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ORIGINAL ARTICLE

Safety and efficacy of ertugliflozin in Asian patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: VERTIS Asia

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Aim: Phase III, randomized, double-blind study evaluating the efficacy and safety of ertugliflozin in Asian patients with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin, including evaluation in the China subpopulation.

Materials and methods: A 26-week, double-blind study of 506 Asian patients (80.2% from mainland China), randomized 1:1:1 to placebo, ertugliflozin 5- or 15 mg, was performed. Primary endpoint was change from baseline in HbA1c at week 26. Secondary endpoints were change from baseline at week 26 in fasting plasma glucose (FPG), body weight (BW), systolic/diastolic blood pressure (SBP/DBP), and proportion of patients with HbA1c <7.0%. Hypotheses for the primary endpoint and FPG and BW secondary endpoints were tested in the China subpopulation.

Results: At week 26, least squares mean (95% CI) change from baseline HbA1c was significantly greater with ertugliflozin 5- and 15 mg versus placebo: −1.0% (−1.1, −0.9), −0.9% (−1.0, −0.8), −0.2% (−0.3, −0.1), respectively. Ertugliflozin significantly reduced FPG, BW and SBP. Reductions in DBP with ertugliflozin were not significant. At week 26, 16.2%, 38.2% and 40.8% of patients had HbA1c <7.0% with placebo, ertugliflozin 5- and 15 mg, respectively. 59.3%, 56.5% and 53.3% of patients experienced adverse events with placebo, ertugliflozin 5- and 15 mg, respectively. Incidence of symptomatic hypoglycaemia was higher for ertugliflozin 15 mg vs placebo. Results in the China subpopulation were consistent.

Conclusions: Ertugliflozin significantly improved glycaemic control and reduced BW and SBP in Asian patients with T2DM. Ertugliflozin was generally well-tolerated. Results in the China subpopulation were consistent with the overall population. ClinicalTrials.gov: NCT02630706.

KEYWORDS

Asia, ertugliflozin, SGLT2 inhibitor, type 2 diabetes mellitus

1 | INTRODUCTION

The global burden of type 2 diabetes (T2DM) is increasing, particularly in Asia.[1] Following current trends, diabetes could affect 693 million adults worldwide by the year 2045.[1] In China, 11.6% (113.9 million) of the adult population are estimated to have diabetes, with T2DM accounting for the vast majority of cases.[2] Several factors are probably contributing to the increased prevalence in the Asian population including urbanization and accompanying obesity, along with increasing age.[3]

Metformin is the standard first-line pharmacological agent for the majority of patients with T2DM.[4] However, because of the

*At time of study conduct.

progressive nature of T2DM, over time many patients fail to maintain adequate glycaemic control on metformin monotherapy, and require additional antihyperglycaemic therapy. Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce renal glucose reabsorption, leading to favourable effects on glycaemic control, blood pressure (BP) and body weight control.[5–8] The insulin-independent mechanism enables their use across the natural progression of T2DM.

Ertugliflozin, a selective inhibitor of SGLT2,[9,10] is currently approved in the United States,[11] the European Union (EU)[12] and other regions including Canada[13] and Australia,[14] as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. Phase III trials have shown that ertugliflozin alone or in combination with metformin or metformin and sitagliptin significantly reduces HbA1c, fasting plasma glucose (FPG), body weight and BP.[15–22] This phase III study assessed the efficacy, safety and tolerability of ertugliflozin relative to placebo in adult Asian patients with T2DM and included a prespecified analysis of the China subpopulation to support the registration of ertugliflozin in China.

2 | METHODS

This was a 26-week, double-blind, placebo-controlled, multicentre, randomized, parallel-group, phase III study in Asian patients with T2DM and inadequate glycaemic control on metformin monotherapy. The final protocol and informed consent documentation were reviewed and approved by the institutional review board or independent ethics committee at each investigational centre. 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 (ClinicalTrials.gov: NCT02630706).

2.1 | Study design and treatment

The trial design is shown in Supporting Information Figure S1. 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/d]), followed by a 2-week, single-blind, placebo run-in period prior to randomization, a 26-week double-blind, placebo-controlled treatment period, and post-treatment telephone contact 14 days after the last dose of blinded study medication. Participants were counselled on appropriate dietary and lifestyle guidelines for T2DM. On day 1 (randomization), each participant was assigned (1:1:1) to oral, once-daily ertugliflozin 5 mg, 15 mg or placebo using a computer-generated randomization code based on the method of random permuted blocks. Randomization was stratified by "Mainland China" and "Other". Participants received glycaemic rescue therapy with open-label glimepiride and dosed according to physician judgement, if they met specific, progressively more stringent, glycaemic thresholds. Participants who received glycaemic rescue therapy remained in the study and continued to receive background metformin and blinded study medication, ertugliflozin or matching placebo.

