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# Efficacy and safety of ertugliflozin in patients with type 2 diabetes mellitus and established cardiovascular disease using insulin: A VERTIS CV substudy

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## Abstract

**Aim:** To assess the efficacy and safety of ertugliflozin in patients with type 2 diabetes mellitus (T2DM) and established atherosclerotic cardiovascular disease (ASCVD) inadequately controlled by insulin.

**Materials and methods:** VERTIS CV was the cardiovascular outcome study for ertugliflozin. Patients were randomly assigned to placebo, or ertugliflozin 5 mg or 15 mg once daily. We report the results of a substudy in patients on a stable dose of insulin ≥20 units/d. The primary endpoint was glycated haemoglobin (HbA1c) change from baseline to 18 weeks. Secondary endpoints were changes in fasting plasma glucose (FPG), body weight (BW), the proportion of patients with HbA1c <53 mmol/mol (<7%), systolic blood pressure (SBP), diastolic blood pressure and insulin dose.

**Results:** Of 8246 patients randomized in VERTIS CV, 1065 were included in the substudy (68.2% men, mean [SD] age 64.8 [7.8] years, T2DM duration 16.7 [9.0] years, HbA1c 8.4 [1.0]%). At week 18, the least squares (LS) mean change from baseline in HbA1c was significantly greater with ertugliflozin 5 mg and 15 mg versus placebo (placebo-adjusted LS mean change −0.58%, 95% confidence interval [CI] −0.71, −0.44 and −0.65%, 95% CI −0.78, −0.51, respectively; $P < 0.001$ for both). Ertugliflozin significantly reduced FPG, BW and SBP. In women, the incidence of genital mycotic infections was higher with ertugliflozin (3.5%) versus placebo (0.0%). The incidence of symptomatic hypoglycaemia was similar across treatment groups.

**Conclusions:** Ertugliflozin added to insulin improved glycaemic control, BW and SBP versus placebo at 18 weeks in patients with T2DM and ASCVD.

KEYWORDS
cardiovascular disease, glycaemic control, insulin therapy, SGLT2 inhibitor, type 2 diabetes

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## 1 | INTRODUCTION

Disease progression in patients with type 2 diabetes mellitus (T2DM) often leads to combination therapy with oral glucose-lowering agents[1] and may ultimately require insulin therapy as a single agent or with other glucose-lowering agents, to maintain glucose control.[2]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a potentially attractive add-on treatment for patients with T2DM inadequately controlled on insulin alone or in combination with metformin. Unlike insulin, SGLT2 inhibitors are not associated with hypoglycaemia when administered as monotherapy or when coadministered with other agents that by themselves do not cause hypoglycaemia.[3] Treatment with SGLT2 inhibitors is also associated with modest reductions in body weight (BW) and blood pressure in patients with T2DM.[4] Diabetes duration is typically longer among patients using insulin.[2] Longer disease duration is associated with a higher risk of end-organ damage, for example, cardiovascular (CV) disease and chronic kidney disease.[5,6] In addition to providing glycaemic control, large outcome studies have demonstrated that SGLT2 inhibitors reduce the risk of CV events, including hospitalization for heart failure, and preserve renal function.[7–13] The effects of the SGLT2 inhibitor ertugliflozin on cardiorenal outcomes in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD) have been assessed in the VERTIS (e**V**aluation of **ERT**ugliflozin eff**I**cacy and **S**afety) CV study.[13–15] In VERTIS CV, approximately 50% of patients were taking insulin at baseline and, in other SGLT2 inhibitor CV outcome studies, 40% to 50% of patients were on insulin at baseline.[7–9,13] Those percentages suggest that substantial numbers of patients with T2DM with or at high risk of ASCVD and kidney events who are using insulin in real-world clinical settings may need additional glycaemic control. Studies have indicated that approximately two-thirds of patients with T2DM treated with basal insulin fail to achieve optimal glycaemic control after 12 months of treatment,[16–18] which suggests a need for additional therapeutic strategies. The present report evaluates glycaemic and cardiometabolic efficacy and safety of ertugliflozin, added to insulin-based therapy, in patients with T2DM and ASCVD inadequately controlled by insulin in an 18-week substudy of VERTIS CV. Assessments of cardiorenal endpoints, which require longer duration of follow-up, were not objectives of the substudy and were previously reported.[13]

## 2 | MATERIALS AND METHODS

VERTIS CV (ClinicalTrials.gov identifier: NCT01986881) was a multicentre, randomized, double-blind, placebo-controlled, parallel-group, event-driven, phase III trial that included a main CV outcomes study and three glycaemic substudies.[13,19] VERTIS CV enrolled two sequential cohorts; it was initiated in 2013 and amended in March 2016, without knowledge of any interim results, to increase the patient population from ~4000 to 8000 to provide sufficient power to evaluate cardiorenal endpoints. Overall, 8246 patients with T2DM and ASCVD were randomized to placebo, or ertugliflozin 5 mg or 15 mg. This 18-week substudy included patients from Cohort 1 on insulin (≥20 units/d). The primary objective was to evaluate the effect of ertugliflozin versus placebo on glycated haemoglobin (HbA1c) and to evaluate ertugliflozin safety and tolerability. Secondary objectives were to evaluate the effect of ertugliflozin on fasting plasma glucose (FPG), BW, the proportion of patients with HbA1c <53 mmol/mol (7%), systolic blood pressure (SBP), diastolic blood pressure (DBP) and insulin dose.

### 2.1 | Study design

On day 1 (randomization), patients were randomly assigned (1:1:1) to oral, once-daily ertugliflozin 5 mg, ertugliflozin 15 mg or placebo, with stratification by substudy and geographic region, using a computer-generated randomization code.

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 Council for Harmonization Good Clinical Practice Guidelines. Written informed consent was obtained from all participants.

