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)

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ABSTRACT

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Introduction: We evaluated efficacy and safety of ertugliflozin, an SGLT2 inhibitor, in type 2 diabetes mellitus (T2DM) inadequately controlled (HbA1c, 7.0–10.5%) on metformin monotherapy (≥1500 mg/day for ≥8 weeks).

Methods: Double-blind, 26-week, multicentre study with ongoing 78-week extension; 621 participants randomized 1:1:1 to placebo, ertugliflozin 5 or 15 mg/day. Primary endpoint: change from baseline in HbA1c at week 26. Secondary efficacy endpoints: change from baseline at week 26 in fasting plasma glucose (FPG), body weight, systolic/diastolic blood pressure (SBP/DBP); participants with HbA1c <7.0% (53 mmol/mol). Pre-specified adverse events (AEs) of special interest and percent change from baseline in bone mineral density (BMD) were also assessed at week 26.

Results: At week 26, the placebo-adjusted least-squares mean change from baseline HbA1c (8.1%) was –0.7% and –0.9% for ertugliflozin 5 and 15 mg, respectively (both $P < 0.001$), to final means of 7.3% and 7.2%, respectively. The odds of HbA1c <7.0% were significantly greater in both ertugliflozin groups vs placebo. Ertugliflozin significantly reduced FPG, body weight, SBP and DBP vs placebo. Incidence of genital mycotic infections was increased in ertugliflozin groups (females: placebo, 0.9%; ertugliflozin 5 mg, 5.5%; 15 mg, 6.3% [$P = 0.032$]; males: 0; 3.1%; 3.2%), as was incidence of urinary tract infections and symptomatic hypoglycaemia. Incidence of hypovolaemia AEs was similar across groups. Ertugliflozin had no adverse impact on BMD at week 26.

Conclusions: Ertugliflozin added to metformin in inadequately controlled T2DM improved glycaemic control, reduced body weight and BP, but increased genital mycotic infections. ClinicalTrials.gov identifier: NCT02033889.

KEYWORDS

bone mineral density, ertugliflozin, SGLT2 inhibitor, type 2 diabetes mellitus

1 INTRODUCTION

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the newest class of oral anti-hyperglycaemic agent (AHA) for the treatment of type 2 diabetes mellitus (T2DM). Several SGLT2 inhibitors (e.g., canagliflozin, dapagliflozin, and empagliflozin) are currently available and have been shown to improve glycaemic control, reduce body weight and blood pressure while being generally well tolerated with a low risk of hypoglycaemia, but consistent genitourinary adverse events (AEs).[1,2] Although there have been no head-to-head comparisons of efficacy or safety, the currently available SGLT2 inhibitors differ in terms of selectivity, the clinical relevance of which, is presently unknown. Ertugliflozin is a highly selective SGLT2 inhibitor with 2000-fold selectivity for SGLT2 over SGLT1 in clinical development for the treatment of T2DM.[3] Phase II studies have shown that ertugliflozin improves glycaemic control and decreases body weight and blood pressure.[4,5] Results from several phase III studies demonstrate that ertugliflozin, administered over 26 weeks, provides clinically meaningful reductions from baseline in glycated haemoglobin (HbA1c), body weight and blood pressure.[6-8] Ertugliflozin is also being developed as a fixed-dose combination (FDC) with sitagliptin and a separate FDC with metformin.

This phase III study assessed the efficacy and safety of ertugliflozin vs placebo in adults with T2DM inadequately controlled on metformin monotherapy. Assessment of bone safety has been an area of interest in the evaluation of SGLT2 inhibitors; therefore, bone mineral density (BMD) and biomarkers of bone turnover were also evaluated. The study population was enriched with women who were ≥3 years postmenopausal to assess BMD changes in this population in addition to the overall cohort.

2 MATERIALS AND METHODS

This 104-week, multicentre, randomized, parallel-group study comprised a 26-week, double-blind, placebo-controlled treatment period (phase A) followed by an ongoing, 78-week, double-blind treatment extension period (phase B). Results from phase A are reported here.

The final protocol and informed consent documentation were reviewed and approved by the Institutional Review Boards or Independent Ethics Committees at each of the

investigational centres participating in the study. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice Guidelines. Written informed consent was obtained from all participants.