2.2 | Participant population

The population comprised Asian men and women aged ≥18 years with T2DM (diagnosed in accordance with American Diabetes Association guidelines)[4] inadequately controlled [HbA1c, 7.0-10.5% (53-91 mmol/mol) inclusive] with metformin monotherapy and with a body mass index (BMI) ≥18.0 kg/m^2. Participants who had received dual antihyperglycaemic agent (AHA) therapy, metformin monotherapy <1500 or ≥1500 mg/d 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/d for ≥8 weeks. To be eligible for study inclusion, these participants underwent a repeat HbA1c measurement for confirmation of HbA1c 7.0 to 10.5% (53-91 mmol/mol) inclusive. Participants were required to be receiving stable doses of BP 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 at screening, and <80% compliance (based on pill count) with the placebo run-in medication. Use of AHAs (other than those approved by the study protocol) was prohibited for the 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. Secondary efficacy endpoints included change from baseline at week 26 in FPG, body weight, systolic BP and diastolic BP, and the proportion of patients with HbA1c <7% (53 mmol/mol) for the secondary hypotheses. Other assessments included the proportion of patients with HbA1c <6.5% (48 mmol/mol) and the proportion of patients requiring glycaemic rescue therapy. Hypotheses for the primary and secondary endpoints were assessed in the overall study population. Hypotheses for the primary endpoint and the secondary endpoints of FPG and body weight were also tested in patients from mainland China (China subpopulation). Laboratory assessments were performed at a central laboratory. Body weight was measured in duplicate using a standardized digital scale. Sitting BP was measured in triplicate using an automated oscillometric device.

2.4 | Safety assessments

Safety assessments included adverse events (AEs), drug-related AEs, serious AEs (SAEs), deaths, discontinuations because of AEs, eGFR change from baseline over time, vital signs and laboratory evaluations. Genital mycotic infection (GMI) by gender, urinary tract infection (UTI), symptomatic hypoglycaemia and hypovolaemia were prespecified AEs of special interest (Tier 1 AEs). Clinical adjudication committees, comprising external panels of independent physicians blinded to patient treatment assignments, evaluated cardiovascular events, fractures, pancreatitis and renal and hepatic events. Potential cases of ketoacidosis were reviewed by an internal blinded case review committee, independent from the study team, to assess whether the cases met a prespecified definition of ketoacidosis. An

external data monitoring committee monitored unblinded, interim data from this study and other phase III studies in the ertugliflozin development programme. There was no interim analysis of efficacy for this study. Safety data were provided to the external data monitoring committee for periodic reviews of safety.

2.5 | Statistical analysis

The sample size was based on the reduction in HbA1c from baseline at week 26, from the patients enrolled from mainland China. Assuming a standard deviation (SD) of 1.0%, a sample size of 105 patients from mainland China per group (315 in total) provided ~95% power to detect a difference in HbA1c change from baseline of 0.5% between each ertugliflozin dose and placebo (and ~90% power for detecting this difference for both doses vs. placebo) using a two-sided 0.05 alpha level test. Assuming a dropout rate of 20% at week 26 (i.e. either patients who discontinued from the study, discontinued study medication or took rescue medication and were censored), ~396 patients from mainland China (132 per group) were to be randomized. In addition, this study was to include ~99 patients from at least two other Asian countries. The total sample size planned for this study was ~495 randomized patients.

2.5.1 | Analysis of efficacy endpoints

Efficacy analyses comprised all randomized patients who received ≥1 dose of study medication. The China subpopulation was assessed in parallel to the overall population. For the China subpopulation, efficacy analyses consisted of patients who were in the full analysis set for overall study population and enrolled from mainland China. For endpoints that used a longitudinal data analysis (LDA) model, at least one measurement (baseline or postbaseline) was required.

Efficacy endpoints were summarized using the excluding glycaemic rescue approach, i.e. efficacy data obtained after the initiation of glycaemic rescue therapy were censored (treated as missing). A sequential testing approach was used to assess the primary and secondary efficacy hypotheses to control the type 1 error rate at the 0.05 level within each population (overall study population and China subpopulation). For each endpoint, the 15-mg dose was tested versus placebo first, followed by the 5-mg dose versus placebo. Each test was performed at the 0.05 level, and testing continued until the first *P*-value was ≥0.05. This testing strategy was used in the overall population for HbA1c, FPG, body weight, HbA1c <7.0% (53 mmol/mol), systolic BP and diastolic BP, and within the China subpopulation for the HbA1c, FPG and body weight endpoints. If any prior *P*-value did not meet the <0.05 criterion, *P*-values for subsequent comparisons were provided for reference only and were considered nominal. In the China subpopulation, the 95% CI and nominal *P*-values were provided for secondary endpoints without statistical hypothesis testing [HbA1c <7.0% (53 mmol/mol), systolic BP and diastolic BP]. Changes from baseline at week 26 were assessed using an LDA model for the ertugliflozin groups that included terms for country (binary, 'Mainland China vs. Other', applicable only for the analyses of the overall study population), treatment (categorical), visit (categorical), treatment by visit interaction, AHA status at study entry (binary) and baseline eGFR (continuous) with baseline constrained to be the same. A logistic regression analysis was used to evaluate the proportion of patients with HbA1c <7.0% (53 mmol/mol) and HbA1c <6.5% (48 mmol/mol) at week 26 using the excluding glycaemic rescue approach. Missing data at week 26 were imputed via a multiple imputation procedure based on the LDA model. The proportion of patients requiring glycaemic rescue therapy up to week 26 was analyzed by treatment using the Miettinen and Nurminen method (stratified by country for the overall population) based on all patients treated.[23]