### 2.2 | Patient population and treatments

Participants in the VERTIS CV trial were eligible if they were age ≥40 years with T2DM (HbA1c 53-91 mmol/mol [7.0%-10.5%], inclusive), and had stable, established ASCVD involving the coronary, cerebrovascular and/or peripheral arterial systems. The specific inclusion and exclusion criteria and the overall VERTIS CV trial design have been previously published.[19] A subset of patients who were receiving insulin ≥20 units/d with or without metformin ≥1500 mg/d and no other glucose-lowering agents were included in this substudy. The protocol required patients to have a stable insulin dose for ≥8 weeks prior to screening and to maintain the same dose for the 18-week duration of the substudy to enable the assessment of the glycaemic effects of ertugliflozin. Insulin total daily dose variations of ±10% during the 8 weeks prior to the screening visit or during the period between the screening visit and randomization were permitted and fulfilled the criterion of stable insulin therapy. Patients using prandial insulin alone were excluded. During the 18-week substudy, changes to the background glucose-lowering treatment were not allowed except when patients met predefined glycaemic rescue thresholds or were experiencing clinically significant hypoglycaemia. The initiation of glycaemic rescue therapy was defined as a change in background glucose-lowering treatment during the first 18 weeks of the substudy that consisted of an increase from baseline in the dose of an existing glucose-lowering agent, or in the addition of a new glucose-lowering agent or a >10% increase in insulin dose, even if the patient did not meet the glycaemic rescue criteria.

## 2.3 | Efficacy assessments

Efficacy assessments were performed at weeks 0 (baseline), 6, 12 and 18. Laboratory assessments were performed at a central laboratory. BW 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 events (AEs), serious AEs (SAEs), deaths and discontinuations because of AEs. Genital mycotic infection (GMI) by gender, urinary tract infection (UTI), symptomatic hypoglycaemia (an event with clinical symptoms reported by the investigator as hypoglycaemia) and hypovolaemia were prespecified AEs of special interest (Tier 1 AEs). For the Tier 1 analysis, AEs of UTIs, GMIs, and hypovolaemia were identified by prespecified sponsor-generated customized MedDRA queries of preferred terms. Tier 2 AEs were those that were not Tier 1 but occurred in ≥4 patients in any treatment arm. Other AEs of interest included documented hypoglycaemia (episodes with a glucose level ≤3.9 mmol/L [70 mg/dL]) and severe hypoglycaemia (episodes that required medical or non-medical assistance, regardless of biochemical documentation). Safety data were reviewed by an external data monitoring committee.

## 2.5 | Statistical methods

The sample size was estimated based on the primary outcome of reduction in HbA1c from baseline at week 18. A planned sample size of 450 patients (150 per group) would provide approximately 98% power (at a two-sided 0.05 alpha level) to detect a true difference of 0.5% in HbA1c reduction from baseline to week 18 between each ertugliflozin dose and placebo, assuming a standard deviation (SD) of 1.0% and a loss to follow-up rate of 10%. With the actual sample size of 1065, the power was >99%.

### 2.5.1 | Patient disposition and baseline characteristics

Demographic and baseline disease characteristics were summarized descriptively in the all-subjects-as-treated population.

### 2.5.2 | Analysis of efficacy endpoints

The primary analysis set for efficacy was the full analysis set, which included all randomized patients who received ≥1 dose of study medication and had ≥1 baseline or post-baseline measurement of the respective endpoint. In the primary analysis approach, efficacy data obtained after the initiation of glycaemic rescue therapy were censored (treated as missing) with the exception of change from baseline in insulin dose and the proportion of patients receiving glycaemic rescue therapy. Sensitivity analyses included data obtained after the initiation of glycaemic rescue therapy.

Changes from baseline at week 18 were assessed using a longitudinal data analysis model that included terms for treatment, visit (categorical), treatment by visit interaction, baseline estimated glomerular filtration rate (eGFR; continuous) and metformin use (binary: yes/no), with mean baseline values constrained to be the same across treatment groups. A logistic regression analysis was used to evaluate the proportion of patients with HbA1c <53 mmol/mol (7.0%) at week 18. The statistical model included terms for treatment, baseline HbA1c, metformin use (binary: yes/no) and baseline eGFR (continuous). For the proportion of patients with HbA1c <53 mmol/mol (7.0%) at week 18, missing data at week 18 were imputed via a multiple imputation procedure based on the longitudinal data analysis model. The proportion of patients requiring glycaemic rescue therapy up to week 18 was analysed using log-rank tests comparing the time-to-event distribution of each dose of ertugliflozin versus placebo. HbA1c reduction from baseline at week 18 was assessed in subgroups, including those based on baseline HbA1c, age, sex and antidiabetic medication use at randomization (insulin ± metformin) using a repeated measures analysis of covariance model.

A stepdown hierarchy approach was used to control the type I error rate across key efficacy endpoints in the following order: HbA1c, FPG, BW, HbA1c <53 mmol/mol (7.0%), SBP and DBP. For each endpoint, the 15-mg dose was tested versus placebo first, followed by the 5-mg dose versus placebo if a statistically significant result was achieved for the 15-mg dose.

### 2.5.3 | Analysis of safety endpoints

Safety analyses used the all-subjects-as-treated population and, with the exception of hypoglycaemia, used the including-rescue approach. For the Tier 1 AEs, the incidence, risk difference, 95% confidence intervals (CIs) and *P* values (not adjusted for multiplicity) were computed. For Tier 2 AEs, 95% CIs were computed. The incidences of all AEs and the AEs resulting in discontinuation from study medication were also summarized. Changes from baseline in lipids were analysed using the longitudinal data analysis method, except for triglyceride levels which were analysed using multiple imputation of missing values together with a robust regression approach.

