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.

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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. The insulin-independent mechanism enables their use across the natural progression of T2DM.

Ertugliflozin, a selective inhibitor of SGLT2, is currently approved in the United States, the European Union (EU) and other regions including Canada and Australia, 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. 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 dose 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) 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/m². 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 m² 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.

#### 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 AEIs 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.

### 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 m². 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.
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%).

### 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 comparisons). 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

### 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 | 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/m²    | 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 m² | 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.

*aCombination blood glucose-lowering agents were counted twice, under each component of the combination.*
TABLE 2  Change from baseline in HbA1c at week 26 for overall population

| Treatment          | Baseline n | Mean (SD) | Week 26 n | Mean (SD) | Change from baseline at week 26 n | Mean (SD) | LS mean (95% CI)* |
|--------------------|------------|-----------|-----------|-----------|----------------------------------|-----------|-------------------|
| 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)² | 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.

²Based 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.

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 genitourinary 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
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.
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. 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.

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. 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.

ACKNOWLEDGMENTS
This study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, in collaboration with Pfizer Inc., New York, NY, USA. Editorial support was provided by Marion James, PhD, of Engage Scientific Solutions (Horsham, UK) and was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, in collaboration with Pfizer Inc., New York.

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., a subsidiary 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., New York, NY, USA. K.L. was an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, at the time of study conduct. P.Y. and S.G.T. were involved in the conception/design of the study. B.L. and Y.C. were involved in the acquisition of data for the study. All authors were involved in data analysis and interpretation of the data.

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

How to cite this article: Ji L, Liu Y, Miao H, et al. Safety and efficacy of ertugliflozin in Asian patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: VERTIS Asia. Diabetes Obes Metab. 2019;21:1474-1482. https://doi.org/10.1111/dom.13681