2.1 Study design

The study included a screening period (during which, if needed, background diabetes medication was adjusted to achieve a minimum 8-week metformin monotherapy stable dose [≥1500 mg/day]), followed by a 2-week, single-blind, placebo run-in period prior to randomization; a double-blind, placebo-controlled, 26-week treatment period; a double-blind, 78-week treatment extension period; and a posttreatment telephone contact 14 days after the last dose of blinded study medication. Participants were counselled on appropriate dietary and lifestyle guidelines for T2DM and asked to maintain these throughout study participation. On day 1 (randomization), each participant was assigned (1:1:1) to placebo, ertugliflozin 5 mg or ertugliflozin 15 mg using a computer-generated randomization code based on the method of random permuted blocks. Randomization was stratified in 4 groups: (1) men, (2) pre-menopausal women, (3) women who were perimenopausal or postmenopausal for <3 years after last menstrual period (LMP), or with bilateral oophorectomy performed <3 years prior to screening, and (4) women who were postmenopausal ≥3 years after LMP, or with bilateral oophorectomy performed ≥3 years prior to screening. 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 (>270 mg/dL) after randomization through week 6, >13.3 mmol/L (>240 mg/dL) after week 6 through week 12, and >11.1 mmol/L (>200 mg/dL) 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 less than –2.5. Participants receiving glycaemic or bone rescue therapy continued to receive ertugliflozin or matching placebo. In phase B, participants randomized to

ertugliflozin continued to receive ertugliflozin; those randomized to placebo received blinded glimepiride (if not rescued during phase A).

2.2 Participant population

The study population comprised men and women aged ≥18 years with T2DM (diagnosed in accordance with American Diabetes Association guidelines[9]) inadequately controlled (HbA1c, 7.0–10.5% [53–91 mmol/mol] inclusive) on metformin monotherapy (≥1500 mg/day for ≥8 weeks) and with BMI 18.0–40.0 kg/m^2.

At screening, participants were receiving either metformin monotherapy ≥1500 mg/day with HbA1c 7.0–10.5% (53–91 mmol/mol) inclusive, metformin monotherapy <1500 mg/day with HbA1c 7.5–11.0% (58–97 mmol/mol) inclusive, or dual combination therapy comprising metformin and one of the following oral AHAs: sulphonylurea, dipeptidyl peptidase-4 inhibitor, meglitinide or alpha-glucosidase inhibitor, with HbA1c 6.5–9.5% (48–80 mmol/mol) inclusive. Participants who had received dual AHA therapy, metformin monotherapy <1500 mg/day or ≥1500 mg/day for <8 weeks were required to adjust their background AHA therapy so that, at a second screening visit, they had received metformin monotherapy at ≥1500 mg/day for ≥8 weeks. To be eligible for study inclusion, these participants underwent a repeat HbA1c measurement for confirmation of HbA1c 7.0–10.5% inclusive. Participants were required to be on stable doses of blood pressure and/or lipid-altering medications for ≥4 weeks prior to randomization.

Key exclusion criteria included type 1 diabetes mellitus, history of ketoacidosis, estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2 according to the 4-variable modification of diet in renal disease equation[10] at screening, <80% compliance (based on pill count) with the placebo run-in medication, documented history of osteoporosis or gender-specific BMD T-score of less than –2.5 at any skeletal site assessed at screening, or any illness that could impact BMD assessment. Those who had received prior therapeutic agents that could confound BMD assessment or affect bone turnover were also excluded. Use of AHAs (other than those approved by the study protocol) and bone active therapeutic agents

(e.g. bisphosphonates) was prohibited for the entire duration of the trial. Participants who had undergone bariatric surgery were also ineligible.

2.3 Efficacy assessments

The primary efficacy endpoint was the change from baseline in HbA1c at week 26. Pre-specified secondary efficacy endpoints were changes from baseline at week 26 in FPG, body weight, systolic and diastolic blood pressure (SBP; DBP). Participants with HbA1c <7.0% (53 mmol/mol) at week 26 and proportions who received glycaemic rescue therapy were also evaluated. Body weight was measured in duplicate using a standardized digital scale. Sitting blood pressure was measured in triplicate using an automated oscillometric device.

2.4 Safety assessments

Safety assessments included adverse event (AE) monitoring, BMD and biomarkers of bone turnover, physical examination, vital signs (including sitting measurements and postural changes in blood pressure and pulse rate) and laboratory evaluations.

AEs of special interest identified *a priori* were termed “Tier 1” safety endpoints. These included symptomatic hypoglycaemia and AEs associated with genital mycotic infection, urinary tract infection (UTI) and hypovolaemia, which were identified according to pre-specified sponsor-generated customized MedDRA queries of preferred terms. Documented hypoglycaemia, defined as episodes with a glucose level ≤3.9 mmol/L (≤70 mg/dL) with or without symptoms, was also assessed. Severe hypoglycaemia was defined as an episode that required assistance, either medical or non-medical.

Bone densitometry of lumbar spine (L1–L4), femoral neck, total hip and distal forearm regions was measured by dual energy X-ray absorptiometry (DXA) at baseline and week 26. DXA scanning procedures were standardized, and all scans were monitored and analysed by a central evaluation facility. Blood was collected for analysis of biochemical markers of rate of bone turnover (carboxy terminal cross-linking telopeptides of Type I

collagen [CTX] and procollagen type 1 N terminal propeptide [P1NP]), parathyroid hormone (PTH, secreted in response to low serum calcium) and lipids.