2.5.2 | Analysis of safety endpoints

Safety analyses included all randomized patients who took ≥1 dose of study medication. With the exception of hypoglycaemia, safety analyses were conducted including using the glycaemic rescue approach. Safety endpoints of a priori interest (Tier 1 AEs of GMI by gender, UTI, symptomatic hypoglycaemia and hypovolaemia) were assessed using 95% confidence intervals (CI), and *P*-values provided without multiplicity control using the Miettinen and Nurminen method.[23]

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

In total, 506 patients were randomized (Supporting Information Table S1), including 406 patients in mainland China. Overall, 465 (92%) patients completed the study medication. The proportion of patients who discontinued the study medication was higher in the placebo group compared with ertugliflozin (Supporting Information Table S1). Patient withdrawal was the most common reason for discontinuation of study medication for both ertugliflozin and placebo. Twenty-six of the 41 (8.1%) patients who discontinued study medication, discontinued from the study (placebo: 10; ertugliflozin 5 mg: 7; ertugliflozin 15 mg: 9).

Baseline demographics and characteristics were similar across treatment groups (Table 1). Overall, 55.5% of patients were male with a mean age (SD) of 56.5 (9.1) years and a mean duration of T2DM of 7.0 (5.1) years. The majority of patients were enrolled in mainland China (80.2%). Baseline HbA1c, FPG and eGFR values were similar across treatment groups. At baseline, mean HbA1c (SD) was 8.1% (0.9) [65.2 (10.1) mmol/mol] and eGFR was 99.3 mL/min/1.73 m^2. The mean duration of T2DM and the proportion of patients on background AHA therapy at screening were similar across the treatment groups. The median metformin dose at randomization was 1500 mg/day for the ertugliflozin and placebo groups with 69.4% of patients on 1500 mg/day at randomization. The baseline demographics and characteristics of patients in the China subpopulation were similar to the overall population and were similar across treatment groups (Supporting Information Table S2).

3.2 | Efficacy

3.2.1 | Overall population

The placebo-adjusted, least squares (LS) mean reduction (95% CI) from baseline in HbA1c at week 26 was −0.8% (−1.0, −0.6) with ertugliflozin 5 mg and −0.7% (−0.9, −0.5) with ertugliflozin 15 mg

TABLE 1 Baseline demographics and characteristics of overall population

	Placebo (n = 167)	Ertugliflozin 5 mg (n = 170)	Ertugliflozin 15 mg (n = 169)	Total (N = 506)
Male, n (%)	88 (52.7)	95 (55.9)	98 (58.0)	281 (55.5)
Age, y	56.9 (9.0)	56.1 (9.0)	56.3 (9.3)	56.5 (9.1)
Age ≥65 y, n (%)	35 (21.0)	28 (16.5)	34 (20.1)	97 (19.2)
Duration of T2DM, y	6.4 (5.1)	7.0 (5.0)	7.5 (5.1)	7.0 (5.1)
Distribution of metformin dose at randomization, n (%)				
1500	113 (67.7)	118 (69.4)	120 (71.0)	351 (69.4)
>1500 and <2000	8 (4.8)	10 (5.9)	8 (4.7)	26 (5.1)
2000	43 (25.7)	35 (20.6)	40 (23.7)	118 (23.3)
>2000 and <3000	3 (1.8)	4 (2.4)	0 (0.0)	7 (1.4)
3000	0 (0.0)	3 (1.8)	1 (0.6)	4 (0.8)
Background AHA therapy at screening,[a] n (%)				
Alpha glucosidase inhibitors	8 (4.8)	11 (6.5)	4 (2.4)	23 (4.5)
Biguanides	167 (100.0)	170 (100.0)	169 (100.0)	506 (100.0)
DPP-4 inhibitors	1 (0.6)	3 (1.8)	5 (3.0)	9 (1.8)
Meglitinide	7 (4.2)	11 (6.5)	5 (3.0)	23 (4.5)
Sulphonylurea	30 (18.0)	34 (20.0)	34 (20.1)	98 (19.4)
Number of agents				
1	121 (72.5)	111 (65.3)	121 (71.6)	353 (69.8)
2	46 (27.5)	59 (34.7)	48 (28.4)	153 (30.2)
Country, n (%)				
China	135 (80.8)	136 (80.0)	135 (79.9)	406 (80.2)
Other	32 (19.2)	34 (20.0)	34 (20.1)	100 (19.8)
Hong Kong	7 (4.2)	10 (5.9)	10 (5.9)	27 (5.3)
Korea, Republic of	9 (5.4)	13 (7.6)	10 (5.9)	32 (6.3)
Philippines	8 (4.8)	7 (4.1)	8 (4.7)	23 (4.5)
Taiwan	8 (4.8)	4 (2.4)	6 (3.6)	18 (3.6)
Body weight, kg	70.1 (12.4)	71.4 (11.1)	69.5 (10.9)	70.3 (11.5)
BMI, kg/m^2	26.1 (3.4)	26.0 (2.8)	25.7 (3.2)	26.0 (3.2)
Baseline HbA1c, %	8.1 (1.0)	8.1 (0.9)	8.1 (0.9)	8.1 (0.9)
Baseline FPG, mg/dL	165.8 (37.6)	170.1 (36.0)	167.3 (41.1)	167.8 (38.3)
Baseline eGFR, mL/min/1.73 m^2	99.9 (20.2)	97.9 (19.2)	100.2 (19.8)	99.3 (19.7)
30 to <60, n (%)	3 (1.8)	2 (1.2)	3 (1.8)	8 (1.6)
60 to <90, n (%)	48 (28.7)	56 (32.9)	50 (29.6)	154 (30.4)
≥90, n (%)	116 (69.5)	112 (65.9)	116 (68.6)	344 (68.0)

