NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ertugliflozin as monotherapy and in dual therapy for treating type 2 diabetes [ID1158]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ertugliflozin as monotherapy and in dual therapy for treating type 2 diabetes [ID1158]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Ertugliflozin as monotherapy and in dual therapy for treating type 2 diabetes

Technical briefing

This slide set is the technical briefing for this appraisal. It has been prepared by the technical team and it is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the appraisal committee meeting and is expected reading for committee members. The submissions made by the company, consultees and nominated experts as well as the ERG report are available for committee members, and are optional reading.

Authors: Juliet Kenny - Technical Lead, Zoe Charles - Technical Adviser

Key issues

- The company has made a case for this appraisal to follow the FTA process (cost comparison) based on ertugliflozin having similar health benefits to dapagliflozin, canagliflozin and empagliflozin, appraised in:
  - TA 390 for monotherapy
  - TA 288 (dapagliflozin), TA 315 (canagliflozin) and TA 336 (empagliflozin) for dual therapy.
- Is the committee satisfied with the evidence for the efficacy and safety of ertugliflozin compared with placebo?
- Does the committee accept the design and reliability of the company's network meta-analyses (NMAs) and/or the ERG's indirect comparisons?
- Does ertugliflozin have similar resource requirements compared with the other recommended treatments?
- Are the lifetime costs and benefits of ertugliflozin likely to be similar to other recommended treatments?
- In light of the above is it reasonable to recommend ertugliflozin in the same way as TAs 390 (mono) and 288, 315 and 336 (dual)?

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The technologies

	Intervention: Ertugliflozin (ERTU)	Comparators: Canagliflozin (CANA); dapagliflozin (DAPA); empagliflozin (EMPA)
Mechanism of action	Sodium–glucose co-transporter 2 inhibitor (SGLT2i)	
Marketing authorisation	Adults aged 18+ with type 2 diabetes to improve glycaemic control: • as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications; • in addition to other medicinal products for the treatment of diabetes	
Dose (administered orally, once daily)	Monotherapy: starting dose 5 mg increasing to 15 mg if needed; combination therapy: individualised using recommended 5 mg or 15 mg dosages	CANA – Monotherapy: starting dose 100 mg increasing to 300 mg if needed; combination therapy: individualised using recommended 100 mg or 300 mg dosages DAPA – Monotherapy and dual therapy: 10 mg EMPA - Monotherapy: starting dose 10 mg increasing to 25 mg if needed; combination therapy: individualised using recommended 10 mg or 25 mg dosages

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Source: Company submission document B, section 31.2, table 2 p10; NICE TAs 390, 288, 315 and 336; electronic medicines compendium (eMC) [https://www.medicines.org.uk/emc accessed October 2018]

Monotherapy: company's clinical effectiveness evidence

VERTIS MONO (Terra 2017) was only ERTU RCT:

- 52-week, multicentre, randomized study (first 26 weeks double blind, placebo controlled)
- 81 centres in USA, Canada, Israel, Italy, Mexico, S. Africa, UK (total n=30 UK patients)
- **Population**: N=461 adults, aged ≥18 years with inadequate glycaemic control (HbA1c 7.0% to 10.5% [53-91 mmol/mol]) despite diet and exercise
- **Outcomes**: include change in HbA1c from baseline to week 26 (primary), HbA1c/glycaemic control, body mass index (BMI), hypoglycaemia (frequency/severity), changes in cardiovascular risk factors, adverse events (AEs)

Baseline characteristics were similar across treatment groups

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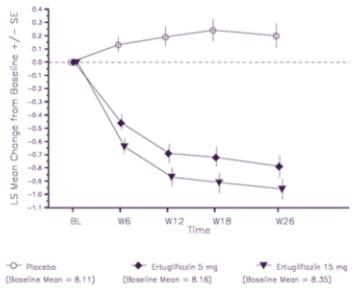
Source: Company submission document B, section 3.1 p20, section 3.2.1 table 11 p21, section 3.3.3, table 16, p39

The all subjects as treated (ASaT) population was used for summarising baseline characteristics. The ASaT consisted of all randomised patients who took at least one dose of study medication.

Patients were diagnosed according to the American Diabetes Association (ADA) guidelines

Monotherapy: clinical effectiveness results (1)

Primary efficacy outcome: HbA1c change from baseline to week 26 - Least Squares mean change (constrained longitudinal data analysis [cLDA] using full analysis set [FAS] population)



Treatment	Differences in LS means vs. PBO at W26 (95% CI; p-Value)
ERTU 5 mg	-0.99 (-1.22, -0.76); <0.001)
ERTU 15 mg	-1.16 (-1.39, -0.93); <0.001)

Analysis of patients with HbA1c <7% (<53 mmol/mol) at week 26 – Logistic regression using multiple imputations (FAS)

Treatment	N	Number (%) with HbA1c <7.0% at W26
PBO	153	20 (13.1)
ERTU 5 mg	156	44 (28.2)
ERTU 15 mg	151	54 (35.8)

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Abbreviations: LS, least squares; SE, standard error; W= week; PBO, placebo

Source: Company submission document B, section 3.6.1, figure 5, p49 and table 21, p50

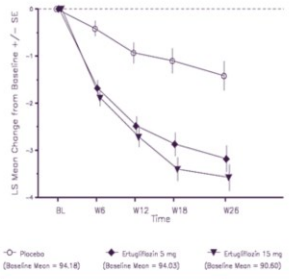
The full analysis set (FAS) population was used for the primary and secondary efficacy outcomes, which included all randomised patients who took at least one dose of study medication and had at least one measurement of the outcome variable (baseline or post-baseline)

A constrained longitudinal data analysis (cLDA) model was used that included terms for treatment (categorical), time, the treatment by time interaction, AHA status at study entry (binary: yes/no), and baseline eGFR (continuous). An unstructured covariance matrix was used to model the correlation among repeated measurements. The Kenward-Roger adjustment was used with restricted (or residual) maximum likelihood (REML) to support appropriate statistical inference. Sensitivity analyses were performed to assess the robustness of the primary model.

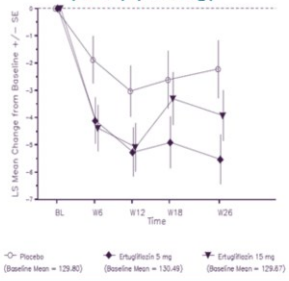
Monotherapy: clinical effectiveness results (2)

Other continuous efficacy outcomes – change from baseline at week 26 - Least Squares mean change (cLDA, FAS)

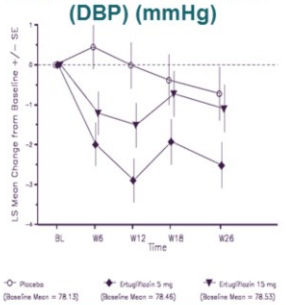
Body Weight (kg)



Systolic blood pressure (SBP) (mmHg)



Diastolic blood pressure (DBP) (mmHg)



Outcome	Differences in LS means vs. PBO at wk 26 (95% CI; p-Value)	
	ERTU 5 mg	ERTU 15 mg
Body Weight (kg)	-1.76 (-2.57, -0.95; <0.001)	-2.16 (-2.98, -1.34; <0.001)
SBP (mmHg)	-3.31 (-5.98, -0.65; 0.015)	-1.71 (-4.40, 0.98; 0.213)
DBP (mmHg)	-1.80 (-3.51, -0.09; 0.039)	-0.37 (-2.09, 1.35; 0.669)

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Abbreviations: cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; FAS, full analysis set

Source: Company submission document B, section 3.6.1, figures 6-8, pp51-53

Monotherapy: adverse events

VERTIS MONO	PBO N = 153	ERTU5 N = 156	ERTU15 N = 152
AEs related to study drug (ER)	19 (12.4)	32 (20.5)	28 (18.4)
Genital mycotic infection (women)	4 (5.6)	**11 (16.4)**	**14 (22.6)**
Genital mycotic infection (men)	1 (1.2)	3 (3.4)	5 (5.6)

ER, analysis excluding events occurring after rescue medication
Bold text = Incidence significantly higher than PBO group

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Abbreviations: AE, adverse event; SAE, Serious adverse event; UTIs, urinary tract infections

Source: Company submission document B, section 3.10.2, table 47, p87

The all subjects as treated (ASaT) population was used for the safety analysis. The ASaT consisted of all randomised patients who took at least one dose of study medication

Patients were prescribed with glycaemic rescue therapy in the form of open-label metformin when exceeding the following thresholds:

- FPG >15.0 mmol/L after randomisation up to week 6
- FPG>13.3 mmol/L after week 6 and up to week 12
- FPG>11.1 mmol/L after week 12 and up to week 26

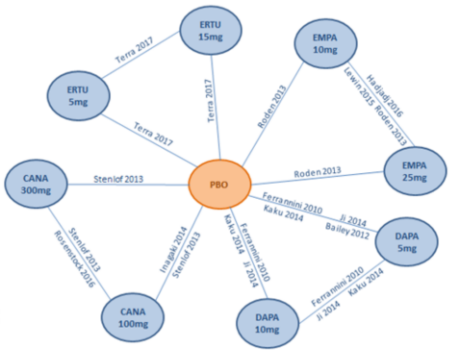
Investigator determined whether events were related to the study drug

Symptomatic hypoglycaemia = Event with clinical symptoms reported

by the investigator as hypoglycaemia

Monotherapy: company's network meta-analysis (NMA)

NMA outcomes:
- Continuous: change in HbA1c, weight and SBP
- Binary: HbA1c in target, UTIs and genital mycotic infections
- All measured at week 24 to 26



Differences between company NMA and TA390:
- Includes publications up to May 2018
- Includes Bailey 2012 – DAPA 5 mg vs. PBO
  - Study was excluded from the AG's NMA in TA 390 because DAPA 5 mg is not licensed
  - Company rational for inclusion: "to allow the comparison of the ERTU lower dose (5 mg) against the DAPA lower dose (5 mg)"
- Excludes Kaku 2014 (DAPA 5 mg and 10 mg vs. PBO) from the base case because:
  - SLR inclusion criteria not met (HbA1c threshold of ≥6.5% not ≥7%)
  - Average baseline HbA1c of patients was lower than other included studies (7.5%)

Company sensitivity analyses showed minimal impact on results

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Abbreviations: SITA, sitagliptin; LINA, linagliptin; SLR, systematic literature review

Source: Company submission document B, section 3.9.1 figure 13, p64

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Monotherapy: company's NMA results

Continuous outcomes

- Change in HbA1c: ERTU 15 mg statistically superior to both doses of DAPA/EMPA
- Weight change: [redacted]
- Change in SBP: CANA 300 mg statistically superior to ERTU 15 mg

Binary outcomes

- HbA1c at target (<7.0%): no significant differences between flozins
- All AEs: no significant differences between flozins
- UTIs: [redacted]

Company's conclusion

- ERTU has similar efficacy and safety in monotherapy to other flozins
- Sensitivity analyses confirmed that the base case results were robust

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Monotherapy: ERG review, clinical effectiveness evidence (1)

Key issues with VERTIS MONO trial

- Patients were randomised to 5 mg/day or 15 mg/day from the start, whereas in practice, patients start on 5 mg and increase to 15 mg. Those who do not respond well to 5 mg might do less well on 15 mg than patients who went straight to 15 mg (same problem noted in CANA and EMPA trials)
- Reservations about the statistical analysis which may have over-estimated the reduction in HbA1c compared with placebo. However independent FDA analysis reports both doses of ERTU are clinically effective, with improvements in HbA1c that are similar to those seen with other flozins

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Source: ERG report, section 3.3 p14

Monotherapy: ERG review, clinical effectiveness evidence (2)

Key issues with company NMA

- Unnecessary, could have compared ERTU against one previously approved flozin (as per ERG's own analysis)
- Consistency with TA 390
  - Company's inclusion of DAPA 5 mg is not appropriate - not relevant dose
  - Company's exclusion of Kaku 2014 is ok - appropriate justification given
  - Overall ERG agree inclusion/exclusion makes minimal impact on results
- Other issues (also applying to TA 390)
  - Some included trials were carried out in East Asian (Japanese and Chinese) populations that have lower baseline BMIs - would have been better to include only trials with similar characteristics to VERTIS MONO
    - Results of NMAs vary according to the trials included (also noted in TA390)
  - The higher doses of several drugs are included - 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

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Source: ERG report, section 3.3 p14

Monotherapy: additional work undertaken by ERG

- As per their comments on company analysis, ERG only compared ERTU against one of the previously approved flozins
- ERG reviewed monotherapy trials and found that CANTATA-M trial (Stenlöf 2013) was the most similar to VERTIS MONO in terms of design and population - concluded that CANA was the most suitable comparator and had similar health benefits to ERTU

Baseline characteristics	VERTIS MONO (ERTU 5 mg)	CANTATA-M (CANA 100 mg)
Mean age (years)	57	55
Mean BMI (kg/m^2)	33	31
Ethnicities	86% white	64% white
Proportion that had previous treatment with glucose lowering drugs	65%	48%
Mean duration of diabetes (years)	5.1	4.5
Mean SBP (mmHg)	130.5	126.7
Mean DBP (mmHg)	78.5	77.7
Mean HbA1c	8.16%	8.1%

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Abbreviations: eGFR, estimated glomerular filtration rate; tx, treatment

Source: ERG report, section 3.4, pp15-17, table 2

Monotherapy trial designs are similar

ERG thought the following trials were less suitable comparators:

- Roden 2013 trial of empagliflozin because it was done mainly in Asians, with a lower baseline BMI (28kg/m^2)
- Ferrannini trial of dapagliflozin because it 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%)

Monotherapy: results of additional work undertaken by ERG

Results (at 26 weeks)	VERTIS MONO (ERTU 5 mg)	CANTATA-M (CANA 100 mg)
Mean HbA1c changes (LS means)	ERTU 5 mg: - 0.79% PBO: + 0.20%	CANA 100 mg: -0.77% PBO: + 0.14%
Mean HbA1c change vs PBO (LS means)	0.99%	0.91%
Mean change in weight vs PBO	1.76kg	1.9kg
Mean change SBP vs PBO (mmHg)	-3.3	-3.7
Mean change DBP vs PBO (mmHg)	-1.8	-1.6
Proportions with urinary tract infections, both sexes	ERTU 5 mg: 7.1% PBO: 8.5%	CANA 100 mg: 7.2% PBO: 4.2%
Proportions with genital tract infection, women	ERTU 5mg: 16.4% PBO: 5.6%	CANA 100 mg: 8.8% PBO: 3.8%

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Source: ERG report, section 3.4, pp15-17, table 2

Dual therapy: company's clinical effectiveness evidence

VERTIS MET (Rosenstock 2018)	VERTIS Factorial (Pratley 2018)
Design: 104-week, multicentre, randomized study (first 26 weeks double blind, placebo controlled)	**Design:** 52-week, multicentre, randomized study (first 26 weeks double blind)
Population: N=621 patients aged ≥18 years with inadequate glycaemic control (HbA1c 7.0% to 10.5% [53-91 mmol/mol]) on metformin therapy at a dose ≥1500 mg/day	**Population**: N=1232 patients aged ≥18 years with inadequate glycaemic control (HbA1c 7.0% ≤11% [≥58 mmol/mol and ≤97 mmol/mol]) on a stable dose of metformin monotherapy
Interventions/Comparators: ERTU 5 mg, ERTU 15 mg and PBO with background metformin	**Interventions/Comparators:** ERTU 5 mg, ERTU 15 mg with background metformin (also included a sitagliptin and ERTU with sitagliptin arms not relevant to this FTA)
Outcomes: change in HbA1c from baseline to week 26 (primary), body weight, blood pressure, proportion of patients with HbA1c <7.0%, AEs	**Outcomes**: change in HbA1c from baseline to week 26 (primary), body weight, blood pressure, proportion of patients with HbA1c <7.0%, AEs
Location: 103 centres worldwide incl. Australia, US and UK (total n=2 UK patients)	**Location:** 242 centres worldwide incl. Canada and US. None in UK

Baseline characteristics were similar between treatment arms

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Source: Company submission document B, section 3.1 p20, section 3.2 tables 12-13 pp2225, section 3.3.1, pp30-35, section 3.3.2 table 15 pp36-37, table 16, p39

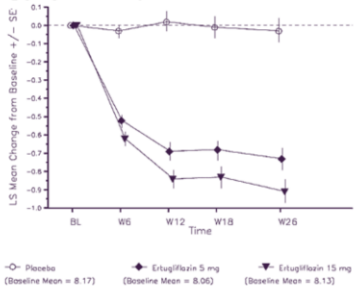
The all subjects as treated (ASaT) population was used for summarising baseline characteristics. The ASaT consisted of all randomised patients who took at least one dose of study medication.

Patients were diagnosed according to the American Diabetes Association (ADA) guidelines

The safety and tolerability of ertugliflozin was evaluated through the assessment of pre-specified adverse events (AEs) following a tiered approach. Tier 1 AEs were AEs of special interest such as genital mycotic infections, UTIs, symptomatic hypoglycaemia and hypovolemia. AEs that were not pre-specified as Tier 1 endpoints were classified as belonging to Tier 2 or Tier 3, based on the number of events observed

Dual therapy: clinical effectiveness results, VERTIS MET (1)

Primary efficacy outcome: HbA1c change from baseline to week 26 - Least Squares mean change (constrained longitudinal data analysis [cLDA] using full analysis set [FAS] population)



Treatment	Differences in LS means vs. PBO at W26 (95% CI; p-Value)
ERTU 5 mg	-0.7 (-0.9, -0.5; <0.001)
ERTU 15 mg	-0.9 (-1.1,- 0.7; <0.001)

Analysis of patients with HbA1c <7% (<53 mmol/mol) at week 26 – Logistic regression using multiple imputations (FAS)

Treatment	N	Number (%) with HbA1c <7.0% at W26
PBO	209	33 (15.8)
ERTU 5 mg	207	73 (35.3)
ERTU 15 mg	205	82 (40.0)

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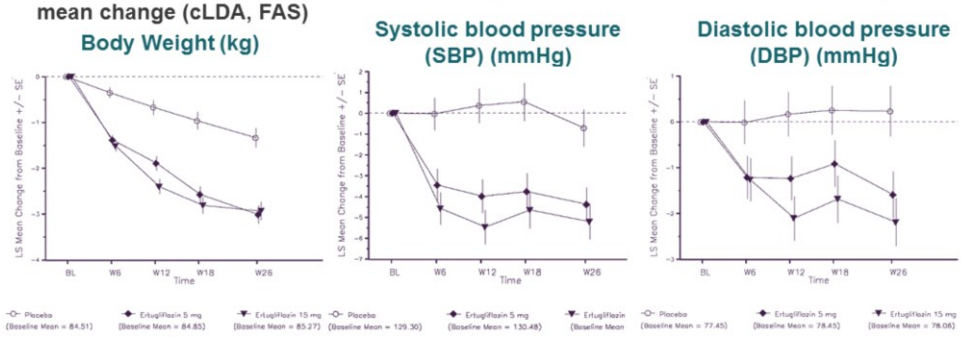
Abbreviations: LS, least squares; SE, standard error; W= week; PBO, placebo

Source: Company submission document B, section 3.6.2 figure 9 p54 and table 22, p55

The full analysis set (FAS) population was used for the primary and secondary efficacy outcomes, which included all randomised patients who took at least one dose of study medication and had at least one measurement of the outcome variable (baseline or post-baseline)

Dual therapy: clinical effectiveness results, VERTIS MET (2)

Other continuous efficacy outcomes – change from baseline at week 26 - Least Squares mean change (cLDA, FAS)



Outcome	Differences in LS means vs. PBO at wk 26 (95% CI; p-Value)	
	ERTU 5 mg	ERTU 15 mg
Body Weight (kg)	-1.67 (-2.24, -1.11; <0.001)	-1.60 (-2.16, -1.03; <0.001)
SBP (mmHg)	-3.68 (-5.96, -1.39; 0.002)	-4.50 (-6.81, -2.19; <0.001)
DBP (mmHg)	-1.82 (-3.24, -0.39; 0.013)	-2.42 (-3.86, -0.98; 0.001)

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Abbreviations: cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; FAS, full analysis set

Source: Company submission document B, section 3.6.2, figures 10-12, pp55-57

Dual therapy: clinical effectiveness results, VERTIS Factorial

Continuous efficacy outcomes – change from baseline at week 26 - Least Squares mean change (cLDA, FAS)

Outcome	Differences in LS means vs baseline (95% CI)	
	ERTU 5mg	ERTU 15mg
HbA1c (%)	-1.02 (-1.14, -0.90)	-1.08 (-1.20, -0.96)
Body Weight (kg)	-2.69 (-3.13, -2.25)	-3.74 (-4.18, -3.29)
SBP (mmHg)	-3.89 (-5.28, -2.50)	-3.69 (-5.08, -2.30)
DBP (mmHg)	-1.11 (-1.96, -0.26)	-0.97 (-1.81, -0.12)

Number (%) of patients with HbA1c <7.0% (raw proportion)	
ERTU 5 mg	ERTU 15mg
66 (26.4)	79 (31.9)

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Abbreviations: cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; FAS, full analysis set; Tx, treatment

Source: Company submission document B, section 3.6.3, tables 23-27, pp57-59

Dual therapy: adverse events

	VERTIS MET			VERTIS Factorial	
Trial arm	PBO N = 209	ERTU5 N = 207	ERTU15 N = 205	ERTU5 N = 250	ERTU15 N = 248
AEs related to study drug (ER)	13 (6.2)	24 (11.6)	25 (12.2)	42 (16.8)	30 (12.1)
Genital mycotic infection (women)	1 (0.9)	6 (5.5)	**7 (6.3)**	6 (4.9)	8 (7.0)
Genital mycotic infection (men)	0 (0)	3 (3.1)	3 (3.2)	6 (4.7)	5 (3.7)

ER, analysis excluding events occurring after rescue medication
Bold text = Incidence significantly higher than PBO group

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Abbreviations: AE, adverse event; SAE, Serious adverse event; UTIs, urinary tract infections

Source: Company submission document B, section 3.10.2, table 47, p87

The all subjects as treated (ASaT) population was used for the safety analysis. The ASaT consisted of all randomised patients who took at least one dose of study medication

Patients in both trials were prescribed with glycaemic rescue therapy in the form of open-label glimepiride or basal insulin when exceeding the following thresholds:

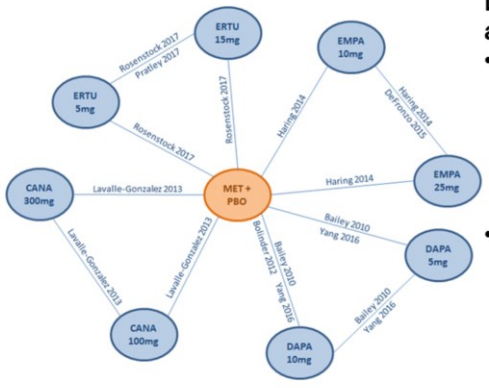
- FPG > 270 mg/dL after randomisation up to week 6
- FPG > 240 mg/dL after week 6 through week 12
- FPG > 200 mg/dL after week 12 through week 26

Investigator determined whether events were related to the study drug

Symptomatic hypoglycaemia = Event with clinical symptoms reported

by the investigator as hypoglycaemia

Dual therapy: company's NMA



NMA outcomes – as per monotherapy

Difference between company NMA and NMAs in TA288, TA315 and TA336

- Excluded Bolinder 2012 (metformin + DAPA 10 mg vs. metformin + PBO) :
  - SLR inclusion criteria not met (HbA1c threshold <7%)
  - primary outcome was change in weight, not change in HbA1c
- Included Yang 2016 (DAPA 10 mg, DAPA 5 mg and PBO all with metformin): published after TA288

Company sensitivity analysis showed minimal impact of excluding Bolinder 2012 but did not test the impact of including DAPA 5 mg

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Abbreviations: SITA, sitagliptin; LINA, linagliptin; SLR, systematic literature review

Source: Company submission document B, section 3.9.1 p61 and figure 14, p64

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Dual therapy: company's NMA results

Continuous outcomes

- Change in HbA1c: ERTU 15 mg statistically superior to other flozins apart from CANA 300 mg
- Weight change: no statistically significant differences between flozins
- Change in SBP: no statistically significant differences between flozins

Binary outcomes

- HbA1c at target (<7.0%): no significant differences between **********
- All AEs / UTIs : no significant differences **********

Company's conclusion

- ERTU has similar efficacy and safety in dual therapy to other flozins
- Sensitivity analyses confirmed that the base case results were robust

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Dual therapy: ERG review, clinical effectiveness evidence

Key issues with VERTIS Met and Factorial trials

- Similar to VERTIS MONO, in particular
  - Patients were randomised to 5 or 15 mg/day from the start – not in line with practice
  - For VERTIS Met, FDA analysis for change in HBA1c gave slightly less favourable results for ERTU compared with placebo

Key issues with company NMA

- As per monotherapy
  - Unnecessary
  - DAPA 5 mg - not relevant dose
  - trials with East Asian/low BMI populations should have been excluded
  - higher doses should have been excluded
- Bolinder 2012 trial was correctly excluded from base case NMA

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Source: ERG report, section 3.2 p12 and 3.3 p14

Dual therapy: additional work undertaken by ERG

- ERG preferred to compare ERTU against one previously approved flozin
- ERG found that Bailey 2012 (DAPA + metformin) was the most similar to VERTIS Met (ERTU + metformin) in terms of design and population - concluded that DAPA (10 mg arm only) was the most suitable comparator and had similar health benefits to ERTU

Baseline characteristics	VERTIS MET		Bailey 2012	
	ERTU 5 mg	PBO	DAPA 10 mg	PBO
Mean age (years)	56.6	56.5	52.7	53.7
Mean BMI (kg/m^2)	30.8	30.7	31.2	31.8
Ethnicities	64.7% white	68.9% white	Mainly white (no % given)	
Duration of diabetes (years)	7.9	8.0	6.1	5.8
Mean SBP (mmHg)	130.5	129.3	126.0	127.7
Mean HbA1c	8.1%	8.2%	7.92 %	8.11%

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Source: ERG report, section 3.4 table 3 pp17-19

ERG thought Haring 2013 (empagliflozin) a less suitable comparator because the ethnic mix in Bailey was more comparable with VERTIS MET

Dual therapy: Results of additional work undertaken by ERG

Results (at 26 weeks)	VERTIS MET		Bailey 2012	
	ERTU 5 mg	PBO	DAPA 10 mg	PBO
HbA1c week 26	7.3%	7.8%	7.13 %	7.79%
HbA1c change from baseline	-0.73%	-0.03%	-0.84%	-0.30%
Proportion of patients achieving HbA1c target of ≤7.0	35.3%	15.8%	40.6%	25.9%
Mean weight change from baseline (kg)	-3.01	-1.33	-2.9	-0.9
Mean SBP change from baseline (mmHg)	-4.38	-0.70	-5.1	-0.2
Mean DBP change from baseline (mmHg)	-1.59	0.23	-1.8	-0.1
Proportions with urinary tract infections	2.9	1.9	7	5
Proportions with genital tract infections	M: 3.1%* F: 5.5%*	M: 0%* F: 0.9%*	M+F: 9%	M+F: 5%

*Genital mycotic infection

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Source: ERG report, section 3.4 table 3 pp17-19

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Company resource use assumptions – monotherapy and dual therapy

- Main NHS resource use associated with flozins = drug acquisition costs
- No difference in other resource use between flozins as per assumptions applied in previous NICE appraisals
- Drug acquisition costs are presented based on publically available list prices (there are no PASs for ERTU or its comparators)
- ERTU **********

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Company resource use assumptions – monotherapy and dual therapy

ERG review

- No major concerns
- Note that incidence of GTI events was higher in the VERTIS MONO trial for ERTU 5mg and 15mg compared with frequency reported in the CANTATA-M trial of CANA 100mg and 300mg – not accounted for in cost comparison analysis
  - If this frequency of mycotic infections in women is accepted, annual cost of treating AEs with ERTU increases – impact of this is that ********** **********)
  - However also note that very high rate of GTI seen in VERTIS MONO was not seen in other trials of ERTU

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Company submission

Cost comparison - monotherapy

Technologies	Acquisition costs per pack (£)	Resource costs (£)	AE costs (£)	Other costs (£)	Annual cost (£)	TOTAL COSTS (£)	Incremental cost to ERTU
ERTU5 or ERTU15	*****	N/A	N/A	N/A	******	*******	-
CANA100 or CANA300 (BNF 2017)	39.20	N/A	N/A	N/A	478.48	478.48	*****
DAPA5 or DAPA10 (BNF 2017)	36.59	N/A	N/A	N/A	478.48	478.48	*****
EMPA10 or EMPA25 (BNF 2017)	36.59	N/A	N/A	N/A	478.48	478.48	*****
Time horizon: 1 year (365.25 days)							

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Company submission

Cost comparison - dual therapy

Technologies	Acquisition costs per pack (£)	Resource costs (£)	AE costs (£)	Other costs (£)	Annual cost (£)	TOTAL COSTS (£)	Incremental cost to ERTU
Met 500* + ERTU 5/15	***** (0.90 + ******)	N/A	N/A	N/A	*******	*******	-
Met 500* + CANA 100/300	40.10 (0.90 + 39.20)	N/A	N/A	N/A	525.96	525.96	*****
Met 500* + DAPA 5/10	37.49 (0.90 + 36.59)	N/A	N/A	N/A	525.96	525.96	*****
Met 500* + EMPA 10/25	37.49 (0.90 + 36.59)	N/A	N/A	N/A	525.96	525.96	*****
Time horizon: 1 year (365.25 days)							

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Technical team recommendation and rationale – monotherapy and dual therapy

Criteria for cost comparison case are met

- The key clinical outcome measures in the ERTU trials and NMAs are consistent with those used in the pivotal trials and cost effectiveness models of the NICE recommended comparators
- Evidence from company NMAs shows that both ERTU 5 and 15 mg have similar clinical effectiveness and safety profile to previously approved flozins in mono and dual therapy – conclusion supported by ERG analysis
- No difference in resource use beyond drug acquisition costs – view supported by ERG. Drug acquisition costs for ERTU *********.

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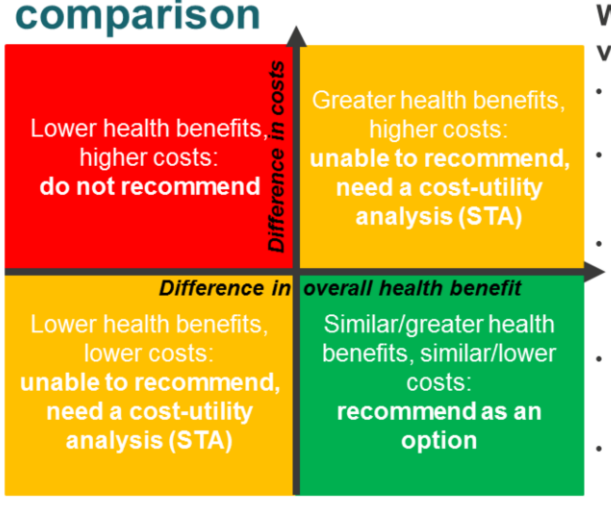
Potential recommendations: cost comparison



What is the committee view on:

- The clinical efficacy and safety of ERTU vs. placebo?
- The design and reliability of the NMA for the purposes of decision making?
- The similarity of the resource requirements of ERTU compared with other recommended treatments?
- Whether the lifetime costs and benefits are likely to be similar to other recommended treatments?
- Whether in light of the above it is reasonable to recommend ERTU in the same way as TAs 390 (mono) and 288, 315 and 336 (dual)?

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Frequently used abbreviations/terms

BMI	Body mass index
CANA	Canagliflozin
DAPA	Dapagliflozin
DBP	Diastolic blood pressure
DPP-4i	Dipeptidyl peptidase 4 inhibitor
EMPA	Empagliflozin
ERTU	Ertugliflozin
Flozins	Ertugliflozin, canagliflozin, dapagliflozin and empagliflozin
HBA_{1c}	Haemoglobin A1c
NMA	Network meta-analysis
mg	Milligram
PBO	Placebo
SBP	Systolic blood pressure
SGLT-2i	Sodium –glucose co-transporter 2 inhibitor

NICE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

Ertugliflozin monotherapy and dual therapy for treating type 2 diabetes mellitus [ID1158] [ACIC]

Document B

Company evidence submission

18th July 2018

File name	Version	Contains confidential information	Date
		Yes	18th July 2018

Contents

Tables and figures

Appendices

Abbreviations

AE	Adverse event
ADA	American Diabetes Association
AG	Assessment group
AHA	Anti-hyperglycaemic agents
ANCOVA	Analysis of covariance
ASaT	All subjects as treated
BC	Base case
BI	Boehringer Ingelheim
BL	Baseline
BMD	Bone mineral density
BMI	Body mass index
CANA	Canagliflozin
CHMP	Committee for Medicinal Products for Human Use
cLDA	Constrained longitudinal data analysis
CI	Confidence interval
CrI	Credible interval
CSR	Clinical study report
DAO	Data as observed
DAPA	Dapagliflozin
DBP	Diastolic blood pressure
DIC	Deviance information criterion
DPP-4i	Dipeptidyl peptidase 4 inhibitor
DSU	Decision support unit
ECG	Electrocardiogram
eCRF	Electronic case report file
EMA	European Medicine Agency
eGFR	Estimated glomerular filtration rate
EMPA	Empagliflozin
EPAR	European assessment report
ER	Excluding rescue (approach)
ERG	Evidence review group
ERTU	Ertugliflozin
FAS	Full analysis set
FDC	Fixed dose combination
FEM	Fixed effect model
FPG	Fasting plasma glucose
GLUT1-4	Glucose transporter 1,2,3 and 4
GP	General practitioner
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
IHD	Ischaemic heart disease
IP	In- patient
IR	Including rescue (approach)
ITT	Intention-to-treat population
IVRS	Interactive voice response system
J2R	Jump to reference analysis
LDL-C	Low-density lipoprotein

LINA	Linagliptin
LS	Least square
MA	Marketing authorization
MAT	Moving annual total
MET	Metformin
Mg	Milligram
MI	Myocardial infarction
MMTT	Mixed meal tolerance test
MSD	Merck Sharp & Dohme Ltd
MTA	Multiple technology appraisal
N	Number of patients per treatment group
NG	NICE guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NPH	Neutral protamine Hagedorn
NSHE	Non-severe hypoglycaemic event
N/A	Not available
OP	Out-patient
PBO	Placebo
PP	Per protocol
PPG	Post-prandial glucose
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
R	Randomisation
RCT	Randomised controlled trial
REM	Random effect model
REML	Restricted (or residual) maximum likelihood
S	Screening
SA	Sensitivity analysis
SAE	Serious adverse event
SAXA	Saxagliptin
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SITA	Sitagliptin
SLR	Systematic literature review
SGLT-1	Sodium-glucose cotransporter-1
SGLT-2i	Sodium-glucose cotransporter-2 inhibitor
SHE	Severe hypoglycaemia
SMBG	Self-monitoring of blood glucose
SmPC	Summary of product characteristics
SU	Sulphonylurea
TA	Technology appraisal
TC	Total cholesterol
T2DM	Type 2 Diabetes Mellitus
UGE	Urinary glucose excretion
UK	United Kingdom
UKPDS	United Kingdom prospective diabetes study
UTI	Urinary tract infections
V	Visit
W	Week

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

Population

This submission focuses on part of the ertugliflozin (Steglatro®) (ERTU) marketing authorisation: monotherapy and dual therapy with metformin. The triple therapy will be assessed separately.

Ertugliflozin is approved for adults aged 18 years and older with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycaemic control:

- as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications;
- in addition to other medicinal products for the treatment of diabetes (*dual therapy as add-on to metformin is the focus in this appraisal*)

Please see Table 1 below for a summary of the NICE decision problem.

Table 1 – The decision problem

	Final scope issued by NICE (June 2018)	Decision problem addressed in the company submission (June 2018)	Rationale if different from the final NICE scope
Population	Adults with T2DM that is inadequately controlled with diet and exercise alone or in whom the use of metformin in considered inappropriate due to intolerance or contraindications *AND* Adults with T2DM that are inadequately controlled on monotherapy	Adults with T2DM that is inadequately controlled with diet and exercise alone or in whom the use of metformin in considered inappropriate due to intolerance or contraindications *AND* Adults with T2DM that are inadequately controlled on monotherapy	
Intervention	Ertugliflozin alone or in a dual therapy regimen	Ertugliflozin alone or in a dual therapy regimen	
Comparator(s)	• Monotherapy: sulphonylureas (SUs), pioglitazone (PIO), DPP-4is and other SGLT-2is (canagliflozin (CANA), dapagliflozin (DAPA), empagliflozin (EMPA)) • Dual therapy: SUs, DPP-4is, PIO and SGLT-2is	• Other SGLT-2is (CANA, DAPA and EMPA) for both monotherapy and dual therapy	The comparators have been confined to other SGLT-2is recommended in published NICE technology appraisal guidance for the same indication
Outcomes	• Mortality. • Complications of diabetes, including cardiovascular, renal and eye. • Haemoglobin A1c (HbA1c)/glycaemic control. • Body mass index (BMI). • Frequency and severity of hypoglycaemia. • Changes in cardiovascular risk factors. • Adverse effects of treatment, including urinary tract infections (UTIs), genital infections and malignancies. • Health-related quality of life (HRQoL).	• Mortality. • Complications of diabetes, including cardiovascular, renal and eye. • HbA1c/glycaemic control. • BMI. • Frequency and severity of hypoglycaemia. • Changes in cardiovascular risk factors. • Adverse effects of treatment, including UTIs, genital infections and malignancies. • HRQoL.	• Mortality was not a pre-specified outcome but it has been reported as number of deaths observed within ertugliflozin RCTs. • HRQoL data were not collected in the ertugliflozin mono and dual therapy randomised controlled trials (RCTs).

