## Title

Efficacy and Safety of Ertugliflozin in Patients with Type 2 Diabetes Inadequately Controlled by Metformin and Sulfonylurea: A Sub-Study of VERTIS CV



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## Authors

Budoff, Matthew J
Davis, Timothy ME
Palmer, Alexandra G
et al.

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# Efficacy and Safety of ERTU in Patients with Type 2 Diabetes Inadequately Controlled by Metformin and Sulfonylurea

Matthew J. Budoff[1] · Timothy M. E. Davis[2] · Alexandra G. Palmer[3] · Robert Frederich[4] · David E. Lawrence[5] · Jie Liu[6] · Ira Gantz[6] · Giuseppe Derosa[7]

*[1]Lundquist Institute, Torrance, CA, USA; [2]Medical School, University of Western Australia, Crawley, Australia; [3]Pfizer Inc., Groton, CT, USA; [4]Pfizer Inc., Collegeville PA, USA; [5]Pfizer Inc., New York, NY, USA; [6]Merck & Co., Inc., Kenilworth, NJ, USA; [7]Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy*

## Introduction

- The combination of metformin and sulfonylureas (SUs) is commonly used to treat type 2 diabetes mellitus (T2DM), due to their glycemic efficacy, low cost, and their complementary mechanisms of action (1, 2).
- When additional glycemic control is needed and a decision is made to add a third oral antihyperglycemic agent (AHA) to the existing metformin/SU regimen, sodium-glucose transporter 2 (SGLT2) inhibitors may be an attractive option.
- The VERTIS (e**V**aluation of **ERTU** eff**I**cacy and **S**afety) CV study evaluated the effects of the SGLT2 inhibitor ertugliflozin (ERTU) on cardiorenal outcomes in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD) (3, 4).

- The efficacy and safety of ERTU, added to metformin and a SU, were assessed in an 18-week sub-study of VERTIS CV.

## Objectives

- The primary objectives were to assess the effect of ERTU vs placebo (PBO) at Week 18 on HbA1c, and to evaluate ERTU safety and tolerability.
- Secondary objectives were to assess the effect of ERTU vs PBO on fasting plasma glucose (FPG), body weight, proportion of patients with HbA1c < 7%, and systolic and diastolic blood pressure (SBP and DBP, respectively).

## Methods

- VERTIS CV (ClinicalTrials.gov identifier: NCT01986881) was a multicenter, randomized, double-blind, PBO-controlled, parallel-group, event-driven study that included a main CV outcomes study and three glycemic sub-studies (3, 4).
- This was an 18-week VERTIS CV sub-study in patients with T2DM and ASCVD with inadequate glycemic control on metformin + SU (**Figure 1**).
- Patients were randomized (1:1:1) to ERTU 5 or 15 mg once daily, or PBO.

### Key eligibility criteria

- Participants were eligible if they were age ≥40 years with T2DM (HbA1c 7.0-10.5%, inclusive), and had stable, established ASCVD involving the coronary, cerebrovascular and/or peripheral arterial systems (3, 4).
- A subset of patients who were receiving metformin (≥ 1500 mg/day) and moderate to high SU (gliclazide [immediate- or modified-release], glimepiride, glipizide, glyburide [micronized and non-micronized], acetohexamide, tolbutamide, or tolazamide) were included in this sub-study.

- Patients were required to have a stable metformin dose and a stable SU dose above a prespecified minimum for ≥8 weeks prior to screening.
- Changes to the background glucose-lowering treatment were not allowed except when patients met pre-defined glycemic rescue thresholds or were experiencing clinically significant hypoglycemia.

**Assessments**

- Change from baseline at Week 18 was calculated for HbA1c, FPG, body weight, SBP, and DBP. The proportion of patients with HbA1c <7.0% and the proportion of patients requiring glycemic rescue therapy were assessed.
- Safety assessments included adverse events (AEs), serious AEs (SAEs), deaths and discontinuations because of AEs.
- Genital mycotic infections (GMIs), urinary tract infections (UTIs), hypoglycemia, and hypovolemia were pre-specified AEs of special interest.

**Statistical methods**

- Efficacy analyses were conducted using the full analysis set (FAS) which included all randomized patients who received ≥1 dose of study medication and had ≥1 baseline or post-baseline measurement of the respective endpoint.
    - Efficacy analyses excluded results obtained after initiation of glycemic rescue therapy with the exception of the proportion of patients receiving glycemic rescue therapy.
- Least squares (LS) mean change from baseline in HbA1c, body weight, FPG, SBP, and DBP were assessed using a constrained longitudinal data analysis (cLDA) model that accounted for treatment, visit (categorical), treatment by visit interaction, baseline estimated glomerular filtration rate (eGFR) (continuous) and metformin use (binary - yes/no).