Changes in renal function were evaluated according to change from baseline in eGFR. The number and proportion of participants meeting pre-specified criteria for orthostatic change in blood pressure (i.e. supine to standing position) were summarized.[11]

2.5 Statistical analysis

The planned sample size of 600 participants (200 per arm) provided >99% power to detect a difference of 0.5% between each ertugliflozin dose and placebo in the change from baseline at week 26 in HbA1c, assuming a standard deviation (SD) of 1.0% based on a 2-sided test at a 5% level of significance. The sample size also provided adequate precision for the comparisons of ertugliflozin vs placebo with respect to change in BMD from baseline at week 26. The half-width of the 95% confidence interval (CI) for the between-treatment difference in BMD was expected to be ± 0.7% from the point estimate, which, based on BMD changes of ~50% of the average change from baseline to week 80 observed for thiazolidinediones, would be precise enough to rule out any clinically relevant change.[12] Efficacy data obtained after initiation of glycaemic rescue therapy were censored (i.e. 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.

2.5.1 Analysis of efficacy endpoints

Efficacy analyses comprised all randomized participants who received ≥1 dose of study medication. For endpoints that used a longitudinal data analysis (LDA) model,[13] at least one measurement (baseline or postbaseline) was required. An ordered testing procedure (HbA1c, FPG, body weight, HbA1c <7.0%, SBP, DBP) was used to control the family-wise

type 1 error rate at the 0.05 level across all key efficacy endpoints. For each endpoint, the 15-mg dose was tested vs placebo first, followed by the 5-mg dose vs placebo. Each test was performed at the 0.05 level, and testing continued until the first *P*-value was ≥0.05. Change from baseline at week 26 in HbA1c, FPG, body weight, SBP and DBP was evaluated using a LDA model that included terms for treatment (categorical), time (categorical), the treatment-by-time interaction, menopausal status randomization stratum (categorical), AHA status at study entry (binary), and baseline eGFR (continuous) with baseline constrained to be the same. No imputation of missing data was performed. A logistic regression analysis was used to evaluate the occurrence of HbA1c of <7.0% (53 mmol/L) at week 26. Missing data at week 26 were imputed via multiple imputation based on the primary longitudinal model. Model-based subgroup analyses of the change from baseline in HbA1c at week 26 were performed using a repeated measures analysis of covariance model. The proportion of participants who received glycaemic rescue therapy in each treatment group was compared using the Miettinen and Nurminen method.[12,14]

2.5.2 Analysis of safety

The safety analysis set included all participants who received ≥1 dose of study medication. For all safety endpoints of *a priori* interest ("Tier 1" AEs), *P*-values and 95% CIs (with no adjustment for multiplicity) were calculated for between-group comparisons using the Miettinen and Nurminen method.[14] The term "significantly" higher or lower has been used when $P < 0.05$. Other safety results have been described as "higher" or "lower" as qualitative assessment only. The "excluding bone rescue therapy" approach was considered primary for BMD, bone biomarker and PTH analyses (however, these data were not censored after initiation of glycaemic rescue therapy). Percent changes in BMD endpoints were analysed using a LDA model as described for HbA1c.

Orthostatic changes in SBP and DBP were defined as reductions of ≥20 or ≥10 mmHg, respectively, after 1 and 3 minutes in the standing position from the supine position (relative to the mean value from measurements taken in the supine position). Percent

changes from baseline in low- and high-density lipoprotein cholesterol (LDL-C; HDL-C) were analysed using the longitudinal method described for HbA1c. Change from baseline in eGFR was summarized descriptively.

3 RESULTS

3.1 Participant disposition and baseline characteristics

In total, 621 participants were randomized (Figure S1). Demographics and baseline characteristics (Table 1) were similar across the treatment groups. The age range was 24 to 79 years and 15.6% of the study population was aged ≥65 years. Approximately 40% of the study population were women who were postmenopausal for ≥3 years. The median metformin dose at baseline was 2000 mg/day in all groups. At baseline, 70% of the overall population was receiving ≥1 antihypertensive medication; 60%, 22%, 21%, and 24% of participants were receiving agents that act on the renin–angiotensin system, beta blockers, calcium channel blockers, and diuretics, respectively. The proportion of participants who discontinued study medication was 9.1%, 2.9% and 7.3% in the placebo, ertugliflozin 5-mg and 15-mg groups, respectively. 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 AE.