Abbreviations: NICE, National Institute of Health and Care Excellence; T2DM, type 2 diabetes mellitus; DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT-2i, sodium –glucose co-transporter 2 inhibitor

B.1.2. Description of the technology being appraised

The summary of product characteristics (SmPC) and the European Public Assessment Report (EPAR) for the indications being appraised have been included in Appendix C.

The technology being appraised (ertugliflozin) is described in Table 2 below:

Table 2 - The technology being appraised - ertugliflozin

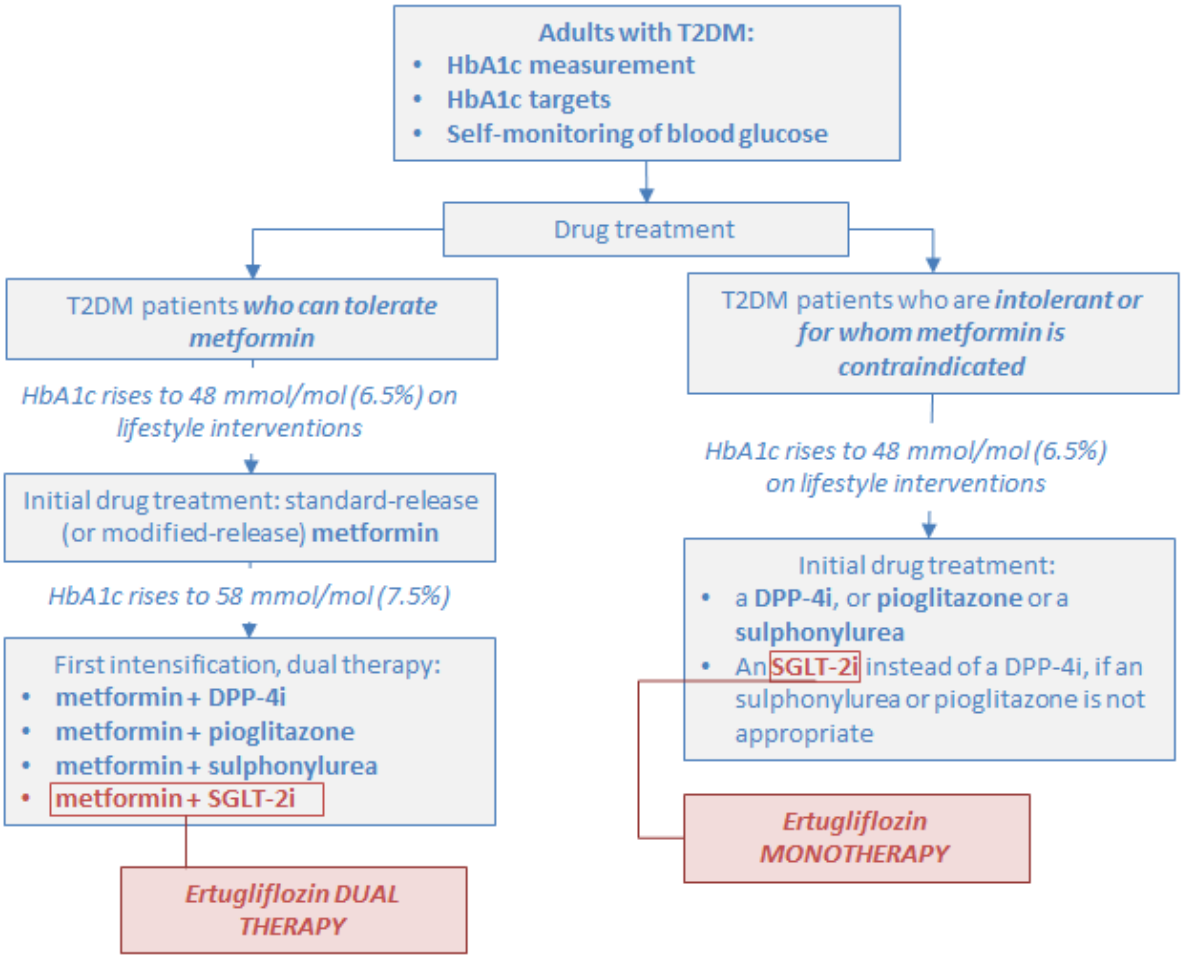
UK approved name and brand name	Ertugliflozin (Steglatro®)
Mechanism of action	Ertugliflozin is an inhibitor of SGLT-2 and possesses a high selectivity over glucose transport via sodium-glucose co-transporter 1 (SGLT-1) and several other glucose transporters (GLUT1-4). Ertugliflozin inhibits renal glucose reabsorption resulting in urinary glucose excretion (UGE) and thereby reducing plasma glucose and HbA1c in patients with T2DM
Marketing authorisation/CE mark status	• Marketing Authorisation (MA) submitted to European Medicine Agency (EMA): 6th February 2017 • CHMP positive opinion: 25th January 2018 • Date of MA: 21st March 2018
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Ertugliflozin has been approved by the EMA for: Adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control: • as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications; • in addition to other medicinal products for the treatment of diabetes.
Method of administration and dosage	Ertugliflozin should be taken orally once daily in the morning, with or without food. In monotherapy, the recommended starting dose of ertugliflozin is 5 mg (ERTU5) once daily. In patients tolerating ertugliflozin 5 mg once daily, the dose can be increased to 15 mg (ERTU15) once daily if additional glycaemic control is needed. In combination therapy the dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability using the recommended daily dose of ertugliflozin 5 mg or ertugliflozin 15 mg.
Additional tests or investigations	N/A
List price and average cost of a course of treatment	• Ertugliflozin (Steglatro®) 5 mg * 28 tablets: £[redacted] per pack • Ertugliflozin (Steglatro®) 15 mg * 28 tablets: £[redacted] per pack
Patient access scheme (if applicable)	N/A

Abbreviations: ERTU, ertugliflozin; SGLT-2i, sodium –glucose co-transporter 2 inhibitor; T2DM, type 2 diabetes mellitus; CHMP, Committee for Medicinal Products for Human Use; mg, milligram; N/A, not available

B.1.3. Health condition and position of the technology in the treatment pathway

The clinical pathway of care depicted below in Figure 1, reflects the latest NICE pathway for "Managing blood glucose in adults with type 2 diabetes" and the algorithm for blood glucose lowering therapy in adults with T2DM included in the NICE Guideline (NG) 28: "Type 2 diabetes in adults"(1), which was revised in April 2017 and accounts for SGLT-2is like ertugliflozin.

Figure 1 - Current T2DM treatment pathway and proposed ertugliflozin monotherapy and dual therapy positioning(1)



Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c; DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT-2i, sodium-glucose cotransporter-2 inhibitor

B.1.4. Equality considerations

MSD has not identified any equality issues.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1. Clinical outcomes and measures

Monotherapy

In 2016 NICE published the Multiple Technology Appraisal (MTA), TA390 (2), which assessed the clinical effectiveness, safety, and cost-effectiveness of the SGLT-2is canagliflozin, dapagliflozin and empagliflozin for the treatment of T2DM; in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control.

The key driver of cost effectiveness was BMI; the assessment group (AG) modelled five BMI scenarios, with a decrement of 0.0061 for each point above a 25 kg/m^2 BMI (as well as a scenario which assumed that BMI has no impact on quality of life). The committee concluded that the BMI scenario where weight gains are maintained, and weight losses rebounded to natural history after 1 year was the most plausible scenario (BMI-2 scenario), but noted that the small quality-adjusted life per year (QALY) difference between treatments made the Incremental cost-effectiveness ratios (ICERs) unstable (2).

Dual Therapy

There were three Technology Appraisals (TAs) published by NICE assessing the SGLT-2is as a treatment option in T2DM in dual therapy. These TAs were TA288 (3), TA315 (4), TA336 (5). The key driver of cost effectiveness in TA288 was the impact of weight change on HRQoL. The committee concluded that the scenario analysis conducted by the Decision Support Unit (DSU) which converged differences in weight profiles between treatment groups at the time of switching to the last treatment was the most appropriate approach. In TA315 HbA1c drift was the key driver of cost effectiveness. The committee and the Evidence Review Group (ERG) accepted the assumption of the manufacturer of extrapolating the 104 weeks of clinical data regarding HbA1c to a lifetime time horizon for canagliflozin.

No key driver of cost-effectiveness was identified in TA336. The impact of the outcomes and the committee's preferred assumptions are summarised in Table 3 below.

Table 3 - Clinical outcomes and measures appraised in published NICE guidance for the comparator(s) (2-5)

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
NICE TA390 (2)	Change in BMI	kg/m2	Yes	Incremental QALYs increased resulting in decreased ICERs.	BMI scenario where weight gains are maintained, and weight losses rebound to natural history after 1 year	NA
NICE TA288 (3)	Impact of weight change on health related quality of life	Health state utilities	Yes	For DAPA vs. SU the incremental QALYs decreased and the ICER increased by £6192 (£8.863 - £2671)	±0.0061 per BMI unit decrease	NA
NICE TA315 (4)	HbA1c drift (increased from 0.14% to 0.24% for CANA)	Percentage (%)	Yes	In dual therapy, for CANA vs. SU, the ICER increased by £28,821 (£30,358 - £1,537) for canagliflozin 100mg and £64, 565 (£69,464 -£4,899) for canagliflozin 300mg)	0.14% annual drift for SGLT-2is	NA
NICE TA336 (5)	NA	NA	NA	NA	NA	NA

Abbreviations: TA, technology appraisal; ICER, incremental cost-effectiveness ratio; BMI, Body Mass Index; HbA1c, haemoglobin A1c; CANA, canagliflozin; DAPA, dapagliflozin; UKPDS, United Kingdom prospective Diabetes study

B.2.2. Resource use assumptions

B.2.2.1 Monotherapy

In TA390 (2), the NICE committee agreed with the AG assumptions on resource use and unit costs. Summarised in Table 4 are the healthcare resource use and unit costs associated with drug acquisition, administration, monitoring, inpatient and outpatient procedures and adverse events. All costs reported in TA390 and the assessment report, are reported in 2014 prices.

Direct Drug Costs

Drug costs were taken from the National Health Service (NHS) drug tariff 2015 (6). Where there were no entries within the NHS drug tariff, list prices were used. Daily doses were assumed to be 60mg for gliclazide MR, 45mg for pioglitazone, 6mg for repaglinide, 100 mg for sitagliptin (SITA), 10mg for dapagliflozin, 25mg for empagliflozin, 300 mg for canagliflozin. Insulin costs were based on a dosing regimen of 0.3IU/kg when initiating neutral protamine Hagedorn (NPH) insulin, rising to 0.55IU/kg upon addition of a bolus injection. The required dosing regimen for a bolus was estimated at 0.2IU/kg. Table 4 below summarises the drug costs used by the AG (7).

Table 4 - Annual direct drug cost (monotherapy)

Treatment	AG drug costs
EMPA10	£476.98
EMPA25	£476.98
DAPA10	£476.98
CANA100	£476.93
CANA300	£476.93
SU (Gliclazide MR)	£62.18
PIO	£20.99
Repaglinide 6 mg	£71.91
DPP-4i (SITA100)	£433.57

Abbreviations: AG, assessment group; EMPA, empagliflozin; DAPA, dapagliflozin; CANA, canagliflozin; SU, sulphonylurea; PIO, pioglitazone; DPP-4I, dipeptidyl peptidase 4 inhibitor

The AG treatment sequencing differed from the company submissions; in the AG model patients added NPH insulin to their treatment whereas in the company submissions patients switched to it. As a result, cost differences between these sequences were maintained throughout the horizon of the model. The AG added an additional £72.26 to the cost of PIO for B-type Natriuretic Peptides (BNP) monitoring (£26.26 for the test and £46.00 for the general practitioner (GP) appointment (8). The testing took place every six months initially and then annually thereafter. A GP appointment cost of £46, was assumed for treatment intensification due to exceeding the 7.5% HbA_{1c} threshold or treatment switch due to drug intolerance. The details of the sequencing used by the AG can be found in Table 5.

Table 5 - Treatment Sequences and Administration Costs (Monotherapy)

Monotherapy	Cost	1st intens.	Cost	2nd intens.	Cost	3rd intens.	Cost
EMPA	£476.98	Glicl. MR	£62.18	Glicl. MR	£62.18		
		EMPA.	£476.98	EMPA.	£476.98	EMPA.	£476.98
				INS	£140.38	Int. INS	£351.36
				SMBG	£51.09	SMBG	£119.54
Total Cost	£476.98		£539.16		£730.63		£947.88
CANA	£476.93	Glicl. MR	£62.18	Glicl. MR	£62.18		
		CANA	£476.93	CANA	£476.93	CANA	£476.93
				INS	£140.38	Int. INS	£351.36
				SMBG	£51.09	SMBG	£119.54
Total Cost	£476.93		£539.11		£730.58		£947.83
DAPA	£476.98	Glicl. MR	£62.18	Glicl. MR	£62.18		
		Dapa.	£476.98	Dapa.	£476.98	Dapa.	£476.98
				INS	£140.38	Int. INS	£351.36
				SMBG	£51.09	SMBG	£119.54
Total Cost	£476.98		£539.16		£730.63		£947.88
SITA	£433.57	Glicl. MR	£62.18	Glicl. MR	£62.18		
		Sita.	£433.57	Sita.	£433.57	Sita.	£433.57
				INS	£140.38	Int. INS	£351.36
				SMBG	£51.09	SMBG	£119.54
Total Cost	£433.57		£495.75		£687.22		£904.47
Pioglitazone	£93.25	Glicl. MR	£62.18	Glicl. MR	£62.18		
		Pio.	£93.25	Pio.	£93.25	Pio.	£93.25
				INS	£140.38	Int. INS	£351.36
				SMBG	£51.09	SMBG	£119.54
Total Cost	£93.25		£155.43		£346.90		£564.15
Gliclazide MR	£62.18	Glicl. MR	£62.18	Glicl. MR	£62.18		
		Pio.	£93.25	Pio.	£93.25	Pio.	£93.25
				INS	£140.38	Int. INS	£351.36
				SMBG	£51.09	SMBG	£119.54
Total Cost	£62.18		£155.43		£346.90		£564.15
Repaglinide	£71.91	Glicl. MR	£62.18	Glicl. MR	£62.18		
		Pio.	£93.25	Pio.	£93.25	Pio.	£93.25
				INS	£140.38	Int. INS	£351.36
				SMBG	£51.09	SMBG	£119.54
Total Cost	£71.91		£155.43		£346.90		£564.15

Abbreviations: Glicl. MR, gliclazide modified release; INS, insulin; Int. INS, intensify insulin; SMBG, self-monitoring blood glucose; EMPA, empagliflozin; CANA, canagliflozin; DAPA dapagliflozin; SITA, sitagliptin; PIO, pioglitazone

Diabetes Complications Costs

The cost of diabetes and its complications were obtained from UKPDS84 (9) and inflated to 2014 costs using the Personal Social Services research Unit (PSSRU) Health Care and Hospital Services (HCHS) index (10). The details of these costs are summarised in Table 6.

Table 6 - Cost of diabetes complications (monotherapy)

	Inpatient costs	Outpatient costs	Total
No event	£472	£547	£1,019
Event year			
Fatal myocardial infarction	£1,564	--	£1,564
Fatal ischaemic heart disease	£3,873	--	£3,873
Fatal stroke	£4,066	--	£4,066
Myocardial infarction	£6,560	£990	£7,550
Ischaemic heart disease	£10,044	£888	£10,932
Stroke	£6,998	£1,122	£8,120
Heart failure	£3,281	£1,007	£4,288
Amputation	£9,816	£2,775	£12,592
Blindness in one eye	£1,393	£1,841	£3,234
Subsequent years			
Myocardial infarction	£1,187	£690	£1,877
Ischaemic heart disease	£1,249	£673	£1,922
Stroke	£1,157	£777	£1,934
Heart failure	£1,515	£1,001	£2,515
Amputation	£1,843	£1,657	£3,499
Blindness in one eye	£466	£759	£1,225

Both Janssen and Boehringer Ingelheim (BI) confined their complication costs to patients' costs. The NICE committee favoured the AG costs which additionally included the outpatient costs.

Adverse Event Costs

To determine the costs of UTIs, the AG assumed treatment to be trimethoprim 200mg twice daily for seven days in males and females, with the number of general practitioner (GP) visits at two and one respectively. The mean total for both males and females was £73. For genital mycotic infections, the treatment was assumed to be a week of fluconazole 200mg in males and three pessaries of clotrimazole 200mg in females. The mean cost for males and females was £51 (7).

To ascertain the cost of severe hypoglycaemic events (SHEs), the AG divided the patients into three groups based on care givers: those treated by family members, those treated by medical practitioners in the community and those treated in hospital. Based on 2007 prices, the costs were £33 (due to NHS follow up costs), £231 and £862 respectively. The AG used figures from the diabetes clinical guideline 87 (now NG28 (1); the assumption of treatment proportion was 9/19 for treatment by family members with the 65% of the remainder treated in hospital. Inflating to 2014 costs, the mean cost for severe hypoglycaemic event was £411 (7).

A summary of the adverse event costs used by the AG is presented in Table 7 below.

Table 7 - Adverse Events Costs (Monotherapy)

Adverse events	Costs
SHE	£411
Non-severe hypoglycaemic event (NSHE)	£0
UTI	£73
Genital mycotic infections	£51

Abbreviations: AG, assessment group; SHE, severe hypoglycaemic event; UTI, urinary tract infection

B.2.2.2 Dual Therapy

For dual therapy healthcare resource use and unit costs were taken from TA418 (11). Although it only considers triple therapy, the resource use is applicable to both dual and triple therapy. TA418 was published in November 2016 and is the latest appraisal of SGLT-2is, reflecting the latest thinking on resource use, assumptions and drivers of the cost-effectiveness of SGLT-2is. All costs were presented in 2014 prices.

Direct Drug Costs

The annual direct costs for all SGLT-2is was the same at £477, the cost of DPP-4i was taken as the weighted average of the market share of DPP-4i £424.50 (see Table 8). A one-off renal function monitoring cost was applied to dapagliflozin at £47 comprising of £45 for a GP appointment and £2 for the test itself (11). This was a conservative approach as it is appropriate for all SGLT-2is (AstraZeneca response to ERG clarification questions); self-monitoring blood glucose (SMBG) and needle use for insulin regimen was not accounted for (12). The annual drug acquisition cost are based on pack prices and summarised below in Table 8.

Table 8 - Annual Direct Drug Costs

Treatment	Share	Annual cost
DAPA10	--	£477
CANA100	--	£477
CANA300	--	£477
EMPA10	--	£477
EMPA25	--	£477
SITA100	71%	£434
Saxagliptin (SAXA) 5mg	10%	£412
Vildagliptin 100mg	3%	£435
Linagliptin (LINA) 5mg	12%	£434
Alogliptin (ALO) 25mg	3%	£347
MET	--	£25.29
SU	--	£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

Abbreviations: 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
Note: Pack costs taken from BNF

Diabetes Complications Costs

The manufacturer (AstraZeneca) sourced complication costs from UKPDS 65 (13). The ERG preferred the updated UKPDS 84 costs which the committee concluded was less questionable. As UKPDS 84 did not provide a cost for renal disease (9) the ERG obtained these values from Lamping et al., 2000 (14) and inflated them using the HCHS index (10). The resulting inflated costs for a fatal event and for a non-fatal event were respectively £36,889 and £36,801. The ERG preferred complication costs are presented in Table 9.

Table 9 - Cost of diabetes complications (dual therapy)

	Male			Female			
	IP	OP	Total	IP	OP	Total	Mean
No event	£596	£569	£1,165	£702	£736	£1,438	£1,285
Event Year							
Fatal MI	£1,765	£569	£2,334	£1,989	£736	£2,725	£2,506
Non-fatal MI	£6,824	£1,012	£7,836	£7,075	£1,179	£8,254	£8,020
Fatal stroke	£4,266	£569	£4,835	£4,490	£736	£5,227	£5,007
Non-fatal stroke	£7,597	£1,144	£8,742	£8,007	£1,312	£9,319	£8,995
Fatal IHD	£4,099	£569	£4,668	£4,333	£736	£5,069	£4,844
Non-fatal IHD	£10,526	£910	£11,436	£10,877	£1,078	£11,955	£11,665
Heart failure	£3,581	£1,029	£4,610	£3,842	£1,196	£5,039	£4,799

Blindness in one eye	£1,672	£1,864	£3,536	£1,886	£2,032	£3,918	£3,704
Amputation	£10,170	£2,800	£12,970	£10,460	£2,968	£13,427	£13,171
Subsequent years							
Non-fatal MI	£1,436	£712	£2,148	£1,631	£879	£2,510	£2,307
Non-fatal stroke	£1,407	£800	£2,206	£1,595	£967	£2,562	£2,363
Non-fatal IHD	£1,511	£694	£2,205	£1,711	£861	£2,572	£2,367
Heart failure	£1,812	£1,023	£2,835	£2,037	£1,190	£3,228	£3,008
Blindness in one eye	£594	£781	£1,374	£706	£948	£1,653	£1,497
Amputation	£2,166	£1,681	£3,847	£2,415	£1,848	£4,263	£4,030

Abbreviations: MI, myocardial infarction; IHD, ischaemic heart disease; IP, inpatient cost; OP, outpatient cost

Adverse Event Costs

The cost for SHEs was the same as to the costs applied in the NICE diabetes clinical guideline modelling, £380 (15) (Table 10). This is slightly lower than the £411 applied in TA390 (2). UTIs and genital mycotic infections were assumed to require a GP visit at £45(15), £51 in TA390 (2). The reason for the lower figures in comparison to the monotherapy costs (TA390) is that in TA390, it was assumed there would be two GP visits for male UTIs(15). Additionally medication costs were included in TA390 but not in TA418.

Table 10 - Adverse event costs (dual therapy)

Adverse events	Costs
SHE	£380
(NSHE	£0
UTI	£45
Genital mycotic infections	£45

Abbreviations: ERG, evidence review group; SHE, severe hypoglycaemic event; NSHE, non-severe hypoglycaemic event, UTI, urinary tract infections

B.3 Clinical effectiveness

B.3.1. Identification and selection of relevant studies

Two systematic literature reviews (SLRs) were conducted to identify clinical studies relevant to this submission. The first SLR was designed to identify randomised controlled trials (RCTs) on the efficacy and safety of ertugliflozin and other pharmacological interventions (other SGLT-2is) for the treatment of adult patients with uncontrolled T2DM. The searches for this SLR were originally conducted on the 19th December 2016 and updated on 11th August 2017 and 8th May 2018.

The second SLR was designed to identify interventional non-RCTs evidence supporting the efficacy and safety of ertugliflozin for the treatment of uncontrolled T2DM. Searches for this SLR were conducted in August 2017 and May 2018. From the second SLR update:

1. RCTs SLR: A total of 1,936 citations were identified:
   - 10 RCTs for ***monotherapy*** were retained and included as evidence supporting the network meta-analysis (NMA) in Section B.3.8. The only ertugliflozin RCT identified as relevant for the purposes of this submission was the VERTIS MONO study
   - 8 RCTs for ***dual therapy***. The ertugliflozin RCTs relevant for the purposes of this submission were the VERTIS MET, VERTIS FACTORIAL and VERTIS SU studies. However, VERTIS SU was not included in the NMA because SUs were not comparators of interest in this submission. Further rationale for the exclusion of this trial is provided in Section B.3.2.4.
2. Non-RCTs SLR: A total of 153 citations were identified but none were included in accordance with the inclusion and exclusion criteria described in Appendix D.

Full details of the SLR process and methods used to identify and select the clinical evidence relevant to the appraisal of ertugliflozin in monotherapy and dual therapy have been included in Appendix D.

B.3.2. List of relevant clinical effectiveness evidence

B.3.2.1 The VERTIS MONO study: evidence supporting ertugliflozin in monotherapy

The efficacy of ertugliflozin monotherapy has been evaluated in a Phase 3, 52-week, multicentre, randomised, parallel – group study which had a 26–week, double-blind, placebo – controlled treatment period (phase A) (16, 17), followed by a 26–week active – controlled treatment period (phase B), in patients with T2DM and with inadequate glycaemic control

despite diet and exercise (16), (17). A summary of ertugliflozin monotherapy clinical trial is presented in Table 11 below.

Table 11 - Clinical effectiveness evidence from VERTIS MONO

Study	**VERTIS MONO (16, 17)**
Study design	A Phase 3, 52-week, multicentre, randomised, parallel – group study divided into two parts: - phase A, a 26–week, double-blind, placebo–controlled treatment period - phase B, a 26–week active–controlled treatment period
Population	People ≥18 years of age with T2DM, diagnosed in accordance with the American Diabetes Association (ADA) guidelines, with inadequate glycaemic control (HbA1c 7.0-10.5% [53-91 mmol/mol], inclusive) despite diet and exercise
Intervention(s)	Ertugliflozin 5 mg (N=156) Ertugliflozin 15 mg (N=152) **Phase A**: the study utilized a double-dummy approach to maintain double-blinding with placebo tablets matching the ertugliflozin missing dose. Patients were instructed to take: - 1 tablet of ertugliflozin 5 mg and 1 tablet of placebo matching ertugliflozin 10 mg - 1 tablet of ertugliflozin 5 mg and 1 tablet of ertugliflozin 10 mg Thus, all patients had to take 2 tablets each day of ertugliflozin or matching placebo until week 26. Patients were prescribed with glycaemic rescue therapy in the form of open-label metformin in Phase A when exceeding the following thresholds: - FPG >15.0 mmol/L after randomisation up to week 6 - FPG>13.3 mmol/L after week 6 and up to week 12 - FPG>11.1 mmol/L after week 12 and up to week 26 **Phase B**: active controlled treatment period where patients remained on their randomised treatment (ertugliflozin 5 or 15 mg) until week 52
Comparator(s)	Placebo (N=153) A single placebo run-in was administered for two weeks prior to Day 1 of Phase A; patients were instructed to take 1 tablet of placebo matching ertugliflozin 5 mg and 1 tablet of placebo matching ertugliflozin 10 mg each morning. **Phase A:** the study utilised a double-dummy approach to maintain double-blinding with a placebo tablet matching the ertugliflozin 5 mg tablet and another tablet matching the ertugliflozin 10 mg tablet. Patients were instructed to take 1 ertugliflozin 5 mg tablet matching placebo and 1 ertugliflozin 10 mg tablet matching placebo each day in the morning. Thus, all patients had to take 2 tablets each day of placebo until week 26 **Phase B**: non-rescued patients in the placebo treatment group received blinded metformin in addition to placebo for ertugliflozin, while non-rescued patients in the ertugliflozin groups received placebo for metformin in addition to ertugliflozin 5 mg or ertugliflozin 15 mg. Patients rescued with metformin in Phase A entered into Phase B and continued to receive open-label metformin in addition to their original randomised treatment
Indicate if trial supports application for marketing authorisation	Yes
Reported outcomes specified in the decision problem	• Mortality • Complications of diabetes, including cardiovascular, renal and eye. • HbA1c/glycaemic control. • BMI

	• Frequency and severity of hypoglycaemia. • Changes in cardiovascular risk factors. • Adverse effects of treatment, including UTIs, genital mycotic infections and malignancies.
All other reported outcomes	- HbA1c <6.5% - FPG - Post-prandial glucose (PPG) - Mixed Meal Tolerance Test (MMTT) - Haemoglobin - Hypovolemia - LDL-C/HDL-C ratio - Apolipoprotein-B - Apolipoprotein A-I - Apolipoprotein A-I - Urine albumin / creatinine ratio (UACR)

Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c; FPG, fasting glucose plasma; ERTU5/10/15, ertugliflozin 5,10 and 15 mg; MET, metformin; PBO, placebo; SHE, severe hypoglycaemic event; BMI, body mass index; UTIs, urinary tract infections

B.3.2.2 The VERTIS MET and VERTIS FACTORIAL studies: evidence supporting ertugliflozin in dual therapy

The efficacy and safety of ertugliflozin in combination with metformin have been studied in 2 multi-centre, randomised, double-blind, placebo - controlled Phase 3 clinical studies.

A summary of the clinical trials involving ertugliflozin in combination therapy with metformin is presented in Table 12 (18, 19) and (20, 21) below.

Table 12 - Clinical effectiveness evidence from VERTIS MET

Study	**VERTIS MET (18, 19)**
Study design	A Phase 3, 104-week, multicentre, randomised, parallel – group study divided into two phases: - phase A, a 26–week, double-blind, placebo–controlled treatment period - phase B, a 78–week active–controlled treatment period
Population	People ≥18 years of age with T2DM, diagnosed in accordance with the ADA guidelines, with inadequate glycaemic control (HbA1c 7.0-10.5% [53-91 mmol/mol], inclusive) on metformin therapy at a dose ≥1500 mg/day.
Intervention(s)	Ertugliflozin 5 mg (N=207) Ertugliflozin 15 mg (N=205) **Phase A**: patients were randomised to ertugliflozin 5 mg or ertugliflozin 15 mg while maintaining metformin at a stable dose of ≥1500 mg/day. Patients were instructed to take: - Ertugliflozin 5 mg : 1 tablet of ertugliflozin 5 mg and 1 tablet of placebo matching ertugliflozin 10 mg - Ertugliflozin 15 mg : 1 tablet of ertugliflozin 5 mg and 1 tablet of ertugliflozin 10 mg 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 up to week 6 - FPG > 240 mg/dL after week 6 through week 12 - FPG > 200 mg/dL after week 12 through week 26

	Phase B: active controlled treatment period where patients remained on their randomised treatment (ertugliflozin 5 mg or ertugliflozin 15 mg) until week 52. The double-blinding was maintained through the use of blinded glimepiride or matching placebo.
Comparator(s)	Placebo (N=209) A single placebo run-in was administered for 2 weeks prior to Day 1 of Phase A, which had the explicit purpose of familiarising the patients with the study treatment regimen and excluding patients who were not compliant with the blinded placebo prior to randomization. **Phase A**: the study utilised a double-dummy approach to maintain double-blinding. Patients were instructed to take 1 ertugliflozin 5 mg tablet matching placebo and 1 ertugliflozin 10 mg tablet matching placebo daily. Thus, all patients had to take 2 tablets each day of placebo until week 26. **Phase B**: non-rescued patients in the placebo treatment group received blinded glimepiride in addition to placebo for ertugliflozin while non-rescued patients in the ertugliflozin groups received placebo for glimepiride in addition to ertugliflozin 5 mg or ertugliflozin 15 mg. Patients rescued with glimepiride in Phase A entered into Phase B and continued to receive open-label glimepiride in addition to their original randomised treatment.
Indicate if trial supports application for marketing authorisation	Yes
Reported outcomes specified in the decision problem	• Mortality • Complications of diabetes, including cardiovascular, renal and eye. • HbA1c / glycaemic control. • BMI • Frequency and severity of hypoglycaemia. • Changes in cardiovascular risk factors. • Adverse effects of treatment, including urinary tract infections, genital infections and malignancies.
All other reported outcomes	- HbA1c <6.5% - Hypovolemia - FPG - Haemoglobin - Patients with rescue therapy needs - Apolipoprotein-B - Apolipoprotein A-I - LDL-C/HDL-C ratio - UACR - Bone mineral density (BMD)

Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c; FPG, fasting glucose plasma; ERTU5/10/15, ertugliflozin 5, 10 and 15 mg; MET, metformin; PBO, placebo; NSHE, non-severe hypoglycaemic event; SHE, severe hypoglycaemic event; BMI, body mass index; UTIs, urinary tract infections; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, triglycerides; GFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio

Table 13 - Clinical effectiveness evidence from VERTIS FACTORIAL

Study	**VERTIS FACTORIAL (20, 21)**
Study design	A Phase 3, 52-week, multicentre, randomised, parallel – group, factorial study of co-administration of ertugliflozin and sitagliptin and administration of the individual agents on the background of metformin, divided into two phases:

<table>
<tr><td></td><td>
- phase A, a 26–week, double-blind, placebo–controlled treatment period
- phase B, a 26–week extension
Treatment arms with ertugliflozin 5 mg and ertugliflozin 15 mg on a background of metformin therapy are the only relevant arms for this submission thus, the other arms will not be discussed from section B.3.3 onwards
</td></tr>
<tr><td>Population</td><td>People ≥18 years of age with T2DM, diagnosed in accordance with the ADA guidelines with inadequate glycaemic control (HbA1c ≥7.5% and ≤11% [≥58 mmol/mol and ≤97 mmol/mol]) on a stable dose of metformin monotherapy</td></tr>
<tr><td>Intervention(s)</td><td>
Ertugliflozin 5 mg (N=250)
Ertugliflozin 15 mg (N=248)
Sitagliptin 100 mg (N=247)

Phase A and B: patients took 3 tablets of study medication once daily in the morning, as per instructions below:
<table>
<tr><th>Background therapy</th><th>Arms</th><th>Medication administered</th></tr>
<tr><td rowspan="9">MET ≥1500 mg/day</td><td rowspan="3">ERTU5</td><td>ERTU5 tablet</td></tr>
<tr><td>Matching PBO for ERTU10</td></tr>
<tr><td>Matching PBO for SITA100</td></tr>
<tr><td rowspan="3">ERTU15</td><td>ERTU5 tablet</td></tr>
<tr><td>ERTU10 tablet</td></tr>
<tr><td>Matching PBO for SITA100</td></tr>
<tr><td rowspan="3">SITA100</td><td>Matching PBO for ERTU5</td></tr>
<tr><td>Matching PBO for ERTU10</td></tr>
<tr><td>SITA100 tablet</td></tr>
</table>
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
</td></tr>
<tr><td>Comparator(s)</td><td>
Ertugliflozin 5 mg / sitagliptin 100 mg (N=243)
Ertugliflozin 15 mg / sitagliptin 100 mg (N=244)

A single placebo run-in was administered for 2 weeks prior to Day 1 of Phase A

Phase A and B: A double-blind/masking technique was used in this study. Ertugliflozin and sitagliptin were packaged identically relative to their matching placebo so that blinding/masking was maintained. Patients were instructed to take the medications as follows:
<table>
<tr><th>Background therapy</th><th>Arms</th><th>Medication administered</th></tr>
<tr><td rowspan="6">MET ≥1500 mg/day</td><td rowspan="3">ERTU5 + SITA100</td><td>ERTU5 tablet</td></tr>
<tr><td>Matching PBO for ERTU10</td></tr>
<tr><td>SITA100 tablet</td></tr>
<tr><td rowspan="3">ERTU15 + SITA100</td><td>ERTU5 tablet</td></tr>
<tr><td>ERTU10 tablet</td></tr>
<tr><td>SITA100 tablet</td></tr>
</table>
</td></tr>
<tr><td>Indicate if trial supports application for marketing authorisation</td><td>Yes</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td>
- Mortality
- Complications of diabetes, including cardiovascular, renal and eye
- HbA1c/glycaemic control.
</td></tr>
</table>

	• BMI • Frequency and severity of hypoglycaemia • Changes in cardiovascular risk factors • Adverse effects of treatment, including urinary tract infections, genital infections and malignancies.
All other reported outcomes	- Hypovolemia - Haemoglobin - Patients with rescue therapy needs - Glucose AUC/Insulin AUC Ratio - Post-prandial urine glucose - Urine glucose excretion rate - FPG - PPG - Apolipoprotein-B - Apolipoprotein A-I - Urinary Albumin / Creatinine ratio (UACR) - LDL-C/HDL-C ratio - β- cell responsivity

Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c; FPG, fasting glucose plasma; PPG, post-prandial glucose; ERTU5/10/15, ertugliflozin 5, 10 and 15 mg; MET, metformin; PBO, placebo; NSHE, non-severe hypoglycaemic event; SHE, severe hypoglycaemic event; BMI, body mass index; UTIs, urinary tract infections; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, triglycerides; GFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio

B.3.2.4 RCTs excluded from further discussion

Error! Reference source not found. lists other RCTs that studied ertugliflozin in combination with other AHAs and that have been excluded from this submission.

Table 14 - RCTs excluded from the submission

Study details	Population	Intervention & Comparator	Rationale for exclusion from decision problem
VERTIS SU (22, 23) Phase 3, completed	Patients with T2DM who have inadequate glycaemic control on MET	MET + ERTU5/15 vs. SU	The dual therapy focus of this submission is ertugliflozin compared to other SGLT-2is on a background of metformin. Additionally, all VERTIS SU endpoints were collected at 52 weeks (Phase A) whereas all the other ertugliflozin (and the other SGLT-2is) RCTs included in this submission were collected and compared at week 26 (Phase A).
VERTIS SITA (24) (25) Phase 3, completed	Patients with T2DM who have inadequate glycaemic control despite diet and exercise	• SITA100 + ERTU5 vs. PBO • SITA100 + ERTU15 vs. PBO	The dual therapy focus of this submission is ertugliflozin compared to other SGLT-2is on a background of metformin and not on a background of diet and exercise and in combination with a DPP-4i.
VERTIS ASIA (26) Phase 3 completed	Asian participants with T2DM who have inadequate glycaemic control on MET	MET + ERTU5/15 vs. PBO	The clinical study report (CSR) is anticipated to be available only in August 2018 and, as a result, data from the VERTIS ASIA trial could not be included in the current submission
VERTIS RENAL (27) (28) Phase 3, completed	Patients with T2DM with stage 3 Chronic Kidney Disease (CKD) who have inadequate glycaemic control on background AHA therapy	• AHA + ERTU5/15 vs. PBO All AHAs excluding MET and other SGLT-2is	This study is confined to patients with stage 3 CKD and it is not generalisable to the population considered in this submission
VERTIS SITA2 (29)	Patients with T2DM who have inadequate glycaemic control on MET and SITA	• MET + SITA100 + ERTU5/15 vs. • MET + SITA100 + PBO	This study is of a triple therapy combination which will be appraised separately

Abbreviations: T2DM, type 2 diabetes mellitus; ERTU5/15, ertugliflozin 5 and 15 mg; MET, metformin; PBO, placebo; AHA, anti-hyperglycaemic agent; HbA1c, haemoglobin A1c; DPP-4i, dipeptidyl peptidase 4 inhibitor; SUs, sulphonylureas; SGLT-2i, sodium-glucose co-transporter 2 inhibitor

B.3.3. Summary of methodology of the relevant clinical effectiveness evidence

Please note for clarity that the ertugliflozin 5 mg and 10 mg doses used in the clinical trials (for ertugliflozin 15 mg, both the 5 mg and 10 mg doses were administered) are not the doses that will be available in the UK; only the 5 mg and 15 mg tablets will be marketed.