Abbreviations: AHA, antihyperglycaemic agents; BMI, body mass index; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; SD, standard deviation; T2DM, type 2 diabetes mellitus.
Data presented are mean (SD) unless otherwise stated.
[a]Combination blood glucose-lowering agents were counted twice, under each component of the combination.

($P < 0.001$ for both comparisons with placebo; Table 2, Figures 1 and 2A). More patients who received ertugliflozin 5 mg (38.2%) and 15 mg (40.8%) compared with placebo (16.2%) had HbA1c <7.0% (53 mmol/mol) at week 26 (Figure 2B). The model-based odds of having an HbA1c <7.0% (53 mmol/mol) at week 26 were significantly greater with ertugliflozin relative to placebo ($P < 0.001$ for both comparisons). More patients who received ertugliflozin 5 mg (14.7%) and 15 mg (15.4%) compared with placebo (2.4%) had HbA1c <6.5% (48 mmol/mol) at week 26. The model-based odds of having an HbA1c <6.5% (48 mmol/mol) at week 26 were greater with ertugliflozin compared with placebo (nominal $P = 0.001$ and nominal $P < 0.001$ for ertugliflozin 15 mg and ertugliflozin 5 mg, respectively). Both ertugliflozin doses provided significantly greater reductions from baseline in FPG (Figure 2C), body weight (Figure 2D) and systolic BP (Figure 2E) compared with placebo ($P < 0.001$ for both comparisons). The LS mean reductions from baseline at week 26 in diastolic BP were greater with ertugliflozin compared with placebo, but the differences were not statistically significant (Figure 2F). By week 26, a larger proportion of patients in the placebo group (9.6%) had received glycaemic rescue therapy compared with the ertugliflozin groups (both <1.2%).

3.2.2 | China subpopulation

The placebo-adjusted, LS mean reduction (95% CI) from baseline in HbA1c at week 26 was −0.8% (−1.0, −0.6) with ertugliflozin 5 mg and −0.7% (−0.9, −0.5) with ertugliflozin 15 mg ($P < 0.001$ for both

TABLE 2 Change from baseline in HbA1c at week 26 for overall population

	Baseline		Week 26		Change from baseline at week 26		
Treatment	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	LS mean (95% CI)[a]
Placebo	166	8.1 (1.0)	132	7.7 (1.0)	167	−0.2 (0.8)	−0.2 (−0.3, −0.1)
Ertugliflozin 5 mg	169	8.1 (0.9)	155	7.1 (0.8)	170	−1.0 (0.9)	−1.0 (−1.1, −0.9)
Ertugliflozin 15 mg	169	8.1 (0.9)	153	7.2 (0.8)	169	−0.9 (0.8)	−0.9 (−1.0, −0.8)
Pairwise comparison			Difference in LS means (95% CI)[a]				*P*-value
Week 26 ertugliflozin 5 mg vs. placebo			−0.8 (−1.0, −0.6)				<0.001
Week 26 ertugliflozin 15 mg vs. placebo			−0.7 (−0.9, −0.5)				<0.001

Abbreviations: AHA, antihyperglycaemic agents; CI, confidence interval; cLDA, constrained longitudinal data analysis; eGFR, estimated glomerular filtration rate; LS, least squares; SD, standard deviation.
For baseline and week 26, n was the number of patients with non-missing assessments at the specific timepoint; for change from baseline at week 26, n was the number of randomized patients who took at least one dose of study medication and had at least one assessment at or after baseline. The mean and SD for the change from baseline are based on non-missing values.
[a]Based on a cLDA model with fixed effects for treatment, time, prior antihyperglycaemic medication (metformin monotherapy or metformin plus another AHA), country (China or other), baseline eGFR (continuous), and the interaction of time by treatment. Time was treated as a categorical variable.

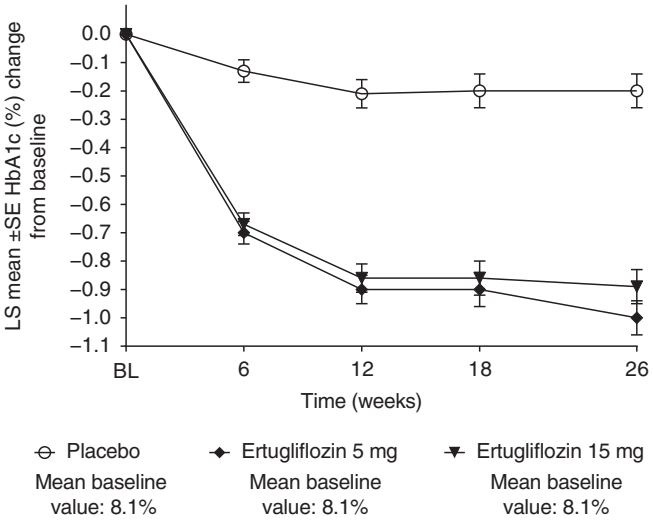

FIGURE 1 Least squares mean change from baseline in HbA1c over time for overall population. Based on cLDA model with fixed effects for treatment, time, antihyperglycaemic medication status at screening, baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable. cLDA, constrained longitudinal data analysis; eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error