# 3 | RESULTS

## 3.1 | Patient disposition and baseline characteristics

Of 8246 patients randomized to VERTIS CV, 1065 with T2DM and ASCVD were included in the substudy (Figure S1). Overall, 979 patients (91.9%) completed the 18-week follow-up period on

**TABLE 1** Baseline demographics and characteristics

| | Placebo (n = 347) | Ertugliflozin 5 mg (n = 348) | Ertugliflozin 15 mg (n = 370) | Total (N = 1065) |
|---|---|---|---|---|
| Men, n (%) | 237 (68.3) | 229 (65.8) | 260 (70.3) | 726 (68.2) |
| Age, years | 64.8 (8.0) | 64.6 (7.6) | 65.0 (7.8) | 64.8 (7.8) |
| Age ≥65 years, n (%) | 184 (53.0) | 176 (50.6) | 197 (53.2) | 557 (52.3) |
| Race, n (%) | | | | |
| White | 306 (88.2) | 294 (84.5) | 334 (90.3) | 934 (87.7) |
| Asian | 15 (4.3) | 20 (5.7) | 14 (3.8) | 49 (4.6) |
| Black | 14 (4.0) | 20 (5.7) | 14 (3.8) | 48 (4.5) |
| Other | 12 (3.5) | 14 (4.0) | 8 (2.2) | 34 (3.2) |
| Ethnicity, n (%) | | | | |
| Non-Hispanic/Latino | 304 (87.6) | 298 (85.6) | 329 (88.9) | 931 (87.4) |
| Hispanic/Latino | 43 (12.4) | 48 (13.8) | 40 (10.8) | 131 (12.3) |
| Unknown | 0 (0.0) | 2 (0.6) | 1 (0.3) | 3 (0.3) |
| Region, n (%) | | | | |
| Europe | 174 (50.1) | 163 (46.8) | 189 (51.1) | 526 (49.4) |
| North America | 96 (27.7) | 95 (27.3) | 99 (26.8) | 290 (27.2) |
| South America | 34 (9.8) | 38 (10.9) | 33 (8.9) | 105 (9.9) |
| South Africa | 18 (5.2) | 23 (6.6) | 19 (5.1) | 60 (5.6) |
| Asia | 13 (3.7) | 19 (5.5) | 17 (4.6) | 49 (4.6) |
| Australia/New Zealand | 12 (3.5) | 10 (2.9) | 13 (3.5) | 35 (3.3) |
| Body weight, kg | 93.1 (17.8) | 93.7 (19.0) | 92.0 (18.6) | 92.9 (18.5) |
| BMI, $kg/m^2$ | 32.5 (5.3) | 32.8 (5.5) | 32.3 (5.7) | 32.5 (5.5) |
| HbA1c, mmol/mol | 68.2 (10.1) | 68.9 (10.3) | 68.1 (10.8) | 68.4 (10.4) |
| HbA1c, % | 8.4 (0.9) | 8.5 (0.9) | 8.4 (1.0) | 8.4 (1.0) |
| FPG, mmol/L | 9.3 (2.9) | 9.6 (3.3) | 9.7 (3.3) | 9.6 (3.2) |
| FPG, mg/dL | 167.4 (51.4) | 173.8 (59.3) | 175.4 (59.5) | 172.3 (57.0) |
| Duration of T2DM, years | 17.2 (9.8) | 16.4 (8.7) | 16.4 (8.4) | 16.7 (9.0) |
| Background glucose-lowering therapy, n (%) | | | | |
| Insulin (with or without metformin) | 347 (100.0) | 348 (100.0) | 370 (100.0) | 1065 (100.0) |
| Basal-bolus | 266 (76.7) | 267 (76.7) | 273 (73.8) | 806 (75.7) |
| Premixed (intermediate-/long-acting and short-acting) insulin alone | 92 (26.5) | 81 (23.3) | 90 (24.3) | 263 (24.7) |
| Intermediate-/long-acting and separate short-acting insulin | 163 (47.0) | 164 (47.1) | 154 (41.6) | 481 (45.2) |
| Other combination/unknown | 11 (3.2) | 22 (6.3) | 29 (7.8) | 62 (5.8) |
| Basal only | 81 (23.3) | 81 (23.3) | 97 (26.2) | 259 (24.3) |
| Insulin + metformin | 209 (60.2) | 203 (58.3) | 221 (59.7) | 633 (59.4) |
| Insulin alone | 138 (39.8) | 145 (41.7) | 149 (40.3) | 432 (40.6) |
| Insulin dose (units/d) | | | | |
| Total daily dose | 73.2 (49.6) | 70.8 (44.1) | 67.3 (41.2) | 70.3 (45.1) |
| Basal-bolus | 80.8 (52.9) | 78.0 (46.0) | 75.7 (43.3) | 78.1 (47.5) |
| Premixed (intermediate-/long-acting and short-acting) insulin | 63.8 (39.2) | 68.1 (38.3) | 63.8 (34.4) | 65.2 (37.3) |
| Intermediate-/long-acting and separate short-acting insulin | 90.7 (57.8) | 83.3 (50.2) | 84.0 (48.2) | 86.0 (52.3) |
| Basal only | 48.3 (23.2) | 46.9 (25.6) | 43.7 (21.7) | 46.1 (23.5) |
| Metformin dose, mg/d | 2081.8 (437.0) | 2084.0 (467.3) | 2088.0 (417.1) | 2084.7 (439.6) |

(Continues)

**TABLE 1** (Continued)

| | Placebo (n = 347) | Ertugliflozin 5 mg (n = 348) | Ertugliflozin 15 mg (n = 370) | Total (N = 1065) |
|---|---|---|---|---|
| Median (range) | 2000 (1500, 3400) | 2000 (1500, 4050) | 2000 (1500, 3000) | 2000 (1500, 4050) |
| eGFR, mL/min/1.73 $m^2$ | 73.1 (21.3) | 74.5 (20.3) | 73.4 (19.7) | 73.7 (20.4) |
| eGFR, n (%) | | | | |
| <30 mL/min/1.73 $m^2$ | 4 (1.2) | 0 (0.0) | 3 (0.8) | 7 (0.7) |
| 30 to <60 mL/min/1.73 $m^2$ | 83 (23.9) | 86 (24.7) | 83 (22.4) | 252 (23.7) |
| 60 to <90 mL/min/1.73 $m^2$ | 192 (55.3) | 177 (50.9) | 209 (56.5) | 578 (54.3) |
| ≥90 mL/min/1.73 $m^2$ | 68 (19.6) | 85 (24.4) | 75 (20.3) | 228 (21.4) |

*Note:* Data are mean (± SD) unless otherwise stated.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; SD, standard deviation; T2DM, type 2 diabetes mellitus.

study medication. The proportion of patients who permanently discontinued the study medication prior to week 18 was similar across treatment groups (placebo: 8.9%; ertugliflozin 5 mg: 6.3%; ertugliflozin 15 mg: 8.9%). Patient withdrawal was the most common reason for discontinuation of study medication.