3.2 Efficacy

Significantly greater reductions in HbA1c at week 26 were observed in both ertugliflozin groups compared with the placebo group ($P < 0.001$ for both comparisons). At week 26, the placebo-adjusted least-squares (LS) mean (95% CI) change from baseline in HbA1c was –0.7% (–0.9, –0.5) and –0.9% (–1.0, –0.7) for the ertugliflozin 5-mg and 15-mg groups, respectively (Table 2; Figures 1A, 1B). Mean (SD) reductions from baseline in HbA1c at week 26 were greater in patients with higher baseline HbA1c levels (<8.0%: placebo, 0 [0.9]; ertugliflozin 5 mg, –0.4 [0.7]; ertugliflozin 15 mg, –0.5 [0.6]; ≥8.0% to <9.0%: –0.3 [0.9]; –0.7 [0.9]; –1.1 [0.8], respectively; ≥9.0%: –0.8 [1.0]; –1.7 [1.1]; –1.8 [0.8], respectively). More

patients who received ertugliflozin 5 mg (35%) and 15 mg (40%) compared with placebo (16%) had HbA1c <7.0% at week 26 (Figure 1C). The model-based odds (95% CI) of HbA1c <7.0% relative to placebo were significantly higher in both the ertugliflozin 5-mg (3.0 [1.8, 5.1]) and 15-mg groups (4.5 [2.6, 7.6]; both $P < 0.001$). Both ertugliflozin doses also provided significantly greater reductions from baseline in FPG (Figure 1D), body weight (Figure 1E), SBP (Figure 1F) and DBP (Figure 1G) compared with placebo. By week 26, a larger proportion of subjects in the placebo group (17.7%) had received glycaemic rescue therapy compared with the ertugliflozin groups (both <3%).

3.3 Safety

3.3.1 Overall AE summary

The overall incidence of AEs was similar across groups. The incidence of AEs resulting in discontinuation from study medication was low (<2%) and similar across groups. The incidence of drug-related AEs was higher in the ertugliflozin groups compared with placebo (Table 3), largely owing to AEs related to genital mycotic infections. The incidence of SAEs was low and similar across groups, and none were reported as drug related by the investigator. There were no cases of ketoacidosis or deaths through week 26.

3.3.2 "Tier 1" AEs/AEs of special interest

In females, the incidence of genital mycotic infections was higher in the ertugliflozin 5-mg group and significantly higher ($P < 0.05$) in the 15-mg group vs placebo (Table 3). In males, the incidence was higher in the ertugliflozin groups vs placebo. Two participants (one each in the ertugliflozin 5-mg and 15-mg groups) discontinued study treatment owing to AEs related to vulvovaginal complaints. The point estimates for the incidences of UTI and symptomatic hypoglycaemia AEs were higher in the ertugliflozin groups vs placebo. One participant in the ertugliflozin 15-mg group discontinued study treatment owing to a UTI. The incidence of hypovolaemia AEs was similar across groups (Table 3). The incidence of documented hypoglycaemia was higher in the ertugliflozin groups (5 mg, 7.2%; 15 mg,

7.8%) vs placebo (4.3%). Two participants, one in the ertugliflozin 5-mg group and one in the placebo group, experienced an episode of severe hypoglycaemia that required non-medical assistance.

There was no notable change from baseline in the occurrence of events meeting orthostatic blood pressure decrease criteria in either ertugliflozin group at weeks 6 (SBP: 5 mg, 2.0%; 15 mg, 2.1%) or 26 (5 mg, 4.0%; 15 mg, 4.2%), and the incidence was similar to placebo (week 6, 3.6%; week 26, 3.7%).

3.3.3 BMD and bone biomarkers

Ertugliflozin had no adverse impact on BMD at week 26 (Table 4). An assessment by subgroup revealed results that were generally similar to those for the overall population (data not shown). Three participants, one in each group, had adjudication-confirmed fractures. One participant (in the ertugliflozin 5-mg group) met bone rescue criteria and received treatment. Mean serum CTX at week 26 was increased in the ertugliflozin groups in a dose-related manner, but mean P1NP and PTH levels at week 26 were similar to baseline (Table S1).

3.3.4 Laboratory parameters

Small mean increases from baseline in magnesium and phosphate were initially observed at week 6 and were maintained through week 26 in both ertugliflozin groups. There was no notable change from baseline in serum calcium (Table S2).

In the ertugliflozin groups, decreases from baseline in eGFR (see Table 1), initially observed at week 6 (3.2 and 3.3 mL/min/1.73 m^2 in the 5-mg and 15-mg groups, respectively), returned to baseline values at week 26. There was no notable change from baseline in the placebo group. The proportion of participants with a >30% decrease in eGFR was low but was higher in ertugliflozin groups (2.0% in both) compared with placebo (0.5%). One participant (0.5%) in the ertugliflozin 15-mg group had a >50% decrease from baseline in eGFR.

At week 26, the LS mean (95% CI) placebo-adjusted percent change from baseline in LDL-C was 2.0% (–6.0, 10.0) in the ertugliflozin 5-mg group and 2.6% (–5.5, 10.7) in the 15-mg group. Baseline values were: placebo, 99.3 mg/dL; ertugliflozin 5 mg, 98.8 mg/dL; ertugliflozin 15 mg, 93.2 mg/dL. Corresponding placebo-adjusted percent changes for HDL-C were: ertugliflozin 5 mg, 4.5% (1.4, 7.6); ertugliflozin 15 mg, 4.4% (1.3, 7.5). Baseline values were: placebo, 48.6 mg/dL; ertugliflozin 5 mg, 48.5 mg/dL; ertugliflozin 15 mg, 48.2 mg/dL.

