100:** +5.2 (95% CI: 2.5, 7.9), p vs. sitagliptin NR **cana300:** +7.2 (95% CI: 4.4, 10.0), p vs. sitagliptin NR
LDL-cholesterol (change from baseline, difference to sitagliptin)	**26 weeks:** ***Change from baseline*** **ertu5:** +8.0% (95% CI: 2.7, 13.3) **ertu15:** +7.9% (95% CI: 2.6, 13.3)	**26 weeks:** ***Change from baseline*** **cana100:** +6.5% (SE 1.7) **cana300:** +10.7% (SE 1.8)

	Ertugliflozin	Canagliflozin
	sita100: +6.7% (95% CI: 1.2, 12.2) **52 weeks:** ***Change from baseline*** **ertu5:** +9.9% (95% CI: 4.4, 15.4) **ertu15:** +9.5% (95% CI: 3.8, 15.1) **sita100:** +10.9% (95% CI: 5.1, 16.6) ***Difference/p versus sitagliptin NR***	**sita100:** +4.1% (SE 1.8) **52 weeks:** ***Change from baseline*** **cana100:** +7.7% (SE 1.7) **cana300:** +8.8% (SE 1.8) **sita100:** +6.0% (SE 1.8) ***Difference to sitagliptin*** **cana100:** 1.7 (95% CI: -2.8, 6.2), p vs. sitagliptin NR **cana300:** 2.8 (95% CI: -1.8, 7.4), p vs. sitagliptin NR
Triglycerides (change from baseline, difference to sitagliptin)	**26 weeks:** ***Change from baseline (median)*** **ertu5:** +0.6% (SD 36.8) **ertu15:** -3.9% (SD 44.3) **sita100:** +0.6% (SD 48.0) **52 weeks:** ***Change from baseline*** **ertu5:** -5.8% (SD 43.3) **ertu15:** -5.3% (SD 38.7) **sita100:** -3.5% (SD 42.9) ***Difference/p versus sitagliptin NR***	**26 weeks:** ***Change from baseline*** **cana100:** +1.6% (SE 2.6) **cana300:** -1.4% (SE 2.6) **sita100:** +1.0% (SE 2.7) **52 weeks:** ***Change from baseline*** **cana100:** +1.9% (SE 2.4) **cana300:** +2.8% (SE 2.4) **sita100:** -0.4% (SE 2.5) ***Difference to sitagliptin*** **cana100:** 2.3 (95% CI: -3.9, 8.5), p=NS vs. sitagliptin **cana300:** 3.2 (95% CI: -3.1, 9.5), p=NS vs. sitagliptin

	Ertugliflozin	**Canagliflozin**
Total cholesterol (change from baseline, difference to placebo)	NR	NR
Adverse effects		
Discontinuation due to AE (%)	**26 weeks:** **ertu5:** 2.4% **ertu15:** 1.2% **sita100:** 0.4% **52 weeks:** **ertu5:** 3.2% **ertu15:** 3.2% **sita100:** 2.8%	**26 weeks:** **cana100:** 4.9% **cana300:** 1.6% **sita100:** 2.2% **52 weeks:** **cana100:** 5.2% **cana300:** 3.3% **sita100:** 4.4%
Hypoglycaemia; *Severe* *Non-severe* *How defined?*	Symptomatic hypoglycaemia (event with clinical symptoms reported by the investigator as hypoglycaemia; biochemical documentation not required): **26 weeks:** **ertu5:** 2.4% symptomatic hypoglycaemia, 5.6% documented hypoglycaemia **ertu15:** 2.4% symptomatic hypoglycaemia, 5.2% documented hypoglycaemia **sita100:** 2.4% symptomatic hypoglycaemia, 3.6% documented hypoglycaemia **52 weeks:** **ertu5:** 2.8% symptomatic hypoglycaemia, 6.8% documented hypoglycaemia, 0 severe	Documented hypoglycaemia (included biochemically confirmed episodes (concurrent fingerstick or plasma glucose ≤3.9 mmol/l) and/or severe episodes (i.e. requiring the assistance of another individual or resulting in seizure or loss of consciousness 26 - **52 weeks:** **cana100:** 6.8% documented hypoglycaemia, n=1 severe hypoglycaemia **cana300:** 6.8% documented hypoglycaemia, 0 severe hypoglycaemia **sita100:** 4.1%, n=1 severe hypoglycaemia Documented hypoglycaemia: included biochemically confirmed episodes (concurrent fingerstick or plasma glucose ≤3.9 mmol/L) Severe episodes: requiring the assistance of another individual or resulting in seizure or loss of consciousness