comparisons with placebo; Supporting Information Table S3, Figures S2 and S3A). More patients who received ertugliflozin 5 mg (35.3%) and 15 mg (42.2%) compared with placebo (18.5%) had HbA1c <7.0% (53 mmol/mol) at week 26 (Supporting Information Figure S3B). The model-based odds of having an HbA1c <7.0% (53 mmol/mol) at week 26 were greater with ertugliflozin relative to placebo (nominal $P < 0.001$ for both comparisons). More patients who received ertugliflozin 5 mg (14.7%) and 15 mg (17.0%) compared with placebo (3.0%) had HbA1c <6.5% (48 mmol/mol) at week 26. The model-based odds of having an HbA1c <6.5% (48 mmol/mol) at week 26 were greater with ertugliflozin compared with placebo (nominal $P < 0.001$ for both comparisons). Both ertugliflozin doses provided significantly greater reductions from baseline in FPG and body weight compared with placebo (Supporting Information Figure S3C, D). The LS mean reductions from baseline at week 26 in systolic BP and diastolic BP were greater with ertugliflozin compared with placebo (Supporting Information Figure S3E, F).

3.3 | Safety

3.3.1 | Overall AE summary

The overall incidence of AEs and drug-related AEs was similar across the treatment groups (Table 3). The incidence of SAEs was higher with ertugliflozin than with placebo (Table 3). No SAEs were considered drug-related with ertugliflozin. One SAE in the placebo group was reported as drug-related by the investigator. The incidence of AEs resulting in discontinuation from study medication was low (<2% of patients in any group). No deaths occurred between the first dose of treatment and 14 days after the final dose of treatment in the study; one death occurred in the China subpopulation in the postrandomization follow-up period (i.e. >14 days after the last dose of study medication). The patient, treated with ertugliflozin 15 mg, was diagnosed with metastatic lung cancer 20 days after the last dose of study medication and died 71 days after the last dose of study medication. There were no confirmed cases of diabetic ketoacidosis in the study population. The incidence of AEs, drug-related AEs, SAEs and discontinuations across treatment groups was similar in the China subpopulation (Supporting Information Table S4).

3.3.2 | Tier 1 AEs/AEs of special interest

The incidence of GMIs was low and similar across treatment groups (Table 3). No patients experienced a complicated genital infection and no GMI AEs led to discontinuation of study medication. The incidence of UTI AEs was similar across groups (Table 3). All UTI AEs were non-serious. No patients experienced a complicated UTI and no UTI AEs led to discontinuation of study medication. The incidence of symptomatic hypoglycaemia was low across the groups, but significantly higher with ertugliflozin 15 mg compared with placebo in the overall population (4.7% vs. 0.6%, $P = 0.019$). The incidence of documented hypoglycaemia [episodes with a glucose level ≤70 mg/dL (≤3.9 mmol/L) with or without symptoms] was higher with ertugliflozin compared with placebo (Table 3). There were no cases of severe hypoglycaemia. The incidence of