Baseline demographics and characteristics were similar across treatment groups (Table 1). Overall, 68.2% of patients were men, and the mean (SD) age was 64.8 (7.8) years and duration of T2DM 16.7 (9.0) years. At baseline, mean (SD) HbA1c was 68.4 (10.4) mmol/mol (8.4 [1.0]%), FPG was 9.6 (3.2) mmol/L (172.3 [57.0] mg/dL) and eGFR was 73.7 (20.4) mL/min/1.73 $m^2$. Overall, 40.6% of patients were on insulin alone and 59.4% of patients were receiving insulin and metformin. The majority of patients (75.7%) received insulin as basal-bolus therapy (separate intermediate-/long-acting insulin and short-acting insulin or premixed intermediate-/long-acting and short-acting insulin). The median (interquartile range) insulin dose at baseline was 58.0 (40-86) units/d (mean [SD] 70.3 [45.1] units/d). For patients on metformin at baseline, the median (range) metformin dose was 2000 (1500-4050) mg/d.

## 3.2 | Efficacy

### 3.2.1 | Glycaemic efficacy

Ertugliflozin 5 mg and 15 mg significantly reduced HbA1c at week 18 compared with placebo (placebo-adjusted LS means change: −0.58% [95% CI −0.71, −0.44] and −0.65% [95% CI −0.78, −0.51], respectively; $P < 0.001$ for both comparisons [Figure 1]); the reductions were greater with ertugliflozin relative to placebo across all subgroup categories, including patients with or without background metformin (Figure 2). More patients who received ertugliflozin 5 mg (20.7%) and 15 mg (21.1%) compared with placebo (10.7%) had an HbA1c level <53 mmol/mol (7.0%) at week 18 (Table 2). The model-based odds of having an HbA1c level <53 mmol/mol (7.0%) at week 18 were greater with ertugliflozin 5 mg and 15 mg relative to placebo (Table 2; $P < 0.001$ for both comparisons). Both ertugliflozin doses provided significantly greater reductions from baseline at week 18 in FPG (Table 2; Figure 2B) compared with placebo. By week 18, the proportion of patients who had received glycaemic rescue therapy was lower with ertugliflozin 5 mg (6.9%) and 15 mg (5.7%) compared with placebo (11.5%). At week 18, a small decrease in the mean (SD) daily insulin dose was observed with ertugliflozin 15 mg compared with placebo (Table 2).

### 3.2.2 | Body weight

Both ertugliflozin doses provided significantly greater reductions from baseline in BW (Table 2; Figure 2C) at week 18 compared with placebo (placebo-adjusted LS mean change −1.6 kg [95% CI −2.1, −1.1] and −1.9 kg [95% CI −2.4, −1.4], respectively; $P < 0.001$ for both comparisons).

### 3.2.3 | Blood pressure

Ertugliflozin 5 mg and 15 mg provided significantly greater reductions from baseline in SBP (Table 2; Figure 2D) compared with placebo (placebo-adjusted LS mean change −2.9 mmHg [95% CI −4.9, −0.8] and −2.3 mmHg [95% CI −4.4, −0.3], respectively; $P < 0.01$ and 0.05, respectively). The placebo-adjusted LS mean reduction from baseline at week 18 in DBP (Table 2; Figure 2E) was −0.6 mmHg (95% CI −1.8, 0.6) for ertugliflozin 5 mg and −0.4 mmHg (95% CI −1.6, 0.8) for ertugliflozin 15 mg (Table 2; $P > 0.05$ for both).

Efficacy results from sensitivity analyses using the including-rescue approach were consistent with the primary analysis approach (Table S1).

## 3.3 | Safety

### 3.3.1 | Overall AE summary

The overall incidence of AEs and SAEs was similar across the treatment groups (Table 3). The incidence of AEs resulting in discontinuation from study medication was low (<4% of patients in any group). There were 11 deaths during the substudy (placebo: n = 1;