	Ertugliflozin	Canagliflozin
	ertu15: 3.2% symptomatic hypoglycaemia, 6.5% documented hypoglycaemia, 2/250 (0.8%) severe **sita100:** 2.8% symptomatic hypoglycaemia, 5.7% documented hypoglycaemia, 0 severe Documented hypoglycaemia: symptomatic and asymptomatic, episodes with a glucose level ≤70 mg/dL [3.9 mmol/L], with or without symptoms Severe hypoglycaemia: episodes that required assistance, either medical or non-medical	
Urinary tract infections	**26 weeks:** **ertu5:** 5.2% **ertu15:** 5.6% **sita100:** 3.2% **52 weeks:** **ertu5:** 8.8% **ertu15:** 8.5% **sita100:** 5.3%	**52 weeks:** **cana100:** 7.9% **cana300:** 4.9% **sita100:** 6.3%
Genital tract infections (by gender)	**26 weeks:** (genital mycotic infections) **ertu5:** 4.7% men, 4.9% women **ertu15:** 3.7% men, 7.0% women **sita100:** 0% men, 1.1% women **52 weeks:** (genital mycotic infections) **ertu5:** 6.3% men, 4.9% women **ertu15:** 5.2% men, 7.0% women	**52 weeks:** **cana100:** 5.2% men, 11.3% women **cana300:** 2.4% men, 9.9% women **sita100:** 1.2% men, 2.6% women

	Ertugliflozin	**Canagliflozin**
	sita100: 0% men, 2.2% women	
Any DKA, amputations, fractures	**52 weeks:** no DKA in relevant comparison groups, 1 fracture each in **ertu5** and **ertu15** group, no amputations reported	**52 weeks:** 1 fracture in cana100 group, no DKA in any relevant group, amputation not reported
Trial quality	Good – no specific quality issues	Good – no specific quality issues

Trial	Method of randomi-sation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	ITT analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Ertugliflozin										
Pratley 2018[5]; VERTIS Factorial trial	*Low risk* Computer-generated schedule	*Low risk* Central randomi-sation; interactive voice response system / integrated web response system	*Low risk* Double-blind: Patients, investigators, contract research personnel (Covance) and the sponsor were blinded to group assignments	*Low risk* The sponsor was unblinded at Week 26 to permit authoring of the Phase A clinical study report. Patients and personnel associated with the conduct of the study at Covance and study sites remained blinded until after completion of Phase B.	*Unclear risk* Observations obtained after initiation of glycaemic rescue therapy were treated as missing in all efficacy analyses. Fewer patients in the E5/S100 (2.5%) and E15/S100 (0.0%) groups received glycaemic rescue therapy by Week 26 compared with patients in the E5 (6.4%), E15 (2.8%) and S100 (6.5%) groups. At Week 52, 11.1% and 10.7% of patients had received rescue medication in the E5/S100 and E15/S100 groups, respectively, compared with 18.4%, 21.0% and 27.9% of patients in the E5, E15 and S100 groups, respectively; i.e. some groups had >20% missing data and the amount of missing data varied between groups.	*Unclear risk* Efficacy analyses included all randomised, treated patients who had ≥1 measurement of the efficacy outcome. Safety analyses included all randomised, treated patients. All safety analyses at Week 26, except the analysis of serious AEs (SAEs) and discontinuations because of AEs, excluded data acquired following initiation of glycaemic rescue. All safety analyses at Week 52, with the exception of those related to hypoglycaemia, included post rescue observations.	*Low risk* Endpoints reported as in the protocol at https://clinicaltrials.gov/ct2/show/NCT02099110	*Low risk* Baseline characteristics were generally similar among groups	*Unclear risk* A sample size of 250 per group (equivalent to a sample size of 220 per group, accounting for information loss as a result of missing data and the correlation among repeated measures) was estimated to provide ~94% power to detect a difference in HbA1c of 0.4% for each pairwise comparison at a given ertugliflozin dose level, assuming a standard deviation (SD) of 1.2% based on a 2-sided test at a 5% α-level. The 5 groups ranged in size from 243 to 250 each and the numbers completing in each group ranged from 217 to 226 (i.e. just below the sample size calculation)	**6/9 low risk**