Ertugliflozin monotherapy

B.3.3.1.a VERTIS MONO key aspects

As noted in Section B.1.1, ertugliflozin monotherapy has been assessed by the EMA for the treatment of patients with T2DM as a monotherapy and combination therapy. All aspects of the included trial methodologies are presented below. For completeness, a summary of the baseline characteristics of the participants in this trial is reported in Section B.3.3.3 (Table 16).

VERTIS MONO Study (16, 17)

Trial design

The VERTIS MONO study is a 52-week, double-blind, multi-center, randomised, parallel-group study with a 26-week, placebo-controlled treatment period (Phase A) followed by a 26-week active-controlled treatment period (Phase B) in people with T2DM and inadequate glycaemic control despite diet and exercise.

Phase A of the study investigated the effect of ertugliflozin 5 mg and ertugliflozin 15 mg orally administered, every day at the same time in the morning over a 26 week period. Phase A was designed to evaluate the efficacy of both the 5 mg and 15 mg oral doses of ertugliflozin on glycaemic control, body weight, and blood pressure following a 26-week dosing period in adult patients with T2DM and inadequate glycemic control on diet and exercise. Phase B was designed to evaluate the longer-term safety and tolerability of ertugliflozin throughout week 52.

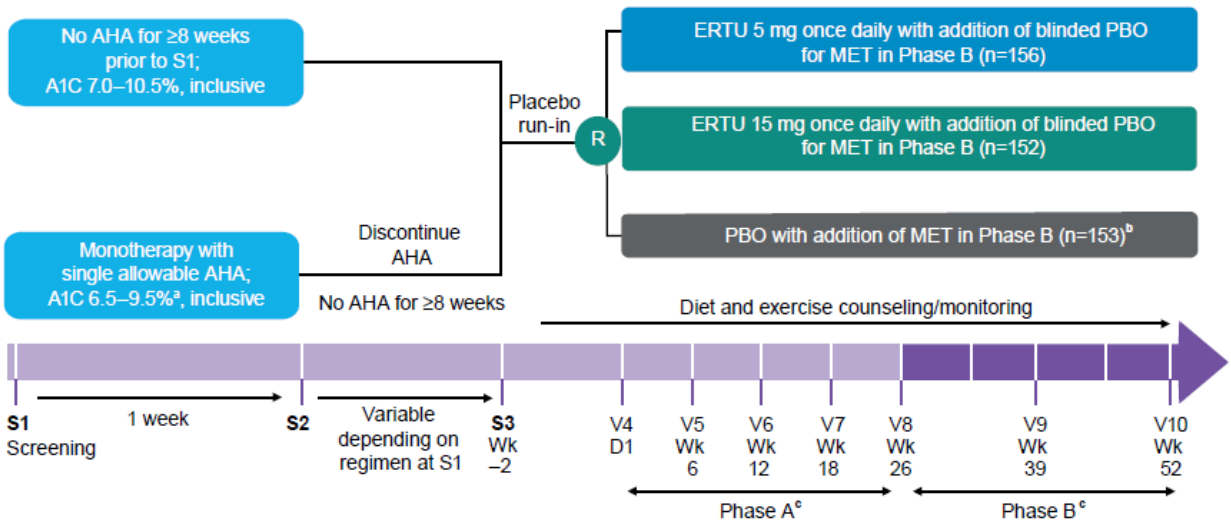
Allocation of patients to treatment groups was conducted using a randomisation system (interactive voice response system [IVRS]). Patient information was entered into the system starting at visit screening 1 (S1) (Please refer to Figure 2) when the patient was assigned to a unique identifier which was retained throughout the duration of participation in the study. On Day 1 (V4), once the inclusion, exclusion and randomisation criteria had been verified, each patient was provided with a patient randomisation number. A computer-generated

randomisation code using the method of random permuted blocks was utilised to assign on Day 1 (V4) patients to 1 of 3 treatment regimens (ertugliflozin 5 mg, ertugliflozin 15 mg or placebo).

A total of 1067 patients were screened for inclusion in the study of which 461 were randomised in a 1:1:1 ratio: 156 were assigned to ertugliflozin 5 mg, 152 to ertugliflozin 15 mg and 153 to placebo as showed in Figure 2 (a more comprehensive participant flow diagram is presented in Appendix D).

Given that the results at week 26 (Phase A) will be providing the evidence of ertugliflozin 5 mg and ertugliflozin 15 mg comparability to the other SGLT-2is in the submission, Phase B of the VERTIS MONO study will not be discussed further. However, for completeness, the main efficacy and safety results of Phase A plus B are reported in Appendix I.

Figure 2 - VERTIS MONO trial design diagram



[a] Patients were ranodmised only if HbA1c at S3 visit was 7.0–10.5%, inclusive.

[b] Blinded MET was administered only in patients who did not receive glycaemic rescue in Phase A. Patients rescued with open-label MET in Phase A continued to receive open-label MET in addition to their ranodmised treatment.

[c] Glycaemic rescue therapy (glimepiride in Phase B) was initiated in patients with FPG >200 mg/dL (11.1 mmol/L) or HbA1c >8.0% (64 mmol/mol).
Patients remained in the study and continued to receive study medication in a blinded fashion unless they met discontinuation criteria.
Abbreviations: HbA1c, haemoglobin A1c; AHA, antihyperglycaemic agent; D, day; ERTU, ertugliflozin; FPG, fasting plasma glucose; MET, metformin; n, number of patients randomised in treatment group; PBO, placebo; R, randomisation; S, screening; V, visit; Wk, week.

Eligibility criteria

Eligible patients were diagnosed with T2DM in accordance with ADA guidelines, aged 18 or older with an HbA1c of 7.0% to 10.5% (53-91 mmol/mol) and without treatment with an AHA for ≥8 weeks prior to screening. During the screening visits, those who were on a single AHA

with an HbA1c between 6.5% and 9.5% (48-80 mmol/mol) were asked to discontinue the AHA for at least 8 weeks and to return for another screening visit. If at the second screening visit the level of HbA1c increased (from 7.0% to 10.5% [53-91 mmol/mol])), they were eligible for enrollment in the study.

The exclusion criteria comprised of patients diagnosed with T1DM, medical history of ketoacidosis, uncontrolled hyperglycaemia (glucose > 15mmol/L), eGFR <55 mL/min/1.73m^2 or serum creatinine ≥115 µmol/L (1.3 mg/dL) in men or ≥106 µmol/L (1.2 mg/dL) in women, or a history of cardiovascular event within 3 months of screening.

Settings and locations

Patients were recruited at 67 sites in 7 countries: USA, Canada, Israel, Italy, Mexico, South Africa and the UK. In the UK, a total of 30 patients were recruited across 19 centres.

Trial drugs and concomitant medications

Ertugliflozin 5 mg and ertugliflozin 15 mg were supplied as immediate-release tablets for oral administration. Tablets were packaged into bottles. Patients receiving glycaemic rescue therapy received treatment with open-label metformin in Phase A.

The most common concomitant drug therapeutic categories were lipid modifying agents (57.5%), agents acting on the renin-angiotensin system (51.0%), and analgesics (39.7%). There were no clinically important differences between treatment groups in concomitant medication categories.

At baseline, 55.7% of patients used blood pressure medications including diuretics, and use was similar for all treatment groups. Diuretic use was 16.7% at baseline, overall. At baseline, use of lipid lowering medication was higher in the ertugliflozin 5 mg and ertugliflozin 15 mg groups (57.1% and 53.3%, respectively) compared to the placebo group (49.0%).

Outcomes specified in the scope

VERTIS MONO study outcomes were all pre-specified and they are consistent with the outcomes described in the scope (see Table 1).

The primary efficacy endpoint was the change from baseline in HbA1c at week 26 followed by pre-specified secondary endpoints all evaluated at week 26 that included: the proportion of patients with HbA1c <7.0%, change from baseline in body weight and in 2-hour PPG, SBP, DBP, mixed meal tolerance test (MMTT for glucose, insulin and C-peptide, proportion of patients with HbA1c <6.5% (48mmo/mol), proportion of patients receiving glycaemic rescue therapy and time to initiation of glycaemic rescue therapy.

The safety and tolerability of ertugliflozin was evaluated through the assessment of pre-specified adverse events (AEs) following a tiered approach. Tier 1 AEs were AEs of special interest such as genital mycotic infections, UTIs, symptomatic hypoglycaemia and hypovolemia. AEs (overall summary, specific terms, and system organ class (SOC) terms) and pre-defined limit of changes (PDLCs) in laboratory parameters that were not pre-specified as Tier 1 endpoints were classified as belonging to Tier 2 or Tier 3, based on the number of events observed. The safety measurements included: clinical monitoring, vital signs, ECGs, adjudicated events (deaths, fractures, pancreatitis, renal and hepatic events), physical examination and laboratory tests (lipids, apolipoproteins and UACR).

Ertugliflozin dual therapy

B.3.3.1.b VERTIS MET and VERTIS FACTORIAL key aspects

As noted in Section B.1.1, ertugliflozin dual therapy has been assessed by the EMA for the treatment of patients with T2DM. All aspects of the methodologies in the included trials are presented below. For completeness, an overview of the baseline characteristics of the participants in these trials is presented in Table 17 (VERTIS MET) and Table 18 (VERTIS FACTORIAL). Additionally, a comparative summary of the methodologies used in the ertugliflozin RCTs is reported in Table 15.

VERTIS MET Study (18, 19)

Trial design

The VERTIS MET study is a 104-week, double-blind, multi-center, randomised, parallel-group study with a 26-week, double-blind, placebo-controlled treatment period (Phase A) followed by a 78-week active-controlled treatment period (Phase B). VERTIS MET was designed to evaluate the efficacy and tolerability of ertugliflozin 5 mg and 15 mg in combination with metformin in people with T2DM and inadequate glycaemic control on metformin monotherapy at a dose ≥1500 mg/day for at least 8 weeks.

VERTIS MET enrolled 621 patients with a diagnosis of T2DM according to ADA guidelines.

The study included a screening period of 1 week, a metformin stable dose period of at least 8 weeks (when patients discontinued and remained off any previous allowable background diabetes therapy except for metformin) and a 2-week single-blind placebo run-in period prior to randomisation (Figure 3).

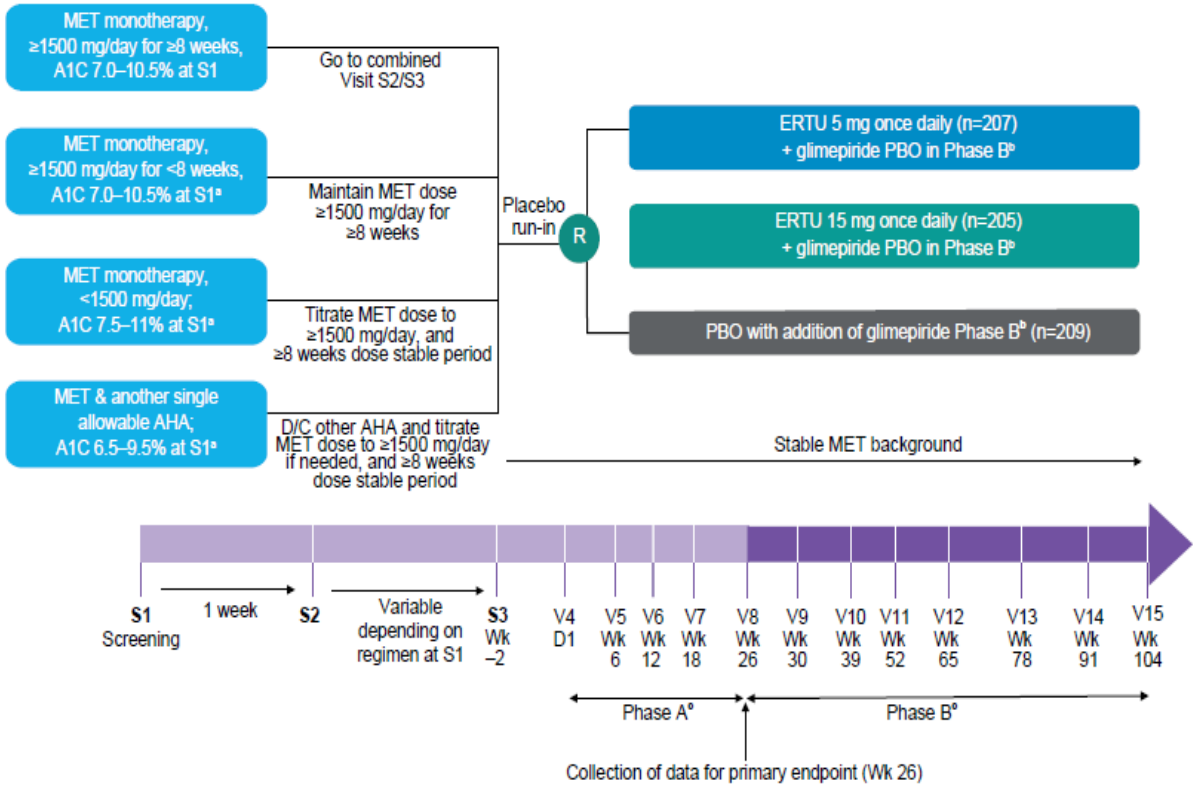
Randomisation to treatment groups proceeded through the use of a randomisation system (IVRS). Patients were randomised (1:1:1) to placebo, ertugliflozin 5 mg or ertugliflozin 15 mg once daily and stratified by gender/menopausal status. Glycaemic rescue therapy with

glimepiride or basal insulin was given to patients exceeding the FPG threshold reported in Table 12.

Phase A of this study was patient, investigator and sponsor blinded. The blinded study medication dispensing and accountability were managed by IVRS and monitored by clinical research associates in addition to the study medication inventory monitoring at each site.

Given that the results at week 26 (Phase A) will be providing the evidence of comparability for ertugliflozin 5 mg and 15 mg against the comparators included in the scope, Phase B of the VERTIS MET study will not be discussed further. However, for completeness, the main efficacy and safety results of Phase A plus B are presented in Appendix I.

Figure 3 – The VERTIS MET trial design diagram



[a] Patients were randomised only if HbA1c at S3 visit was between 7.0-1.05% inclusive
[b] Glimepiride/glimepiride matching placebo was given only to patients in Phase B who did not receive glycaemic rescue therapy in Phase A
Abbreviations: D/C, discontinuation; HbA1c, haemoglobin A1c; AHA, antihyperglycaemic agent; D, day; ERTU, ertugliflozin; FPG, fasting plasma glucose; MET, metformin; n, number of patients randomised in treatment group; PBO, placebo; R, randomisation; S, screening; V, visit; Wk, week.

Eligibility criteria

To be considered for inclusion in the study, male and female patients had to have a diagnosis of T2DM in accordance to ADA guidelines, be aged ≥18 years, have a BMI

between 18.0-40.0 kg/m^2, have inadequate glycaemic control (HbA1c between 7.0-10.5%, inclusive) on metformin therapy (≥1500 mg/day for at least 8 weeks).

During the first screening if:

- patients had received dual therapy with metformin and another AHA, the patients were instructed to discontinue the AHA and continue on metformin monotherapy only
- patients had received metformin monotherapy alone ,1500 mg/day or ≥1500 mg/day for less than 8 weeks, the metformin therapy alone was adjusted

In this way at the second screening every patients was on metformin monotherapy at ≥1500 mg/day for ≥8 weeks and was eligible to enter the study if their HbA1c was still between 7.0-10.5%.

Exclusion criteria included diagnosis of T1DM, FPG >270 mg/dL, eGFR <55 mL/min/1.73m^2, history of ketoacidosis, CV event within 3 months of screening and documented osteoporosis with gender-specific bone mineral density (BMD).

The key eligibility criteria have been summarised in Table 15.

Settings and locations

This study was conducted in 14 countries at 103 study centres: 4 in Australia, 4 in the Czech Republic, 5 in Hong Kong, 10 in Hungary, 5 in Israel, 2 in Mexico, 3 in Poland, 8 in Romania, 5 in the Russian Federation, 10 in Slovakia, 12 in South Africa, 8 in Taiwan, 1 in the United Kingdom (N=2 patients) and 26 in the United States. In total, 122 sites were initiated, and 115 sites screened at least 1 patient.

Trial drugs and concomitant medications

Patients were given ertugliflozin 5 mg, ertugliflozin 15 mg or placebo tablets once daily for 26 weeks at approximately the same time each day without regard for food.

AHAs taken by a patient at any time prior to S1 and non-AHAs taken within 8 weeks prior to S1 were to be recorded on the appropriate electronic case report form (eCRF). Concomitant medications (including any glycaemic rescue therapy) taken during the study were also recorded. Patients had to be on a stable dose of their concomitant medications (if allowed) prior to randomisation.

Outcomes specified in the scope

VERTIS MET study outcomes were pre-specified and they are consistent with the outcomes identified in the scope (Section B.1.1).

The primary efficacy endpoint was the change from baseline in HbA1c at week 26 followed by pre-specified secondary endpoints that included: change in FPG, body weight and blood

pressure (SBP and DBP), proportion of patients with HbA1c <7.0% and patients who received glycaemic rescue therapy.

The safety and tolerability of ertugliflozin was evaluated through the assessment of pre-specified adverse events (AEs) following a tiered approach. Tier 1 AEs were AEs of special interest such as genital mycotic infections, UTIs, symptomatic hypoglycaemia and hypovolemia. AEs (overall summary, specific terms, and system organ class (SOC) terms) and pre-defined limit of changes (PDLCs) in laboratory parameters that were not pre-specified as Tier 1 endpoints were classified as belonging to Tier 2 or Tier 3, based on the number of events observed.

The BMD for lumbar spine, femoral neck, hip and distal forearm regions was measured both at baseline and at week 26.

VERTIS FACTORIAL Study (20, 21)

Trial design

The VERTIS FACTORIAL study is a 52-week, double-blind, multi-center, randomised, parallel-group, factorial study with a 26-week, double-blind, placebo-controlled treatment period (Phase A) followed by a 26-week extension (Phase B). VERTIS FACTORIAL assesses the efficacy and tolerability of ertugliflozin and sitagliptin given together or alone, with metformin in participants with T2DM and inadequate glycemic control on metformin monotherapy at a dose ≥1500 mg/day for at least 8 weeks.

VERTIS FACTORIAL enrolled 1232 patients with a diagnosis of T2DM according to ADA guidelines. The study included a screening period, a metformin stable dose period for at least 8 weeks (when patients discontinued and remained off any previous allowable background diabetes therapy except for metformin), and a 2-week single-blind PBO run-in period prior to randomisation (Figure 4).

Randomisation occurred centrally using an IVRS. Patients were assigned randomly using a computer-generated randomisation schedule to 1 of the following 5 treatment groups (1:1:1:1:1 ratio): ertugliflozin 5 mg, ertugliflozin 15 mg, sitagliptin 100 mg, ertugliflozin 5 mg + sitagliptin 100 mg and ertugliflozin 15 mg + sitagliptin 100 mg once daily and stratified by participation in the mixed meal tolerance test (MMTT).

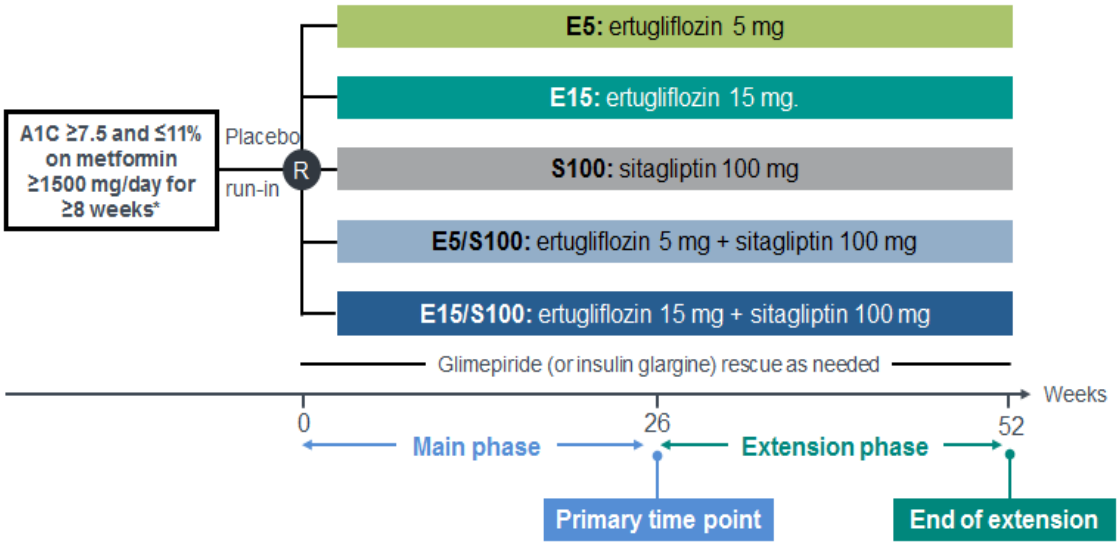
During the double-blind treatment period, patients who met progressively more stringent glycaemic rescue criteria were to receive open-label glimepiride rescue medication (or insulin glargine, if open-label glimepiride was not considered appropriate by the investigator).

A double-blind/masking technique was used in this study. Ertugliflozin and sitagliptin were packaged identically relative to their matching placebos so that blinding was maintained. The patient, the investigator, Sponsor personnel and personnel from the Sponsors' designees,

who were involved in the treatment or clinical evaluation of the patients, were unaware of treatment group assignments.

Given that the results at week 26 (Phase A) will be providing the evidence of comparability for ertugliflozin 5 mg and 15 mg against the comparators included in the scope, Phase B of VERTIS FACTORIAL study will not be discussed further. However, for completeness, the main efficacy and safety results of Phase A plus B are presented in Appendix I.

Figure 4 - VERTIS FACTORIAL trial design diagram



* Patients on one of those regimens were eligible to enter the screening period if they met the following criteria after the dose titration/stabilization period: on metformin ≥1500 mg/day for <8 weeks or on metformin <1500 mg/day and HbA1c≥8.0% and ≤11.5%

Abbreviations: HbA1c, haemoglobin A1c; AHA, antihyperglycaemic agent; D, day; E, ertugliflozin; S100, sitagliptin 100 mg; MET, metformin; n, number of patients randomised in treatment group; R, randomisation

Eligibility criteria

To be considered for inclusion in the study, male and female patients had to have a diagnosis of T2DM in accordance with ADA guidelines, be aged ≥18 years, have a BMI ≥ 18.0 kg/m2, have inadequate glycaemic control on metformin therapy (≥1500 mg/day for at least 8 weeks with HbA1c ≥7.5% and ≤11.0% (≥58 mmol/mol and ≤97 mmol/mol) or <1500 mg/day but with HbA1c ≥8.0% and ≤11.5% (≥64 mmol/mol and ≤102 mmol/mol)).

The exclusion criteria included diagnosis of T1DM, eGFR <60 mL/min/1.73 m^2, history of ketoacidosis, CV event within 3 months of screening, history of malignancies or being affected by HIV or liver disease.

The key eligibility criteria have been summarized in Table 15.

Settings and locations

The trial was conducted in 21 countries, including 242 trial centres: 4 in Canada, 19 in Argentina, 7 in Chile, 8 in Colombia, 15 in Mexico, 52 in the United States, 4 in Italy, 19 in Russia, 7 in Bulgaria, 13 in Romania, 11 in Hungary, 13 in Poland, 12 in Slovakia, 12 in Ukraine, 9 in the Czech Republic, 4 in Finland, 10 in Israel, 7 in Malaysia, 7 in the Philippines, 3 in Thailand and 6 in New Zealand.

Trial drugs and concomitant medications

Patients were given ertugliflozin 5 mg, ertugliflozin 15 mg and sitagliptin 100 mg as a single agent or as a dual combination of these 3 agents or their related matching placebo dose once daily (a total of 3 tablets per day) for 52 weeks (26 weeks for Phase A) at approximately the same time each day without regard for food.

The AHAs taken by the patient at any time prior to screening, and any other medications taken within 8 weeks of screening were recorded on the appropriate electronic case report form (eCRF). Concomitant medications (including glycaemic rescue therapy) taken during the trial were also recorded.

Outcomes specified in the scope

The VERTIS FACTORIAL study outcomes were pre-specified and they are consistent with the outcomes identified in the scope (Section B.1.1)

The primary efficacy endpoint was the change from baseline in HbA1c at week 26. The secondary endpoints were all evaluated at week 26 as change from baseline: FPG, body weight and SBP and proportion of patients with HbA1c <7.0% (53 mmol/mol).

The safety and tolerability of ertugliflozin was evaluated through the assessment of pre-specified adverse events (AEs) following a tiered approach. Tier 1 AEs were AEs of special interest: genital mycotic infections, UTIs, symptomatic hypoglycaemia and hypovolemia. All other AEs and changes in laboratory parameters that were not pre-specified as Tier 1 endpoints were classified as belonging to Tier 2 or Tier 3, based on the number of events observed.

B.3.3.2 Comparative summary of the methodology of the ertugliflozin RCTs

Table 15 - Comparative summary of the methodology of the ertugliflozin RCTs for mono and dual therapy

	VERTIS MONO (16, 17)	VERTIS MET (18, 19)	VERTIS FACTORIAL (20, 21)
	Monotherapy	**Dual therapy**	
Location	• 81 study centres • 7 countries: Canada, Israel, Italy, Mexico, South Africa, United Kingdom and United States (including centres that did not randomised patients)	• 103 study centres • 14 countries: Australia, Czech Republic, Hong Kong, Hungary, Israel, Mexico, Poland, Romania, Russia, Slovakia, South Africa, Taiwan, United Kingdom and United States	• 242 study centres • 21 countries: Argentina, Bulgaria, Canada, Chile, Colombia, Czech Republic, Finland, Hungary, Israel, Italy, Malaysia, Mexico, New Zealand, Philippines, Poland, Romania, Russia, Slovakia, Thailand, Ukraine and United States
Trial design	• Phase 3 • Double-blind, multi-center, randomised, parallel-group, placebo-controlled (patients, investigator and sponsor personnel blinded)	• Phase 3 • Double-blind, multi-center, randomised, parallel-group, placebo-controlled (patients, investigator and sponsor personnel blinded)	• Phase 3 • Double-blind, multi-center, randomised, parallel-group, placebo-controlled, factorial (patients, investigator and sponsor personnel blinded)
Eligibility criteria for participants	• Diagnosis of T2DM • Age ≥18 years • BMI between ≥18.0 kg/m2 • Inadequate glycaemic control with no prior allowable oral AHA for ≥8 weeks and with an HbA1c between 7.0-10.5%, inclusive	• Diagnosis of T2DM • Age ≥18 years • BMI between 18.0-40.0 kg/m2 • Inadequate glycaemic control on metformin therapy at a dose of ≥1500 mg/day with an HbA1c between 7.0-10.5%, inclusive	• Diagnosis of T2DM • Age ≥18 years • BMI ≥18.0 kg/m2 • Inadequate glycaemic control on metformin therapy at a dose of ≥1500 mg/day with HbA1c ≥7.5% and ≤11.0% or on metformin <1500 mg/day and with an HbA1c ≥8.0% and ≤11.5%
Trial drugs	Intervention ERTU5 (N=156) and ERTU15 (N=152) tablets for 26 weeks taken once daily on a background of metformin	Intervention *On background of metformin* ERTU5 (N=207) and ERTU15 (N=205) tablets for 26 weeks taken once daily	Intervention *On background of metformin* ERTU5 (N=250) and ERTU15 (N=248), tablets for 26 weeks taken once daily
	Comparator PBO (N=153)	Comparator *On background of metformin* PBO (N=209)	Comparator *On background of metformin* SITA100 (N=247) ERTU5 + SITA100 (N=243)

	VERTIS MONO (16, 17)	VERTIS MET (18, 19)	VERTIS FACTORIAL (20, 21)
	Monotherapy	**Dual therapy**	
			ERTU15 + SITA100 (N=244)
Concomitant medications	Permitted (stable doses prior to and after randomisation) • Metformin if needed for glycaemic rescue therapy • Thyroid replacement medication • Blood pressure or lipid-altering medications • Hormonal Replacement Therapy and Birth Control Medications • Weight loss medication if weight stable Disallowed • Any other AHA with the exception of the protocol-approved agents • Bromocriptine (Cycloset) • Colesevelam (Welchol) • Weight-loss medications	Permitted (stable doses prior to and after randomisation) • Metformin • Glimepiride or basal insulin if needed for glycaemic rescue therapy • Thyroid replacement medication • Blood pressure or lipid-altering medications • Calcium supplementation • Hormonal Replacement Therapy and Birth Control Medications • Weight loss medication if weight stable Disallowed • Any other AHA with the exception of the protocol-approved agents • Bone-active medications (e.g. bisphosphonates) • Weight-loss medications • Bromocriptine (Cycloset) • Colesevelam (Welchol)	Permitted (stable doses prior to and after randomisation) • Metformin • Sitagliptin • Glimepiride or insulin glargine if needed for glycaemic rescue therapy • Thyroid replacement medication • Blood pressure or lipid-altering medications • Hormonal Replacement Therapy and Birth Control Medications • Supplements and/or Traditional Medicines • Weight loss medication if weight stable Disallowed • Any other AHA with the exception of the protocol-approved agents • Corticosteroids • Weight-loss medications • Bromocriptine (Cycloset) • Colesevelam (Welchol)
Primary outcome (including scoring methods and timing of assessment)	Change from baseline in HbA1c to Week 26 HbA1c was measured by the central laboratory at: • Screening visit: 1 and 3 • After randomisation: day 1, week 6, 12, 18 and 26 Rescue visit: if needed and at time of discontinuation	Change from baseline in HbA1c to Week 26 HbA1c was measured by the central laboratory at: • Screening visit: 1 and 3 • After randomisation: day 1, week 6, 12, 18 and 26 Rescue visit: if needed and at time of discontinuation	Change from baseline in HbA1c to Week 26 HbA1c was measured by the central laboratory at: • Screening visit: 1 and 3 • After randomisation: day 1, week 6, 12, 18 and 26 Rescue visit: if needed and at time of discontinuation
Pre-planned subgroups	To assess whether the treatment effect at Week 26 was consistent across various subgroups, the between-group treatment effect (with a nominal 95% CI) for the primary endpoint was estimated and plotted within each category of the following classification variables: baseline HbA1c levels (by	To assess whether the treatment effect at week 26 was consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint was estimated and plotted within each category of the following classification variables: baseline HbA1c levels (by categories: <8.0%; ≥8.0% to <9%;	To assess whether the treatment effect at week 26 was consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint was estimated and plotted within each category of the following classification variables: baseline HbA1c levels (by categories: <8.0%; ≥8.0% and <9%; ≥9% and <10%;≥10%.), age categories, gender,

	VERTIS MONO (16, 17)	VERTIS MET (18, 19)	VERTIS FACTORIAL (20, 21)
	Monotherapy	Dual therapy	
	categories: <8.0%; ≥8.0% to <9%; and ≥9%), age categories, gender, race, ethnicity and baseline AHA status	and ≥9%), age categories, gender, race and ethnicity	race and ethnicity

Abbreviations: T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, haemoglobin A1c; MET, metformin; ERTU, ertugliflozin; PBO, placebo; SITA, sitagliptin; AHA, anti-hyperglycaemic agent

B.3.3.3 Baseline characteristics of the ertugliflozin RCTs

Baseline characteristics of participants were similar across treatment groups, as shown in Tables 18 and 19.

Table 16 – The baseline characteristics of participants in the VERTIS MONO trial by treatment groups (All Subjects as Treated = ASaT)

VERTIS MONO (16, 17)	PBO	ERTU5	ERTU15	TOTAL
N	153	156	152	461
Demographics				
Age, mean (SD) years	56.1 (10.9)	56.8 (11.4)	56.2 (10.8)	56.4 (11.0)
Gender, n (%)	M: 82 (53.6) F: 71 (46.4)	M: 89 (57.1) F: 67 (42.9)	M: 90 (59.2) F: 62 (40.8)	M: 261 (56.6) F: 200 (43.4)
Body weight (kg), mean (SD)	94.2 (25.2)	94.0 (25.4)	90.6 (18.3)	92.9 (23.2)
BMI, mean (SD) kg/m^2	33.3 (6.8)	33.2 (7.4)	32.5 (5.7)	33.0 (6.7)
Disease indicators				
Disease duration (years), mean (SD)	4.63 (4.52)	5.11 (5.09)	5.22 (5.55)	4.99 (5.07)
Background AHA therapy status at screening:				
Currently on AHA, n (%)	77 (50.3)	85 (54.5)	78 (51.3)	240 (52.1)
Previously treated, n (%)	13 (8.5)	17 (10.9)	21 (13.8)	51 (11.1)
Never treated, n (%)	63 (41.2)	54 (34.6)	53 (34.9)	170 (36.9)
HbA1c %, mean (SD)	8.11 (0.92)	8.16 (0.88)	8.35 (1.12)	8.21 (0.98)
HbA1c mmol/mol, mean (SD)	65.18 (10.04)	65.72 (9.57)	67.80 (12.19)	66.22 (10.69)
FPG mmol/L, mean (SD)	10.0 (2.5)	10.0 (2.7)	9.9 (2.7)	10.0 (2.6)
eGFR mL/min/1.73m^2, mean (SD)	86.2 (19.4)	88.5 (18.4)	88.3 (18.0)	87.7 (18.6)

Abbreviations: ERTU, ertugliflozin; PBO, placebo; mg, milligram; n, sample size; BMI, Body Mass Index; kg, kilogram; AHA, anti-hyperglycaemic agent; HbA1c, haemoglobin A1c; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; SD, standard deviation; M, male; F, female

Table 17 – The baseline characteristics of participants in the VERTIS MET trial by treatment groups (ASaT)

VERTIS MET (18, 19)	PBO	ERTU5	ERTU15	TOTAL
N	209	207	205	621
Demographics				
Age, mean (SD) years	56.5 (8.7)	56.6 (8.1)	56.9 (9.4)	56.6 (8.8)
Gender, n (%)	M: 98 (46.9) F: 111 (53.1)	M: 97 (46.9) F: 110 (53.1)	M: 93 (45.4) F: 112 (54.6)	M: 288 (46.4) F: 333 (53.6)
Body weight (kg), mean (SD)	84.5 (17.1)	84.8 (17.2)	85..3 (17.5)	84.9 (16.9)
BMI, mean (SD) kg/m^2	30.7 (4.7)	30.8 (4.8)	31.1 (4.5)	30.9 (4.7)
Disease indicators				
Disease duration (years), mean (SD)	8.04 (6.34)	7.87 (6.08)	8.07 (5.52)	7.99 (5.98)
Background AHA therapy at screening:				
Metformin, n (%)	209 (100.0)	207 (100.0)	204 (99.5)	620 (99.8)
DPP-4i, n (%)	7 (3.3)	6 (2.9)	8 (3.9)	21 (3.4)
Other AHAs, n (%)	0 (0.0)	3 (1.4)	2 (1.0)	5 (0.8)
Sulfonamides, urea derivates, n (%)	62 (29.7)	57 (27.5)	45 (22.0)	164 (26.4)
No. agents 1	140 (67.0)	141 (68.1)	151 (73.7)	432 (69.6)
No. agents 2	69 (33.0)	66 (31.9)	54 (26.3)	189 (30.4)
HbA1c %, mean (SD)	8.17 (0.90)	8.06 (0.89)	8.13 (0.93)	8.12 (0.91)
HbA1c mmol/mol, mean (SD)	65.78 (9.81)	64.59 (9.70)	65.33 (10.17)	65.23 (9.89)
FPG mmol/L, mean	9.4	9.3	9.3	9.3
eGFR mL/min/1.73m^2, mean (SD)	91.6 (19.8)	88.9 (17.5)	91.0 (20.6)	90.5 (19.3)

Abbreviations: ERTU, ertugliflozin; PBO, placebo; mg, milligram; n, sample size; BMI, body mass index; kg, kilogram; AHA, anti-hyperglycaemic agent; HbA1c, haemoglobin A1c; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; SD, standard deviation; M, male; F, female

Table 18 – The baseline characteristics of participants in the VERTIS FACTORIAL trial by treatment groups (ASaT)

VERTIS FACTORIAL (20, 21)	ERTU5	ERTU15
N	250	248
Demographics		
Age, mean (SD) years	55.1 (10.1)	55.3 (9.5)
Gender, n (%)	Male: 127 (50.8) Female: 123 (49.2)	Male: 134 (54.0) Female: 114 (46.0)
Body weight (kg), mean (SD)	88.6 (22.2)	88.0 (20.3)
BMI, mean (SD) kg/m^2	31.8 (6.2)	31.5 (5.8)
Disease indicators		
Disease duration (years), mean (SD)	7.07 (5.39)	7.34 (5.42)
Background AHA therapy at screening:		
MET, n (%)	250 (100.0)	248 (100.0)
Insulins and analogs for injection, n (%)	1 (0.4)	0 (0.0)
No. agents 1	249 (99.6)	248 (100.0)
No. agents 2	1 (0.4)	0 (0.0)
HbA1c %, mean (SD)	8.57 (1.05)	8.57 (1.01)
HbA1c mmol/mol*	70.2	70.2
FPG mmol/L, mean	10.2	9.9
eGFR mL/min/1.73m^2, mean (SD)	91.9 (20.6)	92.8 (21.4)

Abbreviations: ERTU, ertugliflozin; PBO, placebo; MET, metformin; mg, milligram; n, sample size; BMI, Body Mass Index; kg, kilogram; AHA, anti-hyperglycaemic agent; HbA1c, haemoglobin A1c; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; SD, standard deviation
*HbA1c values manually converted from DCCT units - % to IFCC units - mmol/mol

B.3.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details of VERTIS MONO, VERTIS MET and VERTIS FACTORIAL trial populations, hypothesis objective, statistical analysis and data management are summarised in Table 19 below.