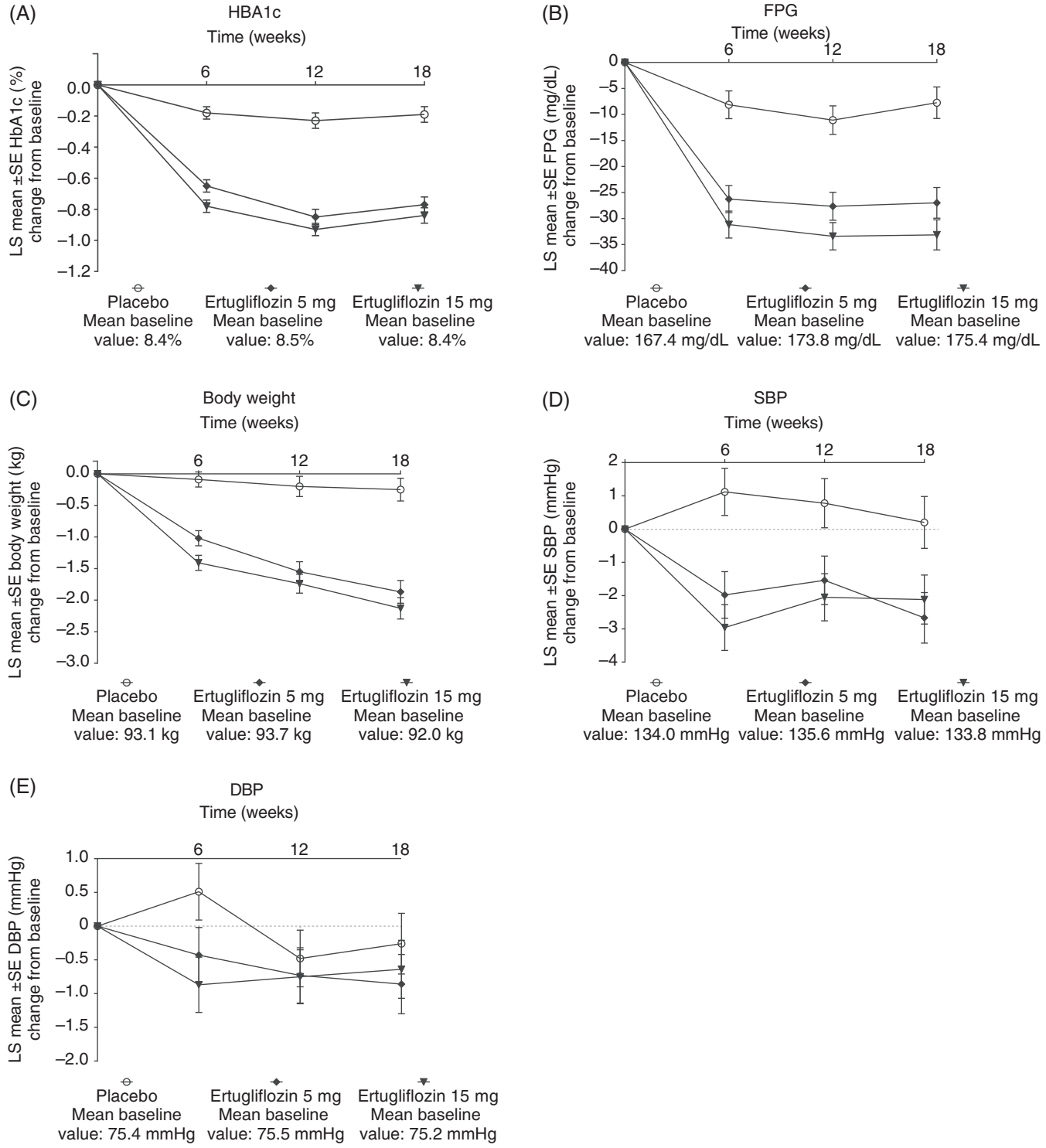


**FIGURE 1** Efficacy outcomes over time. Least squares (LS) mean change from baseline in: (A) glycated haemoglobin (HbA1c); (B) fasting plasma glucose (FPG); (C) body weight; (D) systolic blood pressure (SBP) and (E) diastolic blood pressure (DBP) from baseline to week 18. SE, standard error

ertugliflozin 5 mg: n = 4; ertugliflozin 15 mg: n = 6; Table 3; Figure S1), seven patients experienced fatal AEs that occurred in the on-treatment period, and four patients had fatal AEs that occurred more than 14 days after the last dose of study medication (ertugliflozin 5 mg: n = 1; ertugliflozin 15 mg: n = 3).

### 3.3.2 | Tier 1 prespecified AEs

In women, the incidence of GMIs was higher with ertugliflozin 5 mg (3.4%; $P = 0.05$) and ertugliflozin 15 mg (3.6%; $P = 0.04$) compared with placebo (0.0%; Table 3). In men, there were small differences in