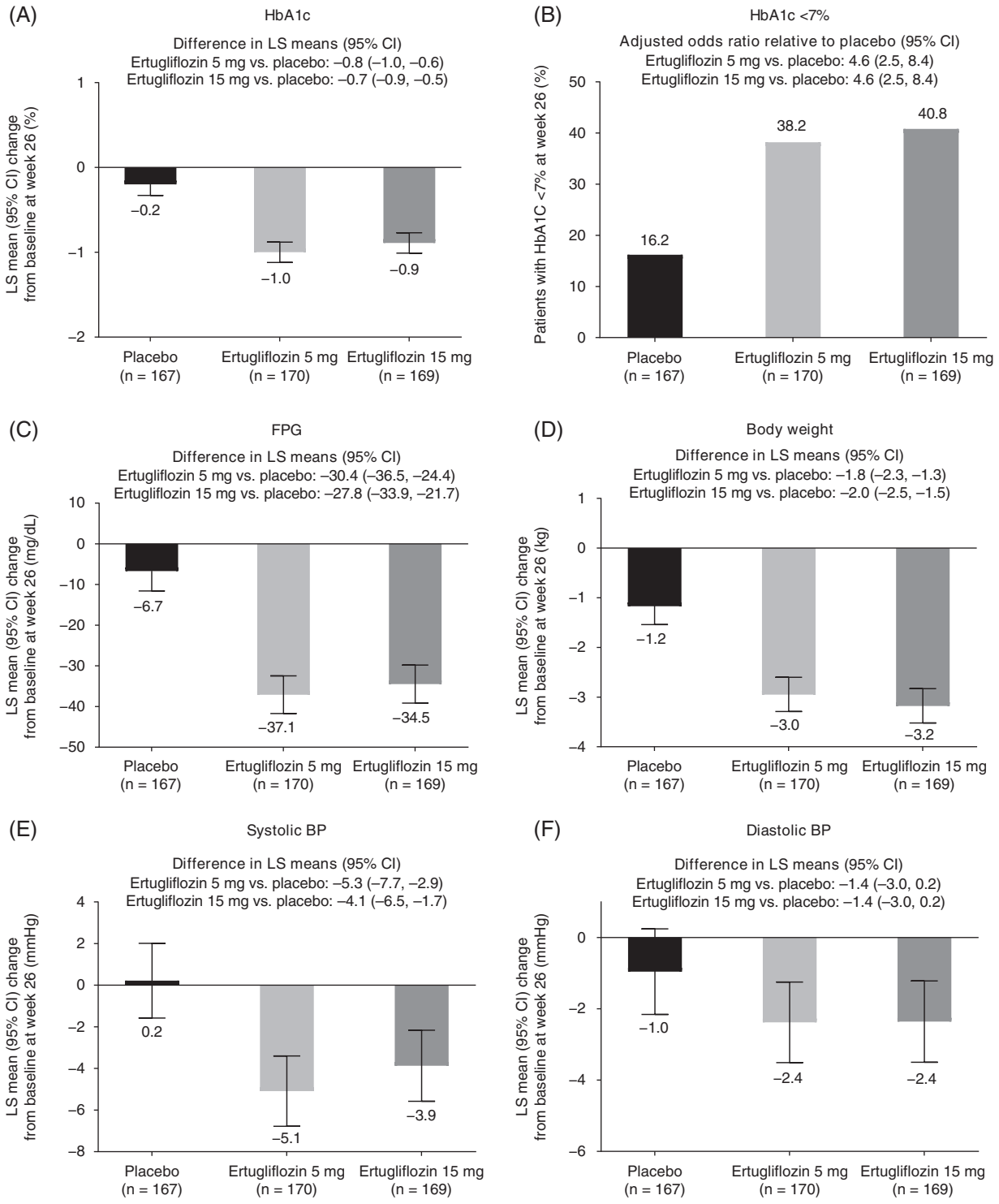

FIGURE 2 Efficacy outcomes in overall population: A, least squares mean change from baseline in HbA1c at week 26; B, proportion of patients with HbA1c <7% at week 26; C, LS mean change from baseline in FPG at week 26; D, LS mean change from baseline in body weight at week 26; E, LS mean change from baseline in systolic BP at week 26; F, LS mean change from baseline in diastolic BP at week 26; BP, blood pressure; CI, confidence interval; FPG, fasting plasma glucose; LS, least squares

hypovolaemia was low across treatment groups. The incidence of Tier 1 AEs across treatment groups for the China subpopulation was generally similar to the overall subpopulation (Supporting Information Table S4).

3.3.3 | Laboratory parameters

Changes from baseline through week 26 in relevant laboratory parameters are shown in Supporting Information Table S5.

TABLE 3 Summary of adverse events for overall population

Event, n (%)	Placebo (n = 167)	Ertugliflozin 5 mg (n = 170)	Ertugliflozin 15 mg (n = 169)
≥1 AE			
Overall	99 (59.3)	96 (56.5)	90 (53.3)
Drug-related[a]	23 (13.8)	29 (17.1)	24 (14.2)
≥1 SAE			
Overall	2 (1.2)	9 (5.3)	10 (5.9)
Drug-related[a]	1 (0.6)	0	0
Discontinuations			
Because of AE	3 (1.8)	2 (1.2)	1 (0.6)
Because of drug-related[a] AE	1 (0.6)	1 (0.6)	0
Because of SAE	0	1 (0.6)	1 (0.6)
Because of drug-related[a] SAE	0	0	0
Deaths[b]	0	0	0
Tier 1AEs			
GMI (women)	1 (1.3)	2 (2.7)	1 (1.4)
GMI (men)	1 (1.1)	2 (2.1)	2 (2.0)
UTI	4 (2.4)	3 (1.8)	2 (1.2)
Symptomatic hypoglycaemia	1 (0.6)	4 (2.4)	8 (4.7)
Hypovolaemia	1 (0.6)	0	1 (0.6)
Other selected AEs			
Documented hypoglycaemia[c]	5 (3.0)	11 (6.5)	14 (8.3)

Abbreviations: AE, adverse event; GMI, genital mycotic infection; SAE, serious adverse event; UTI, urinary tract infection.
For all AEs, this table contains events that occurred between the first dose of treatment and 14 d after the final dose of treatment.
[a]Assessed as related to the study drug by the investigator.
[b]No deaths occurred between the first dose of treatment and 14 d after the final dose of treatment in the study; there was one death in the China subpopulation in the all postrandomization follow-up period (>14 d after the last dose of study medication). The patient, treated with ertugliflozin 15 mg, was diagnosed with metastatic lung cancer 20 d after the last dose of study medication and died 71 d after the last dose of study medication.
[c]Episodes with a glucose level ≤70 mg/dL (≤3.9 mmol/L) with or without symptoms.