Table 19 - Summary of the statistical analyses for all ertugliflozin trials

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Monotherapy				
VERTIS MONO (NCT01958671 2016) (16, 17)	Ertugliflozin is superior to placebo in patients with T2DM and inadequate glycaemic control despite diet and exercise	• The full analysis set (FAS) population was used for the primary and secondary efficacy outcomes, which included all randomised patients who took at least one dose of study medication and had at least one measurement of the outcome variable (baseline or post-baseline). A constrained longitudinal data analysis (cLDA) model was used that included terms for treatment (categorical), time, the treatment by time interaction, AHA status at study entry (binary: yes/no), and baseline eGFR (continuous). An unstructured covariance matrix was used to model the correlation among repeated measurements. The Kenward-Roger adjustment was used with restricted (or residual) maximum likelihood (REML) to support appropriate statistical inference. Sensitivity analyses were performed to assess the robustness of the primary model. Analysis of Covariance (ANCOVA) was conducted utilising the last observation carried forward (LOCF). Other outcomes were summarised descriptively and graphically by treatment group and time point.	The study had greater than 99% power to detect a difference of 0.6% between each ertugliflozin dose and placebo based on the inclusion of approximately 450 patients (150 per arm), allowing for a dropout rate of up to 20% and assuming a standard deviation (SD) of 1.0 based on a 2-sided test at 5% level of significance. Type I error at an alpha level of 0.05 was controlled for with an ordered testing procedure across all key efficacy endpoints	Efficacy • To explore the impact of missing data on the conclusions of the primary analysis, the cLDA model used the maximum likelihood principle to estimate the parameters and account for missing data in an implicit fashion; additionally the tipping point analysis and a jump-to-reference (J2R) analysis were performed Safety • In the absence of safety data the safety analysis used the data as observed approach (DAO), i.e. no imputation for missing data/missing value excluded Patient withdrawal For withdrawn patients, the investigator inquired about the reason for withdrawal, requested the patient return all unused study medication and return for an early termination (ET) visit, and followed up with the patient regarding any unresolved AEs. If the patient discontinued study

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		• The ASaT population was used for the safety analysis, time-to-rescue analysis and for summarizing baseline characteristics, patient disposition and compliance. The ASaT consisted of all ranodmised patients who took at least one dose of study medication Safety analyses were based on the observed data. Descriptive statistics were used to summarize results and changes from baseline in clinical laboratory tests and in vital signs. Furthermore, a 3-tier approach was used to summarise AEs; for tier-1 and 2 AEs, the percentage of patients with incident AE, the risk difference, its 95% confidence interval, and p-value were provided. The confidence intervals and p-values were not adjusted for multiplicity and were provided for screening purposes only. For Tier-3 AEs, only within-group incidence proportions were tabulated.		medication and also withdrew consent for disclosure of future information, no further evaluations were performed, and no additional data were collected.
Dual therapy				
VERTIS MET (NCT02033889 2016) (18) (19)	Ertugliflozin is superior to placebo in patients with T2DM and inadequate glycaemic control on a stable dose of metformin monotherapy	• The FAS population was used for most efficacy endpoints and also for the BMD endpoints (labelled as BMD FAS), which included all ranodmised patients who took at least one dose of study medication and had at least one measurement of the outcome variable (baseline or post-baseline). A cLDA, based on the FAS was used to evaluate the change from baseline in HbA1c at week 26 as the primary efficacy analysis. The statistical model included terms for treatment, visit, the treatment by visit interaction,	The study had at least 99% power to detect a difference of 0.5% between each ertugliflozin dose and placebo based on the inclusion of approximately 600 patients (200 per arm), allowing for a dropout rate of up to 20%. All statistical tests were	Efficacy • Missing data were accounted for in an implicit fashion through the use of a cLDA model that used the maximum likelihood principle for estimation • Impact of missing data was explored through sensitivity analyses (e.g. tipping point analysis and J2R) Safety • In the absence of safety data the safety analysis used DAO, i.e. no imputation for missing data/missing

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		menopausal status randomization stratum (categorical), AHA status at study entry and baseline eGFR (continuous). The treatment difference in terms of mean change from baseline to a given time point was estimated and tested with this model. An unstructured covariance matrix was used to model the correlation among repeated measurements. The Kenward-Roger adjustment was used with restricted (or residual) maximum likelihood (REML) to make appropriate statistical inference. Nominal p-values have been computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect (ordered testing) rather than formal tests of hypotheses. The proportion of patients with HbA1c <7% at week 26 was analysed using a logistic regression model. • The ASaT population was used for the safety analysis (except BMD endpoints), time-to-rescue analysis and for summarizing baseline characteristics, patient disposition and compliance. It consisted of all ranodmised patients who took at least one dose of study medication Safety analyses were based on the observed data. Descriptive statistics were used to summarize results and changes from baseline in clinical laboratory tests.	conducted at the alpha=0.05 (2-sided) level with a standard deviation of 1.0. Type I error at an alpha level of 0.05 was controlled for using an ordered testing procedure across all efficacy endpoints. If ertugliflozin 15 mg vs. placebo was significant at 0.05 level, then ertugliflozin 5 mg vs. placebo was tested.	value excluded Patient withdrawal Patients may have been withdrawn from the study at any time at their own request, or they may have been withdrawn at any time at the discretion of the investigator for safety or behavioural reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site. If a patient did not return for a scheduled visit, every effort was made to contact the patient. For withdrawn patients, the investigators inquired about the reason for withdrawal, requested the patient return all unused study medication, requested the patient return for an early termination visit, and followed-up with the patient regarding any unresolved AEs. If the patient discontinued study medication and also withdrew consent for disclosure of future information, no further evaluations were performed, and no additional data were collected.
VERTIS	Ertugliflozin	• The FAS population was used for most of the	The study had 94%	Efficacy

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
FACTORIAL (NCT02099110 2016) (20, 21)	in combination with sitagliptin is superior to each of these single agents in patients with T2DM and inadequate glycaemic control on a stable dose of metformin monotherapy	primary and secondary efficacy endpoints, which included all ranodmised patients who took at least one dose of study medication and had at least one measurement of the outcome variable (baseline or post-baseline). The primary analysis model for continuous efficacy endpoints was a cLDA model proposed by Liang and Zeger (2000, (30)). This model assumed a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. The model included terms for treatment, baseline eGFR, time, and the interaction of time by treatment. All hypotheses were evaluated separately for each ertugliflozin dose level. As a supportive analysis, an ANCOVA model in the FAS population was also used for the primary efficacy endpoint. The ANCOVA model included treatment, baseline eGFR and baseline value. • The ASaT population was used for the safety analysis, consisting of all ranodmised patients who took at least one dose of study medication Safety and tolerability were assessed following a tiered-approach. Symptomatic hypoglycaemia and AEs associated with UTIs, male and female genital mycotic infections, and hypovolemia were considered as pre-specified safety parameters (Tier 1) for which p-values and 95% confidence intervals (CIs) for between treatment differences were provided using the Miettinen and Nurminen method (1985, (31)). Other safety parameters were considered Tier 2 or Tier 3. Tier 2 events parameters were assessed via point estimates with 95% CIs provided for	power to detect a difference of 0.4% for each of the pairwise comparison based on the inclusion of approximately 1250 patients (250 per arm), assuming a standard deviation of 1.2 based on a 2-sided test at a 5% level of significance. The power for success for both pairwise comparisons at a given ertugliflozin dose level was approximately 89%. Type I error at an alpha level of 0.05 was controlled using an ordered testing procedure across all efficacy endpoints.	• Missing data were accounted for using the last observation carried forward analysis (LOCF) • Impact of missing data was explored through sensitivity analyses (e.g. tipping point analysis and J2R) Safety • In the absence of safety data the safety analysis used DAO, i.e. no imputation for missing data/missing value excluded Patient withdrawal If a patient withdrew consent to participating in the trial, no further evaluation was performed, and no additional data was collected. Patients who discontinued treatment with study medication for reasons other than withdrawn consent were asked to attend the clinic for a Study Medication Discontinuation Visit followed by a post-treatment telephone call 14 days after the last dose of study medication. Thereafter, patients were followed by telephone contacts according to the study visit schedule until the end of the trial. The purpose of the telephone contacts, as well as the 14-day post treatment telephone call, was to evaluate if the patient experienced any SAEs or events eligible for adjudication. For a patient indicating an intention to stop active participation in the trial, the

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		between-group comparisons; point estimates by treatment group were provided for Tier 3 safety parameters. For Tier 3 parameters, summary statistics for baseline, on-treatment, and change (or percent change) from baseline values were provided by treatment group		investigator clarified with the patient if he/she was willing to continue in the study off of study medication with contact at intervals (as described above) to provide a brief and focused update on health status.

Full details of the numbers of participants eligible to enter the abovementioned trials are included in Appendix D.

B.3.5. Quality assessment of the relevant clinical effectiveness evidence

B.3.5.1 Validity of the RCTs results

The quality of each source of evidence provided in Section 3.2 has been appraised in order to assess the validity and robustness of the overall design and execution of the ertugliflozin RCTs.

B.3.5.2 Quality assessment methods

The York Centre for Reviews and Dissemination quality assessment tool (32), 2009 was chosen to assess the quality and risk of bias of the RCTs identified through the SLR, which incorporates the criteria for assessment of risk of bias and generalisability suggested by NICE (FTA template guide, Section 3.5.2.)

In total, three clinical trials have been identified as providing robust evidence in supporting ertugliflozin in mono and dual therapy relevant to this submission:

- **Monotherapy** (SGLT-2i only): VERTIS MONO study
- **Dual therapy** (metformin + SGLT-2i): VERTIS MET and VERTIS FACTORIAL studies

B.3.5.3 Routine clinical practice in England

As noted in the NG28 (15), the assessment of HbA1c levels is the most effective diagnosis measure for the control and management of T2DM. The change in HbA1c over time is the primary efficacy outcome of all ertugliflozin trials presented in Section B.3.2, which reflects current clinical practice in England for evaluating treatments in patients with T2DM. The remaining secondary efficacy (change in weight, FPG, SBP) and safety (AEs, hypoglycaemia, UTIs and genital mycotic infections) outcomes are all clinically relevant to both physicians and patients

B.3.5.4 Summary of results of the quality assessment of the ertugliflozin RCTs

As can be seen in Table 20, the results indicate that all ertugliflozin studies are of good quality. All clinical trials were randomised, double-blind and reported pre-specified outcomes. None of the ertugliflozin studies presented true intention-to-treat (ITT) analyses; all of them presented analyses based on populations who had received at least one dose of the study drug (FAS for efficacy endpoints and ASaT for safety and tolerability endpoints).

Please refer to Appendix D for a complete quality assessment of each trial.

Table 20 - Summary of quality assessment for the trials reporting ertugliflozin in monotherapy and combination therapy

Study ID and publications	VERTIS MONO (16, 17)	VERTIS MET (18, 19)	VERTIS FACTORIAL (20, 21)
	Monotherapy	Dual therapy	
Was the randomisation method adequate?	Yes	Yes	Yes
Was the allocation adequately concealed?	NR	NR	NR
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis?	No	No	No
Did the authors of the study publication declare any conflicts of interest?	Yes	Yes	Yes

Abbreviations: ID, identity; ERTU, ertugliflozin; NR, not reported

B.3.6. Clinical effectiveness results of the relevant trials

All data from the ertugliflozin clinical trials are presented excluding glycaemic rescue therapy to avoid the confounding influence of the rescue therapy (e.g. metformin, glimepiride or insulin glargine).

As described in Table 19, the FAS population was used for the majority of the efficacy endpoints, whereas the ASaT was used for all safety and tolerability outcomes.

All outcomes analysed followed a planned testing procedure with ertugliflozin 15 mg assessed first, followed by ertugliflozin 5 mg. If a test in the ordered testing procedure did not meet statistical significance, subsequent tests were considered nominal and were thus

not used for declaring statistical significance but only as a measure of strength of association between the endpoint and the treatment effect.

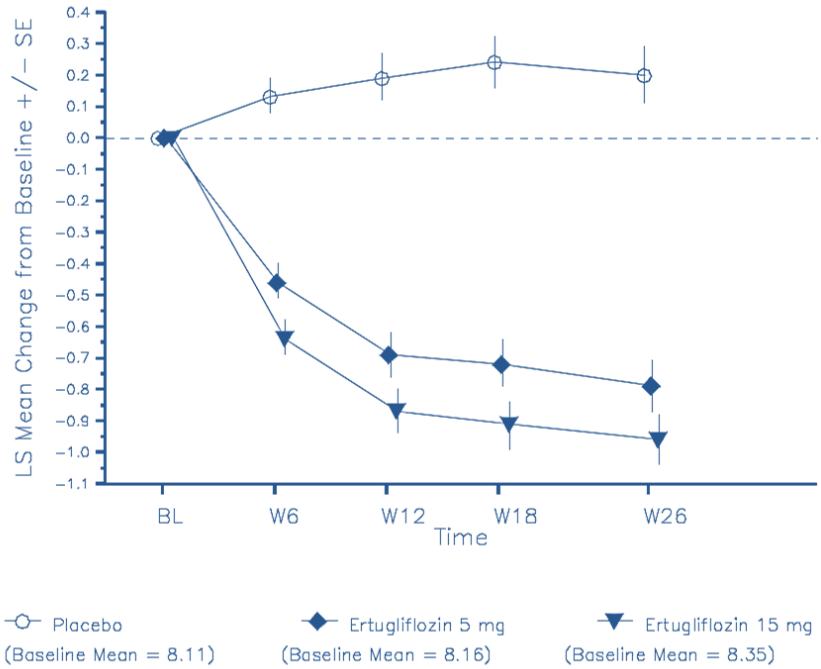
B.3.6.1 VERTIS MONO: Phase A - Primary efficacy outcome at week 26

HbA1c change from baseline to week 26

Figure 5 presents the results of the primary analysis of change from baseline in HbA1c to week 26 using the cLDA model in the FAS population. The least square (LS) mean reductions from baseline in HbA1c to week 26 were significantly greater in the ertugliflozin 5 mg and ertugliflozin 15 mg groups compared to the placebo group.

Initial reductions in mean HbA1c at week 6 were followed by smaller subsequent reductions at each time point to week 26. The point estimate of the reduction in HbA1c was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point. In the placebo group, there was a small increase from baseline in HbA1c throughout the study.

Figure 5 - HbA1c change from baseline to week 26 (primary efficacy outcome) – LS mean change (cLDA, FAS)



	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-0.99 (-1.22, -0.76)	<0.001
ERTU15	-1.16 (-1.39, -0.93)	<0.001

Abbreviations: HbA1c, haemoglobin A1c; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; ERTU, ertugliflozin; PBO, placebo; FAS, full analysis set

The corresponding changes from baseline to week 26 for HbA1c in mmol/mol are:

- ertugliflozin 5 mg versus placebo = [95%CI] = -10.82 [-13.33, -8.30]
- ertugliflozin 15 mg versus placebo = [95%CI] = -12.67 [-15.20, -10.13]

VERTIS MONO: Phase A - Secondary efficacy outcomes at week 26

Proportion of patients with HbA1c <7.0% (<53 mmol/mol) at week 26

Table 21 shows the analysis of the proportion of patients with HbA1c <7.0% (<53 mmol/mol) at week 26. The raw proportions of patients with an HbA1c <7.0% in the ertugliflozin 5 mg group (28.2% of patients) and the ertugliflozin 15 mg group (35.8% of patients) were twice as great and almost three times greater, respectively, than in the placebo group (13.1% of patients). The odds of having an HbA1c <7.0% at week 26, using multiple imputation for patients with missing week 26 data, were significantly greater in both ertugliflozin groups compared to the placebo group (p<0.001).

Table 21 - Analysis of patients with HbA1c <7% (<53 mmol/mol) at week 26 – Logistic regression using multiple imputations (FAS)

Treatment	N	Number (%) of patients with HbA1c <7.0% (raw proportion)	Adjusted Odds Ratio (OR) relative to PBO*		
			Point estimate	95% CI	p-Value
PBO	153	20 (13.1)			
ERTU5	156	44 (28.2)	3.59	(1.85, 6.95)	<0.001
ERTU15	151	54 (35.8)	6.77	(3.46, 13.24)	<0.001

Abbreviations: HbA1c, haemoglobin A1c; ERTU, ertugliflozin; PBO, placebo; FAS, full analysis set
*Adjusted odds ratio based on a logistic regression model fitted with fixed effects for treatment, prior antihyperglycaemic medication (yes, no) and covariates for baseline HbA1c and baseline eGFR (continuous). Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis.

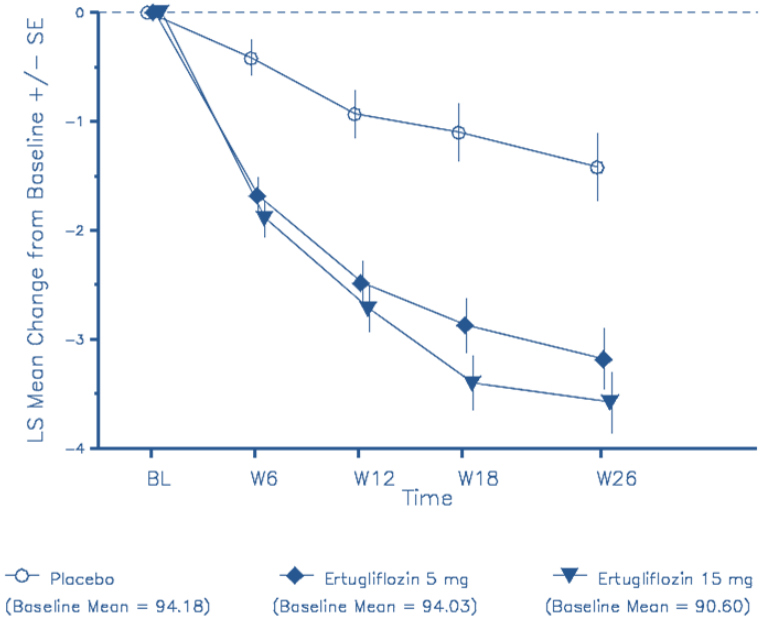
Body weight change from baseline to week 26

Figure 6 shows the results of the analysis of change from baseline to week 26 in body weight.

In both ertugliflozin groups and in the placebo group, body weight decreased from baseline to week 6 and continued to decrease at each subsequent time point to week 26 with the magnitude of the decrease numerically greater in both ertugliflozin groups than in the placebo group at each time point. Changes from baseline in body weight to week 26 were numerically greater in the ertugliflozin 15 mg group compared to the ertugliflozin 5 mg group.

The LS mean reductions from baseline in body weight to week 26 were significantly greater in the ertugliflozin 5 mg and ertugliflozin 15 mg groups compared to the placebo group (p<0.001 for both comparisons).

Figure 6 - Body Weight (kg) change from baseline to week 26 - LS mean change (cLDA, FAS)



	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-1.76 (-2.57, -0.95)	<0.001
ERTU15	-2.16 (-2.98, -1.34)	<0.001

Abbreviations: kg, kilogram; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; ERTU, ertugliflozin; PBO, placebo; FAS, full analysis set

Systolic blood pressure (SBP) change from baseline to week 26

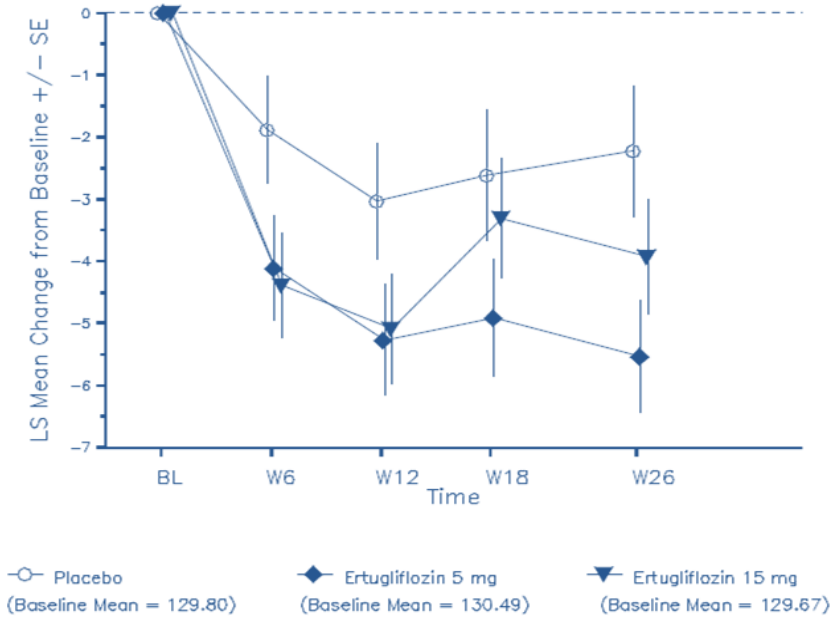
Figure 7 shows the results of the analysis of change from baseline in sitting SBP to week 26. The LS mean reduction from baseline in SBP to week 26 was numerically (but not significantly) greater in the ertugliflozin 15 mg group compared to the placebo group and the reduction was greater in the ertugliflozin 5 mg group compared to the placebo group (nominal value for ertugliflozin 5 mg p=0.015 as ertugliflozin 15 mg was not statistically significant). All subsequent outcomes in the ordered testing procedure were therefore ineligible for statistical testing.

In both ertugliflozin groups, SBP decreased from baseline to week 6 and through week 12, increased at week 18 and then decreased at week 26. In the placebo group, SBP decreased from baseline to week 12 and then increased slightly to week 26. Reductions from baseline

in SBP to week 26 were numerically greater in the ertugliflozin 5 mg group compared to the ertugliflozin 15 mg group.

An evaluation of the proportions of patients taking antihypertensive medication, including diuretics, at baseline and week 26 was conducted and no meaningful difference in the proportions of patients taking antihypertensive medication at week 26 relative to baseline was observed in the ertugliflozin or placebo groups.

Figure 7 - SBP (mmHg) at week 26 - LS mean change from baseline over time (cLDA, FAS)



	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-3.31 (-5.98, -0.65)	0.015
ERTU15	-1.71 (-4.40, 0.98)	0.213

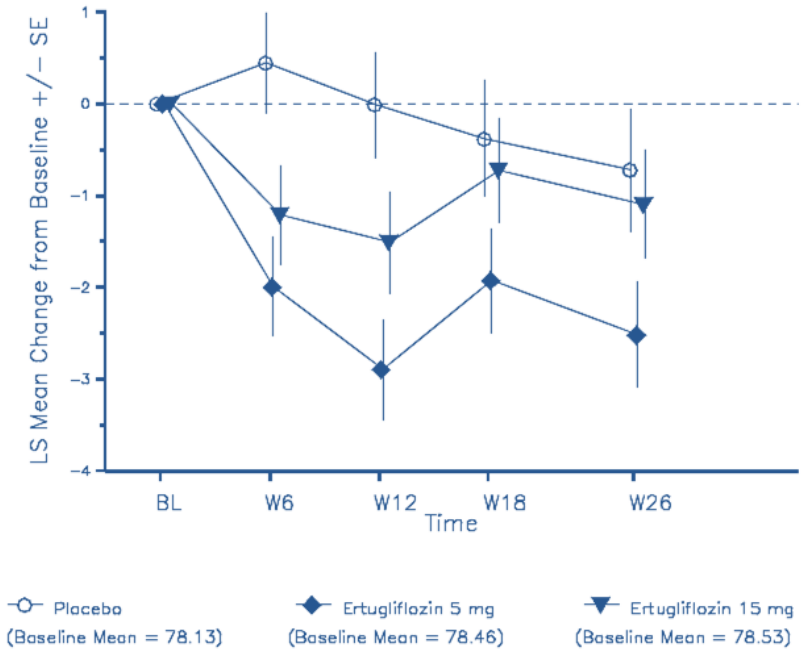
Abbreviations: SBP, systolic blood pressure; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; ERTU, ertugliflozin; PBO, placebo; FAS, full analysis set

Diastolic blood pressure (DBP) change from baseline to week 26

Figure 8 shows the results of the analysis of change from baseline in DBP to week 26. The LS mean reductions from baseline in DBP to week 26 were greater in the ertugliflozin 5 mg group compared to the placebo group (nominal p=0.039) and numerically greater in the ertugliflozin 15 mg group compared to the placebo group.

Similar to SBP, DBP decreased from baseline to week 12 in both ertugliflozin groups, increased at week 18 and then decreased at week 26. In the placebo group, there were no clinically meaningful mean changes in DBP.

Figure 8 - DBP (mmHg) at week 26 - LS mean change from baseline (cLDA, FAS)



	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-1.80 (-3.51, -0.09)	0.039
ERTU15	-0.37 (-2.09, 1.35)	0.669

Abbreviations: DBP, diastolic blood pressure;; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; ERTU, ertugliflozin; PBO, placebo; FAS, full analysis set

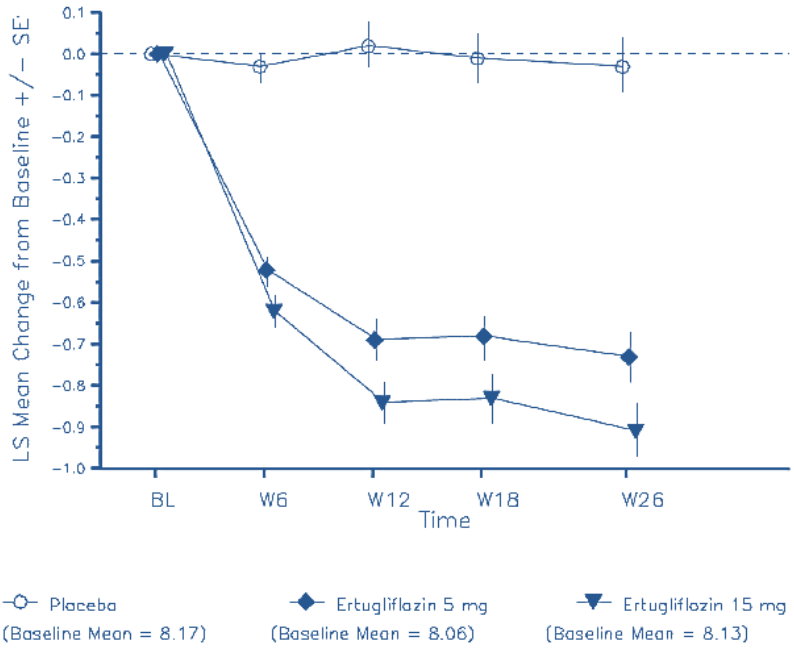
Please note that all other secondary efficacy outcomes (FPG, PPG, HbA1c<6.5% and MMTT, patients receiving glycaemic rescue therapy and time to initiation of glycaemic rescue therapy) are included in Appendix H for completeness.

B.3.6.2 VERTIS MET: Phase A - Primary efficacy outcome at week 26

HbA1c change from baseline to week 26

Figure 9 shows the results of the primary analysis of change from baseline in HbA1c at week 26 using the cLDA model for the FAS population. The LS mean reductions from baseline in HbA1c at week 26 were significantly greater in the ertugliflozin 5 mg and ertugliflozin 15 mg groups compared to the placebo group.

Figure 9 - HbA1c (%) change from baseline at Week 26 (primary endpoint) - LS mean change (cLDA, FAS)



	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-0.7 (-0.9, -0.5)	<0.001
ERTU15	-0.9 (-1.1,- 0.7)	<0.001

Abbreviations: HbA1c, haemoglobin A1c; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; ERTU, ertugliflozin; PBO, placebo; FAS, full analysis set

The corresponding changes from baseline to week 26 for HbA1c in mmol/mol were:

- ertugliflozin 5 mg versus placebo = [95%CI] = -7.66 [-9.52, -5.81]
- ertugliflozin 15 mg versus placebo = [95%CI] = -9.60 [-11.46, -7.73]

VERTIS MET: Phase A - Secondary efficacy endpoints

Proportion of patients with HbA1c <7.0% (<53 mmol/mol)

Table 22 shows the analysis of the proportions of patients with HbA1c <7.0% (<53 mmol/mol) at week 26. The raw proportions of patients with an HbA1c <7.0% in the ertugliflozin 15 mg group and the ertugliflozin 5 mg group were over two-times greater than in the placebo group. The model-based odds were significantly greater in both ertugliflozin groups compared to the placebo group (p<0.001 for both ertugliflozin doses).

Table 22 - Analysis of patients with HbA1c <7% (<53 mmol/mol) at week 26 – Logistic regression using multiple imputations (FAS)

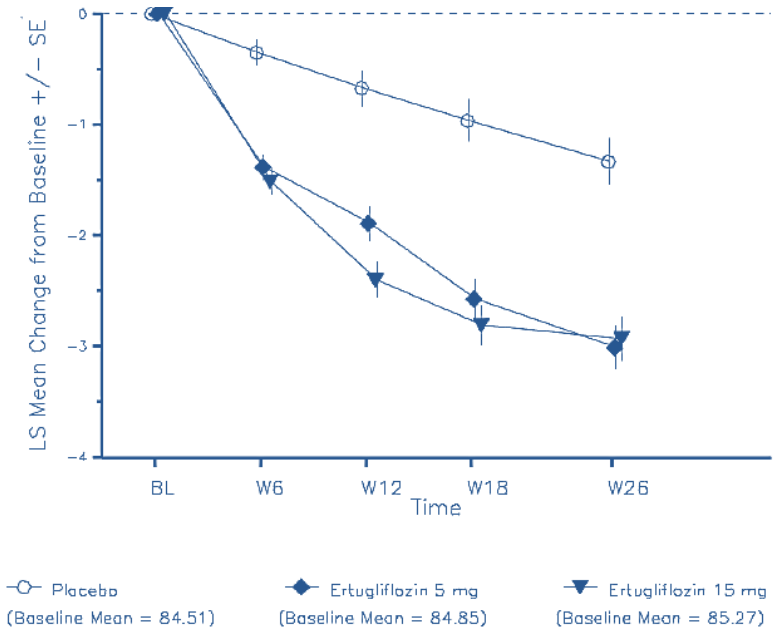
Treatment	N	Number (%) of patients with HbA1c <7.0% (raw proportion)	Adjusted OR relative to PBO*		
			Point estimate	95% CI	p-Value
PBO	209	33 (15.8)			
ERTU5	207	73 (35.3)	3.03	(1.81, 5.06)	<0.001
ERTU15	205	82 (40.0)	4.48	(2.64, 7.62)	<0.001

Abbreviations: HbA1c, hemoglobin A1c; CI, confidence interval; N, number of patients in treatment group; FAS, full analysis set; OR, odd ratio; ERTU, ertugliflozin; PBO, placebo
*Adjusted odds ratio based on a logistic regression model fitted with fixed effects for treatment, prior antihyperglycaemic medication (yes, no) and covariates for baseline HbA1c and baseline eGFR (continuous). Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis.

Body weight change from baseline to week 26

Figure 10 shows the results of the analysis of change from baseline in body weight at week 26. The LS mean change from baseline in body weight to week 26, were significantly greater in the ertugliflozin groups compared to the placebo group.

Figure 10 - Body Weight (kg) change from baseline to week 26 - (cLDA; FAS)



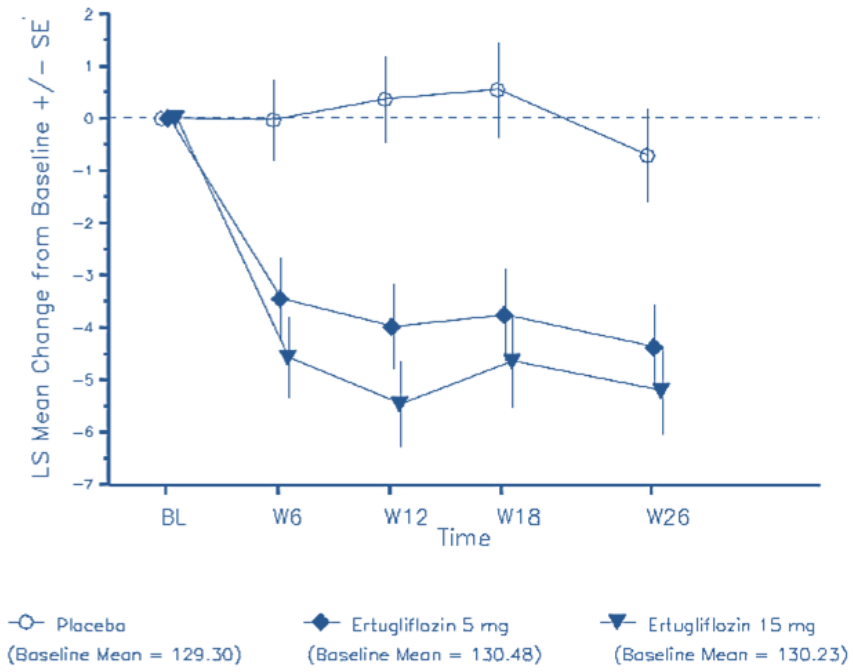
	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-1.67 (-2.24, -1.11)	<0.001
ERTU15	-1.60 (-2.16, -1.03)	<0.001

Abbreviations: kg, kilogram; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; ERTU, ertugliflozin; PBO, placebo; FAS, full analysis set

SBP change from baseline to week 26

Figure 11 shows the results of the analysis of change from baseline in SBP to week 26. The LS mean reductions from baseline in SBP at week 26 were significantly greater in the ertugliflozin 15 mg group (-5.20 (-6.87, -3.54)) and the ertugliflozin 5 mg group (-4.38 (-6.01, -2.75)) compared to the placebo group. LS mean differences compared to placebo were statistically significant for both ertugliflozin doses (p<0.001 and p=0.002 respectively).

Figure 11 - SBP (mmHg) change from baseline to week 26 - (cLDA; FAS)



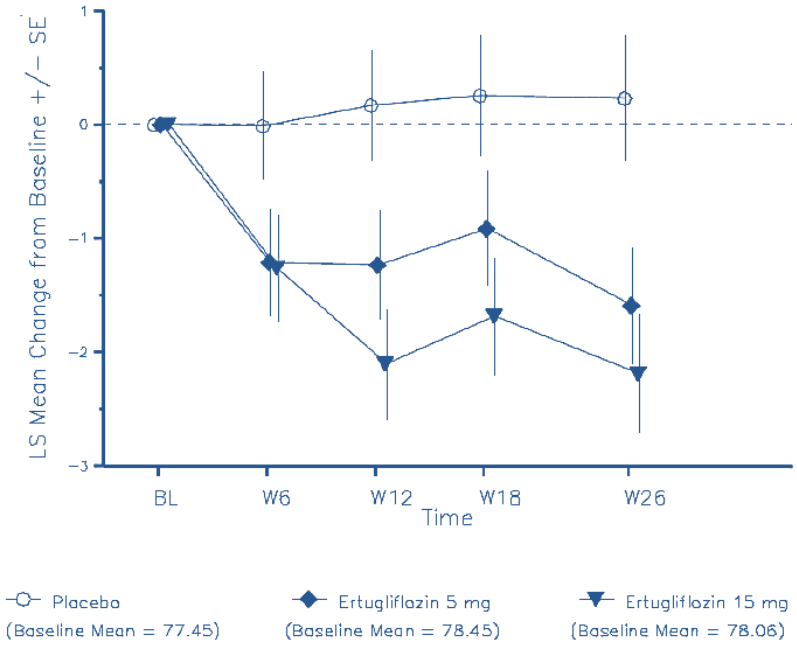
	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-3.68 (-5.96, -1.39)	0.002
ERTU15	-4.50 (-6.81, -2.19)	<0.001

Abbreviations: SBP, systolic blood pressure; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; ERTU, ertugliflozin; PBO, placebo; FAS, full analysis set

DBP change from baseline to week 26

Figure 12 shows the results of the analysis of change from baseline in DBP to week 26. The LS mean reductions from baseline in DBP to week 26 were significantly greater in the ertugliflozin 15 mg group and the ertugliflozin 5 mg group compared to the placebo group.

Figure 12 - DBP (mmHg) change from baseline to week 26 - (cLDA; FAS)



	Differences in LS means (95% CI) vs. PBO at week 26	*P*-value
ERTU5	-1.82 (-3.24, -0.39)	0.013
ERTU15	-2.42 (-3.86, -0.98)	0.001

Abbreviations: DBP, diastolic blood pressure; BL, baseline; cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; ERTU, ertugliflozin; PBO, placebo; FAS, full analysis set

B.3.6.3 VERTIS FACTORIAL: Phase A – Primary Efficacy Endpoints

HbA1c change from baseline to week 26

As mentioned in Section B.3.2.2, VERTIS FACTORIAL is a 5-arm study that was designed to investigate the combination therapy of ertugliflozin and sitagliptin on a metformin background compared to the use of each of these agents alone (i.e. pairwise comparisons); therefore, only the LS means for the primary and secondary endpoints in the ertugliflozin 5 mg and ertugliflozin 15 mg arms are reported below, as data supporting this submission and in accordance with their inclusion in the network meta-analysis (NMA) (see Section B.3.8.1). Table 23 shows the results of the primary analysis of change from baseline in HbA1c at week 26 using the cLDA model in the FAS population.