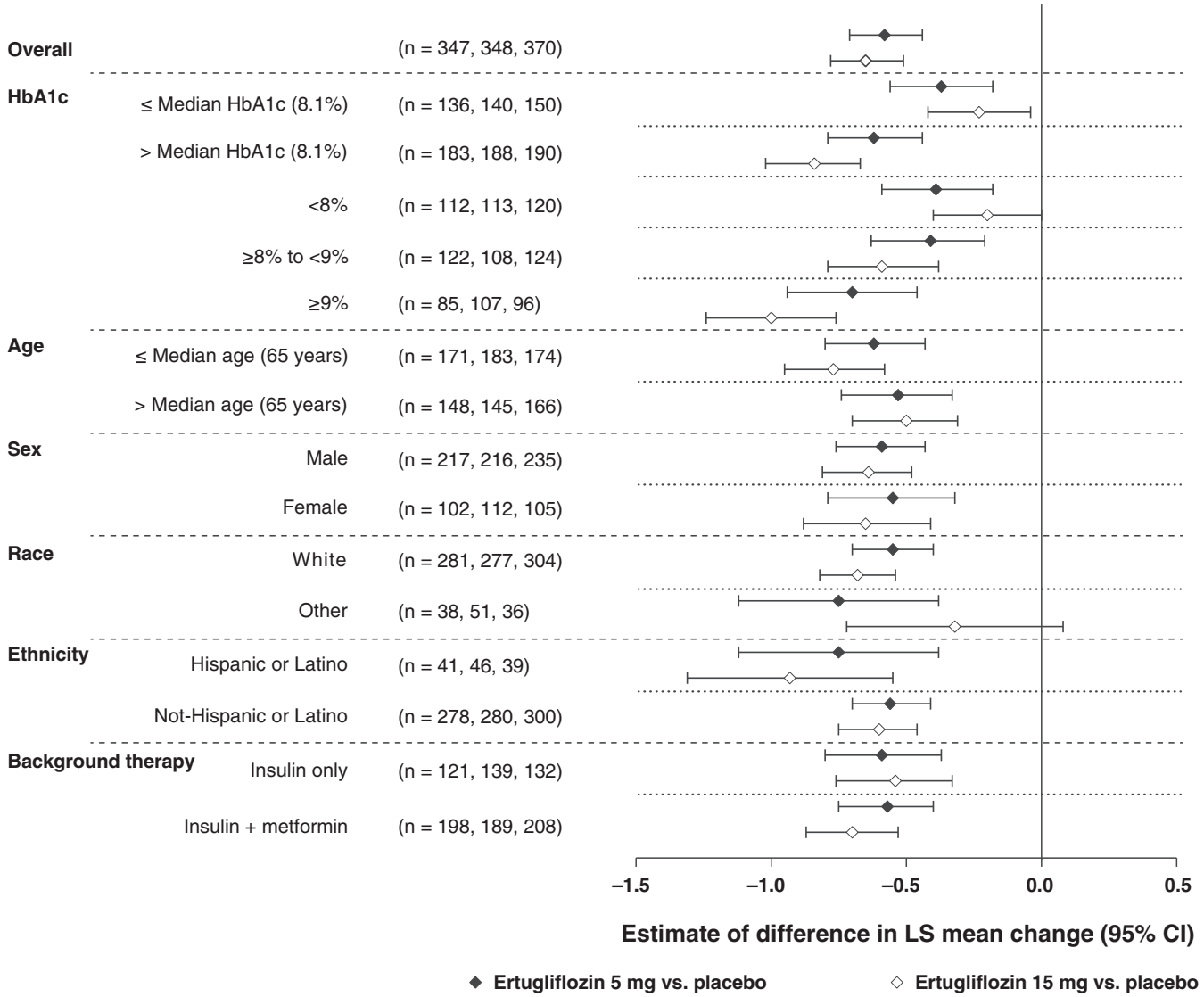


**FIGURE 2** Least squares (LS) mean change from baseline in glycated haemoglobin (HbA1c) at week 18 by subgroup. Point estimate and 95% confidence intervals (CIs) are shown. The median age (65 years) and median HbA1c (8.1%) were derived from the overall patient population of the main study. (n = n1, n2, n3): the number of patients in each treatment group in the full analysis set (ie, randomized patients who took at least one dose of study medication and had a baseline measurement and at least one assessment after baseline). n1 = the number of patients in the placebo group, n2 = the number of patients in the ertugliflozin 5 mg group, n3 = the number of patients in the ertugliflozin 15 mg group

the incidence of GMI with ertugliflozin 5 mg (1.7%) and 15 mg (2.7%) compared with placebo (0.8%). There were no SAEs of GMI, and no patients discontinued study medication due to a GMI. The incidence of UTI AEs was similar across treatment groups (Table 3). Two patients experienced AEs (ertugliflozin 15 mg: n = 1, placebo: n = 1) of UTI, which included one SAE (placebo: n = 1) of UTI that led to discontinuation of study medication.

The incidences of symptomatic, documented and severe hypoglycaemia were similar across the treatment groups (Table 3). A higher number of per-patient episodes of documented and severe hypoglycaemia was observed with ertugliflozin relative to placebo (Table 3). The incidence of hypovolaemia was low (<2.5%) and similar across treatment groups. There were five patients with SAEs of hypovolaemia (ertugliflozin 5 mg: n = 1, ertugliflozin 15 mg: n = 1, placebo: n = 3) and one with an AE of hypovolaemia (ertugliflozin 15 mg) that led to discontinuation of study medication.

### 3.3.3 | Laboratory assessments

Changes from baseline in lipids are reported in Table S2.

## 4 | DISCUSSION

This VERTIS CV substudy demonstrated that, in patients with T2DM and ASCVD receiving insulin ≥20 units/d, ertugliflozin provided clinically meaningful reductions from baseline in HbA1c and FPG at week

**TABLE 2** Key efficacy endpoints at week 18

| | | Placebo (n = 347) | Ertugliflozin 5 mg (n = 348) | Ertugliflozin 15 mg (n = 370) |
|---|---|---|---|---|
| Primary endpoint | | | | |
| HbA1c, mmol/mol | Baseline, mean (SD) | 68.2 (10.1) | 68.9 (10.3) | 68.1 (10.8) |
| | Week 18, mean (SD) | 64.9 (12.8) | 60.2 (10.3) | 59.0 (9.6) |
| | LS mean change from baseline at week 18 (95% CI) | −2.1 (−3.2, −1.0) | −8.4 (−9.4, −7.3) | −9.1 (−10.2, −8.1) |
| | Difference in LS mean vs placebo at week 18 (95% CI) | — | −6.3 (−7.8, −4.8)* | −7.1 (−8.5, −5.6)* |
| HbA1c, % | Baseline, mean (SD) | 8.4 (0.9) | 8.5 (0.9) | 8.4 (1.0) |
| | Week 18, mean (SD) | 8.1 (1.2) | 7.7 (0.9) | 7.6 (0.9) |
| | LS mean change from baseline at week 18 (95% CI) | −0.19 (−0.29, −0.09) | −0.77 (−0.86, −0.67) | −0.84 (−0.93, −0.74) |
| | Difference in LS mean vs placebo at week 18 (95% CI) | — | −0.58 (−0.71, −0.44)* | −0.65 (−0.78, −0.51)* |
| Secondary endpoints | | | | |
| FPG, mmol/L | Baseline, mean (SD) | 9.3 (2.9) | 9.7 (3.3) | 9.7 (3.3) |
| | Week 18, mean (SD) | 8.8 (2.9) | 8.0 (2.4) | 7.8 (2.6) |
| | LS mean change from baseline at week 18 (95% CI) | −0.4 (−0.8, −0.1) | −1.5 (−1.8, −1.2) | −1.8 (−2.2, −1.5) |
| | Difference in LS mean vs placebo at week 18 (95% CI) | — | −1.1 (−1.5, −0.7)* | −1.4 (−1.8, −1.0)* |
| Body weight, kg | Baseline, mean (SD) | 93.3 (17.9) | 93.8 (19.1) | 92.1 (18.6) |
| | Week 18, mean (SD) | 92.5 (18.1) | 91.5 (18.4) | 89.8 (17.3) |
| | LS mean change from baseline at week 18 (95% CI) | −0.3 (−0.6, 0.1) | −1.9 (−2.2, −1.5) | −2.1 (−2.5, −1.8) |
| | Difference in LS mean vs placebo at week 18 (95% CI) | — | −1.6 (−2.1, −1.1)* | −1.9 (−2.4, −1.4)* |
| Patients with HbA1c <53 mmol/mol (7%) | n (%) at week 18 | 37 (10.7) | 72 (20.7) | 78 (21.1) |
| | Odds ratio vs placebo at week 18 (95% CI) | — | 2.6 (1.6, 4.1)* | 2.5 (1.6, 3.8)* |
| SBP, mmHg | Baseline, mean (SD) | 134.0 (15.3) | 135.6 (14.3) | 133.8 (14.5) |
| | Week 18, mean (SD) | 133.8 (15.2) | 132.2 (13.8) | 132.2 (14.6) |
| | LS mean change from baseline at week 18 (95% CI) | 0.2 (−1.3, 1.7) | −2.7 (−4.2, −1.2) | −2.1 (−3.6, −0.7) |
| | Difference in LS mean vs placebo at week 18 (95% CI) | — | −2.9 (−4.9, −0.8)** | −2.3 (−4.4, −0.3)*** |
| DBP, mmHg | Baseline, mean (SD) | 75.4 (9.2) | 75.5 (8.9) | 75.2 (8.8) |
| | Week 18, mean (SD) | 74.8 (9.6) | 74.5 (9.0) | 74.9 (9.4) |
| | LS mean change from baseline at week 18 (95% CI) | −0.3 (−1.1, 0.6) | −0.9 (−1.7, 0.0) | −0.6 (−1.5, 0.2) |
| | Difference in LS mean vs placebo at week 18 (95% CI) | | −0.6 (−1.8, 0.6)[a] | −0.4 (−1.6, 0.8)[a] |
| Patients who received glycaemic rescue therapy[b] | n (%) at week 18 | 40 (11.5) | 24 (6.9) | 21 (5.7) |
| | Difference in percentage estimate vs placebo at week 18 (95% CI) | — | −4.6 (−9.1, −0.3) | −5.9 (−10.2, −1.8) |
| Other endpoint | | | | |
| Insulin dose, units/d | Baseline, mean (SD) | 73.2 (49.6) | 70.8 (44.1) | 67.3 (41.2) |
| | Week 18, mean (SD) | 73.0 (49.5) | 70.0 (45.1) | 64.9 (41.6) |
| | Change from baseline at week 18, mean (SD) | −0.3 (11.5) | −0.7 (10.1) | −2.1 (10.2) |