4 DISCUSSION

In this study, the addition of ertugliflozin at doses of 5 mg and 15 mg once daily to metformin monotherapy over 26 weeks improved glycaemic control and reduced body weight, SBP and DBP without impacting BMD, but it increased the incidence of genital mycotic infections.

With both doses of ertugliflozin, decreases in HbA1c were clinically relevant and consistent with reports for other SGLT2 inhibitors.[1,2,15] Treatment with ertugliflozin also resulted in significant improvements relative to placebo in other glycaemic measures, including FPG, and in the proportion of participants with HbA1c <7%. In addition, treatment with ertugliflozin resulted in significantly greater reductions in body weight, SBP and DBP at week 26 relative to placebo. Although this trial was not designed to formally compare the two ertugliflozin doses tested, the 15-mg dose appeared to be associated with slightly greater reductions in the primary and key secondary endpoints, except for body weight loss, which was similar between the two doses.

The incidence of genital mycotic infections was more frequent in ertugliflozin groups vs placebo. This is a known class effect of SGLT2 inhibitors, and these findings are consistent with the increased relative risk for genital mycotic infections reported in a meta-analysis of SGLT2 inhibitors.[16] Consistent with reports for dapagliflozin[17] and canagliflozin,[18] in the current study there was a trend for a higher incidence of UTI AEs in ertugliflozin groups vs placebo, but there were no cases of complicated UTIs. Symptomatic hypoglycaemia and documented hypoglycaemic events were infrequent.

Bone safety remains an area of interest for SGLT2 inhibitors. The strongest evidence for bone safety involves assessment of fracture risk. However, assessment of BMD and bone biomarkers can also be informative. Potentially disparate effects on fracture are noted for SGLT2 inhibitors based on indirect comparisons of phase III results. In the canagliflozin program, an increase in fractures was noted as early as 12 weeks.[19] While no imbalance of fractures was evident in the dapagliflozin program, increased incidence was observed in a study of individuals with moderate renal impairment.[20] The incidence of bone fractures in patients treated with empagliflozin was low and similar to placebo,[21] and was confirmed by pooled analysis.[22]

In a study in patients aged 55–80 years, at 2 years, individuals randomized to canagliflozin 100 or 300 mg had placebo-adjusted declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively.[23,24] In the same study, at week 26, canagliflozin was associated with increases in CTX, a biomarker of bone resorption, of 16.2% and 23.9%, respectively, and decreases in P1NP, a biomarker of bone formation, of 5.5% and 6.8%, respectively.[25] No meaningful changes from baseline in markers of bone turnover or BMD in patients who received dapagliflozin added to metformin were reported after either 50[26] or 102 weeks.[27] However, the dapagliflozin study was small (n=182) and did not have a population enriched with older participants.

Through 26 weeks, ertugliflozin had no adverse impact on BMD in either the overall population or the cohort of women postmenopausal for ≥3 years. The study protocol also includes BMD assessment at weeks 52 and 104; these data, along with future pooled analyses of fracture risk in the phase III program, will inform on bone safety outcomes associated with longer-term treatment with ertugliflozin. Participants in ertugliflozin groups had increased serum CTX compared with those in the placebo group. Levels of P1NP and PTH did not differ between groups through 26 weeks. The clinical relevance of these laboratory findings, coupled with the lack of change in BMD at week 26 in particular, is unclear. Longer-term data on bone biomarkers and PTH will be available when the 78-week extension phase is completed.

Small increases in HDL-C and LDL-C were noted with ertugliflozin, consistent with reports of other SGLT2 inhibitors.[28] SGLT2 inhibitors have also been associated with transient increases in serum creatinine and decreases in eGFR.[29] In this study, there was an initial decrease in eGFR at week 6 in ertugliflozin groups (without dose effect), but by week 26 values had returned to baseline and were similar to placebo.

5 CONCLUSIONS

In participants with T2DM who had inadequate glycaemic control on metformin monotherapy, the addition of ertugliflozin for 26 weeks provided meaningful improvements in glycaemic control and significant reductions in body weight, SBP and DBP. Ertugliflozin was generally well tolerated; however, it was associated with a higher incidence of genital mycotic infections compared with placebo.

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FIGURE LEGENDS

FIGURE 1 Efficacy outcomes: (A) LS mean (± SE) change from baseline in HbA1c at week 26; (B) LS mean (95% CI) change from baseline in HbA1c at week 26; (C) proportion of participants with HbA1c <7% at week 26. LS mean change from baseline at week 26 in (D) FPG; (E) body weight; (F) SBP; and (G) DBP.

FIGURE S1 Participant disposition.