Table 23 - HbA1c (%) changes from baseline to week 26 - LS mean change (FAS)

Treatment	Baseline		Week 26		Differences in LS means (95% CI)	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)
ERTU5	244	8.57 (1.047)	217	7.41 (0.926)	250	-1.02 (-1.14, -0.90)
ERTU15	247	8.57 (1.006)	217	7.41 (1.036)	248	-1.08 (-1.20, -0.96)

Abbreviations: HbA1C, haemoglobin A1c; ERTU, ertugliflozin; CI, confidence interval; FAS, Full Analysis Set; LS, least squares; N, number of patients in the FAS; SD, standard deviation

The corresponding changes from baseline to week 26 for HbA1c in mmol/mol are:

- ertugliflozin 5 mg [95%CI] = -11.19 [-12.51, -9.87]
- ertugliflozin 15 mg [95%CI] = -11.77 [-13.09, -10.45]

VERTIS FACTORIAL: Phase A - Secondary endpoints

Proportion of patients with HbA1c <7.0% (<53 mmol/mol)

The proportion of patients with HbA1c values <7.0% (<53 mmol/mol) at week 26 is shown in Table 24. Respectively 26% and 32% of the patients in the ertugliflozin 5 mg and ertugliflozin 15 mg groups had an HbA1c <7.0% at week 26.

Table 24 - Number of patients with HbA1c <7% (<53 mmol/mol) at week 26 - (FAS)

Treatment	N	Number (%) of patients with HbA1c <7.0% (raw proportion)
ERTU5	250	66 (26.4)
ERTU15	248	79 (31.9)

Abbreviations: HbA1C, haemoglobin A1c; ERTU, ertugliflozin; FAS, full analysis set; LS, least squares; N, number of patients in the FAS; SD, standard deviation

Body weight change from baseline to week 26

Table 25 shows the results of the analysis of change from baseline in body weight at week 26. The magnitude of the decrease in body weight was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point.

Table 25 - Body Weight (kg) change from baseline to week 26 - (cLDA; FAS)

Treatment	Baseline		Week 26		Differences in LS means (95% CI)	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)*
ERTU5	250	88.56 (22.18)	219	85.09 (21.10)	250	-2.69 (-3.13, -2.25)
ERTU15	248	87.98 (20.33)	219	83.80 (20.15)	248	-3.74 (-4.18, -3.29)

Abbreviations: kg, kilogram; ERTU, ertugliflozin; FAS, full analysis set; CI, confidential interval; cLDA, constrained longitudinal data analysis LS, least squares; N, number of patients; SD, standard deviation
*Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycaemic medication, baseline eGFR (continuous), menopausal status randomisation stratum and the interaction of time by treatment. Time was treated as a categorical variable.

SBP change from baseline to week 26

Table 26 shows the results of the analysis of change from baseline in SBP to week 26. The size of reductions in SBP was similar in the two ertugliflozin-treated groups.

Table 26 - SBP (mmHg) change from baseline to week 26 - (cLDA; FAS)

Treatment	Baseline		Week 26		Differences in LS means (95% CI)	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)*
ERTU5	250	129.68 (12.478)	218	125.45 (12.190)	250	-3.89 (-5.28, -2.50)
ERTU15	248	128.94 (12.515)	220	152.16 (12.705)	248	-3.69 (-5.08, -2.30)

Abbreviations: SBP, systolic blood pressure; ERTU, ertugliflozin; FAS, Full Analysis Set; cLDA, constrained longitudinal data analysis LS, least squares; N, number of patients in the FAS; SD, standard deviation; CI, confidential interval
*Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycaemic medication, baseline eGFR (continuous), menopausal status randomisation stratum and the interaction of time by treatment. Time was treated as a categorical variable.

DBP change from baseline to week 26

Table 27 shows the results of the analysis of change from baseline in DBP to week 26. The size of reductions in DBP in the two ertugliflozin-treated groups was small.

Table 27 - DBP (mmHg) change from baseline to week 26 - (cLDA; FAS)

Treatment	Baseline		Week 26		Differences in LS means (95% CI)	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)*
ERTU5	250	77.87 (7.76)	218	76.56 (7.96)	250	-1.11 (-1.96, -0.26)
ERTU15	248	77.49 (7.27)	220	76.40 (6.67)	248	-0.97 (-1.81, -0.12)

Abbreviations: DBP, diastolic blood pressure; ERTU, ertugliflozin; FAS, Full Analysis Set; cLDA, constrained longitudinal data analysis LS, least squares; N, number of patients in the FAS; SD, standard deviation; CI, confidential interval
*Based on the cLDA model with fixed effects for treatment, time, prior antihyperglycaemic medication, baseline eGFR (continuous), menopausal status randomisation stratum and the interaction of time by treatment. Time was treated as a categorical variable.

B.3.7. Subgroup analysis

Ertugliflozin provides similar or greater health benefits to the comparators (dapagliflozin, empagliflozin and canagliflozin) in the full adult populations considered across mono and dual therapy. As a result no subgroup analyses are reported. However, for completeness, pre-defined subgroup analyses for the primary efficacy outcome (reduction in HbA1c) are presented in Appendix E. Furthermore, post-hoc analyses have been performed on HbA1c by band baseline. Analyses were also performed on blood pressure by band baseline in accordance with the concomitant use or not of antihypertensive agents (e.g. beta-blockers).

B.3.8. Meta-analysis

Based on the current data availability for the SGLT-2is in mono and dual therapy, an indirect and mixed treatment comparison was considered to be the most appropriate methodology (see Section B.3.9).

B.3.9. Indirect and mixed treatment comparisons

B.3.9.1 Summary of trials

Trials included in the NMA were identified through the SLR and are presented in Table 28 for mono and dual therapy. An overview of the baseline characteristics of all included studies for the two populations is provided in Appendix D.

The full networks of evidence identified in the SLR for ertugliflozin in monotherapy and dual therapy are presented in Figure 13 and Figure 14, respectively. It should be noted that the evidence networks are based solely on the treatments compared in the studies identified. As all outcomes of interest were not reported in each trial, outcome-specific evidence networks are reported in Appendix J for completeness.

Ertugliflozin monotherapy NMA

The studies included in the NMA were consistent with those identified in TA390 (Table 28) with some minor exceptions:

- MSD's NMA includes publications up to May 2018
- Bailey et al., 2012 (33) (dapagliflozin vs. placebo) was excluded from the AG's NMA because dapagliflozin 5 mg is "not a licensed dose of dapagliflozin used" (7). MSD included this study in the NMA to allow the comparison of the ertugliflozin lower dose (5 mg) against the dapagliflozin lower dose (5 mg). However, a sensitivity analysis dropping Bailey et al., 2012 and all the other studies containing dapagliflozin 5 mg (Table 28) were performed to assess the impact on the NMA results.

- Kaku et al., 2014 (34) (dapagliflozin 5 mg and 10 mg vs. placebo) was excluded from the base case NMA for two reasons:
    - Having an HbA1c threshold of ≥6.5%, Kaku et al., 2014 did not meet the inclusion criterion of HbA1c ≥7% for study inclusion in the SLR. The approach was consistent with the ertugliflozin trial designs and intended to reduce heterogeneity between included studies.
    - As would be anticipated with a lower HbA1c study threshold, the average baseline HbA1c of this study was lower than other included studies (7.5%) (Table 28). Excluding this study from the base case was considered to be conservative, as the lower baseline HbA1c and subsequent change in HbA1c would have reduced the average effect of dapagliflozin as noted by the AG in TA390 (7). However, a sensitivity analysis including the study was performed to assess the impact on the NMA results.

Ertugliflozin dual therapy NMA

The studies included in the NMA were consistent with those included in TA288 (dapagliflozin) (3) , TA315 (canagliflozin) (4) and TA336 (empagliflozin) (5), with the exception of Bolinder et al., 2012 (35) (metformin + dapagliflozin 10 mg vs. metformin + placebo) which was excluded from the base case as:

- The study had a lower HbA1c criterion than the MSD SLR for study inclusion (HbA1c ≥7%).
- As would be expected with a lower inclusion criterion, the mean baseline HbA1c for Bolinder et al., 2012 (35) (7.2%) was lower than the average of the studies included in the SLR (8%).
- The primary outcome of this study was change in weight as opposed to change in HbA1c.

A sensitivity analysis including Bolinder et al., 2012 was conducted to assess the impact on the NMA results (35).

Table 28- Summary of the RCTs used to carry out the NMA

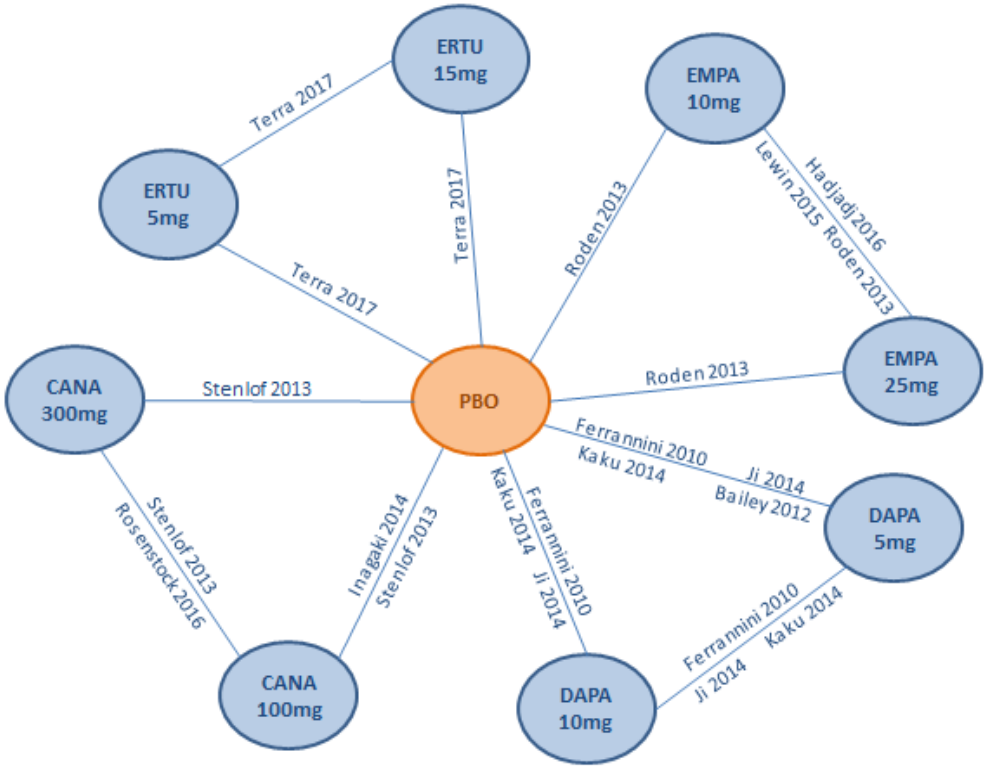
Trial identifier	ERTU5	ERTU15	CANA100	CANA300	DAPA5	DAPA10	EMPA10	EMPA25
Monotherapy								
NCT00528372** Bailey et al., 2012 (33)					✓			
NCT00528372** Ferrannini et al., 2010 (36)					✓ (TA390)	✓ (TA390)		
NCT01719003 Hadjadj et al., 2016 (37)							✓	✓
NCT01413204 Inagaki et al., 2014 (38)			✓ (TA390)					
NCT01095653 Ji et al., 2014 ** (39)					✓ (TA390)	✓ TA390)		
NCT01294423 Kaku et al., 2014** (34)					✓ (TA390)	✓ (TA390)		
NCT01422876 Lewin et al., 2015 (40)							✓ (TA390)	✓ (TA390)
NCT01177813 Roden et al., 2013 /(41)							✓ (TA390)	✓ (TA390)
NCT01809327 Rosenstock et al., 2016 /(42)			✓	✓				
NCT01081834 Stenlof et al., 2013 (43)			✓ (TA390)	✓ (TA390)				
NCT01958671 VERTIS MONO Terra (16)	✓	✓						
Dual therapy – MET background therapy								
NCT00528879 Bailey et					✓	✓		

Trial identifier	ERTU5	ERTU15	CANA100	CANA300	DAPA5	DAPA10	EMPA10	EMPA25
al., 2010 (44)					**(TA288 – TA336)**	**(TA315 – TA288 – TA336)**		
NCT00855166 Bolinder et al., 2012** (35)						✓ **(TA315 – TA288 – TA336)**		
NCT02099110 VERTIS FACTORIAL Pratley et al., 2017 (21)	✓	✓						
NCT02033889 VERTIS MET Rosenstock et al., 2017 (19)	✓	✓						
NCT01422876 DeFronzo et al., 2015 (45)							✓ **(TA336)**	✓ **(TA336)**
NCT01159600 Haring et al., 2014 (46)							✓ **(TA336)**	✓ **(TA336)**
NCT01106677 Lavalle-Gonzalez et al., 2013 (47)			✓ **(TA315 – TA336)**	✓ **(TA315 – TA336)**				
NCT01095666 Yang et al., 2016 (48)					✓	✓		

Abbreviations: TA, technology appraisal; SA, sensitivity analysis; CSR, clinical study report; ERTU, ertugliflozin; PBO, placebo; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin
** Studies included/excluded through sensitivity analysis

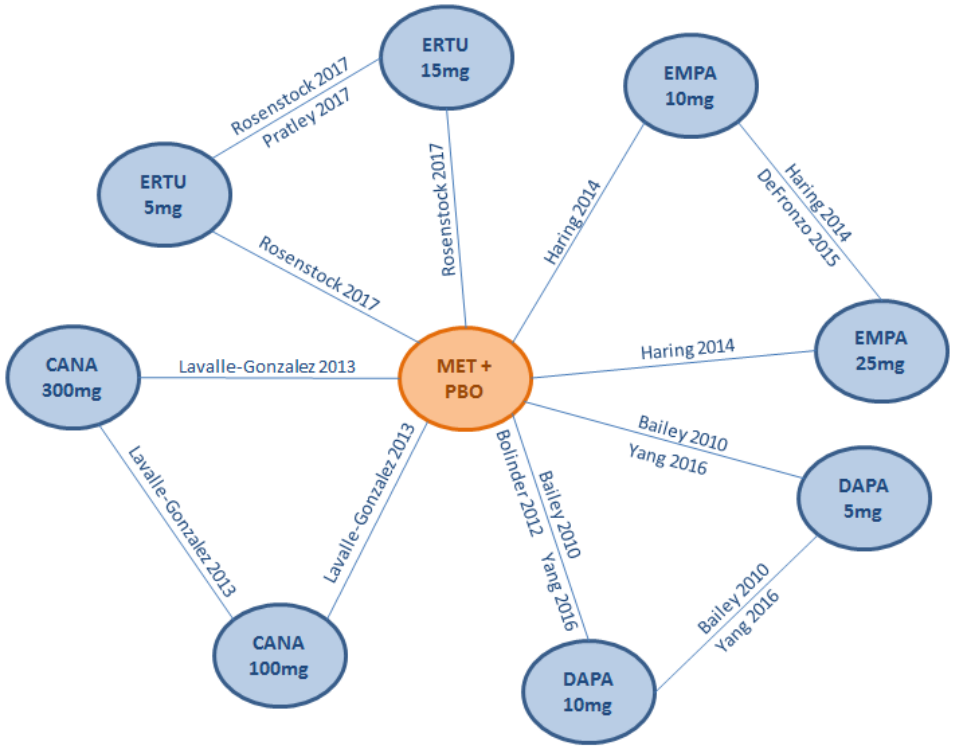
Please refer to Appendix D for full details of the methodology for the NMA, the baseline characteristics and outcomes of the studies included in the NMA.

Figure 13 - Full network of evidence – MONOTHERAPY



Abbreviations: PBO, placebo; SITA, sitagliptin; LINA, linagliptin; EMPA, empagliflozin; DAPA, dapagliflozin; mg, milligram

Figure 14 - Full network of evidence – DUAL THERAPY



Abbreviations: PBO, placebo; ERTU, ertugliflozin; CANA, canagliflozin; EMPA, empagliflozin; DAPA, dapagliflozin; MET, metformin; mg, milligram

B.3.9.2 NMA base case definition

The NMA base case was defined as follows:

- The FAS population was used in all ertugliflozin trials for efficacy outcomes.
- The ASaT population was used in all ertugliflozin trials for safety outcomes.
- The outcome time point was either 24 or 26 weeks for all the included studies.
- The efficacy outcomes assessed were: HbA1c, weight, SBP and HbA1c at target (i.e. <7%).
- The safety outcomes assessed were: overall AEs, UTIs, genital mycotic infections.

B.3.9.3 NMA results

The NMAs conducted consisted of both continuous and binary outcomes. For the continuous outcomes (change in HbA1c, weight and SBP) the median of the mean difference from baseline is presented. The median odds ratio (OR) is presented for binary outcomes (HbA1c in target, UTIs and genital mycotic infections). Additional binary safety outcomes (NSHE and SHE) were not considered appropriate for inclusion in the NMA due to the number of zero events across all lines of therapy.

The results of the NMA are summarised in both forest plots and tables by line of therapy. NMA summary statistics are also provided in Appendix P, to give context for the model selection (random effect model (REM) or fixed effect model (FEM)).

The forest plots display the results obtained from comparing each SGLT-2i to placebo. Within tables, the median differences and ORs were reported for continuous and binary outcomes, respectively. The associated 95% credible intervals (CrI) for the selected base cases were also included. Significant results, defined as a CrI not including 0 for continuous outcomes and 1 for binary outcomes, were highlighted in bold in the tables. Results for the non-selected model and the deviance information criterion (DIC) can be found in Appendix L.

B.3.9.3.1 Monotherapy NMA

The results are broken down into continuous efficacy outcomes (Figure 15 and Table 29, Figure 16 and Table 30, Figure 17 and Table 31), binary efficacy outcomes (Figure 18 and Table 32) and binary safety outcomes (Figure 19 and Table 33, Figure 20 and Table 34).

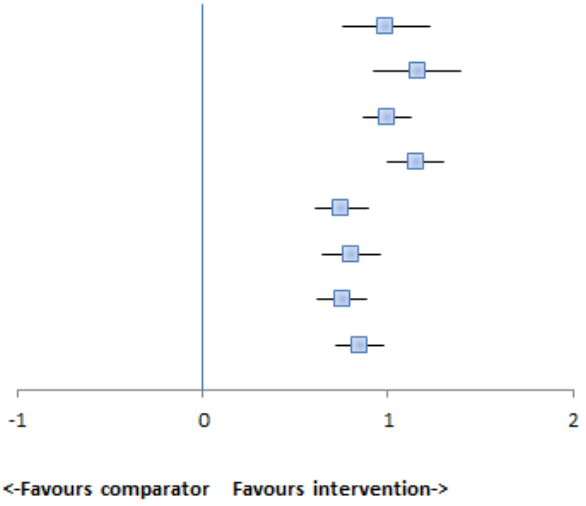
- **Continuous efficacy outcomes**

HbA1c (%) change from baseline to week 26

For change from baseline in HbA1c, ertugliflozin 5 and 15 mg and canagliflozin 100 and 300 mg had the largest effect sizes when compared with placebo (Figure 15). Ertugliflozin 15 mg was statistically significantly better that both doses of dapagliflozin and empagliflozin (Table 29).

Figure 15 - Base case - HbA1c (%) change from baseline to week 24 - 26 (continuous outcome – FEM)

Comparison	Median DIFF	[95% CrI]
ERTU5 vs. PBO	0.99	[0.75, 1.23]
ERTU15 vs. PBO	1.16	[0.93, 1.40]
CANA100 vs. PBO	1.00	[0.86, 1.13]
CANA300 vs. PBO	1.15	[1.00, 1.30]
DAPA5 vs. PBO	0.75	[0.60, 0.89]
DAPA10 vs. PBO	0.80	[0.64, 0.96]
EMPA10 vs. PBO	0.75	[0.62, 0.88]
EMPA25 vs. PBO	0.85	[0.72, 0.98]



Abbreviations: HbA1c, haemoglobin A1c; FEM, fixed effect model; vs, versus; CrI, credible interval

Table 29 - HbA1c change (%) median difference (95% CrI) Base Case: FEM

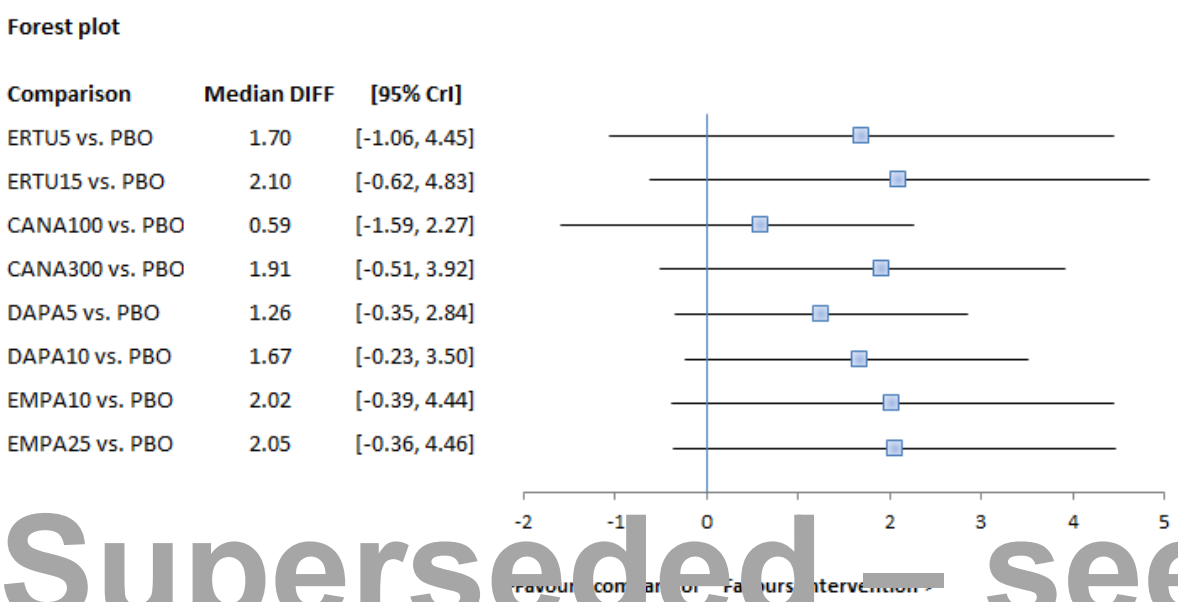
	ERTU5	ERTU15
CANA100	0.01 (-0.27 to 0.28)	[redacted]
CANA300	[redacted]	-0.01 (-0.29 to 0.27)
DAPA5	-0.24 (-0.52 to 0.04)	[redacted]
DAPA10	[redacted]	**-0.36 (-0.65 to -0.08)**
EMPA10	-0.24 (-0.51 to 0.03)	[redacted]
EMPA25	[redacted]	**-0.31 (-0.58 to -0.04)**

Bold values indicate significant results (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

Weight change (kg) change from baseline to week 26

Ertugliflozin 15 mg had the largest reduction in weight from baseline when compared with placebo (Figure 16). However, there were no statistically significant differences between SGLT-2is (Table 30).

Figure 16 - Base case - Weight (kgs) change from baseline to week 24 - 26 (continuous outcome – REM)



Abbreviations: kg, kilogram; REM, random effect model; vs, versus; CrI, credible interval

Table 30 - Weight Change (kgs) median difference (95% CrI) Base Case: REM

	ERTU5	ERTU15
CANA100	-1.1 (-4.73 to 2)	[redacted]
CANA300	[redacted]	-0.19 (-3.91 to 3.12)
DAPA5	-0.45 (-3.64 to 2.73)	[redacted]
DAPA10	[redacted]	-0.42 (-3.77 to 2.84)
EMPA10	0.32 (-3.33 to 3.98)	[redacted]
EMPA25	[redacted]	-0.04 (-3.7 to 3.59)

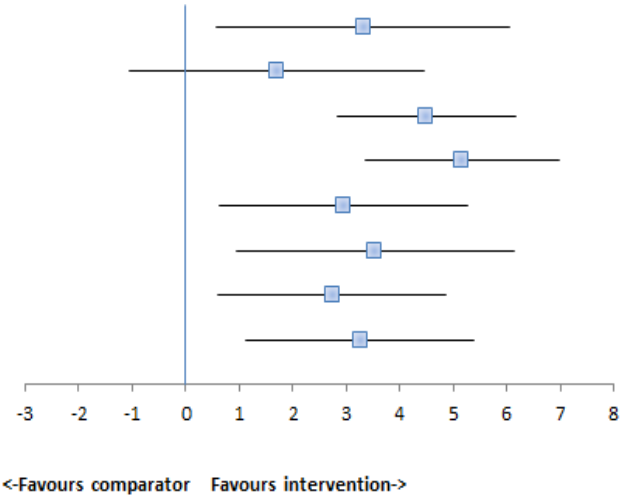
Bold values indicate significant results (CrI does not include 0)
Abbreviations: CrI, credible interval; REM, random effect model

SBP (mmHg) change from baseline to week 26

Canagliflozin 100 mg and 300 mg had the largest effect size in SBP when compared to placebo (Figure 17). Canagliflozin 300 mg was statistically significantly better than ertugliflozin 15 mg in reducing SBP (Table 31).

Figure 17 - Base case - SBP (mmHg) change from baseline to week 24 - 26 (continuous outcome – FEM)

Comparison	Median DIFF	[95% CrI]
ERTU5 vs. PBO	3.31	[0.58, 6.06]
ERTU15 vs. PBO	1.70	[-1.05, 4.46]
CANA100 vs. PBO	4.49	[2.82, 6.16]
CANA300 vs. PBO	5.16	[3.34, 6.98]
DAPA5 vs. PBO	2.94	[0.63, 5.26]
DAPA10 vs. PBO	3.53	[0.95, 6.13]
EMPA10 vs. PBO	2.73	[0.59, 4.87]
EMPA25 vs. PBO	3.26	[1.12, 5.39]



Abbreviations: SBP, systolic blood pressure; FEM, fixed effect model; vs, versus; CrI, credible interval

Table 31 - SBP Change (mmHg) median difference (95% CrI) Base Case: FEM

	ERTU5	ERTU15
CANA100	1.17 (-2.04 to 4.39)	[redacted]
CANA300	[redacted]	**3.45 (0.15 to 6.76)**
DAPA5	-0.37 (-3.96 to 3.23)	[redacted]
DAPA10	[redacted]	1.83 (-1.96 to 5.63)
EMPA10	-0.58 (-4.06 to 2.9)	[redacted]
EMPA25	[redacted]	1.55 (-1.94 to 5.05)

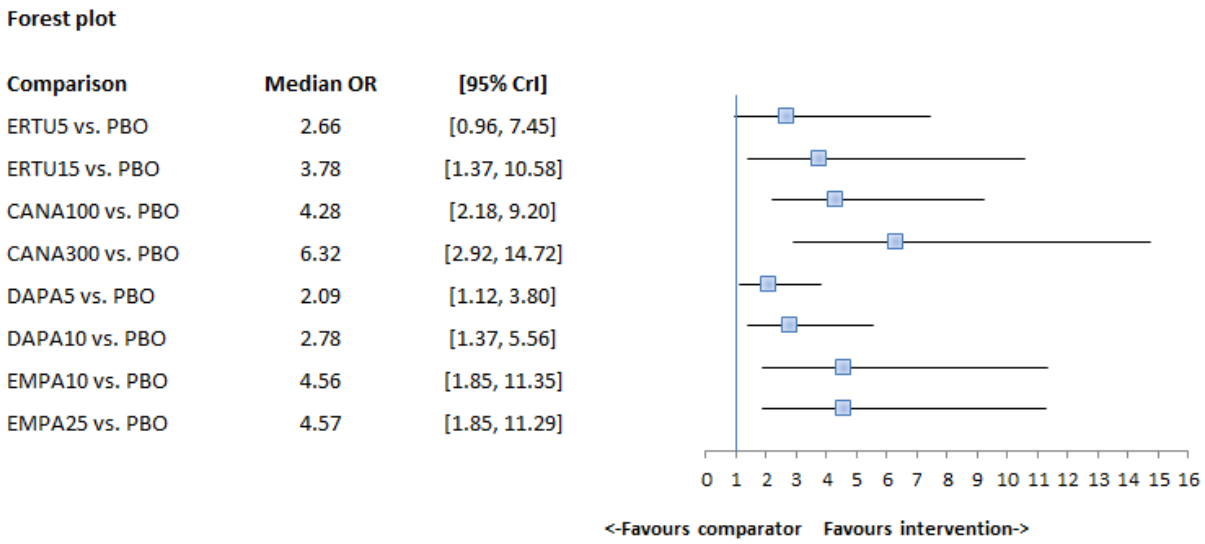
Bold values indicate significant results (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

- **Binary efficacy outcome**

HbA1c <7.0% (<53 mmol/mol) at week 26

For HbA1c in target (<7.0%), ertugliflozin 15 mg, canagliflozin 100 and 300, dapagliflozin 5 and 10 mg and empagliflozin 10 and 25 mg were significantly better than placebo (Figure 18). Canagliflozin 300 mg had the largest median OR versus placebo (Figure 18). There were no significant differences in the indirect comparison between SGLT-2is (Table 32).

Figure 18 - Base case – HbA1c (%) within target at week 24 - 26 (binary outcome – REM)



Abbreviations: HbA1c, haemoglobin A1c; REM, random effect model; vs, versus; CrI, credible interval; OR, odd ratio

Table 32 - HbA1c in target (<7.0%) median odds ratio (95% CrI) Base Case: REM

	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA5	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

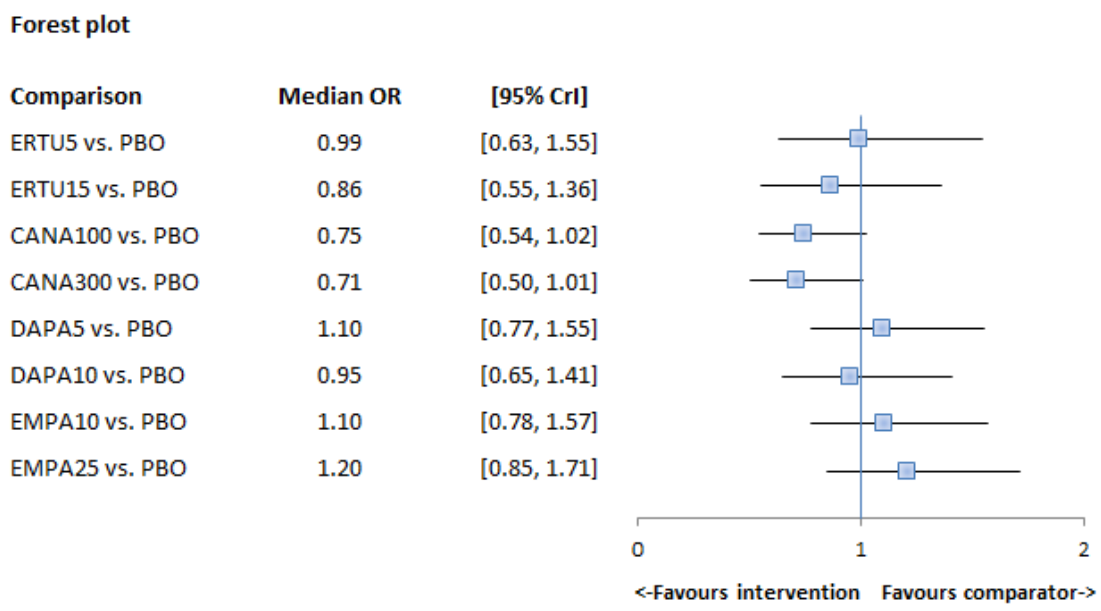
Bold values indicate significant results (CrI does not include 1)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; REM, random effect model

- **Binary safety outcomes**

AEs at week 26

There were no significant differences between SGLT-2is and placebo (Figure 19) or between SGLT-2is (Table 33) for AEs.

Figure 19 - Base case – AEs at week 24 - 26 (binary outcome – FEM)



Abbreviations: AEs, adverse events; FEM, fixed effect model; vs, versus; CrI, credible interval; OR, odd ratio

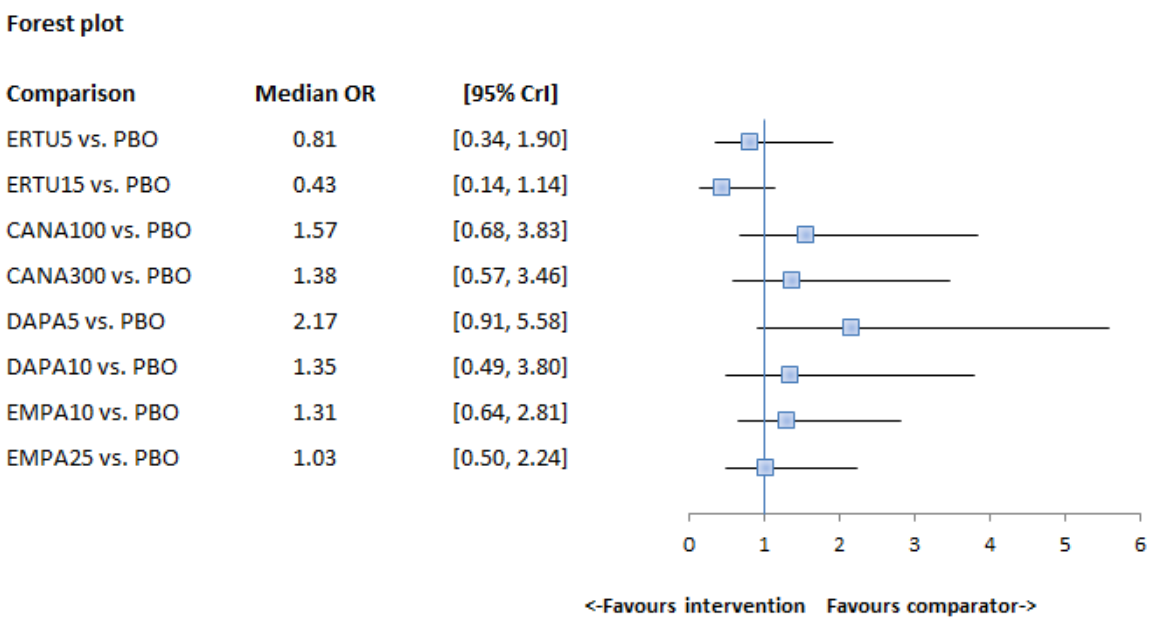
Table 33 - AEs median odds ratio (95% CrI) Base Case: FEM

	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA5	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Bold values indicate significant results (CrI does not include 1)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

For UTIs, ertugliflozin 5 and 15 mg had the smallest ORs, indicating that both doses of ertugliflozin resulted in fewer events than the other SGLT-2is when compared with placebo (Figure 20). [redacted] had significantly [redacted] (Table 34).

Figure 20 - Base case – UTIs at week 24 - 26 (binary outcome – FEM)



Abbreviations: UTIs, urinary tract infections; FEM, fixed effect model; vs, versus; CrI, credible interval; OR, odd ratio

Table 34 - UTIs median odds ratio (95% CrI) Base Case: FEM

	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA5	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Bold values indicate significant results (CrI does not include 1)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

All included studies reported genital mycotic infections but both the FEM and the REM did not converge for this outcome, attributed to insufficient sample size and small numbers of patients affected by genital mycotic infections in the included studies. Non-converged results are available in Appendix M.

B.3.9.3.2 Dual therapy NMA

The dual therapy NMA results are divided into continuous efficacy outcomes (Figure 21 and Table 35, Figure 22 and Table 36, Figure 23 and Table 37), binary efficacy outcomes (Figure 24 and Table 38) and binary safety outcomes (Figure 25 and Table 39, Figure 26 and Table 40).

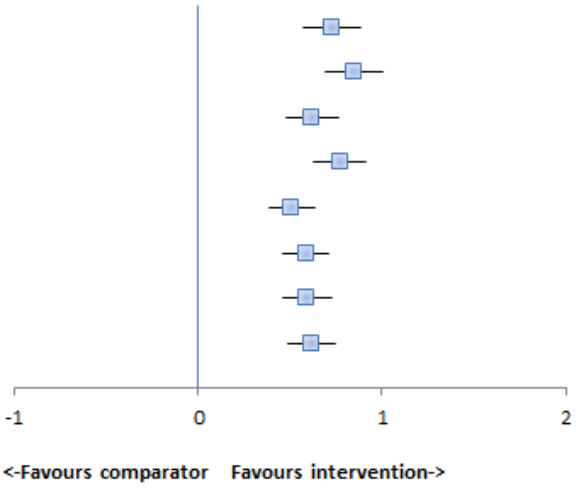
- **Continuous efficacy outcomes**

HbA1c (%) change from baseline to week 26

For continuous efficacy outcomes ertugliflozin 15 mg had the largest effect size for change from baseline in HbA1c (Figure 21) when compared with placebo. Ertugliflozin 5 mg was statistically significantly better than dapagliflozin 5 mg and ertugliflozin 15 mg was superior to all the other SGLT-2is apart from canagliflozin 300 mg in the indirect comparison (Table 35).