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LS, least squares; SBP, systolic blood pressure; SD, standard deviation.

*$P < 0.001$.

**$P < 0.01$.

***$P < 0.05$.

[a]Since the ertugliflozin 15 mg versus placebo comparison for DBP was not significant at the $P = 0.05$ level, the prespecified hypothesis-testing sequence stopped and the testing of ertugliflozin 5 mg versus placebo for DBP was not performed.

[b]Patients received glycaemic rescue therapy if confirmed FPG was >15.0 mmol/L between randomization and week 6, >13.3 mmol/L during weeks 6-12, or >11.1 mmol/L during weeks 12-18. The criteria for initiation of glycaemic rescue therapy are defined in the methodology.

**TABLE 3** Summary of adverse events

| Event, n (%) | Placebo (n = 347) | Ertugliflozin 5 mg (n = 348) | Ertugliflozin 15 mg (n = 370) |
|---|---|---|---|
| ≥1 AE | 212 (61.1) | 206 (59.2) | 231 (62.4) |
| ≥1 SAE | 37 (10.7) | 33 (9.5) | 27 (7.3) |
| Discontinuations | | | |
| Due to AE | 13 (3.7) | 9 (2.6) | 14 (3.8) |
| Due to SAE | 4 (1.2) | 3 (0.9) | 2 (0.5) |
| Death[a] | 1 (0.3) | 4 (1.1) | 6 (1.6) |
| Tier 1 pre-specified AEs | | | |
| UTI | 14 (4.0) | 11 (3.2) | 15 (4.1) |
| Hypovolaemia | 5 (1.4) | 7 (2.0) | 9 (2.4) |
| GMI (men)[b] | 2 (0.8) | 4 (1.7) | 7 (2.7) |
| GMI (women)[c] | 0 (0.0) | 4 (3.4) | 4 (3.6) |
| Symptomatic hypoglycaemia[d] | 99 (28.5) | 92 (26.4) | 98 (26.5) |
| Documented and severe hypoglycaemia | | | |
| Patients with documented hypoglycaemia[e] | 130 (37.5) | 137 (39.4) | 144 (38.9) |
| Total number of episodes[f] | 762 | 826 | 873 |
| Patients with 1 episode | 34 (9.8) | 31 (8.9) | 34 (9.2) |
| Patients with 2 episodes | 19 (5.5) | 24 (6.9) | 25 (6.8) |
| Patients with ≥3 episodes | 77 (22.2) | 82 (23.6) | 85 (23.0) |
| Patients with severe hypoglycaemia[g] | 12 (3.5) | 13 (3.7) | 19 (5.1) |
| Total number of episodes[f] | 26 | 27 | 62 |
| Patients with 1 episode | 7 (2.0) | 7 (2.0) | 11 (3.0) |
| Patients with 2 episodes | 3 (0.9) | 4 (1.1) | 2 (0.5) |
| Patients with ≥3 episodes | 2 (0.6) | 2 (0.6) | 6 (1.6) |

*Note:* For all AEs, this table contains events that occurred between the first dose of treatment and 14 days after the final dose of treatment, with the exception of death which is reported for the overall study period whether the AE occurred between the first dose of treatment and 14 days after the final dose of treatment or with AE onset more than 14 days after the last dose of study medication.

Abbreviations: AE, adverse event; GMI, genital mycotic infection; SAE, serious adverse event; UTI, urinary tract infection.

[a]Of the 11 deaths in the substudy, eight were adjudicated to be cardiovascular deaths (including the one patient in the placebo group), one was attributable to metastatic gastric cancer, one was attributable to stroke and the remaining death was of unknown cause (lost to follow-up).

[b]N = 237 for placebo, 229 for ertugliflozin 5 mg and 260 for ertugliflozin 15 mg.

[c]N = 110 for placebo, 119 for ertugliflozin 5 mg and 110 for ertugliflozin 15 mg.

[d]Symptomatic hypoglycaemia was defined as an event with clinical symptoms reported by the investigator as hypoglycaemia (biochemical documentation not required).

[e]Documented hypoglycaemia was defined as an episode with a glucose level ≤3.9 mmol/L (≤70 mg/dL) with or without symptoms.

[f]All applicable episodes were counted, including multiple episodes in the same patient.

[g]Severe hypoglycaemia was defined as an episode of symptomatic hypoglycaemia that required assistance, either medical or nonmedical, regardless of whether such assistance was obtained, and regardless of biochemical documentation.

18 compared with placebo. Additionally, more patients met the HbA1c target of <53 mmol/mol (7.0%) and a lower proportion of patients required glycaemic rescue medication with ertugliflozin compared with placebo. Other benefits of ertugliflozin compared with placebo were modest decreases in BW and SBP.