TABLE 1 Baseline demographics and treatment characteristics

	Placebo (N=209)	**Ertugliflozin 5 mg (N=207)**	**Ertugliflozin 15 mg (N=205)**	**Total (N=621)**
Male, n (%)	98 (46.9)	97 (46.9)	93 (45.4)	288 (46.4)
Age, years ± SD	56.5 ± 8.7	56.6 ± 8.1	56.9 ± 9.4	56.6 ± 8.8
Duration of T2DM, years ± SD	8.0 ± 6.3	7.9 ± 6.1	8.1 ± 5.5	8.0 ± 6.0
Background AHA therapy at screening, n (%)[1]				
Metformin	209 (100.0)	207 (100.0)	204 (99.5)[2]	620 (99.8)
DPP-4 inhibitors	7 (3.3)	6 (2.9)	8 (3.9)	21 (3.4)
Other blood glucose lowering agents	0 (0)	3 (1.4)	2 (1.0)	5 (0.8)
Sulphonamides, urea derivatives	62 (29.7)	57 (27.5)	45 (22.0)	164 (26.4)
Number of agents				
1	140 (67.0)	141 (68.1)	151 (73.7)	432 (69.6)
2	69 (33.0)	66 (31.9)	54 (26.3)	189 (30.4)
Race, n (%)				
Asian	31 (14.8)	34 (16.4)	35 (17.1)	100 (16.1)
Black or African American	19 (9.1)	22 (10.6)	23 (11.2)	64 (10.3)
Multiple	15 (7.2)	17 (8.2)	14 (6.8)	46 (7.4)
White	144 (68.9)	134 (64.7)	133 (64.9)	411 (66.2)
Region, n (%)				

	Placebo (N=209)	Ertugliflozin 5 mg (N=207)	Ertugliflozin 15 mg (N=205)	Total (N=621)
North America	55 (26.3)	61 (29.5)	53 (25.9)	169 (27.2)
South America	9 (4.3)	4 (1.9)	8 (3.9)	21 (3.4)
Europe	76 (36.4)	74 (35.7)	74 (36.1)	224 (36.1)
Asia	26 (12.4)	27 (13.0)	32 (15.6)	85 (13.7)
South Africa	39 (18.7)	35 (16.9)	37 (18.0)	111 (17.9)
Australia/New Zealand	4 (1.9)	6 (2.9)	1 (0.5)	11 (1.8)
Body weight, kg	84.5 ± 17.1	84.8 ± 17.2	85.3 ± 16.5	84.9 ± 16.9
BMI, kg/m^2	30.7 ± 4.7	30.8 ± 4.8	31.1 ± 4.5	30.9 ± 4.7
HbA1c, %	8.2 ± 0.9	8.1 ± 0.9	8.1 ± 0.9	8.1 ± 0.9
FPG, mmol/L	9.4 ± 2.3	9.3 ± 2.5	9.3 ± 2.5	9.3 ± 2.4
eGFR[3], $mL/min/1.73\ m^2$	91.6 ± 19.8	88.9 ± 17.5	91.0 ± 20.6	90.5 ± 19.3
Stratification factor: menopausal status				
Men	97 (46.4)	97 (46.9)	93 (45.4)	287 (46.2)
Women				
Pre-menopausal	16 (7.7)	17 (8.2)	16 (7.8)	49 (7.9)
Perimenopausal or <3 years postmenopausal	9 (4.3)	10 (4.8)	11 (5.4)	30 (4.8)
≥3 years postmenopausal	87 (41.6)	83 (40.1)	85 (41.5)	255 (41.1)

Data are mean ± SD or n (%) where indicated.
Abbreviations: AHA, anti-hyperglycaemic agent; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; SD, standard deviation; T2DM, type 2 diabetes mellitus.
[1] Combination blood glucose lowering agents are counted twice, under each component of the combination.

	Placebo (N=209)	Ertugliflozin 5 mg (N=207)	Ertugliflozin 15 mg (N=205)	Total (N=621)
[2] One patient was not on metformin at the first screening visit but started at the second screening visit. [3] n numbers for eGFR were: placebo, 202; ertugliflozin 5 mg, 199; ertugliflozin 15 mg, 201; total, 602.				

TABLE 2 Change from baseline in HbA1c (%) at week 26

Treatment	Baseline		Week 26		Change from baseline at week 26		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS mean (95% CI)[1]
Placebo	207	8.2 (0.9)	151	7.8 (1.1)	209	–0.2 (0.9)	0.0 (–0.2, 0.1)
Ertugliflozin 5 mg	205	8.1 (0.9)	191	7.3 (0.8)	207	–0.7 (0.9)	–0.7 (–0.8, –0.6)
Ertugliflozin 15 mg	201	8.1 (0.9)	186	7.2 (0.8)	205	–1.0 (0.9)	–0.9 (–1.0, –0.8)

Pairwise comparison	Difference in LS means (95% CI)[1]	*P*-value[1]
Week 26 ertugliflozin 5 mg vs placebo	–0.7 (–0.9, –0.5)	<0.001
Week 26 ertugliflozin 15 mg vs placebo	–0.9 (–1.0, –0.7)	<0.001

Based on the full analysis set, excluding data after initiation of glycaemic rescue therapy.
Abbreviations: AHA, anti-hyperglycaemic agent; CI, confidence interval; cLDA, constrained longitudinal data analysis; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; LS, least-squares; SD, standard deviation.
[1] Based on cLDA model with fixed effects for treatment, time, prior AHA (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status randomization stratum (men, pre-menopausal women, women perimenopausal or <3 years postmenopausal, women ≥3 years postmenopausal) and the treatment-by-time interaction. Time was treated as a categorical variable.