    - HbA1c reduction from baseline at Week 18 was assessed in subgroups, including those based on baseline HbA1c, age, sex, race, ethnicity, and use of metformin using a repeated measures analysis of covariance model.
- A logistic regression analysis was used to evaluate the proportion of patients with HbA1c <7.0% at Week 18 that included terms for treatment, baseline HbA1c, metformin use (binary - yes/no) and baseline eGFR (continuous).
- The proportion of patients requiring glycemic rescue therapy up to Week 18 was analyzed using log-rank tests comparing the time-to-event distribution of ERTU vs PBO.
- Safety analyses used the all subjects as treated (ASaT) population and, with the exception of hypoglycemia, used the including rescue approach.

**Results**

- Of 8246 patients randomized to VERTIS CV, 330 patients with T2DM and ASCVD were included in the sub-study (**Figure 1**).
    - Overall, 313 (94.8%) patients completed the 18-week follow-up period on study medication.
    - Patient withdrawal was the most common reason for treatment discontinuation.
- Baseline demographics and characteristics were similar across treatment groups (**Table 1**).

**Efficacy**

- At Week 18, ERTU 5 mg and 15 mg significantly reduced HbA1c vs PBO (**Figure 2A**).

- Reductions in HbA1c were greater with ERTU vs PBO across all subgroup categories, irrespective of baseline HbA1c, age, gender, or race (**Figure 3**).
- More patients who received ERTU 5 mg and 15 mg vs PBO had HbA1c <7.0% at Week 18 (**Figure 2B**).
- At Week 18, greater reductions from baseline in FPG, and body weight were observed with ERTU vs PBO (**Figure 2C and 2D**).
- Reduction in SBP with ERTU 15 mg vs PBO was not significant ($P > 0.05$) so further hypothesis testing of SBP and DBP was stopped (**Figure 2E and 2F**).
- By Week 18, the proportion of patients who had received glycemic rescue therapy was lower with ERTU 5 mg (7.0%) and 15 mg (2.7%) vs PBO (10.3%).

### Safety

- A summary of overall safety is provided in **Table 2**, with incidence of AEs of special interest presented in **Table 3**.

## Conclusion

- ERTU as add-on therapy to metformin and SU in patients with T2DM and ASCVD resulted in significantly greater reductions in HbA1c, FPG, and body weight than PBO but did not provide statistically significant improvements in blood pressure.
- ERTU was generally well tolerated with a safety profile consistent with the SGLT2 inhibitor class.
- ERTU is a suitable candidate add-on therapy in patients with T2DM who are inadequately controlled with metformin and SU.