4 | DISCUSSION

Ertugliflozin 5 and 15 mg once daily in addition to metformin monotherapy over 26 weeks significantly improved glycaemic control and reduced body weight and systolic BP in Asian patients with T2DM. Treatment with ertugliflozin also resulted in significant improvements relative to placebo in other glycaemic measures, including FPG, and in the proportion of patients with HbA1c <7% (53 mmol/mol).

Both the 5 mg and 15 mg doses of ertugliflozin were evaluated in the global phase III programme.[15,16,18–22,24] Ertugliflozin 5 mg and 15 mg provide effects on urinary glucose excretion and HbA1c that are >80% and >90% of the maximum response for these endpoints, respectively.[25] In a pooled analysis of three placebo-controlled studies, ertugliflozin 15 mg produced incremental HbA1c lowering of 0.15% relative to ertugliflozin 5 mg.[26] One of the studies included in this pooled analysis evaluated ertugliflozin added to metformin monotherapy, and showed placebo-adjusted changes in HbA1c of −0.70% and −0.88% for ertugliflozin 5 mg and 15 mg, respectively.[15] On the basis of the results from the phase III programme, the approved ertugliflozin labelling in the United States and EU recommends a starting dose of 5 mg, increasing to 15 mg if therapy is well-tolerated and if additional glycaemic control is needed.[11,14]

In the current study, the efficacy on HbA1c was similar between ertugliflozin 5 mg and 15 mg but the estimated mean was ~0.1% greater for ertugliflozin 5 mg relative to ertugliflozin 15 mg in both the overall population and China subpopulation. A pooled analysis of three other placebo-controlled studies (N = 1544) assessing the efficacy and safety of ertugliflozin by race showed no notable differences in HbA1c, body weight and SBP reductions between racial subgroups.[27] In the analysis, the placebo-adjusted LS mean change (95% CI) in HbA1c at week 26 was −0.8% (−1.1, −0.5) with ertugliflozin 5 mg and −1.0% (−1.3, −0.8) with ertugliflozin 15 mg for Asian patients (n = 221). The results from the current study in Asian patients may therefore reflect a stochastic finding given that both ertugliflozin 5 mg and 15 mg are near the top end of the dose–response curve.

In addition, in this current study of Asian patients, both the point estimates of the reduction in body weight and the proportion of patients with HbA1c <7.0% (53 mmol/mol) at week 26 were greater for ertugliflozin 15 mg relative to 5 mg in both the overall population and the China subpopulation.

The baseline patient characteristics in the current study are typical of an Asian population, with mean weight and BMI lower than in VERTIS MET, a previous study of ertugliflozin in a Western population.[15] Despite this lower mean baseline weight, ertugliflozin resulted in significantly greater reductions in body weight with a magnitude similar to that observed in the overall phase III programme, and significantly greater reductions from baseline in systolic BP at week 26 relative to placebo, showing that ertugliflozin reduces body weight in populations with lower mean BMI as well as in populations with higher BMIs.[15]

Ertugliflozin was generally well-tolerated in the overall population and China subpopulation. The incidence of UTI, GMIs and hypovolaemia-related AEs was low and similar across treatment groups in both the overall population and China subpopulation. An increased incidence of GMIs is often observed with SGLT2 inhibitors because of the associated glucosuria. In a pooled analysis of three placebo-controlled studies, ertugliflozin increased the incidence of GMIs.[26] In the current study, the similar incidence of GMI with ertugliflozin and placebo could reflect a chance finding given the sample size in the study and prior available data with ertugliflozin and other SGLT2 inhibitors. In the overall population, the incidence of symptomatic hypoglycaemia and episodes of documented hypoglycaemia were higher with ertugliflozin 15 mg compared with placebo. However, the number of patients with symptomatic hypoglycaemia was low (ertugliflozin 5 mg: 4; ertugliflozin 15 mg: 8). Therefore, these differences were not deemed to be clinically meaningful. Hypoglycaemia results for the China subpopulation were generally similar to the overall population.

The majority of patients (80%) included in this study were residents of mainland China. Efficacy and safety results in the China subpopulation were similar to the overall study population. In the China subpopulation, ertugliflozin added once daily to metformin monotherapy over 26 weeks significantly improved glycaemic control and

reduced body weight. Clinically meaningful improvements were observed in other endpoints including the proportion of patients with HbA1c <7% (53 mmol/mol) and reductions in systolic BP and diastolic BP.

In conclusion, in Asian patients with T2DM and inadequate glycaemic control on metformin monotherapy, the addition of ertugliflozin (15 mg and 5 mg) improves glycaemic control and reduces body weight and BP over 26 weeks. Ertugliflozin treatment was associated with a significantly greater proportion of patients achieving HbA1c <7% (53 mmol/mol) relative to placebo. Ertugliflozin was generally well-tolerated. Efficacy and safety results in the China subpopulation were consistent with the overall population.

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CONFLICT OF INTEREST

L.J., Y.L., H.M. and Y.X. declare no conflicts of interest. Y.M. is an employee of Pfizer (China) R&D Co. S.P. and S.G.T. are employees of Pfizer Inc. S.L. is an employee of MSD China. S.H. is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. M.Y., P.Y. and W.W. were employees of Pfizer (China) R&D Co. at the time of study conduct. B.L. and Y.Q. were employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, at the time of study conduct. S.G.T. owns stocks in Pfizer Inc. S.P., M.Y., Y.M. and P.Y. own stocks in Pfizer (China) R&D Co., and S.H. owns stocks in Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc, Kenilworth, NJ, USA.