TABLE 3 Summary of overall safety and selected AEs

n (%)[1]	Placebo (N=209)	Ertugliflozin 5 mg (N=207)	Ertugliflozin 15 mg (N=205)
Overall safety			
One or more AEs	94 (45.0)	88 (42.5)	103 (50.2)
AEs related to study drug	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)
Death	0 (0)	0 (0)	0 (0)
AE leading to discontinuation of study medication	3 (1.4)	3 (1.4)	3 (1.5)
Tier 1 AEs			
Genital mycotic infection (women)	1 (0.9)	6 (5.5)	7 (6.3)[2]
Genital mycotic infection (men)	0 (0)	3 (3.1)	3 (3.2)
UTI	2 (1.0)	6 (2.9)	7 (3.4)
Symptomatic hypoglycaemia	4 (1.9)	7 (3.4)	7 (3.4)
Hypovolaemia	1 (0.5)	1 (0.5)	2 (1.0)
Other selected AEs			
Documented hypoglycaemia[3]	9 (4.3)	15 (7.2)	16 (7.8)
Pollakiuria	0 (0)	3 (1.4)	3 (1.5)
Dizziness	1 (0.5)	3 (1.4)	1 (0.5)

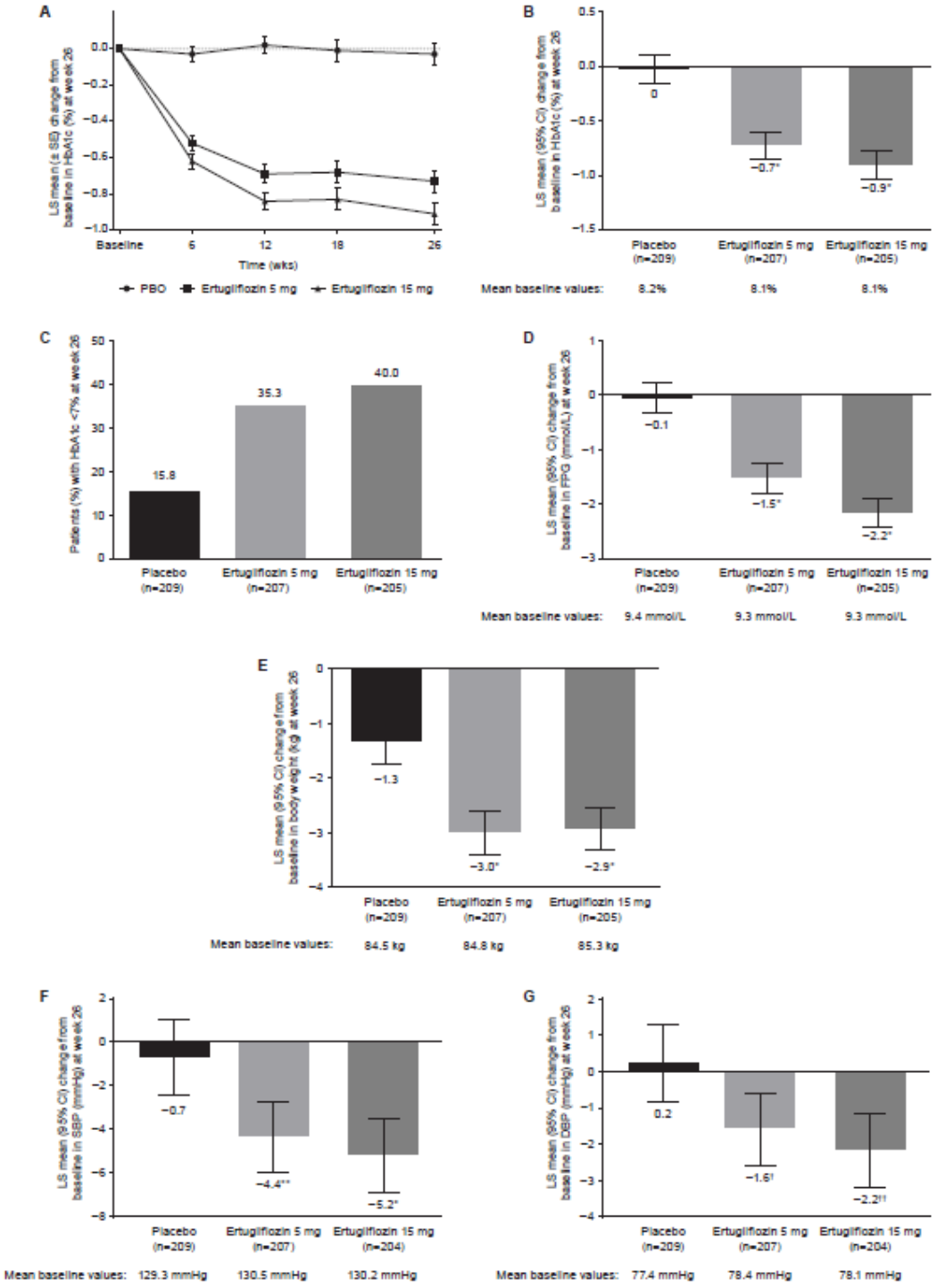
Data are shown as n (%).
Abbreviations: AE, adverse event; SAE, serious adverse event; UTI, urinary tract infection.
[1] The "including rescue" approach (analysis including data obtained after the initiation of glycaemic rescue therapy) was the primary analysis for SAEs, deaths and discontinuations due to AEs. The "excluding rescue" approach (analysis excluding events occurring after glycaemic rescue medication) was the primary analysis for all other endpoints.
[2] Incidence significantly higher (P = 0.032) vs placebo group.
[3] Episodes with a glucose level ≤3.9 mmol/L (70 mg/dL) with or without symptoms.