Figure 21 - Base case – HbA1c (%) change from baseline to week 24 - 26 (continuous outcome – FEM)

Comparison	Median DIFF	[95% CrI]
ERTU5 vs. PBO	0.73	[0.57, 0.89]
ERTU15 vs. PBO	0.85	[0.69, 1.01]
CANA100 vs. PBO	0.62	[0.48, 0.76]
CANA300 vs. PBO	0.77	[0.63, 0.91]
DAPA5 vs. PBO	0.51	[0.38, 0.64]
DAPA10 vs. PBO	0.59	[0.46, 0.71]
EMPA10 vs. PBO	0.59	[0.46, 0.72]
EMPA25 vs. PBO	0.62	[0.49, 0.75]



Background therapy: metformin

Abbreviations: HbA1c, haemoglobin A1c; FEM, fixed effect model; vs, versus; CrI, credible interval

Table 35 - HbA1c change (%) median difference (95% CrI) Base Case: FEM

	ERTU5	ERTU15
CANA100	-0.11 (-0.32 to 0.1)	[redacted]
CANA300	[redacted]	-0.08 (-0.29 to 0.13)
DAPA5	**-0.22 (-0.42 to -0.02)**	[redacted]
DAPA10	[redacted]	**-0.26 (-0.46 to -0.06)**
EMPA10	-0.14 (-0.34 to 0.07)	[redacted]
EMPA25	[redacted]	**-0.23 (-0.44 to -0.03)**

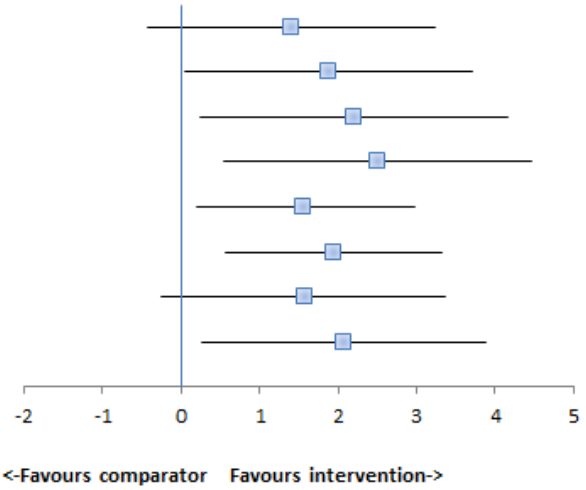
Bold values indicate significant results (CrI does not include 0)
Background therapy: metformin
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

Weight (kg) change from baseline to week 26

Canagliflozin 100 and 300 mg and empagliflozin 25 mg had the larger effect size for change in weight (Figure 22). With the exception of empagliflozin 10 mg and ertugliflozin 5 mg (which approached statistical significance), all SGLT-2is were significantly superior to placebo on weight reduction. There were no significant differences between any SGLT-2i (Table 36).

Figure 22 - Base case - Weight change from baseline to week 24 - 26 (continuous outcome – REM)

Comparison	Median DIFF	[95% CrI]
ERTU5 vs. PBO	1.41	[-0.44, 3.24]
ERTU15 vs. PBO	1.87	[0.04, 3.72]
CANA100 vs. PBO	2.20	[0.25, 4.16]
CANA300 vs. PBO	2.50	[0.55, 4.46]
DAPA5 vs. PBO	1.55	[0.20, 2.98]
DAPA10 vs. PBO	1.94	[0.56, 3.33]
EMPA10 vs. PBO	1.58	[-0.25, 3.38]
EMPA25 vs. PBO	2.06	[0.26, 3.89]



Background therapy: metformin

Abbreviations: kg, kilogram; REM, random effect model; vs, versus; CrI, credible interval

Table 36 - Weight Change (kgs) median difference (95% CrI) Base Case: REM

	ERTU5	ERTU15
CANA100	0.79 (-1.88 to 3.49)	[redacted]
CANA300	[redacted]	0.63 (-2.05 to 3.31)
DAPA5	0.15 (-2.12 to 2.49)	[redacted]
DAPA10	[redacted]	0.06 (-2.23 to 2.38)
EMPA10	0.17 (-2.41 to 2.74)	[redacted]
EMPA25	[redacted]	0.19 (-2.38 to 2.78)

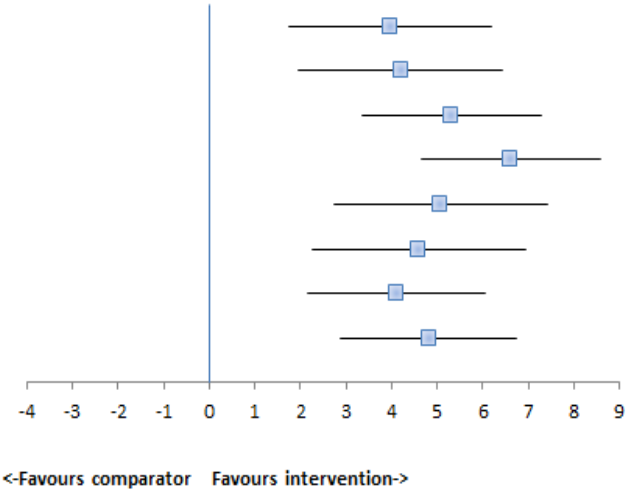
Bold values indicate significant results (CrI does not include 0)
Background therapy: metformin
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; REM, random effect model

SBP (mmHg) change from baseline to week 26

For the SBP outcome, all SGLT-2is superior to placebo (Figure 23); canagliflozin 300 mg produced the largest effect size versus placebo. No other significant differences between SGLT-2is were identified in the indirect comparison (Table 37).

Figure 23 - Base case – SBP change from baseline to week 24 - 26 (continuous outcome – FEM)

Comparison	Median DIFF	[95% CrI]
ERTU5 vs. PBO	3.97	[1.75, 6.19]
ERTU15 vs. PBO	4.20	[1.96, 6.43]
CANA100 vs. PBO	5.31	[3.34, 7.27]
CANA300 vs. PBO	6.61	[4.65, 8.57]
DAPA5 vs. PBO	5.07	[2.72, 7.41]
DAPA10 vs. PBO	4.59	[2.25, 6.93]
EMPA10 vs. PBO	4.10	[2.17, 6.04]
EMPA25 vs. PBO	4.80	[2.86, 6.74]



Background therapy: metformin
Abbreviations: SBP, systolic blood pressure; FEM, fixed effect model; vs, versus; CrI, credible interval

Table 37 - SBP Change (mmHg) median difference (95% CrI) Base Case: FEM

	ERTU5	ERTU15
CANA100	1.34 (-1.62 to 4.29)	[redacted]
CANA300	[redacted]	2.42 (-0.55 to 5.37)
DAPA5	1.1 (-2.13 to 4.33)	[redacted]
DAPA10	[redacted]	0.4 (-2.83 to 3.63)
EMPA10	0.13 (-2.82 to 3.07)	[redacted]
EMPA25	[redacted]	0.61 (-2.34 to 3.56)

Background therapy: metformin (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

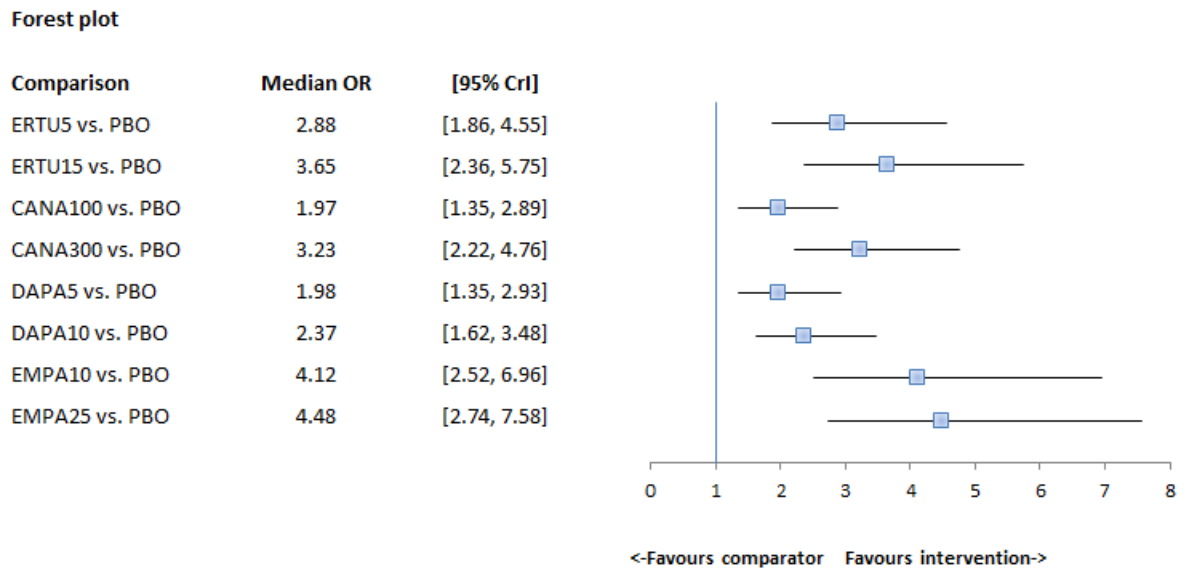
- **Binary efficacy outcome**

HbA1c in target (<7.0%) at week 26

Results show that empagliflozin 10 and 25 mg had the largest median OR for HbA1c in target (<7.0%) when compared to placebo, followed by ertugliflozin 15 mg and canagliflozin 300mg (Figure 24). All SGLT-2is were superior to placebo. In the indirect comparison,

[redacted] was superior to the [redacted] (Table 38). No other differences were found between SGLT-2is.

Figure 24 - Base case – HbA1c (%) within target (<7.0%) at week 24 - 26 (binary outcome – FEM)



Background therapy: metformin
Abbreviations: HbA1c, haemoglobin A1c; FEM, fixed effect model; vs, versus; CrI, credible interval; OR, odd ratio

Table 38 - HbA1c in target (<7.0%) median odd ratio (95% CrI) Base Case: FEM

	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA5	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

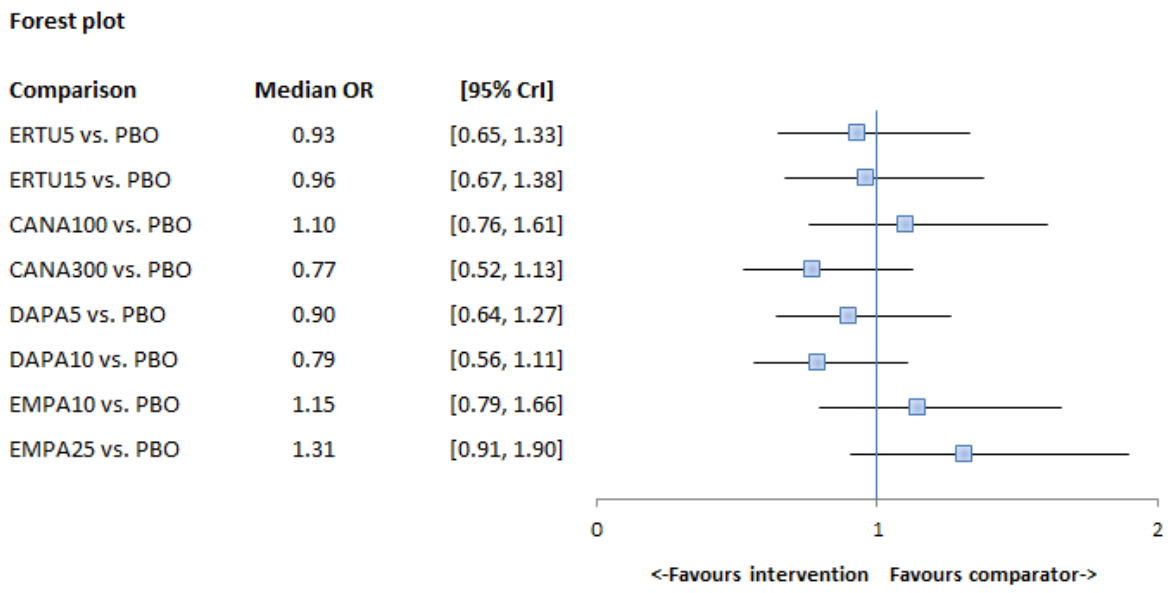
Background therapy: metformin (CrI does not include 1)
Bold values indicate significant results
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

- **Binary safety outcomes**

AEs at week 26

For AEs and UTIs, no statistically significant differences were found for the SGLT-2is compared with placebo (Figure 25 and Figure 26) or with each other (Table 39 and Table 40).

Figure 25 - Base case – AEs at week 24 - 26 (binary outcome – FEM)



Background therapy: metformin
Abbreviations: AEs, adverse events; FEM, fixed effect model; vs, versus; CrI, credible interval; OR, odd ratio

Table 39 - AEs median odds ratio (95% CrI) Base Case: FEM

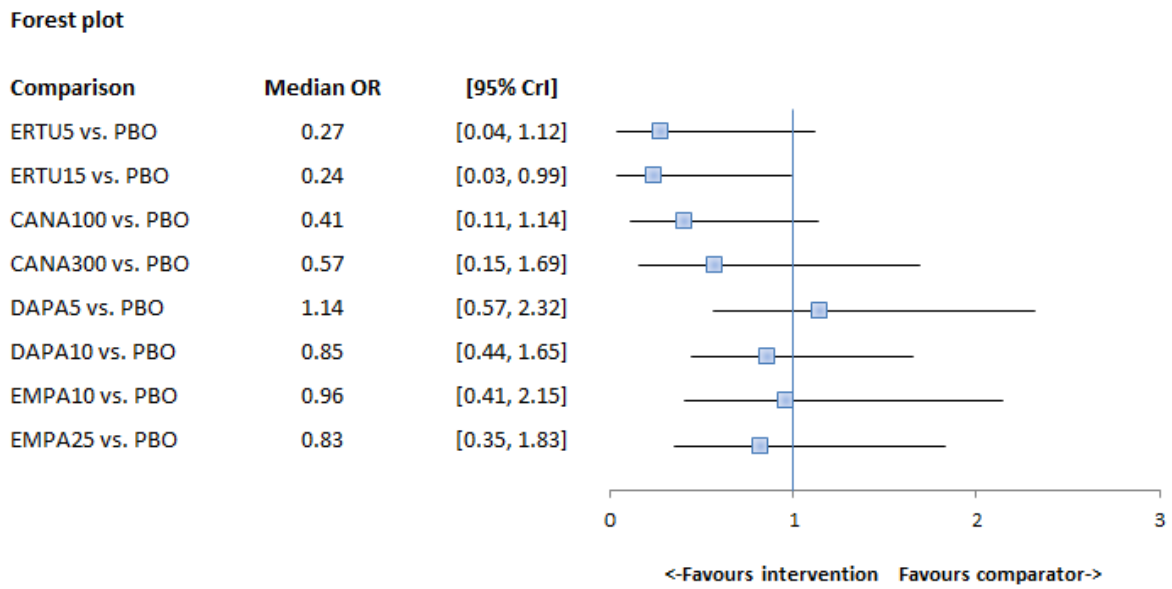
	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA5	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Background therapy: metformin (CrI does not include 1)
Bold values indicate significant results
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

UTIs at week 26

For UTIs, ertugliflozin (both doses) had the smallest median OR (fewer events occurred). Ertugliflozin 15 mg had significantly less UTIs than placebo (Figure 26). No significant differences were found between SGLT-2is in the indirect comparison (Table 40).

Figure 26 - Base case – UTIs at week 24 - 26 (binary outcome – FEM)



Background therapy: metformin
Abbreviations: UTIs, urinary tract infections; FEM, fixed effect model; vs, versus; CrI, credible interval; OR, odd ratio

Table 40 - UTIs median odds ratio (95% CrI) Base Case: FEM

	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA5	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Background therapy: metformin (CrI does not include 1)
Bold values indicate significant results
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

Lavelle-Gonzalez et al., 2013 (47) did not report genital mycotic infections during the time period of interest (24-26 weeks); as a result, canagliflozin could not be linked to the network. Neither the FEM nor the REM converged for the genital mycotic infection outcome, attributed

to insufficient number of studies and small numbers of patients affected, particularly in the placebo arms. Non-converged results are available in Appendix M.

B.3.9.4 Assessment of heterogeneity and inconsistency

Heterogeneity

The statistical heterogeneity in treatment effect estimates was evaluated using between study variance (i.e. square root of the standard deviation of underlying effects across trials) with 95% CrI (49), where the REM converged. Heterogeneity was also assessed via assessment of study quality, which is presented in details in Appendix D.

It is possible that between-study heterogeneity may have been present. It is also important to note, there is no method, (statistical or otherwise) to remove all heterogeneity, particularly when data is scarce.

Inconsistency

Inconsistency, which occurs due to an imbalance of effect modifiers between treatment comparison and leads to biased estimates of treatment effect (50), was assessed by performing a series of Bucher tests to test for conflicts between direct and indirect evidence. Where significant inconsistency ($p<0.05$) was found, the studies identified as causing the potential inconsistency were investigated further through sensitivity analyses to determine whether specific effect modifiers could be identified. Consistency was also checked by assessing closed loops (50).

- *Monotherapy*: there were 3 closed loops tested for inconsistency – both doses of empagliflozin and placebo, both doses of canagliflozin and placebo and both doses of dapagliflozin plus placebo. The outcomes, change in HbA1c, change in weight and HbA1c in target were tested. No significant differences were identified in any of the outcomes or loops, indicating no evidence of inconsistency between direct evidence from the trials and indirect evidence from the NMA.
- *Dual therapy*: there were 3 closed loops with direct and indirect evidence – empagliflozin, ertugliflozin and dapagliflozin doses and placebo loops. The outcomes, change in HbA1c, change in weight and HbA1c in target were tested for inconsistency. No significant differences were identified in any of the outcomes or loops, indicating no discrepancy between the NMA and trial data.

Full details of the closed loop tests are reported in Appendix O.

B.3.9.4 Sensitivity analyses

- **Sensitivity analyses – monotherapy**

Sensitivity analyses were run for two outcomes: HbA1c change, the primary outcome of the RCTs, and weight change which was found to influence the cost-effectiveness of TA390 via the impact on health state utilities. Two sensitivity analyses were performed for each of these outcomes - removing dapagliflozin 5 mg as a comparator and adding Kaku et al., 2014 (34) (dapagliflozin 5 and 10 mg), in accordance with the explanations given in Section B.3.9.1. Additional sensitivity analyses, such as meta-regression, were not possible due to the small number of included studies.

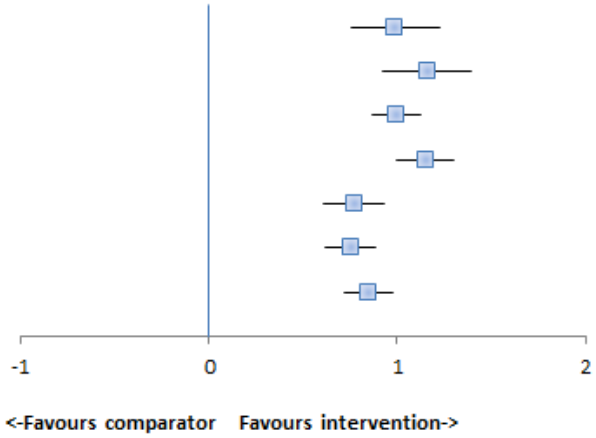
Sensitivity analysis 1 (SA1): removing dapagliflozin 5 mg as comparator

The studies that included dapagliflozin 5 mg were: Bailey et al., 2012 (33), Ferrannini et al.(36), 2010 and Ji et al., 2014 (39).

Low-dose of dapagliflozin was not considered a relevant comparator in TA390 due to primarily being prescribed for patients with impaired hepatic function (51). The sensitivity analysis was run using the model selected in the base case. As shown in Figure 27 and Table 41, removing dapagliflozin 5 mg did not change the base case results for ertugliflozin when considering the baseline change in HbA1c.

Figure 27 -SA1 – HbA1c (%) change from baseline to week 24 - 26 removing dapagliflozin 5 mg (continuous outcome – FEM)

Comparison	Median DIFF	[95% CrI]
ERTU5 vs. PBO	0.99	[0.75, 1.23]
ERTU15 vs. PBO	1.16	[0.92, 1.40]
CANA100 vs. PBO	1.00	[0.86, 1.13]
CANA300 vs. PBO	1.15	[1.00, 1.30]
DAPA10 vs. PBO	0.77	[0.61, 0.93]
EMPA10 vs. PBO	0.75	[0.62, 0.88]
EMPA25 vs. PBO	0.85	[0.72, 0.98]



Abbreviations: SA, sensitivity analysis; HbA1c, haemoglobin A1c; fixed effect model; vs, versus; CrI, credible interval

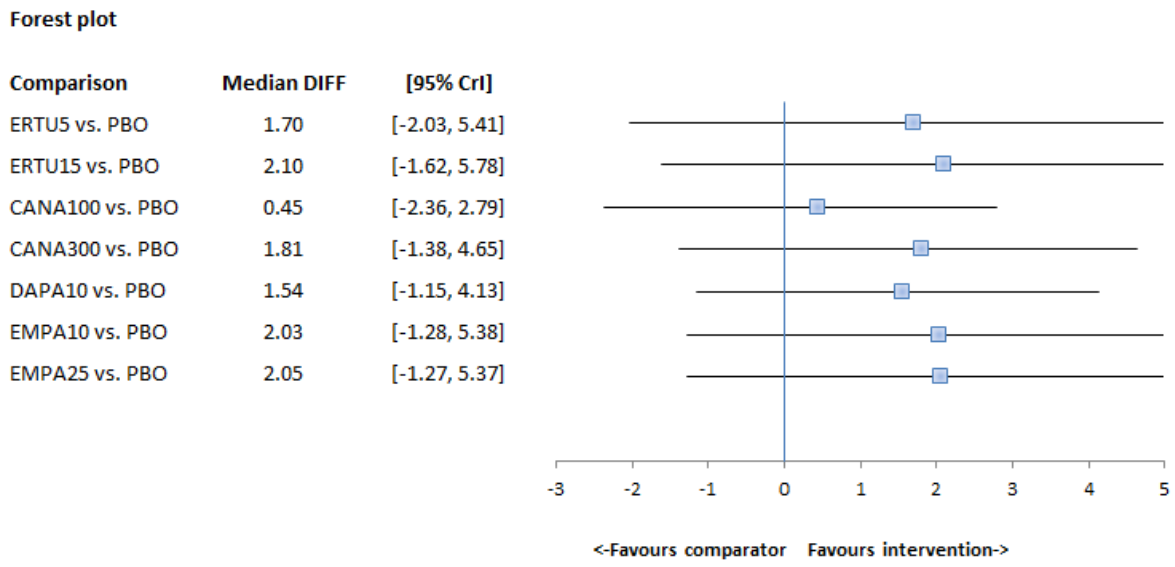
Table 41 - HbA1c change (%) median difference (95% CrI) SA1: FEM

	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Bold values indicate significant results (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

Furthermore, removing dapagliflozin 5 mg did not impact on the base case findings for the weight change from baseline in monotherapy. None of the comparisons were statistically significant (Figure 28).

Figure 28 - SA1 – Weight change from baseline to week 24 - 26 rmoving dapagliflozin 5 mg (continuous outcome – REM)



Abbreviations: SA, sensitivity analysis; kg, kilogram; fixed effect model; vs, versus; CrI, credible interval

Table 42 - Weight Change (kgs) median difference (95% CrI) SA1: REM

	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Bold values indicate significant results (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; REM, random effect model

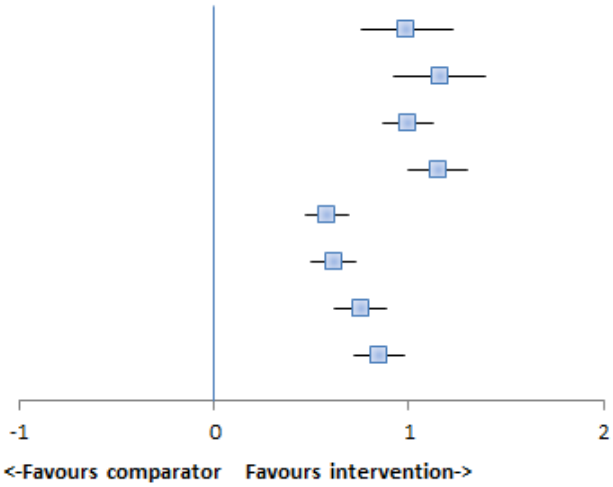
Sensitivity analysis 2 (SA2): adding Kaku et al., 2014

As mentioned in Section B.3.8.1, Kaku et al., 2014 (34) was initially excluded from the SLR and NMA as it did not meet the inclusion criterion of all subjects having uncontrolled HbA1c (≥7%) by having a lower threshold (≥6.5%). The average baseline HbA1c of this study was therefore lower than other included studies. MSD's inclusion criterion of HbA1c ≥7.0% was developed to be consistent with the ertugliflozin trial designs and to reduce heterogeneity of included studies. Moreover, excluding this study from the base case was considered to be conservative, as the lower baseline HbA1c and subsequent change in HbA1c reduced the average effect of dapagliflozin. This study was included in a sensitivity analysis to assess the impact on the NMA results.

As shown in Figure 29, adding Kaku et al., 2014 (34) for the HbA1c change from baseline outcome, resulted in a reduction of the median difference of dapagliflozin doses versus placebo (0.58 vs 0.75 in the base case). Consequently, [redacted] became significantly more effective versus both doses of [redacted] (Table 43). There were no other significant differences between the base case and sensitivity analyses for ertugliflozin.

Figure 29 - SA2 – HbA1c (%) change from baseline to week 24 - 26 including Kaku et al., 2014 (continuous outcome – FEM)

Comparison	Median DIFF	[95% CrI]
ERTU5 vs. PBO	0.99	[0.75, 1.23]
ERTU15 vs. PBO	1.16	[0.92, 1.40]
CANA100 vs. PBO	1.00	[0.86, 1.13]
CANA300 vs. PBO	1.15	[1.00, 1.30]
DAPA5 vs. PBO	0.58	[0.47, 0.69]
DAPA10 vs. PBO	0.61	[0.50, 0.73]
EMPA10 vs. PBO	0.75	[0.62, 0.88]
EMPA25 vs. PBO	0.85	[0.72, 0.98]



Abbreviations: SA, sensitivity analysis; HbA1c, haemoglobin A1c; fixed effect model; vs, versus; CrI, credible interval

Table 43 - HbA1c change (%) median difference (95% CrI) SA2: FEM

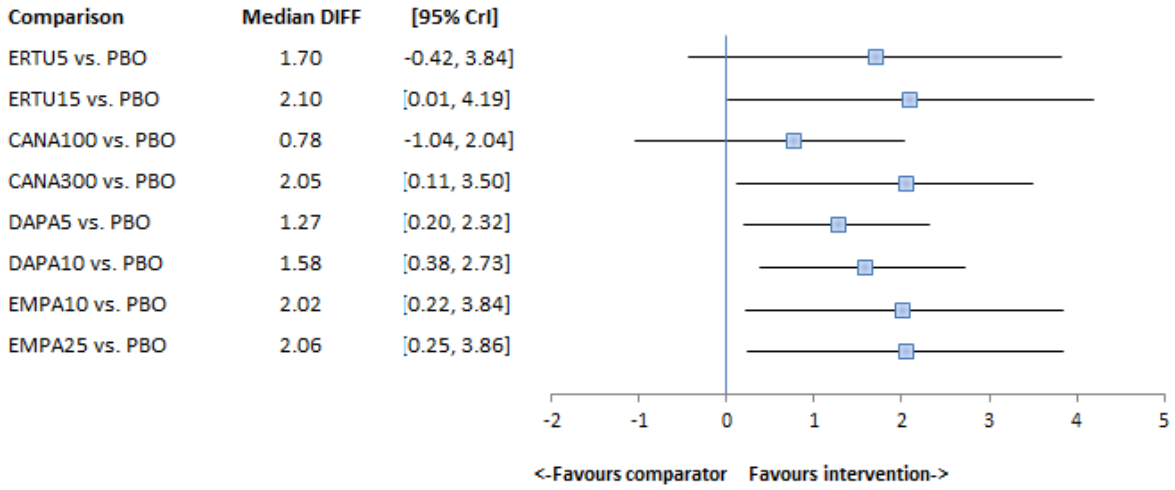
	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA5	[redacted]	[redacted]

DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Bold values indicate significant results (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; REM, random effect model

For weight change from baseline, including Kaku et al., 2014 (34) resulted in ertugliflozin 15 mg becoming significantly more effective versus placebo. There were no other significant differences between ertugliflozin doses and other SGLT-2is of comparable doses as depicted in Figure 30 and Table 44 below.

Figure 30 - SA2 – Weight change from baseline to week 26 including Kaku et al., 2014 (continuous outcome – REM)



Abbreviations: SA, sensitivity analysis; kg, kilogram; fixed effect model; vs, versus; CrI, credible interval

Table 44 - Weight Change (kgs) median difference (95% CrI) SA2: REM

	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]
	[redacted]	[redacted]

Bold values indicate significant results (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; REM, random effect model

- **Sensitivity analyses – dual therapy**

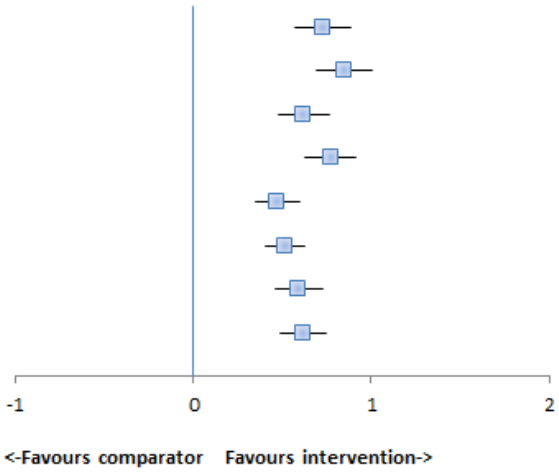
Sensitivity analysis 3 (SA3): adding Bolinder et al., 2012

Two sensitivity analyses were run for the dual therapy NMA, assessing the impact of including Bolinder et al, 2012 (35) on the key outcomes of HbA1c change and weight change. This study was originally excluded as the HbA1c threshold inclusion criterion was too low (6.5%≤ HbA1c ≤8.5%) and the primary outcome for the study was weight change, not HbA1c change. Additionally, the SD and standard error (SE) were unavailable for HbA1c. For this outcome, the SE was estimated by assuming the same SD as Yang et al., 2016 (48) and dividing it by the square root of the sample size of Bolinder et al., 2012.

Results versus placebo show that no changes occur and that findings were consistent with the base case (Figure 31). However, Table 45 shows that adding Bolinder et al., 2012 resulted in [redacted] becoming significantly more effective versus the higher and lower doses of [redacted].

Figure 31 - SA3 – HbA1c (%) change from baseline to week 24 - 26 including Bolinder et al., 2012 (continuous outcome – FEM)

Comparison	Median DIFF	[95% CrI]
ERTU5 vs. PBO	0.73	[0.57, 0.89]
ERTU15 vs. PBO	0.85	[0.69, 1.01]
CANA100 vs. PBO	0.62	[0.48, 0.76]
CANA300 vs. PBO	0.77	[0.63, 0.91]
DAPA5 vs. PBO	0.47	[0.35, 0.60]
DAPA10 vs. PBO	0.51	[0.40, 0.62]
EMPA10 vs. PBO	0.59	[0.46, 0.72]
EMPA25 vs. PBO	0.62	[0.49, 0.75]



Abbreviations: SA, sensitivity analysis; HbA1c, haemoglobin A1c; fixed effect model; vs, versus; CrI, credible interval

Table 45 - HbA1c change (%) median difference (95% CrI) SA3: FEM

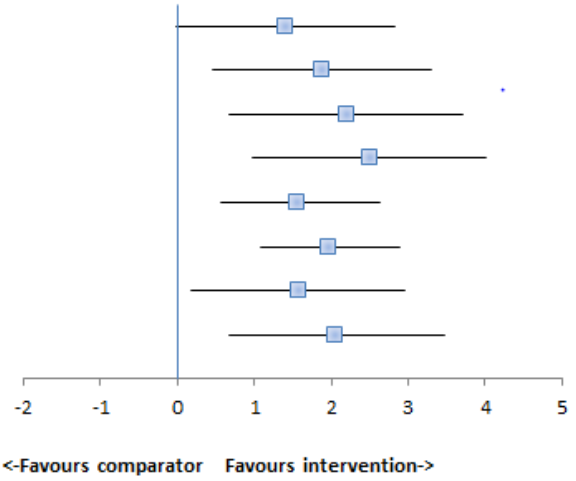
	ERTU5	ERTU15
CANA100	-0.11 (-0.32 to 0.1)	[redacted]
CANA300	[redacted]	[redacted]
DAPA5	[redacted]	[redacted]
DAPA10	**-0.22 (-0.42 to -0.02)**	[redacted]
EMPA10	-0.14 (-0.34 to 0.07)	[redacted]
EMPA25	[redacted]	[redacted]

Bold values indicate significant results (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; FEM, fixed effect model

Similar to the finding for HbA1c above, adding Bolinder et al., 2012 (35) did not change the results compared to the base case for weight change (Figure 32) and the comparison of SGLT-2is continued to show no significant differences (Table 46).

Figure 32 - SA3 – Weight (kgs) change from baseline to week 24 - 26 including Bolinder et al., 2012 (continuous outcome – REM)

Comparison	Median DIFF	[95% CrI]
ERTU5 vs. PBO	1.41	[-0.03, 2.84]
ERTU15 vs. PBO	1.87	[0.46, 3.32]
CANA100 vs. PBO	2.20	[0.68, 3.72]
CANA300 vs. PBO	2.50	[0.98, 4.02]
DAPA5 vs. PBO	1.57	[0.56, 2.64]
DAPA10 vs. PBO	1.98	[1.09, 2.89]
EMPA10 vs. PBO	1.58	[0.17, 2.97]
EMPA25 vs. PBO	2.06	[0.67, 3.47]



Abbreviations: SA, sensitivity analysis; kg, kilogram; fixed effect model; vs, versus; CrI, credible interval

Table 46 - Weight Change (kgs) median difference (95% CrI) SA3: REM

	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA5	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Bold values indicate significant results (CrI does not include 0)
Abbreviations: HbA1c, haemoglobin A1c; CrI, credible interval; REM, random effect model

B.3.9.5 Uncertainties in the indirect and mixed treatment comparisons

The SGLT-2is NMAs developed for mono and dual therapies have potential limitations. In the absence of any head to head evidence it was only possible to compare the SGLT-2is (canagliflozin, dapagliflozin empagliflozin and ertugliflozin) in both lines of therapy via an indirect comparison. The number of available studies that could be incorporated in the NMAs was low (11 in monotherapy and 8 in dual therapy). Ertugliflozin has only been considered in one combination therapy in this submission, as an add-on to metformin, which does not

reflect the full range of potential uses for ertugliflozin. Limited combination treatments were also noted for canagliflozin in the ERG report for TA315 (4).

The evidence availability in the public domain was limited and in some cases the limited reporting of data resulted in some continuous outcomes being extracted using graph digitizer software. This in turn, could have affected the precision of treatment effect data included for evidence synthesis. Some outcomes, such as genital mycotic infections and hypoglycaemia, suffered from not only a lack of data but also frequent zero events.

Between-study heterogeneity may have been present in the NMAs. In monotherapy therapy the mean baseline HbA1c tended to be over 8% which is above the 7.5% recommended by NICE in NG28 (15) and may suggest greater reductions than will be seen in practice in the NHS in England and Wales. In most cases patients were randomised to a single dose e.g. canagliflozin 100mg or 300mg, and this does not reflect clinical practice where patients will be titrated to the maximum dose. In monotherapy some of the trials were conducted in East Asian populations who had a lower baseline BMI than European patients which could have potentially influenced weight reduction. It was not possible to control for potential effect modifiers through meta-regression due to the small number of studies available. However, these potential issues do not appear to have impacted on the NMA results which were consistent with published NMAs of other SGLT-2is and the sensitivity analyses conducted for mono and combination therapy, confirmed the robustness of the base case NMA results.

B.3.10. Adverse reactions

B.3.10.1 Evidence from VERTIS MONO

Ertugliflozin was well tolerated. Details on overall AEs incidence across arms, drug-related AEs, genital mycotic infections, UTIs, discontinuation and SAEs are reported in Table 47.

As shown in Table 47, there was a numerically higher incidence (not statistically significant) in the placebo group compared to the ertugliflozin 5 and 15 mg groups of drug-related AEs, AEs of genital mycotic infections and AEs related to osmotic diuresis (e.g. pollakiuria). The incidence of AEs leading to discontinuation of study medication was lower in the ertugliflozin arms (2.0% to 2.6%) than in the placebo arm (3.3%).

The incidence of SAEs was generally low, but numerically higher in the ertugliflozin 5 mg group (4.5%), relative to the ertugliflozin 15 mg group (1.3%) and the placebo group (1.3%); no SAEs were reported as drug-related by the investigator. No specific SAE were observed and no deaths occurred in this phase of the study.

Events associated with hypoglycaemia, whether reported as AEs or documented as symptomatic or asymptomatic were infrequent in ertugliflozin and placebo groups. The overall incidence of UTIs was numerically lower in the ertugliflozin 5 mg and ertugliflozin 15

mg groups (7.1% and 3.9%, respectively) relative to the placebo group (8.5%). There were no complicated UTIs.

Genital mycotic infections were more common in female patients receiving ertugliflozin (16.4% for ertugliflozin 5mg and 22.6% for ertugliflozin 15 mg) compared with placebo (5.6%). In male subjects, genital mycotic infections were numerically higher in ertugliflozin subjects (3.4% and 5.6% in the 5 mg and 15 mg groups, respectively) as compared to placebo (1.2%); the majority of the events resolved within 2 to 3 weeks. More patient in the placebo arm reported AEs of hypovolemia (3.9%) than in the ertugliflozin 5mg (1.3%) and 15mg (2.0%) arms.

Notably, there was no signal for an increase in the occurrence of blood pressure changes meeting the criteria for orthostatic hypotension with either dose of ertugliflozin relative to placebo, nor was there evidence of supine or orthostatic changes in heart rate, consistent with the lack of an increase in AEs of hypovolemia.

There were no clinically meaningful changes in safety laboratory parameters. The 4 patients who met the eGFR pre-defined limit of change (PDLC) criteria (decrease from baseline >30%) did not meet withdrawal criteria. Patients meeting the PDLC criterion for haemoglobin increase >2.0 g/dL with increases above ULN (3 in the ertugliflozin 15 mg group) did not have associated AEs.