Author contributions

All authors critically reviewed the draft manuscript and approved the final version of the manuscript for publication. M.Y., W.W., Y.M., S.P., P.Y. and S.G.T. were involved in the conception/design of the study. L.J., Y.L., H.M. and Y.X. were involved in the acquisition of data for the study. All authors were involved in data analysis and interpretation of the data.

Data accessibility

Upon request, and subject to certain criteria, conditions and exceptions (see www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (a) for indications that have been approved in the United States and/or EU or (b) in programs that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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REFERENCES

1. International Diabetes Federation. *IDF Diabetes Atlas*. 8th ed. Brussels, Belgium: International Diabetes Federation; 2017.
2. Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. *JAMA*. 2013;310:948-959.
3. Li H, Oldenburg B, Chamberlain C, et al. Diabetes prevalence and determinants in adults in China mainland from 2000 to 2010: a systematic review. *Diabetes Res Clin Pract*. 2012;98:226-235.
4. Fitchett D, Inzucchi SE, Lachin JM, et al. Cardiovascular mortality reduction with empagliflozin in patients with type 2 diabetes and cardiovascular disease. *J Am Coll Cardiol*. 2018;71:364-367.
5. El Masri D, Ghosh S, Jaber LA. Safety and efficacy of sodium-glucose cotransporter 2 (SGLT2) inhibitors in type 1 diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2018;137:83-92.
6. Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Sodium-glucose co-transporter-2 inhibitors as add-on therapy to insulin for type 1 diabetes mellitus: systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2018;20:1755-1761.
7. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab*. 2016;18:783-794.
8. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes*. 2017;24:73-79.
9. Kalgutkar AS, Tugnait M, Zhu T, et al. Preclinical species and human disposition of PF-04971729, a selective inhibitor of the sodium-dependent glucose cotransporter 2 and clinical candidate for the treatment of type 2 diabetes mellitus. *Drug Metab Dispos*. 2011;39:1609-1619.
10. Miao Z, Nucci G, Amin N, et al. Pharmacokinetics, metabolism, and excretion of the antidiabetic agent ertugliflozin (PF-04971729) in healthy male subjects. *Drug Metab Dispos*. 2013;41:445-456.
11. FDA. Steglatro (ertugliflozin) *Prescribing Information*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209803s000lbl.pdf. Accessed March 2019.
12. EMA. Ertugliflozin (Steglatro) *Summary of Product Characteristics*. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004315/WC500246918.pdf. Accessed March 2019.
13. CADTH. *CADTH Common Drug Review Submissions*. https://www.cadth.ca/ertugliflozin. Accessed February 2019.
14. Australian Government Department of Health. *Prescription Medicines: Registration of New Chemical Entities in Australia*. https://www.tga.gov.au/prescription-medicines-registration-new-chemical-entities-australia. Accessed February 2019.
15. Rosenstock J, Frias J, Pall 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 Obes Metab*. 2018;20:520-529.
16. Pratley RE, Eldor R, Raji A, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: the VERTIS FACTORIAL randomized trial. *Diabetes Obes Metab*. 2018;20:1111-1120.

17. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2018 executive summary. *Endocr Pract*. 2018;24:91-120.
18. Miller S, Krumins T, Zhou H, et al. Ertugliflozin and sitagliptin co-initiation in patients with type 2 diabetes: the VERTIS SITA randomized study. *Diabetes Ther*. 2018;9:253-268.
19. Grunberger G, Camp S, Johnson J, et al. Ertugliflozin in patients with stage 3 chronic kidney disease and type 2 diabetes mellitus: the VERTIS RENAL randomized study. *Diabetes Ther*. 2018;9:49-66.
20. Aronson R, Frias J, Goldman A, Darekar A, Lauring B, Terra SG. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. *Diabetes Obes Metab*. 2018;20:1453-1460.
21. Terra SG, Focht K, Davies M, 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 Obes Metab*. 2017;19:721-728.
22. Hollander P, Liu J, Hill J, et al. Ertugliflozin compared with glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin: the VERTIS SU randomized study. *Diabetes Ther*. 2018;9:193-207.
23. Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med*. 1985;4:213-226.
24. Dagogo-Jack S, Liu J, Eldor R, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: the VERTIS SITA2 placebo-controlled randomized study. *Diabetes Obes Metab*. 2018;20:530-540.
25. Amin NB, Wang X, Jain SM, Lee DS, Nucci G, Rusnak JM. Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. *Diabetes Obes Metab*. 2015;17:591-598.
26. Liu J, Tarasenko L, Terra SG, et al. Effects of ertugliflozin in monotherapy or combination therapy in patients with type 2 diabetes: a pooled analysis of placebo-controlled studies. *Diab Vasc Dis Res*. 2019. In press.
27. Liu J, Pong A, Huyck S, et al. Efficacy and safety of ertugliflozin across racial groups in patients with type 2 diabetes mellitus. *Diabetes*. 2018;67(Supplement 1):1132-P.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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