TABLE 4 Percent change from baseline to week 26 in BMD measured by DXA

	Baseline		Week 26		Change (%) from baseline at week 26			Change (%) from baseline vs placebo
Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**LS mean (95% CI)[1]**	**Difference in LS means (95% CI)[1]**
Lumbar spine								
Placebo	209	1.15 (0.181)	191	1.15 (0.184)	191	0.20 (2.919)	0.22 (–0.20, 0.65)	–
Ertugliflozin 5 mg	207	1.13 (0.184)	200	1.13 (0.188)	200	0.00 (3.191)	–0.01 (–0.42, 0.41)	–0.23 (–0.83, 0.37)
Ertugliflozin 15 mg	204	1.10 (0.168)	190	1.11 (0.169)	189	0.15 (2.884)	0.12 (–0.31, 0.55)	–0.10 (–0.71, 0.50)
Femoral neck								
Placebo	209	0.92 (0.167)	191	0.92 (0.166)	191	–0.42 (3.296)	–0.40 (–0.89, 0.09)	–
Ertugliflozin 5 mg	207	0.92 (0.162)	200	0.92 (0.165)	200	–0.10 (3.237)	–0.10 (–0.57, 0.38)	0.30 (–0.38, 0.99)
Ertugliflozin 15 mg	205	0.89 (0.153)	190	0.89 (0.152)	190	0.33 (3.797)	0.30 (–0.19, 0.79)	0.70 (0.00, 1.39)
Total hip								
Placebo	209	1.06 (0.154)	191	1.06 (0.156)	191	–0.62 (1.963)	–0.63 (–0.92, –0.34)	–
Ertugliflozin 5 mg	207	1.07 (0.150)	200	1.06 (0.155)	200	–0.54 (2.013)	–0.55 (–0.83, –0.27)	0.08 (–0.33, 0.48)
Ertugliflozin 15 mg	205	1.04 (0.138)	190	1.04 (0.138)	190	–0.36 (2.177)	–0.36 (–0.65, –0.07)	0.27 (–0.15, 0.68)
Distal forearm								
Placebo	209	0.81 (0.136)	191	0.81 (0.133)	190	0.07 (3.049)	0.06 (–0.35, 0.47)	–
Ertugliflozin 5 mg	204	0.81 (0.137)	200	0.81 (0.138)	197	–0.14 (2.692)	–0.15 (–0.55, 0.24)	–0.21 (–0.78, 0.35)
Ertugliflozin 15 mg	205	0.79 (0.134)	189	0.80 (0.134)	189	–0.08 (2.826)	–0.13 (–0.53, 0.28)	–0.19 (–0.76, 0.39)

Data are excluding bone rescue approach.
Abbreviations: AHA, anti-hyperglycaemic agent; BMD, bone mineral density; CI, confidence interval; cLDA, constrained longitudinal data analysis; DXA, dual energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; LS, least-squares; SD, standard deviation.
[1] Based on cLDA model with fixed effects for treatment, time, prior anti-hyperglycaemic medication (metformin monotherapy or metformin + another AHA), baseline eGFR (continuous), menopausal status randomization stratum (men, pre-menopausal women, women perimenopausal or <3 years postmenopausal, women ≥3 years postmenopausal) and the treatment-by-time interaction. Time was treated as a categorical variable.

[FIGURE 1]



*P < 0.001 vs placebo; **P = 0.002 vs placebo; †P = 0.013; ††P = 0.001. Excluding data after initiation of glycaemic rescue therapy. CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LS, least-squares; PBO, placebo; SBP, systolic blood pressure; SE, standard error.