The pattern of changes in eGFR from baseline was consistent with prior findings in the SGLT2i class. By week 6, ertugliflozin treatment reduced eGFR by approximately 3 to 4 mL/min/1.73 m2. In the ertugliflozin 5 mg group, the eGFR had returned to baseline by week 26 (0.5 mL/min/1.73 m2). For the ertugliflozin 15 mg group, there was a return to baseline; however eGFR was still 1.3 mL/min/1.73 m2 lower than baseline at Week 26.

These transient reductions in eGFR may reflect an acute osmotic diuretic effect along with effects on tubuloglomerular feedback and resulting afferent arteriolar vasoconstriction.

Analyses of lipid parameters showed a greater increase in high-density lipoprotein cholesterol in the ertugliflozin groups than in the placebo group at week 26. In addition, for LDL, apolipoprotein B, apolipoprotein A-1, and TC there was a greater increase in the ertugliflozin 15 mg group than in the placebo group compared to a numerically greater increase in the ertugliflozin 5 mg group than placebo. Lipid effects with ertugliflozin treatment on other lipid parameters were generally neutral and similar to placebo.

Changes in ECG parameters over time were not clinically meaningful between the 3 treatment groups.

More information on safety evaluations and laboratory values is provided in Appendix H.

B.3.10.2 Summary of adverse reactions

Table 47 - Safety outcomes for VERTIS MONO at week 26

VERTIS MONO (16)	PBO N = 153	ERTU5 N = 156	ERTU15 N = 152
One or more AEs (ER)	80 (52.3)	82 (52.6)	85 (55.9)
AEs related to study drug (ER)[1]	19 (12.4)	32 (20.5)	28 (18.4)
One or more SAE (IR)	2 (1.3)	7 (4.5)	2 (1.3)
SAE related to study drug[1] (IR)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation (IR)	5 (3.3)	4 (2.6)	3 (2.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Tier 1 AEs (ER)			
Genital mycotic infection (women)	4 (5.6)	11 (16.4)[2]	14 (22.6)[2]
Genital mycotic infection (men)	1 (1.2)	3 (3.4)	5 (5.6)
UTIs	13 (8.5)	11 (7.1)	6 (3.9)
Symptomatic hypoglycaemia[3]	2 (1.3)	2 (1.3)	4 (2.6)
Hypovolemia	6 (3.9)	2 (1.3)	3 (2.0)
Other AEs (ER)			
Pollakiuria	1 (0.7)	3 (1.9)	3 (2.0)
Polyuria	0	3 (1.9)	2 (1.3)
Nocturia	2 (1.3)	1 (0.6)	0
Dizziness	6 (3.9)	1 (0.6)	2 (1.3)

Data are presented as n, (%)
[1]Determined by the investigator to be related to the study drug
[2]Incidence significantly higher than PBO group
[3]Event with clinical symptoms reported by the investigator as hypoglycaemia
Abbreviations: ERTU, ertugliflozin; PBO, placebo; AE, adverse event; SAE, Serious adverse event; UTIs, urinary tract infections; ER, analysis excluding events occurring after rescue medication; IR, analysis including events occurring after rescue medication

B.3.10.3 Evidence from VERTIS MET

VERTIS MET (NCT02033889 2016) (18, 19)

Ertugliflozin was well tolerated. Details on overall AEs incidence across arms, drug related AEs, genital mycotic infections, UTIs, discontinuation and SAEs are reported in Table 48. The overall incidence of AEs was similar between the ertugliflozin treatment groups and the placebo group. Drug-related AEs were reported more frequently in the ertugliflozin groups than in the placebo group, with no dose-related difference. A similar incidence of one or more SAEs was observed for the ertugliflozin 15 mg group and the placebo group, with a numerically lower incidence in the ertugliflozin 5 mg group. No SAEs were reported as drug-

related by the investigator. The incidence of AEs resulting in discontinuation from study medication was low (<2% of subjects in any group) and similar across the treatment groups. AEs of hypoglycaemia, or events of documented symptomatic or asymptomatic hypoglycaemia, were infrequent in both ertugliflozin and placebo groups. However, incidences were numerically higher in the ertugliflozin groups compared to placebo. One patient in the ertugliflozin 5 mg arm and 1 patient in the placebo group experienced an episode of severe hypoglycaemia which required non-medical assistance.

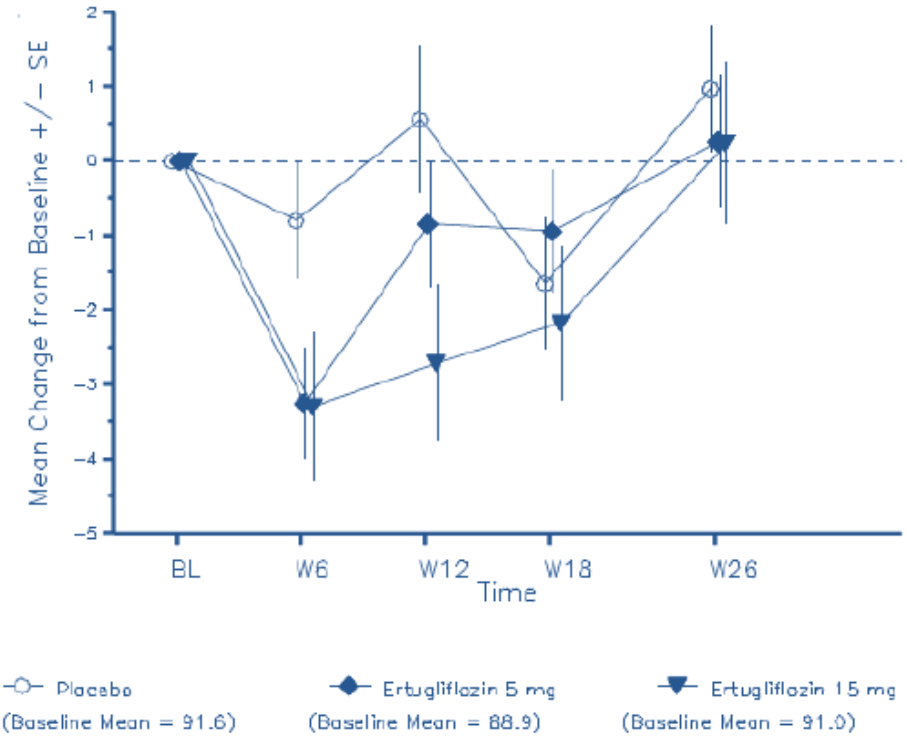
The incidence of AEs associated with UTI was low, however numerically higher in the ertugliflozin 5 mg and ertugliflozin 15 mg groups relative to the placebo group. No patients experienced a complicated UTI. Genital mycotic infections in female patients were significantly higher (p-value= 0.032) in the ertugliflozin 15 mg group compared to placebo and numerically higher in the ertugliflozin 5 mg group compared to placebo. In male patients, the incidence of genital mycotic infections was numerically higher in ertugliflozin patients (3.1%) as compared to placebo (0.0%). One patient in the ertugliflozin 15 mg group and 2 patients in the ertugliflozin 5 mg group reported complicated genital mycotic infections while on treatment. Each of these complicated events resolved and none led to discontinuation of study medication.

SGLT-2is have been associated with transient increases in serum creatinine and decreases in eGFR. In this study, there was an initial decrease in eGFR at week 6 in the ertugliflozin groups (without any dose effect) and at week 26, mean eGFR had returned to baseline for the ertugliflozin groups and was similar to placebo (Figure 33). Incidence of eGFR PDLC (at least 1 occurrence of a decrease from baseline >30% in eGFR) occurred infrequently, but was numerically higher in the ertugliflozin groups than the placebo group. No patient discontinued the study medication due to renal and urinary disorders.

SGLT-2is have also been associated with other changes in laboratory values. In this study, there were small mean increases in haemoglobin in the ertugliflozin groups relative to the placebo group and more patients in the ertugliflozin groups met the criterion of haemoglobin increase >2.0 g/dL.

The clinical significance of these small changes is unknown. When compared to placebo, there was a numerical increase in LDL-C of 2.6% and 2.0% for ertugliflozin 15 mg and ertugliflozin 5 mg, respectively. This was accompanied by an increase in HDL-C that was higher in the ertugliflozin groups compared to the placebo group; for urinary albumin / creatinine ration (UACR) there were no notable changes at week 26 across treatment groups (median baseline UACR was in the normoalbuminuric range of 9-10.5 mg/g). Further detailed information on these laboratory safety measures is provided in Appendix H.

Figure 33 - Mean Change from Baseline in eGFR (mL/min/1.73 m2) Over Time (Mean ± SE; All Subjects as Treated; Phase A: Excluding Rescue Approach



Abbreviations: SE, standard error; BL, baseline; eGFR, estimated glomerular filtration rate; W, week

B.3.10.4 Summary of adverse reactions

Table 48 - Summary of adverse events for VERTIS MET at week 26

VERTIS MET (NCT02033889 2016) (18)	PBO N = 209	ERTU5 N = 207	ERTU15 N = 205
Overall Safety[a], n (%)			
One or more AEs	94 (45.0)	88 (42.5)	103 (50.2)
AEs related to study drug[a]	13 (6.2)	24 (11.6)	25 (12.2)
One or more SAEs	8 (3.8)	3 (1.4)	7 (3.4)
SAE related to study drug	0 (0)	0 (0)	0 (0)
AEs leading to discontinuation	3 (1.4)	3 (1.4)	3 (1.5)
Death	0 (0)	0 (0)	0 (0)
Tier 1 AEs[a]			
Genital mycotic infection (women)	1 (0.9)	6 (5.5)	7 (6.3)[b]
Genital mycotic infection (men)	0 (0)	3 (3.1)	3 (3.2)
UTIs	2 (1.0)	6 (2.9)	7 (3.4)
Symptomatic hypoglycaemia[3]	4 (1.9)	7 (3.4)	7 (3.4)
Hypovolemia	1 (0.5)	1 (0.5)	1 (0.5)
Other AEs by SOC			

VERTIS MET (NCT02033889 2016) (18)	PBO N = 209	ERTU5 N = 207	ERTU15 N = 205
Metabolism disorders (dyslipidemia)	3 (1.4)	2 (1.0)	2 (1.0)
Vascular disorders (hypertension)	1 (0.5)	2 (1.0)	0 (0)
Eye disorders (diabetic retinopathy)	2 (1.0)	1 (0.5)	1 (0.5)
Cardiac disorders[c]	1 (0.5)	3 (1.4)	7 (3.4)
Hepatobiliary disorders[d]	3 (1.4)	0 (0)	1 (0.5)

[a] Excluding rescue approach
[b] Incidence significantly higher versus placebo (p=0.032)
[c] Including: acute coronary syndrome, acute myocardial infarction, cardiac failure chronic and myocardial infarction
[d] Including: cholecystitis, cholecystitis chronic and cholelithiasis
Abbreviations: ERTU, ertugliflozin; PBO, placebo; AE, adverse events; SAE, serious adverse event; UTIs, urinary tract infections

B.3.10.5 Evidence from VERTIS FACTORIAL

VERTIS FACTORIAL (NCT02099110 2016) (20)

The overall incidences of AEs, SAEs and drug-related AEs were not notably different across the two treatment groups. The most commonly reported drug-related AEs in the ertugliflozin-treated groups were those associated with genital mycotic infections. Likewise, discontinuation of study medication due to an AE occurred with a low incidence in both treatment groups (<3%). Table 50 summarises the overall AEs.

Class-related AEs, including male and female genital mycotic infections, UTIs, and hypovolemia, were pre-specified as Tier 1 safety endpoints. In both men and women, the incidences of genital mycotic infections in the ertugliflozin groups were similar.

Similar to other SGLT-2is (52), treatment with ertugliflozin resulted in modest reductions from baseline in mean eGFR at week 6 (Table 49). These decreases were followed by a return to baseline in the ertugliflozin 5 mg group, and an increase toward baseline in the ertugliflozin 15 mg group at week 26. Five patients in the ertugliflozin-treated groups discontinued study medication for protocol-specified renal discontinuation criteria. Of the 5 ertugliflozin-treated patients who discontinued study medication, post-treatment values were not available for 1 patient and eGFR levels returned to or near to baseline eGFR levels after discontinuation of study medication in 3 of the other 4 patients.

The incidence of eGFR decreased and/or blood creatinine increase was low across the ertugliflozin groups, ranging from 0.8 to 2.4%. All eGFR decreases/creatinine increases reported as AEs in the ertugliflozin treated patients were non-serious, and most resolved on-

treatment or after discontinuation of study medication. No renal-related clinical AEs were serious but one resulted in study drug discontinuation.

Small mean increases in haemoglobin were seen in the two ertugliflozin-treated groups. Additionally, modest mean percentage increases in LDL-C were seen in each of the treatment groups at week 26 and the proportions of patients whose albuminuria status (UACR) shifted between categories during the course of the study were similar across the treatment groups. Similarly, there did not appear to be any treatment-related trends in the number of patients whose albuminuria progressed or regressed during the course of the study. Further information on these laboratory values is provided in Appendix H.

Table 49 - eGFR (mL/min/1.73m2) summary statistics of change from baseline over time (ASaT: Excluding rescue approach)

Treatment	N	Time point	Change from baseline at time point		
		Median (SD)	Mean (SD)	SE	Median
Baseline					
ERTU5 ERTU15	250 248	91.9 (20.6) 92.8 (21.4)	---	---	---
Week 6					
ERTU5 ERTU15	244 239	89.5 (19.9) 88.7 (20.9)	-2.5 (12.8) -3.4 (12.5)	0.8 0.8	- 3.0 - 3.0
Week 26					
ERTU5 ERTU15	218 217	93.6 (20.5) 91.7 (21.0)	0.5 (13.5) -0.9 (14.6)	0.9 1.0	- 1.0 0.0

Abbreviations: eGFR, estimated glomerular filtration rate; ASaT, all subjects as treated; SD, standard deviation; SE, standard error; ERTU, ertugliflozin

B.3.10.6 Summary of adverse reactions

Table 50 - Summary of adverse events for VERTIS FACTORIAL at week 26

VERTIS FACTORIAL (NCT02099110 2016) (20)	ERTU5 N = 250	ERTU15 N = 248
Overall Safety[a], n (%)		
One or more AEs	128 (51.2)	107 (43.1)
AEs related to study drug	42 (16.8)	30 (12.1)
One or more SAEs	8 (3.2)	3 (1.2)
SAEs related to study drug	0 (0.0)	0 (0.0)
AEs leading to discontinuation	3 (1.2)	3 (1.2)
Death	0 (0.0)	0 (0.0)
Tier 1 AEs[a]		

VERTIS FACTORIAL (NCT02099110 2016) (20)	ERTU5 N = 250	ERTU15 N = 248
Genital mycotic infection (women)	6 (4.9)	8 (7.0)
Genital mycotic infection (men)	6 (4.7)	5 (3.7)
UTIs	13 (5.2)	14 (5.6)
Symptomatic hypoglycaemia	6 (2.4)	6 (2.4)
Hypovolemia	4 (1.6)	2 (0.8)
Other AEs by SOC		
Metabolism disorders (dyslipidemia)	1 (0.4)	2 (0.8)
Vascular disorders (hypertension)	4 (1.6)	2 (0.8)
Eye disorders (diabetic retinopathy)	2 (0.8)	0 (0.0)
Cardiac disorders[b]	8 (3.2)	2 (0.8)
Hepatobiliary disorders[c]	3 (1.2)	1 (0.4)

[a] Excluding rescue approach
[b] Including: acute coronary syndrome, acute myocardial infarction, cardiac failure chronic and myocardial infarction
[c] Including: cholecystitis, cholecystitis chronic and cholelithiasis
Abbreviations: ERTU, ertugliflozin; PBO, placebo; AE, adverse events; SAE, Serious adverse event; UTIs, urinary tract infections

B.3.10.9 Conclusions on the safety of the technology being appraised

The overall safety profile of ertugliflozin observed in all RCTs is consistent with that reported in similarly designed efficacy and safety studies of other SGLT-2is (45, 53, 54). Both the 5 mg and 15 mg doses of ertugliflozin had similar safety profile.

In conclusion, treatment with ertugliflozin over 26 weeks is well-tolerated with an acceptable safety profile when administered as monotherapy and dual therapy.

B.3.11. Conclusions about comparable health benefits and safety

B.3.11.1 & B.3.11.2 Main conclusion and differences in effectiveness

The findings of the NMA show that ertugliflozin and its comparators (canagliflozin, dapagliflozin and empagliflozin) were similar in terms of efficacy and safety. There were some examples where statistically significant differences were found between the SGLT-2is in the indirect comparison. In monotherapy, the high (15 mg) dose of ertugliflozin produced significant reduction in HbA1c (%) change compared to both the low (5 mg and 10 mg) and high (10 mg and 25 mg) doses of dapagliflozin and empagliflozin. The high (300 mg) dose of canagliflozin had significantly lower SBP than the high (15 mg) dose of ertugliflozin. [redacted] high (15 mg) dose had significantly lower incidence of UTIs than the low [redacted] dose of [redacted]

In dual therapy, the low (5 mg) dose of ertugliflozin reduced HbA1c (%) change significantly compared to the low (5 mg) dose of dapagliflozin. The high (15 mg) dose of ertugliflozin significantly reduced HbA1c (%) change compared to low ([redacted]) dose [redacted], and high (10 mg and 25 mg) dose dapagliflozin and empagliflozin. High dose ([redacted] also had significantly more patients within HbA1c at target than low ([redacted]) dose [redacted]

The sensitivity analyses conducted on the NMA confirmed that the base case results were robust and that ertugliflozin is at least as efficacious and well tolerated as its comparators canagliflozin, dapagliflozin and empagliflozin.

B.3.11.3 Evidence on the clinical or biological plausibility of similarities in health benefits

Clinical or biological plausibility

Ertugliflozin like canagliflozin, dapagliflozin and empagliflozin is biologically defined as a SGLT-2i. Ertugliflozin and the other SGLT-2is possess a high selectivity over glucose transport and inhibit renal glucose reabsorption resulting in urinary glucose excretion (UGE) and thereby reducing plasma glucose and HbA1c.

In line with the decision problem, ertugliflozin and its comparators should follow the same clinical pathway in the treatment of T2DM in monotherapy (when diet and exercise do not provide benefit) and dual therapy (in combination with metformin), as they are considered to produce similar effects in the population treated as shown in the NMAs (Section B.3.8). Ertugliflozin has demonstrated significant improvement in HbA1c in T2DM subjects, alongside reducing body weight and blood pressure as additional benefits. It is well tolerated and its safety profile is similar to that of other SGLT-2i in the same indications as shown in Section B.3.8. Like its comparators, ertugliflozin is administered orally once daily.

B.3.11.4 Clinical assumption driving cost-effectiveness

As described in Section B.2.1 the key clinical assumptions that drive the cost-effectiveness of ertugliflozin monotherapy in TA390 (2) was the BMI scenario applied to duration of treatment effect on weight loss and impact on disutility. For combination therapy in TA288 (3), the key driver of cost effectiveness was the impact of weight change on HRQoL. In TA315 (4) HbA1c drift was the key driver of cost effectiveness.

Based on the pharmacological and clinical similarities between ertugliflozin and its comparators, it can be expected that the clinical assumptions driving the cost-effectiveness for TAs 390, 288 and 315 (2), (3), (4) also apply to ertugliflozin.

B.3.12 On-going studies

VERTIS ASIA (26) is a RCT that investigated the efficacy and safety of ertugliflozin 5 and 15 mg versus placebo in Asian participants with T2DM who have inadequate glycaemic control on metformin therapy. It was completed in December 2017 and the clinical study report (CSR) is anticipated to be available in August 2018 and, as a result, relevant data from VERTIS ASIA could not be included in the current submission.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Ertugliflozin and its comparators (SGLT-2is) are predominantly used in the primary healthcare setting, with some use in secondary care. SGLT-2is are commissioned by clinical commissioning groups (CCGs). The main NHS resource use associated with ertugliflozin and its comparators are drug acquisition costs. However, ertugliflozin is [redacted] than the other SGLT-2i. There is no difference in resource use between ertugliflozin and its comparators, as per the assumptions applied in TAs 390, 315, 288, 336 and 418 (2-5, 11).

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

Due to no differences in administration, monitoring, diabetes treatment and AEs costs between ertugliflozin and its comparators, the cost comparison has been confined to drug acquisition costs alone. This is consistent with the resource use assumptions applied in TAs 390, 315, 288, 336 and 418 (2-5, 11).

A one year time horizon is used in the cost comparison analysis. As a time horizon of one year was applied, a discount rate will not be applied.

B.4.2.2 Intervention and comparators' acquisition costs

Table 51 presents the drug acquisition costs, dosage, and annual cost of ertugliflozin and the comparators. It should be noted that T2DM is a long-term condition, and patients are likely to remain on SGLT-2i for a number of years, rather than receive a single course of treatment. The drug acquisition costs presented are based on publically available list prices. There are no PASs for ertugliflozin or its comparators.

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

As assumed in TAs 390, 315, 288, 336 and 418 (2-5, 11), there are no differences in the health care resource use associated with the initiation and administration of ertugliflozin and the comparators and, as a result, the resource use costs have been excluded from this analysis. For a summary of the health care resource use and unit costs associated with SGLT-2is treatment, please see Section B.2.2.

Table 51 - Acquisition costs of the intervention and comparator technologies

Abbreviations:

	ERTU	CANA (55)	DAPA (51)	EMPA(56)
Pharmaceutical formulation	5mg or 15mg	100mg or 300mg	5mg or 10mg	10mg or 25mg
(Anticipated) care setting	Primary care	Primary care	Primary care	Primary care
Acquisition cost (excluding VAT) *	[redacted] per 28 pack (list price)	£39.20 per 30 pack (list price)	£36.59 per 28 pack (list price)	£36.59 per 28 pack (list price)
Method of administration	Oral	Oral	Oral	Oral
Doses	1 tablet	1 tablet	1 tablet	1 tablet
Dosing frequency	Once Daily	Once Daily	Once Daily	Once Daily
Dose adjustments	If lower dose tolerated, switch to maximum strength	If lower dose tolerated, switch to maximum strength	If lower dose tolerated, switch to maximum strength	If lower dose tolerated, switch to maximum strength
Average length of a course of treatment	Long term	Long term	Long term	Long term
Average cost of a course of treatment (acquisition costs only)	[redacted] per annum	£478.48 per annum	£478.48 per annum	£478.48 per annum
(Anticipated) average interval between courses of treatment	N/A	N/A	N/A	N/A
(Anticipated) number of repeat courses of treatment	On-going	On-going	On-going	On-going

ERTU, ertugliflozin; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; mg, milligram; N/A, not available

B.4.2.4 Adverse reaction unit costs and resource use

There are no adverse reaction unit costs or resource use that should be considered for this analysis.

B.4.2.5 Miscellaneous unit costs and resource use

There are no miscellaneous unit costs or resource use that should be considered for this analysis.

B.4.2.6 Clinical expert validation

No clinical expert validation of resource use and unit costs, beyond that of TA418 (11), has been undertaken. As the clinical pathway (NG28) (15) has not been substantially altered since TA418 was issued and no new comparator treatments have been approved by NICE, it was assumed that clinical validation was not necessary.

B.4.2.7 Uncertainties in the inputs and assumptions

As the assumptions are consistent with those recommended by the committee in TAs 390, 315, 288, 336 (2-5), and the only inputs in the cost comparison analysis are the drug acquisition costs which are publically available list prices there are no uncertainties surrounding the input parameters.

B.4.3 Base-case results

The base case analysis is presented in Table 52 below for mono and dual therapy. For monotherapy the comparison was between the SGLT-2is only and for dual therapy the comparison was on a background of 2000 mg of metformin. As metformin costs are the same for all comparators, the differences in acquisition costs stems from the SGLT-2i price. Canagliflozin, dapagliflozin and empagliflozin all have an annual cost of £478.48 (£1.31 per day * 365.25 days). Ertugliflozin however, is [redacted] to the NHS with an annual cost of [redacted] (£[redacted] per day * [redacted] days), producing an annual [redacted]

B.4.4 Sensitivity and scenario analyses

No sensitivity or scenario analysis was conducted as the cost comparison analysis is based on drug acquisition cost alone (list price).

Table 52 - Base-case results of the cost comparison analysis

Technologies	Acquisition costs per pack (£)	Resource costs (£)	AE costs (£)	Other costs (£)	Annual cost (£)	TOTAL COSTS (£)	Incremental cost to ERTU
Monotherapy							
ERTU5 or ERTU15	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	-
CANA100 or CANA300 (BNF 2017, (55))	39.20	N/A	N/A	N/A	478.48	478.48	[redacted]
DAPA5 or DAPA10 (BNF 2017)	36.59	N/A	N/A	N/A	478.48	478.48	[redacted]
EMPA10 or EMPA25 (BNF 2017)	36.59	N/A	N/A	N/A	478.48	478.48	[redacted]
Dual Therapy							
Met 500* + ERTU 5/15	[redacted] (0.90 + [redacted])	N/A	N/A	N/A	[redacted]	[redacted]	-
Met 500* + CANA 100/300	40.10 (0.90 + 39.20)	N/A	N/A	N/A	525.96	525.96	[redacted]
Met 500* + DAPA 5/10	37.49 (0.90 + 36.59)	N/A	N/A	N/A	525.96	525.96	[redacted]
Met 500* + EMPA 10/25	37.49 (0.90 + 36.59)	N/A	N/A	N/A	525.96	525.96	[redacted]
1 year time horizon (365.25 days)							

Abbreviations: ERTU, ertugliflozin; CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin; mg, milligram; Met, metformin; Sita, sitagliptin; N/A, not available; AE, adverse event, *- (Met 500 pack size cost is for 28 days of 500mg; at a dose of 2000mg, four packs are needed every 28 days)

B.4.5 Subgroup analysis

As mentioned in Section B.3.7 no clinically relevant subgroups were identified. No subgroup analysis was required.

B.4.6 Interpretation and conclusions of economic evidence

The cost comparison analysis demonstrated that ertugliflozin is a [redacted] alternative therapy to the other NICE approved SGLT-2is (canagliflozin, dapagliflozin and empagliflozin). The finding is robust as the analysis is based on the TAs 390, 315, 288, 336 (2-5), committee assumptions for common resource use. The results of the cost comparison analysis are generalisable to adults with T2DM in England and Wales who require an SGLT-2i as mono or dual therapy with metformin.

It should be noted that the treatment of T2DM is individualised for each patient and that all existing treatments have advantages and disadvantages and it is possible that not all T2DM patients will achieve and maintain their target HbA1c levels. The introduction of ertugliflozin adds an additional treatment option in the SGLT-2i class. The SGLT-2i mechanism of action increases renal glucose excretion providing clinically significant glucose reduction alongside a decrease in blood pressure and weight loss.

In summary, it can be concluded that the introduction of ertugliflozin will result in a [redacted] therapy for the NHS in England and Wales, supporting its implementation as a valuable treatment alternative for patients with T2DM.

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Fast track appraisal: cost-comparison case

Ertugliflozin monotherapy and dual therapy for treating type 2 diabetes mellitus [ID1158] [redacted]

ERRATA

Replacement pages for incorrect data in the MSD Document B submission and Appendices

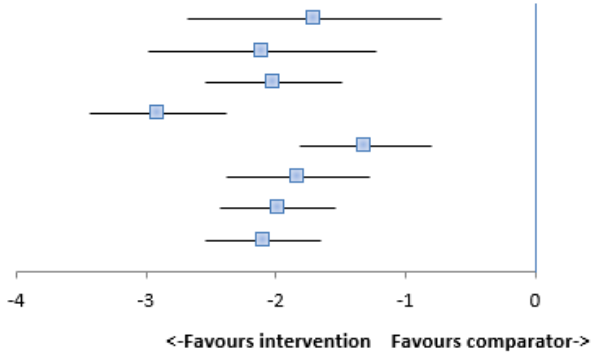
11th December 2018

Weight change (kg) change from baseline to week 26

Canagliflozin 300 mg had the largest reduction in weight from baseline when compared with placebo (**Error! Reference source not found.**). In the indirect comparison, [redacted] was superior to [redacted] (Table 30).

Figure 16 - Base case - Weight (kgs) change from baseline to week 24 - 26 (continuous outcome –

Comparison	Median DIFF	[95% CrI]
ERTU5 vs. PBO	-1.70	[-2.68, -0.72]
ERTU15 vs. PBO	-2.10	[-2.98, -1.23]
CANA100 vs. PBO	-2.01	[-2.54, -1.48]
CANA300 vs. PBO	-2.91	[-3.44, -2.38]
DAPA5 vs. PBO	-1.31	[-1.81, -0.80]
DAPA10 vs. PBO	-1.82	[-2.38, -1.27]
EMPA10 vs. PBO	-1.98	[-2.43, -1.53]
EMPA25 vs. PBO	-2.10	[-2.55, -1.65]



Abbreviations: kg, kilogram; REM, random effect model; vs, versus; CrI, credible interval

Table 30 - Weight Change (kgs) median difference (95% CrI) Base Case: FEM

	ERTU5	ERTU15
CANA100	[redacted]	[redacted]
CANA300	[redacted]	[redacted]
DAPA5	[redacted]	[redacted]
DAPA10	[redacted]	[redacted]
EMPA10	[redacted]	[redacted]
EMPA25	[redacted]	[redacted]

Bold values indicate significant results (CrI does not include 0)
Abbreviations: CrI, credible interval; FEM, fixed effect model

SBP (mmHg) change from baseline to week 26

Canagliflozin 100 mg and 300 mg had the largest effect size in SBP when compared to placebo Figure 17. Canagliflozin 300 mg was statistically significantly better than ertugliflozin 15 mg in reducing SBP Table 31.

Table 16: Baseline characteristics of all included studies across the mono and dual therapy indication

Study	Arms	N	Age (years)	Duration of disease (years)	% Female	HbA1c (%)	Weight (kg)	BMI (kg/m2)	SBP (mmHg)	DBP (mmHg)	FPG (mg/dL)
Monotherapy studies identified											
Bailey et al., 2012 (NCT00528372)**	**PBO**	68	53.5	1.1	46%	7.8	90.0	32.5	129	80	161
	DAPA5	68	51.3	1.4	53%	7.9	85.4	31.0	126	78	157
	Total/Avg	136	52.4	1.3	49%	7.9	87.7	31.7	127	79	159
Ferrannini et al., 2010 (NCT00528372) **	**PBO**	75	52.7	0.5	59%	7.8	88.8	32.3	NR	NR	160
	DAPA5	64	52.6	0.3	52%	7.9	87.6	31.9	NR	NR	162
	DAPA10	70	50.6	0.5	51%	8.0	94.2	33.6	NR	NR	167
	Total/Avg	209	52.0	0.4	54%	7.9	90.2	32.6	NA	NA	163
Hadjadj et al., 2016 (NCT01719003)	**EMPA10**	156	53.1	NR	43%	8.6	83.8	30.3	128	79	169
	EMPA25	143	53.3	NR	49%	8.9	83.1	30.6	128	79	176
	Total/Avg	299	53.2	NA	46%	8.7	83.5	30.5	128	79	173
Inagaki et al., 2014 (NCT01413204)	**PBO**	93	58.2	5.6	35%	8.0	68.6	25.9	128	78	163
	CANA100	90	58.4	4.7	34%	8.0	69.1	25.6	127	78	158
	Total/Avg	183	58.3	5.2	35%	8.0	68.8	25.7	128	78	160
Ji et al., 2014 (NCT01095653) **	**PBO**	132	49.9	1.3	34%	8.4	72.2	25.9	124	79	167
	DAPA5	128	53.0	1.2	34%	8.1	68.9	25.2	124	77	154
	DAPA10	133	51.2	1.7	35%	8.3	70.9	25.8	124	78	162
	Total/Avg	393	51.4	1.4	35%	8.3	70.7	25.6	124	78	161
Kaku et al., 2014 (NCT01294423) **	**PBO**	87	60.4	5.3	40%	7.5	66.0	25.2	127	NR	140
	DAPA5	86	58.6	4.6	42%	7.5	65.8	24.9	122	NR	138
	DAPA10	88	57.5	4.9	40%	7.5	69.7	26.1	126	NR	139
	Total/Avg	261	58.8	4.9	41%	7.5	67.2	25.4	125	NR	139
Lewin et al., 2015 (NCT01422876)	**EMPA10**	132	53.9	NR	52%	8.1	87.8	31.5	129	79	160
	EMPA25	133	56.0	NR	42%	8.0	86.7	31.2	129	79	153
	Total/Avg	265	55.0	NA	47%	8.0	87.3	31.4	129	79	157
Roden et al., 2013 (NCT01177813)	**PBO**	228	54.9	NR	46%	7.9	78.2	28.7	130	79	NR
	EMPA10	224	56.2	NR	37%	7.9	78.4	28.3	133	79	NR
	EMPA25	224	53.8	NR	35%	7.9	77.8	28.2	130	78	NR

Study	Arms	N	Age (years)	Duration of disease (years)	% Female	HbA1c (%)	Weight (kg)	BMI (kg/m2)	SBP (mmHg)	DBP (mmHg)	FPG (mg/dL)
	Total/Avg	676	55.0	NA	39%	7.9	78.1	28.4	131	79	153
Rosenstock et al., 2016 (NCT01809327)	**CANA100**	230	54.0	3.5	56%	8.8	90.2	32.4	129	79	196
	CANA100	234	55.8	3.3	48%	8.8	93.0	32.6	130	79	193
	Total/Avg	464	54.9	3.4	52%	8.8	91.6	32.5	130	79	195
Stenlof et al., 2013 (NCT01081834)	**PBO**	192	55.7	4.2	54%	8.0	87.6	31.8	128	77	167
	CANA100	195	55.1	4.5	58%	8.1	85.8	31.3	127	78	173
	CANA300	197	55.3	4.3	55%	8.0	86.9	31.7	129	79	173
	Total/Avg	584	55.4	4.3	56%	8.0	86.8	31.6	128	78	171
Terra et al., 2017 (NCT01958671/VERTIS MONO 2013)	**PBO**	153	56.1	4.6	46%	8.1	94.2	33.3	130	78	180
	ERTU5	156	56.8	5.1	43%	8.2	94.0	33.2	130	78	180
	ERTU15	151	56.2	5.2	40%	8.4	90.6	32.5	130	78	178
	Total/Avg	460	56.4	5.0	43%	8.2	92.9	33.0	130	78	179
Dual therapy studies identified											
Bailey et al., 2010 (NCT00528879)	**MET + PBO**	134	53.7	5.8	45%	8.1	87.7	31.8	128	NR	165
	MET + DAPA5	133	54.3	6.4	48%	8.2	84.7	31.4	127	NR	169
	MET + DAPA10	132	52.7	6.1	42%	7.9	86.3	31.2	126	NR	156
	Total/Avg	399	53.6	6.1	45%	8.1	86.2	31.5	127	NR	163
Bolinder et al., 2012 (NCT00855166) **	**MET + PBO**	91	60.8	5.5	44%	7.2	90.9	31.7	NR	NR	150
	MET + DAPA10	89	60.6	6.0	45%	7.2	92.1	32.1	NR	NR	148
	Total/Avg	180	60.7	5.7	44%	7.2	91.5	31.9	NR	NR	149
Pratley et al., 2017 (NCT02099110 / VERTIS FACTORIAL)	**MET + ERTU5**	250	55.1	7.1	49%	8.6	88.6	31.8	130	NR	184
	MET + ERTU15	248	55.3	7.3	46%	8.6	88.0	31.5	129	NR	180
	Total/Avg	498	55.2	7.2	48%	8.6	88.3	31.7	129	NR	182
Rosenstock et al., 2017 (NCT02033889 / VERTIS MET)	**MET + PBO**	209	56.5	7.9	53%	8.2	84.5	30.7	129	NR	169
	MET + ERTU5	207	56.6	8.1	53%	8.1	84.8	30.8	130	NR	168
	MET + ERTU15	204	56.9	8.0	55%	8.1	85.3	31.1	130	NR	168

Methods and outcomes of studies included in indirect or mixed treatment comparison

Table 17 displays the outcomes reported in the included studies for each intervention and by line of therapy according to those specified in the scope (see section B.1.1 of Document B).