The SGLT2 inhibitors are attractive agents to use in combination with exogenous insulin because the two classes of agents have complementary mechanisms of action on reducing blood glucose. Insulin promotes cellular uptake of glucose in peripheral tissues, especially fat and skeletal muscle, and decreases gluconeogenesis from the liver[20]; whereas SGLT2 inhibitors decrease the reabsorption of glucose excreted from the kidney.[21] In addition, SGLT2 inhibitors counterbalance the undesirable effect of weight gain with insulin therapy.

The efficacy and safety of ertugliflozin reported here are similar to studies of other SGLT2 inhibitors added to background insulin. In a substudy of the CANagliflozin CardioVascular Assessment Study (CANVAS), canagliflozin added to insulin therapy (≥20 IU/d) in patients with T2DM with prevalent ASCVD or at increased risk of ASCVD, improved glycaemic control and decreased BW and SBP at 18 weeks.[22] In that study, a greater incidence of hypoglycaemia was observed in the canagliflozin groups, compared with placebo. In two studies in patients with T2DM where empagliflozin was added-on to multiple daily injections of insulin (basal or prandial ± metformin) or added-on to basal insulin (≥20 IU/d ± metformin and/or sulphonylureas), empagliflozin improved glycaemic control and reduced BW with a similar incidence of hypoglycaemia to placebo at

18 weeks (episodes of hypoglycaemia were not reported).[23,24] In a study in patients with T2DM with dapagliflozin added-on to insulin (≥30 IU/d ± metformin ± another oral agent), dapagliflozin improved glycaemic control, stabilized insulin dosing and reduced BW with a higher incidence of hypoglycaemic episodes, compared with placebo, at 24 weeks.[25] A comparison of the reductions in daily insulin dose in this current substudy with dose reductions reported in studies of other SGLT2 inhibitors is confounded by the differences in study design and timepoints at which dose differences were assessed.[22–24,26]

Ertugliflozin (5 and 15 mg) was generally well tolerated in patients with T2DM and ASCVD receiving insulin, and the safety profile was consistent with other SGLT2 inhibitors.[27] The overall occurrence of AEs, SAEs and discontinuations due to AEs was similar across treatment groups. The majority of deaths were adjudicated to be CV in nature; CV safety is reported as part of the overall VERTIS CV study.[13] The occurrence of GMIs was higher in women with ertugliflozin versus placebo, but the overall percentage of patients affected was low and there were no discontinuations of study medication due to GMIs. The occurrence of UTIs and hypovolaemia were also low and similar across treatment groups. Although the number of episodes of documented and severe hypoglycaemia was numerically higher with ertugliflozin, the overall incidence of symptomatic and documented hypoglycaemia was similar across treatment arms. Numerically larger reductions in insulin dose were observed in the ertugliflozin groups relative to placebo; as is the case when other classes of antihyperglycaemic agents are added to insulin (or insulin secretagogue), a lower dose of insulin (or insulin secretagogues) may be required to minimize the risk of hypoglycaemia.[28,29]

The results of this substudy have the potential to be clinically impactful in that benefits were readily and safely achieved in a population that is typically difficult to manage in clinical practice (ie, patients with long-standing T2DM and established ASCVD inadequately controlled on insulin therapy). The benefits of improved glycaemic control and reduction of BW and SBP observed with ertugliflozin, together with the potential reduction in the risk for hospitalization for heart failure[13,14] and renal outcomes[13,15] observed with ertugliflozin compared with placebo in the overall VERTIS CV study,[13] could alter disease outcome in this important population.

There are a number of potential limitations to the present study, including its relatively short duration and the characteristics of the population studied, which was restricted to patients with T2DM and prevalent ASCVD. However, as the 18-week duration was sufficient to observe a plateau in HbA1c response, the results will assist clinicians in setting expectations for glycaemic control for patients with T2DM initiating ertugliflozin on background insulin. This substudy protocol required patients to maintain a stable insulin dose for 18 weeks which is not necessarily aligned to clinical practice, where insulin doses might be increased to improve glycaemic control. However, this design enabled the assessment of the glycaemic effects of ertugliflozin. Assessment of longer-term glycaemic efficacy would have been confounded by changes in insulin dose that were allowed after week 18 at the discretion of the investigator, in line with applicable local guidelines. In studies of other SGLT2 inhibitors added to insulin, glycaemic control observed at earlier placebo-controlled timepoints (18-24 weeks) was generally similar to that observed over the longer treatment period (48-104 weeks); however, any conclusions about the longer-term maintenance of glycaemic effects in those studies must consider changes in study design at the end of placebo-controlled periods and analysis methods.[22,23,26] In addition, this substudy did not assess long-term safety as changes in glucose-lowering regimen, doses of background glucose-lowering agents and the addition of agents beyond the placebo-controlled period could confound results, especially with regard to assessment of hypoglycaemia. Although this substudy only included a subset of patients (Cohort 1) on insulin ≥20 U/d in VERTIS CV, the patient numbers provided sufficient power to evaluate endpoints and the sample size was larger than analogous studies.[23,25] While this substudy was conducted exclusively in patients with T2DM and ASCVD, previous studies with ertugliflozin have demonstrated consistent glycaemic efficacy and safety when given as a monotherapy or in combination with metformin and/or other glucose-lowering agents as second- or third-line treatment.[30–36] Therefore, the findings are likely to be more broadly applicable to patients with T2DM without prevalent ASCVD.

In conclusion, ertugliflozin added to insulin (≥20 units/d) in patients with T2DM and ASCVD provided clinically meaningful improvements in glycaemic control and also provided benefits in BW and SBP versus placebo. Ertugliflozin was generally well tolerated, with the most frequent treatment-related AEs being GMIs in women. These findings suggest that ertugliflozin may be a useful treatment option in patients with T2DM receiving insulin who need additional glycaemic control.

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## CONFLICT OF INTEREST

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Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and own stock in 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. Michelle Greenberg, Silvina Gallo and Harry Shi were involved in the conception/design of the study. Ildiko Lingvay was involved in the acquisition of data for the study. All authors were involved in data analysis and interpretation of the data.

## DATA AVAILABILITY STATEMENT

Upon request, and subject to certain criteria, conditions and exceptions (see https://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 (1) for indications that have been approved in the US and/or EU or (2) in programmes 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.

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