Table 17: Outcomes reported by included studies informing the NMA

Reference	Arms	N	HbA1c change (%)	Weight change (kg)	SBP (mm/hg)	DBP (mm/hg)	HbA1c in target (%)	NSHE (%)	SHE (%)	UTIs (%)	GTIs (%)	AEs (%)
Monotherapy												
Bailey 2012*	PBO	68	0.20	-1.0	0.8	0.2	38%	0%	0.0%	1%	3%	60%
	DAPA5	68	-0.82	-2.7	-4.6	-1.9	48%	1%	0.0%	3%	3%	57%
Ferrannini 2010*	PBO	75	-0.23	-2.2	-0.9	-0.7	32%	3%	0.0%	4%	1%	60%
	DAPA5	64	-0.77	-2.8	-2.3	-1.7	44%	0%	0.0%	13%	8%	58%
	DAPA10	70	-0.89	-3.2	-3.6	-2.0	51%	3%	0.0%	6%	13%	69%
Hadjadj 2016	EMPA25	143	-1.36	-2.4	-2.4	-1.0	32%	1%	0.0%	8%	5%	59%
	EMPA10	156	-1.35	-2.4	-2.2	-1.7	43%	1%	0.0%	8%	6%	63%
Inagaki 2014	PBO	93	0.29	0.5	-2.7	-1.8	7%	3%	0.0%	1%	1%	59%
	CANA100	90	-0.74	2.6	-7.8	-4.4	31%	7%	0.0%	1%	2%	66%
Ji 2014*	PBO	132	-0.29	-0.3	0.8	0.4	20%	2%	0.0%	3%	1%	64%
	DAPA5	128	-1.04	-1.6	-1.2	-1.3	45%	1%	0.0%	4%	3%	62%
	DAPA10	133	-1.11	-2.3	-2.3	-1.6	49%	1%	0.0%	4%	5%	61%
Kaku 2014*	PBO	87	-0.06	-0.8	-0.5	NR	NR	0%	0.0%	2%	1%	52%
	DAPA5	86	-0.41	-2.1	-3.3	NR	NR	0%	0.0%	0%	1%	48%
	DAPA10	88	-0.45	-2.2	-3.2	NR	NR	2%	0.0%	2%	2%	65%
Lewin 2015	EMPA 25	133	-0.95	-2.1	NR	NR	42%	1%	0.0%	10%	4%	69%
	EMPA 10	132	-0.83	-2.3	NR	NR	39%	3%	0.0%	16%	5%	81%
Roden 2013	PBO	228	0.08	-0.3	-0.3	-0.5	11%	0%	0.0%	5%	0%	61%
	EMPA10	224	-0.66	-2.3	-2.9	-1.0	32%	0%	0.0%	7%	3%	55%
	EMPA25	224	-0.78	-2.5	-3.7	-1.9	39%	0%	0.0%	5%	4%	61%
Rosenstock 2016	CANA100	230	-1.37	-2.8	-2.2	-1.1	39%	3%	0.0%	1%	2%	37%
	CANA300	234	-1.42	-3.7	-2.4	-1.7	43%	4%	0.0%	2%	4%	40%

Reference	Arms	N	HbA1c change (%)	Weight change (kg)	SBP (mm/hg)	DBP (mm/hg)	HbA1c in target (%)	NSHE (%)	SHE (%)	UTIs (%)	GTIs (%)	AEs (%)
Stenlof 2013	PBO	192	0.14	-0.5	0.4	-0.1	21%	3%	0.0%	4%	2%	53%
	CANA100	195	-0.77	-2.5	-3.3	-1.7	45%	4%	0.0%	7%	6%	61%
	CANA300	197	-1.03	-3.4	-5.0	-2.1	62%	3%	0.0%	5%	7%	60%
Terra 2017	PBO	153	0.20	-1.4	-2.2	-0.7	13%	1%	0.0%	8%	3%	52%
	ERTU5	156	-0.79	-3.1	-5.5	-2.5	28%	1%	0.0%	7%	9%	53%
	ERTU15	151	-0.96	-3.5	-3.9	-1.1	36%	3%	0.7%	4%	13%	56%
Dual therapy – background therapy MET												
Bailey 2010	PBO	134	-0.30	-0.9	-0.2	/	25%	3%	0%	8%	5%	64%
	DAPA5	133	-0.70	-3.0	-4.3	/	35%	4%	0%	7%	13%	69%
	DAPA10	132	-0.84	-2.9	-5.1	/	44%	4%	0%	8%	9%	73%
Bolinder 2012*	PBO	91	-0.10	-0.9	NR	/	NR	3%	0.0%	2%	0%	40%
	DAPA10	89	-0.39	-3.0	NR	/	NR	2%	0.0%	7%	3%	43%
VERTIS FACTORIAL	ERTU5	250	-1.02	-2.7	-3.9	/	26%	6%	0.0%	5%	5%	51%
	ERTU15	248	-1.08	-3.7	-3.7	/	32%	5%	0.4%	6%	5%	43%
VERTIS MET	ERTU5	207	-0.73	-3.0	-4.4	/	35%	7%	0.5%	3%	4%	43%
	ERTU15	204	-0.91	-2.9	-5.2	/	40%	8%	0.0%	3%	5%	50%
	PBO	209	-0.03	-1.3	-0.7	/	16%	4%	0.5%	1%	0%	45%
DeFronzo 2015	EMPA10	140	-0.62	-3.2^	NR	/	33%	4%	0.0%	14%	9%	74%
	EMPA25	137	-0.66	-2.5^	NR	/	28%	1%	0.0%	12%	8%	70%
Häring 2014	PBO	207	-0.13	-0.5	-0.4	/	11%	0%	0.0%	5%	0%	59%
	EMPA10	217	-0.70	-2.1	-4.5	/	35%	2%	0.0%	5%	4%	57%
	EMPA25	213	-0.77	-2.5	-5.2	/	35%	1%	0.0%	6%	5%	50%
Lavalle-González 2013	PBO	181	-0.17	-1.1	1.5	/	30%	NR	NR	2%	NR	67%
	CANA100	365	-0.79	-3.3	-3.8	/	45%	NR	NR	5%	NR	64%
	CANA300	360	-0.94	-3.6	-5.1	/	58%	NR	NR	4%	NR	72%
Yang 2016	PBO	139	-0.23	-0.7	1.8	/	18%	2%	0.0%	5%	0%	52%
	DAPA5	146	-0.82	-1.8	-4.1	/	33%	1%	0.0%	4%	2%	52%
	DAPA10	149	-0.85	-2.6	-2.5	/	33%	1%	0.0%	7%	1%	55%

Table 69: Weight Change (kgs) Median Difference (95% CrI): Random Effects

	PBO	ERTU5	ERTU15	CANA100	CANA300	DAPA5	DAPA10	EMPA10	EMPA25
PBO		**-1.7 (-2.83 to -0.57)**	**-2.1 (-3.14 to -1.06)**	**-2.01 (-2.7 to -1.32)**	**-2.91 (-3.63 to -2.19)**	**-1.3 (-1.91 to -0.67)**	**-1.8 (-2.46 to -1.07)**	**-1.99 (-2.7 to -1.32)**	**-2.09 (-2.76 to -1.38)**
ERTU5	**1.7 (0.57 to 2.83)**		-0.4 (-1.3 to 0.5)	-0.31 (-1.64 to 1.01)	-1.21 (-2.55 to 0.12)	0.4 (-0.87 to 1.69)	-0.09 (-1.4 to 1.25)	-0.29 (-1.62 to 1.02)	-0.39 (-1.7 to 0.94)
ERTU15	**2.1 (1.06 to 3.14)**	0.4 (-0.5 to 1.3)		0.09 (-1.16 to 1.34)	-0.81 (-2.07 to 0.46)	0.8 (-0.4 to 2.02)	0.31 (-0.92 to 1.59)	0.11 (-1.15 to 1.34)	0.01 (-1.22 to 1.27)
CANA100	**2.01 (1.32 to 2.7)**	0.31 (-1.01 to 1.64)	-0.09 (-1.34 to 1.16)		**-0.9 (-1.46 to -0.33)**	0.71 (-0.2 to 1.65)	0.22 (-0.73 to 1.23)	0.01 (-0.97 to 0.98)	-0.08 (-1.03 to 0.91)
CANA300	**2.91 (2.19 to 3.63)**	1.21 (-0.12 to 2.55)	0.81 (-0.46 to 2.07)	**0.9 (0.33 to 1.46)**		**1.61 (0.67 to 2.57)**	**1.11 (0.15 to 2.15)**	0.91 (-0.09 to 1.9)	0.82 (-0.15 to 1.83)
DAPA5	**1.3 (0.67 to 1.91)**	-0.4 (-1.69 to 0.87)	-0.8 (-2.02 to 0.4)	-0.71 (-1.65 to 0.2)	**-1.61 (-2.57 to -0.67)**		-0.5 (-1.18 to 0.23)	-0.7 (-1.64 to 0.21)	-0.79 (-1.71 to 0.14)
DAPA10	**1.8 (1.07 to 2.46)**	0.09 (-1.25 to 1.4)	-0.31 (-1.59 to 0.92)	-0.22 (-1.23 to 0.73)	**-1.11 (-2.15 to -0.15)**	0.5 (-0.23 to 1.18)		-0.2 (-1.22 to 0.74)	-0.29 (-1.29 to 0.67)
EMPA10	**1.99 (1.32 to 2.7)**	0.29 (-1.02 to 1.62)	-0.11 (-1.34 to 1.15)	-0.01 (-0.98 to 0.97)	-0.91 (-1.9 to 0.09)	0.7 (-0.21 to 1.64)	0.2 (-0.74 to 1.22)		-0.09 (-0.59 to 0.45)
EMPA25	**2.09 (1.38 to 2.76)**	0.39 (-0.94 to 1.7)	-0.01 (-1.27 to 1.22)	0.08 (-0.91 to 1.03)	-0.82 (-1.83 to 0.15)	0.79 (-0.14 to 1.71)	0.29 (-0.67 to 1.29)	0.09 (-0.45 to 0.59)	

Bold values indicate significant results.

Table 70: SBP Change (mmHg) Median Difference (95% CrI): Random Effects

	PBO	ERTU5	ERTU15	CANA100	CANA300	DAPA5	DAPA10	EMPA10	EMPA25
PBO		-3.32 (-6.89 to 0.25)	-1.71 (-5.29 to 1.88)	**-4.5 (-6.84 to -2.2)**	**-5.22 (-7.91 to -2.65)**	**-2.96 (-5.65 to -0.25)**	**-3.53 (-6.61 to -0.47)**	-2.74 (-5.78 to 0.31)	**-3.25 (-6.29 to -0.21)**
ERTU5	3.32 (-0.25 to 6.89)		1.61 (-1.81 to 5.06)	-1.18 (-5.44 to 3.06)	-1.9 (-6.39 to 2.48)	0.36 (-4.11 to 4.83)	-0.21 (-4.93 to 4.48)	0.59 (-4.12 to 5.29)	0.07 (-4.63 to 4.75)
ERTU15	1.71 (-1.88 to 5.29)	-1.61 (-5.06 to 1.81)		-2.79 (-7.07 to 1.47)	-3.51 (-8.01 to 0.88)	-1.25 (-5.73 to 3.24)	-1.82 (-6.55 to 2.89)	-1.03 (-5.74 to 3.66)	-1.55 (-6.23 to 3.15)
CANA100	**4.5 (2.2 to 6.84)**	1.18 (-3.06 to 5.44)	2.79 (-1.47 to 7.07)		-0.72 (-2.84 to 1.31)	1.54 (-2 to 5.12)	0.96 (-2.87 to 4.82)	1.76 (-2.03 to 5.6)	1.25 (-2.55 to 5.09)
CANA300	**5.22 (2.65 to 7.91)**	1.9 (-2.48 to 6.39)	3.51 (-0.88 to 8.01)	0.72 (-1.31 to 2.84)		2.26 (-1.46 to 6.09)	1.69 (-2.31 to 5.77)	2.48 (-1.48 to 6.57)	1.97 (-2 to 6.05)
DAPA5	**2.96 (0.25 to 5.65)**	-0.36 (-4.82 to 4.11)	1.25 (-3.24 to 5.73)	-1.54 (-5.12 to 2)	-2.26 (-6.09 to 1.46)		-0.58 (-3.68 to 2.54)	0.22 (-3.84 to 4.27)	-0.3 (-4.37 to 3.76)
DAPA10	**3.53 (0.47 to 6.61)**	0.21 (-4.48 to 4.93)	1.82 (-2.89 to 6.55)	-0.96 (-4.82 to 2.87)	-1.69 (-5.77 to 2.31)	0.58 (-2.54 to 3.68)		0.8 (-3.52 to 5.11)	0.28 (-4.02 to 4.6)
EMPA10	2.74 (-0.31 to 5.78)	-0.59 (-5.29 to 4.12)	1.03 (-3.66 to 5.74)	-1.76 (-5.6 to 2.03)	-2.48 (-6.57 to 1.48)	-0.22 (-4.27 to 3.84)	-0.8 (-5.11 to 3.52)		-0.52 (-2.86 to 1.83)
EMPA25	**3.25 (0.21 to 6.29)**	-0.07 (-4.75 to 4.63)	1.55 (-3.15 to 6.23)	-1.25 (-5.09 to 2.55)	-1.97 (-6.05 to 2)	0.3 (-3.76 to 4.37)	-0.28 (-4.6 to 4.02)	0.52 (-1.83 to 2.86)	

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Single technology appraisal

Ertugliflozin as monotherapy or in a dual therapy regimen for treating type 2 diabetes [ID1158]

Dear [redacted],

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 18 July 2018 from MSD. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Friday 24 August 2018.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted], Technical Lead ([redacted]). Any procedural questions should be addressed to [redacted], Project Manager ([redacted]).

Yours sincerely

[redacted]
Heath Technology Assessment Adviser
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. In table 2 of Terra et al 2017 (Diab Ob Metab 2017/19/721-728), the number of patients on placebo at week 26 is 89. Please explain why this figure differs from the figures presented in the submission (Figure 6, in appendix D) and in the CONSORT diagram in a supplement to the published paper. There it is stated that 77.8% (119 patients) completed 26 weeks of follow-up on placebo, and that only 6 discontinued it because of lack of efficacy, or 10 if we include those listed as having hyperglycemia.

A2. Please explain how hyperglycemia was defined? Raised plasma glucose but below threshold for rescue?

A3. In Table 26 of Appendix D it is stated that 39 of the placebo patients were on rescue therapy at week 26 (ASaT population). These figures do not match the CONSORT diagram. Please explain this discrepancy.

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.

A5. Blood pressure rose at the 18 week visit with ertugliflozin 15 mg in the VERTIS MONO trial, and (less so) in the VERTIS MET trial. Furthermore, reductions in systolic blood pressure were greater in dual therapy than in monotherapy, despite similar baseline characteristics. Do you have any explanation for these results?

Section B: Clarification on cost data

The ERG has no questions.

Section C: Textual clarifications and additional points

The ERG has no questions

MSD Response to Clarification Questions on Fast track appraisal: cost-comparison case – ertugliflozin in mono and dual therapy for treating type 2 diabetes [ID1158]

Section A: Clarification on effectiveness data

A1. In table 2 of Terra et al 2017 (Diab Ob Metab 2017/19/721-728), the number of patients on placebo at week 26 is 89. Please explain why this figure differs from the figures presented in the submission (Figure 6, in appendix D) and in the CONSORT diagram in a supplement to the published paper. There it is stated that 77.8% (119 patients) completed 26 weeks of follow-up on placebo, and that only 6 discontinued it because of lack of efficacy, or 10 if we include those listed as having hyperglycaemia.

Response

The figures reported in Table 2 of Terra et. al. (2017) (1) differ to the CONSORT diagram and its analogue figure 6 in Appendix D as they are reporting different information. The CONSORT diagram presents the number of patients who completed Phase A of the VERTIS MONO study (n=119), took the medication from randomisation until week 26, whilst Table 2 of Terra et al. (1) presents the number of patients in the placebo arm (n=89) with results (no missing value and did not require glycaemic rescue) for the HbA1c change from baseline at week 26.

Please note that subjects receiving glycaemic rescue medication continued to receive blinded study medication and remain in the study to provide longer-term safety data, unless they met specific protocol discontinuation criteria (please see the response to question A2). Therefore, a subject receiving glycaemic rescue would only be reported within the CONSORT diagram in case of discontinuation from the study.

A2. Please explain how hyperglycaemia was defined? Raised plasma glucose but below threshold for rescue?

Response

The criteria for hyperglycaemia for the purposes of discontinuation from treatment or for discontinuation from the study (VERTIS MONO clinical study report (CSR) Section 6.7.2 (2)) were:

- Patients who continue to exceed the glycaemic threshold values after at least 4 weeks of taking metformin rescue therapy at a dose of 1000 mg twice a day or maximum tolerated dose, or at least 2 weeks of taking glimepiride rescue therapy at a dose of ≥4 mg/day or the maximum tolerated dose.
- Fasting plasma glucose (FPG) consistently >11.1 mmol/L or HbA1c >8.0% after visit 8/week 26 through to the end of the trial. Please note that a consistent value for FPG was defined as a repeat measurement performed within 7 days of notification from the central laboratory.
- For the purpose of an adverse event, the definition of hyperglycaemia was based on investigator judgment.

The protocol specified progressively stricter glycaemic rescue criteria. Metformin was the glycaemic rescue medication used in Phase A (weeks 0 - 26) and glimepiride was used in Phase B (weeks 26 - 52) (2). The specific criteria for glycaemic rescue were as follows (also reported in Table 11, Section B.3.2 of Document B):

- FPG values >15.0 mmol/L after day 1 through week 6;
- >13.3 mmol/L after week 6 through week 12;
- >11.1 mmol/L after week 12 through week 26;
- >11.1 mmol/L or HbA1c >8.0% after week 26.

A3. In Table 26 of Appendix D it is stated that 39 of the placebo patients were on rescue therapy at week 26 (ASaT population). These figures do not match the CONSORT diagram. Please explain this discrepancy.

Response

The number of patients on rescue therapy in the placebo arm (n=39) is not specified in the CONSORT diagram and the number cannot be estimated from it, as it only displays the number of patients who discontinued the medication.

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 (1) 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.

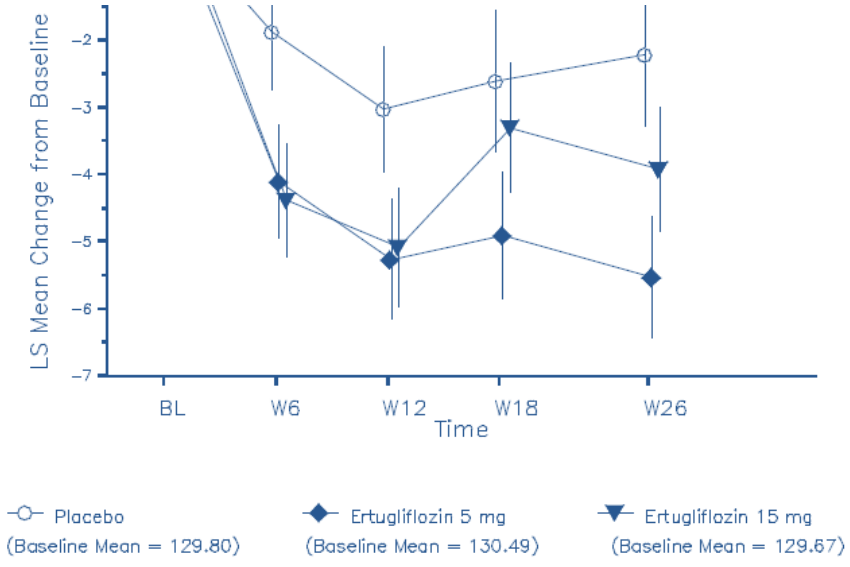
A5. Blood pressure rose at the 18 week visit with ertugliflozin 15 mg in the VERTIS MONO trial, and (less so) in the VERTIS MET trial. Furthermore, reductions in systolic blood pressure were greater in dual therapy than in monotherapy, despite similar baseline characteristics. Do you have any explanation for these results?

Response

In the VERTIS MONO study, systolic blood pressure decreased from baseline for both ertugliflozin groups at all time points. In both ertugliflozin groups, systolic blood pressure decreased from baseline at week 6 through week 12, increased at week 18 and then decreased at week 26. In the placebo group, systolic blood pressure decreased from baseline through week 12 and then increased slightly through week 26. The "rise" in systolic blood pressure at week 18 in the ertugliflozin 15 mg group noted by the reviewer likely reflects a stochastic finding. As seen in Figure 1 below (Figure 7, Section B.3.6.1 of Document B), the LS mean reduction from baseline for ertugliflozin 15 mg was approximately 5 mmHg at week 12 and approximately 3.5 mmHg at week 18.

The ertugliflozin LS mean changes from baseline in systolic blood pressure were very similar between VERTIS MONO and VERTIS MET. As shown in Table 2 below, (Table 28 of the VERTIS MONO CSR (2)), LS mean changes from baseline in systolic blood pressure were -5.54 and -3.93 mmHg for ertugliflozin 5 mg and 15 mg, respectively. In the VERTIS MET study (3)(4), LS mean changes from baseline in systolic blood pressure were -4.38 and -5.20 mmHg for ertugliflozin 5 mg and 15 mg, respectively. These results are in line with available data from the SGLT-2i class that show an approximate 4 mmHg reduction in systolic blood pressure in a general T2DM population.

Figure 1 - Systolic blood pressure (mmHg): LS mean change from baseline over time (cLDA) (FAS, excluding rescue approach)



Abbreviations: BL, baseline; W, week; LS, least square; cLDA, constrained longitudinal data analysis; FAS, full analysis set

Table 1 - Systolic blood pressure (mmHg): change from baseline at week 26 (cLDA) (FAS, excluding rescue approach)

Treatment	Baseline		Week 26		Change from baseline at week 26		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS mean (95% CI) †
PBO	150	129.80 (14.464)	91	128.14 (14.356)	152	-1.82 (10.875)	-2.22 (-4.30, -0.14)
ERTU5	155	130.49 (13.511)	132	125.01 (12.874)	156	-5.84 (9.876)	-5.54 (-7.32, -3.76)
ERTU15	152	129.67 (14.208)	126	125.55 (14.560)	152	-3.49 (12.427)	-3.93 (-5.74, -2.12)
Pairwise comparison			**Differences in LS means (95% CI)**				**p-value**
ERTU5 vs. PBO			-3.31 (-5.98, -0.65)				0.015
ERTU15 vs PBO			-1.71 (-4.40, 0.98)				0.213

Abbreviations: CI, confidence interval; cLDA, constrained longitudinal data analysis; eGFR, estimated glomerular filtration rate; FAS, full analysis set; LS, least squares; N, number of subjects in FAS; SD, standard deviation.

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point; for change from baseline at Week 26, N is the number of subjects in the FAS (i.e. randomized subjects who took at least 1 dose of study medication and had at least one assessment at or after baseline). The Mean and SD for the change from baseline are based on non-missing values.

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

References

1. Terra SG, Focht K, Davies M, Frias J, Derosa G, Darekar A, et al. Phase III, efficacy and safety study of ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. Diabetes, Obesity and Metabolism. 2017;19(5):721-8.
2. Terra SG. Clinical Study Report: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study with a 26-Week Extension to Evaluate the Efficacy and Safety of ertugliflozin Monotherapy in the Treatment of Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control despite Diet and Exercise. 2016.
3. Terra SG. Clinical Study report: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study with a 78-Week Extension to Evaluate the Efficacy and Safety of Ertugliflozin in Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control on Metformin Monotherapy. 2016.
4. Rosenstock J, Frias J, Páll D, Charbonnel B, Pascu R, Saur D, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). Diabetes, Obesity and Metabolism. 2018;20(3):520-9.

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Clinical expert statement

Ertugliflozin in a triple therapy regimen for treating type 2 diabetes [ID1160] and

Ertugliflozin as monotherapy or in a dual therapy regimen for treating type 2 diabetes [ID1158]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor John Wilding**
2. Name of organisation	**University of Liverpool and Aintree University Hospital NHS Foundation Trust**

3. Job title or position	**Professor of Medicine**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve symptoms of hyperglycaemia, to reduce development and progression of complications, whilst minimising adverse events.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in HbA1c by at least 5mmol/mol (0.5%) that is sustained for at least one year Reduction in the development of micro and macrovsacular complications of diabetes
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Initially with lifestyle (diet and exercise), metformin 1st line drug and sequential addition of additional drugs and insulin as outlined in NICE TA 288 and others. Active management of risk factors for cardiovascular disease. Treatment of complications if they arise.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes NICE CG87; however ADA / EASD guidelines are more up to date.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Would fit as 2nd or 3rd line treatment or as 1st line if metformin not tolerated or contraindicated. Three other drugs in SGLT2i class with very similar effects are already in the guidelines.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes would fit in same place as other SGLT2 inhibitors.

• How does healthcare resource use differ between the technology and current care?	Similar as drugs in class already in use.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary care and specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil specific
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Similar to other drugs in the class.
• Do you expect the technology to increase length of life more than current care?	Possible, but we don't yet have CV outcomes data for ertugliflozin that we do for the other SGLT2i so currently unknown.

• Do you expect the technology to increase health-related quality of life more than current care?	Possible but no data available
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Less effective in people with renal impairment (eGFR < 45ml/min due to mode of action in kidneys
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Similar to other SGTL2 inhibitors

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	N/A
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Possible when CV outcome trial data is available. Weight loss might provide some addition benefit
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	The class as a whole is innovative, but this is 4th drug in class – no clear differences from others.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The class provides new benefits (reduced heart failure, CV death, major adverse cardiovascular events and probably reduced progression of renal disease) that has not yet been shown for ertugliflozin.
• Does the use of the technology address any particular unmet need of the patient population?	Yes as other drugs in class reduce risk of important outcomes as outlined above.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Main adverse event is risk of fungal genetic infections which can be problematic for some people. Rarely patients can develop diabetic ketoacidosis Lower limb amputations emerged as a possible risk in CANVAS trial with canagliflozin
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Lowering of HbA1c predicts reduced micro and macrovascular adverse events in diabetes. However beneficial effects of SGLT2i on CV and renal disease seems independent of reductions in glycaemia.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Rare adverse events such as DKA were not seen in the trials
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA418, TA390, TA336, TA315, TA288]?	Yes 3 major trials have reported EMPA-REG outcome CANVAS DECLARE TIMI-58 1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373(22): 2117-28. 2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377(7): 644-57. 3. Stephen D. Wiviott, Itamar Raz, Marc P. Bonaca et al Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes New England Journal of Medicine 2018 DOI: 10.1056/NEJMoa1812389

	These show reduced heart failure hospitalisation, mortality and in some cases reduce major adverse CV events. This seems to be a class effect (see meta-analysis below) but the results of the VERTIS trial with ertugliflozin are not yet reported. Thomas A. Zelniker, Stephen D. Wiviott, Itamar Raz, Kyungah Im, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo HM Furtado, Deepak L Bhatt, Lawrence A. Leiter, Darren K. McGuire, John PH Wilding, Marc S. Sabatine SGLT2 Inhibitors for Primary and Secondary Prevention of Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus: A Meta-Analysis of Cardiovascular Outcomes Trials Lancet 2018 http://dx.doi.org/10.1016/S0140-6736(18)32590-X Secondary analysis of these trials also suggests renoprotective events definitive trials are underway
22. How do data on real-world experience compare with the trial data?	Extensive Real World evidence with other drugs in class shows clinical effects and improved CV outcomes that are consistent with the clinical trial data.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Ertugliflozin is an effective SGLT2 inhibitor; glucose lowering, weight loss and blood pressure reduction are similar to other drugs in the class
- Favourable CV outcome data are present for empagliflozin, canagliflozin and dapagliflozin. This is probably a class effect but no data yet available for ertugliflozin
- Current NICE guidelines do not reflect new CV outcome data with SGLT2i that has led to changes in most other international guidelines that support use of the class in patients with pre-existing cardiovascular disease
- Emerging data also suggest SGLT2i are renoprotective in diabetes
-

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Ertugliflozin in a triple therapy regimen for treating type 2 diabetes [ID1160] and

Ertugliflozin as monotherapy or in a dual therapy regimen for treating type 2 diabetes [ID1158]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Stephen Charles BAIN**
2. Name of organisation	**Swansea University & ABMU Health Board, South West Wales**

3. Job title or position	**Professor of Medicine (Diabetes) & Honorary Consultant Physician**
4. Are you (please tick all that apply):	☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology?
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ other (I have not had sight of this document – I have been told that this is the 'norm')
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Ertugliflozin is a selective sodium glucose-cotransporter 2 (SGLT-2) inhibitor, which reduces hyperglycaemia in people with type 2 diabetes (T2DM) by reducing the renal reabsorption of filtered glucose. This leads to a reduction in glycosylated haemoglobin (HbA1c) along with secondary benefits of weight reduction and blood pressure lowering. There is a presumption that the fall in HbA1c will reduce the long-term risk of specific microvascular complications of T2DM such as retinopathy, neuropathy and nephropathy although there is currently no evidence that the progression of the underlying pathogenesis of T2DM is slowed. For other agents in the SGLT-2 inhibitor class, trials have shown a reduction in cardiovascular disease (compared with standard glucose lowering therapies) as well fewer hospitalisations for heart failure and improved preservation of renal function.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction in HbA1c of 0.4% (~4 mmol/mol) is generally regarded as indicating a clinically significant glucose-lowering effect. Medicines in the SGLT-2 inhibitor class typically provide much bigger falls in HbA1c than this.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The management of T2DM in the UK is sub-optimal with huge numbers of people having poor glucose control, as assessed by HbA1c and as recommended by the current NICE guidelines (NG28). Modern therapies offer the potential for potent glucose lowering but without the adverse effects of hypoglycaemia and weight gain. Two of the newer classes of glucose-lowering agents (SGLT-2 inhibitors and GLP-1 mimetics) also provide cardiovascular protection.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE produced a new guideline for the management of T2DM in 2015 (NG28), which was updated in 2016. This forms the basis for the management of T2DM across England & Wales.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway allows for choice between second and third-line agents but is seen as out-of-date as it does not include data from positive cardiovascular outcome trials (CVOTs) of the SGLT-2 inhibitors and GLP-1 mimetics, which have been published since September 2015 (i.e. before the publication of NG28). These results have been incorporated into over 25 diabetes guidelines around the world and recently consolidated in the publication (October 2018) of a consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). The ADA/EASD document recommends that after metformin failure, the presence of atherosclerotic cardiovascular disease (ASCVD), heart failure and/or chronic kidney disease should influence the choice of glucose-lowering class (with preference for SGLT-2 inhibitors and GLP-1 mimetics). My experience relates to Wales but applies equally to England.
• What impact would the technology have on the current pathway of care?	Ertugliflozin would provide an additional (forth) choice of SGLT-2 inhibitor, whenever this class is thought the most appropriate for managing a person with T2DM.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Ertugliflozin, used according to licence, would have similar indications to other medicines in the SGLT-2 inhibitor class.

• How does healthcare resource use differ between the technology and current care?	No. It may be that ertugliflozin has advantages over other members of the SGLT-2 inhibitor class but direct head-to-head studies have yet to be performed.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	SGLT-2 inhibitors can (and should) be initiated and monitored in primary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional resources, given that we already have three SGLT-2 inhibitors available in the UK. It is possible (and actually desirable) that the use of this class of glucose-lowering medications will increase but this will apply equally in the current situation where three drugs recommended by the guidelines.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, as per the SGLT-2 inhibitor class.
• Do you expect the technology to increase length of life more than current care?	The use of SGLT-2 inhibitors in appropriate patients with T2DM has been shown to extend life in CVOTs.
• Do you expect the	I would expect ertugliflozin to have similar benefits on health-related quality of life as the other agents in the

technology to increase health-related quality of life more than current care?	SGLT-2 inhibitor class.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Currently the trial data from CVOTs in people with T2DM suggest that most benefit accrues in those cases with pre-existing cardiovascular disease.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	The use of ertugliflozin should not pose any additional difficulties or issues over the use of the three currently available SGLT-2 inhibitors.

or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Any rules would be that those that apply to the currently available SGLT-2 inhibitors. Currently this means stopping drug when the estimated glomerular filtration rate (eGFR) drops below 45mL/min. Since people with T2DM should have their kidney function checked on a regular basis, no additional testing is required.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	In addition to the benefit of glucose-lowering, the technology assessment needs to take into account mortality, CV morbidity, heart failure, renal, weight and blood pressure lowering effects of the SGLT-2 inhibitors.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	No, this is an addition to the currently available SGLT-2 inhibitors.

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No, this is an addition to the currently available SGLT-2 inhibitors.
• Does the use of the technology address any particular unmet need of the patient population?	No more (or less) than any of the currently available SGLT-2 inhibitors.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The major side-effect of the SGLT-2 inhibitors is genital mycotic infections, which are usually easily treated with over-the-counter anti-fungal creams. Urinary frequency and infection may be reported (there is still debate about the latter) and diabetic ketoacidosis (DKA) has been included in the SGLT2-inhibitor class label, but is rare. Fournier's gangrene is now also included as adverse side-effect but is extremely rare.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Given our knowledge about the SGLT-2 inhibitor class, I feel that there can be some extrapolation from studies of the other three agents.

• If not, how could the results be extrapolated to the UK setting?	Not applicable.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Cardiovascular, heart failure and mortality outcomes are hard end-points which will be reported for ertugliflozin in due course. The surrogate markers of HbA1c, weight and blood pressure reduction have been measured and published.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, HbA1c reduction is a well-established surrogate (as are weight and blood pressure).
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The post-licence observation of DKA for the SGLT-2 inhibitor class was not anticipated (although there are several hypotheses which might explain it); I am not aware of any specific issues with ertugliflozin.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator	No, although studies of the use of SGLT-2 inhibitors and GLP-1 mimetics are beginning to be published

treatment(s) since the publication of NICE technology appraisal guidance [TA418, TA390, TA336, TA315, TA288]?	and more data will become available in the near future.
22. How do data on real-world experience compare with the trial data?	Generally the experience with the SGLT-2 inhibitor class, in terms of glucose-lowering and weight reduction, has been better than that reported in the clinical trials. This may reflect the higher HbA1c levels at treatment initiation in 'real-life' (termed 'clinical inertia') versus lower HbA1c baseline levels in clinical trials.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	Not applicable.

Key messages
24. In up to 5 bullet points, please summarise the key messages of your statement. • Ertugliflozin will be the fourth SGLT-2 inhibitor to be made available in the UK • SGLT-2 inhibitors are a highly effective class of glucose-lowering medicines • SGLT-2 inhibitors have the secondary benefits of weight reduction and blood pressure lowering • SGLT-2 inhibitors reduce cardiovascular morbidity and mortality in appropriate patients with T2DM • SGLT-2 inhibitors are generally well-tolerated

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Ertugliflozin in monotherapy and dual therapy: NICE appraisal ID1158

Produced by Warwick Evidence

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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

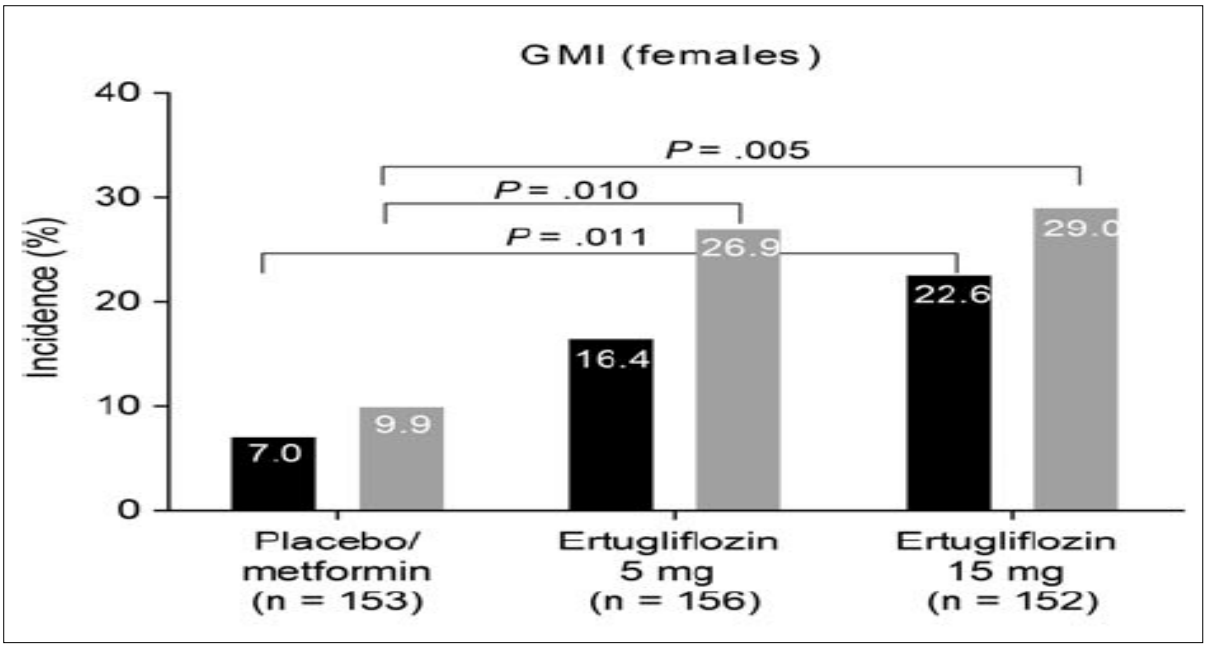
Adverse event	**Monotherapy**	**Dual therapy**	**Comparison**
Urinary tract infections	£73	£45	It was assumed that in monotherapy males

			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**

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ertugliflozin as monotherapy or in a dual therapy regimen for treating type 2 diabetes [ID1158]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 20 November 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 14 it is stated that "Ertugliflozin 5 mg daily has similar effects on HbA1c, weight loss, SBP and proportion achieving target as the other flozins". The revised NMA results for weight change, which had not been seen by the ERG at the time of producing the report, show canagliflozin 300mg was significantly better at weight loss than ertugliflozin 5mg	Proposed amendment, "Ertugliflozin 5 mg daily has similar effects on HbA1c, weight loss, SBP and proportion achieving target as the other low dose flozins"	Accuracy	No error by ERG. The ERG does not regard this finding as important because it is comparing the higher dose of canagliflozin with the lower dose of ertugliflozin. Patients start on the lower dose and have the dose increased if response is insufficient. The correct comparator for canagliflozin 300mg would be ertugliflozin 15 mg. No change required

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG
On page 14 it is stated for ertugliflozin 15 mg that "It was reported to have more effect on SBP than canagliflozin 300, but not than canagliflozin 100 mg."	Proposed amendment, "Canagliflozin 300mg was reported to have more effect on SBP than ertugliflozin 15 mg".	Accuracy	Accepted. Though we note that this is one of 12 comparisons with 95% CIs. No change made.

This is incorrect. Canagliflozin 300mg had more effect on SBP than Ertugliflozin 15mg.			

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 14 it is stated that “Other outcomes are similar” The revised NMA results for weight change, which had not been seen by the ERG at the time of producing the report, show canagliflozin 300 mg are significantly better than ertugliflozin 5 mg.	Proposed amendment, “Other outcomes are similar by dose of flozins”	Accuracy	No error by ERG. Response as for issue 1 above. No change required.