## Figures and Tables

**Figure. 1** Study flow diagram

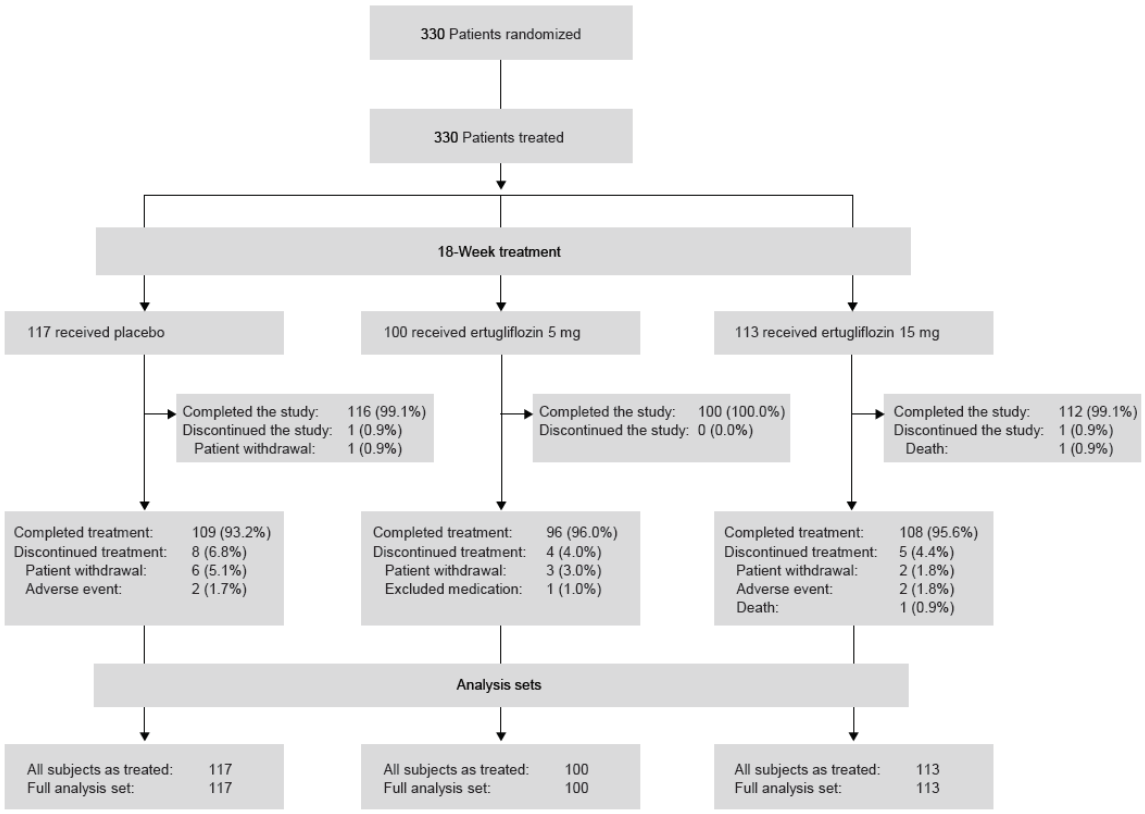
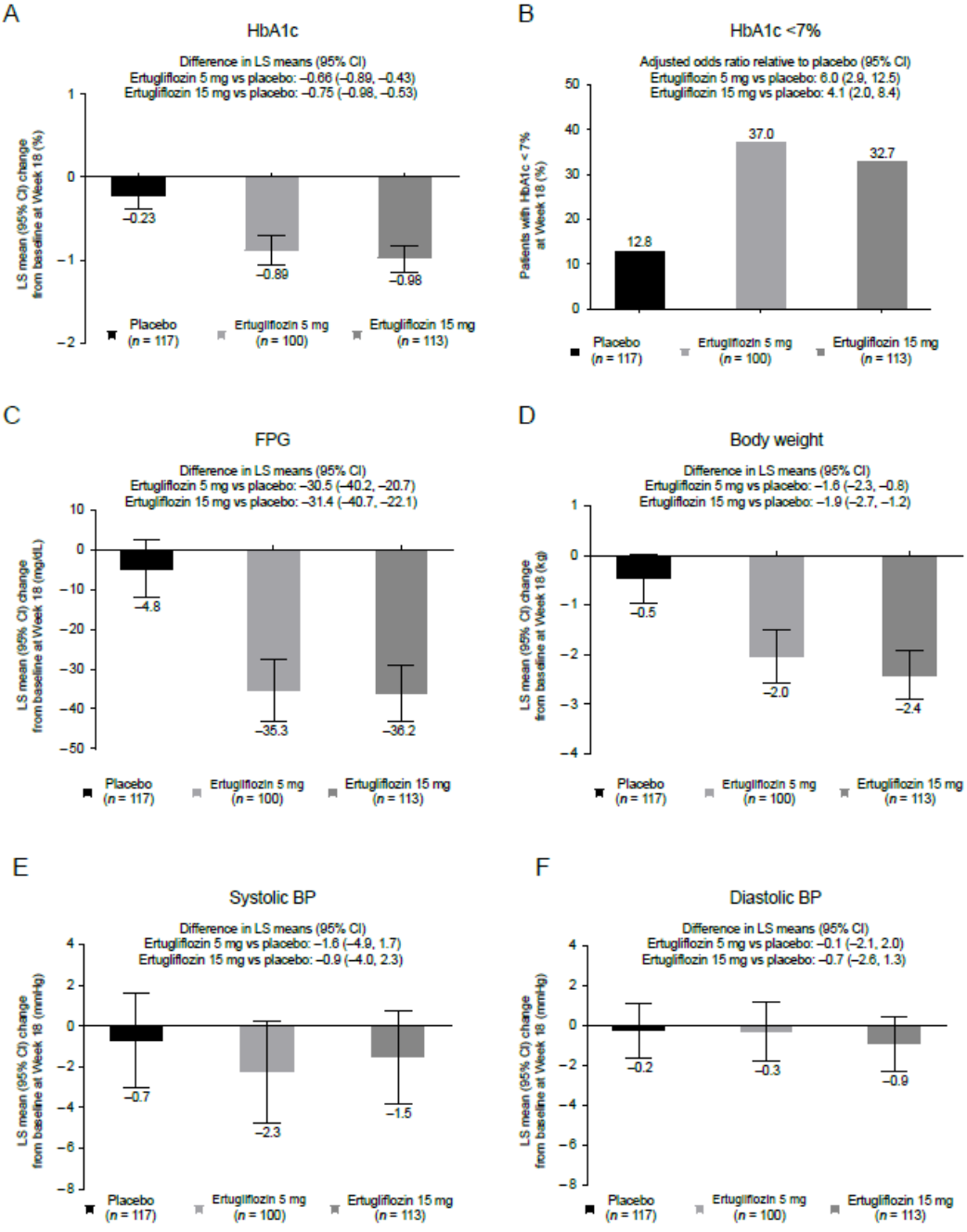


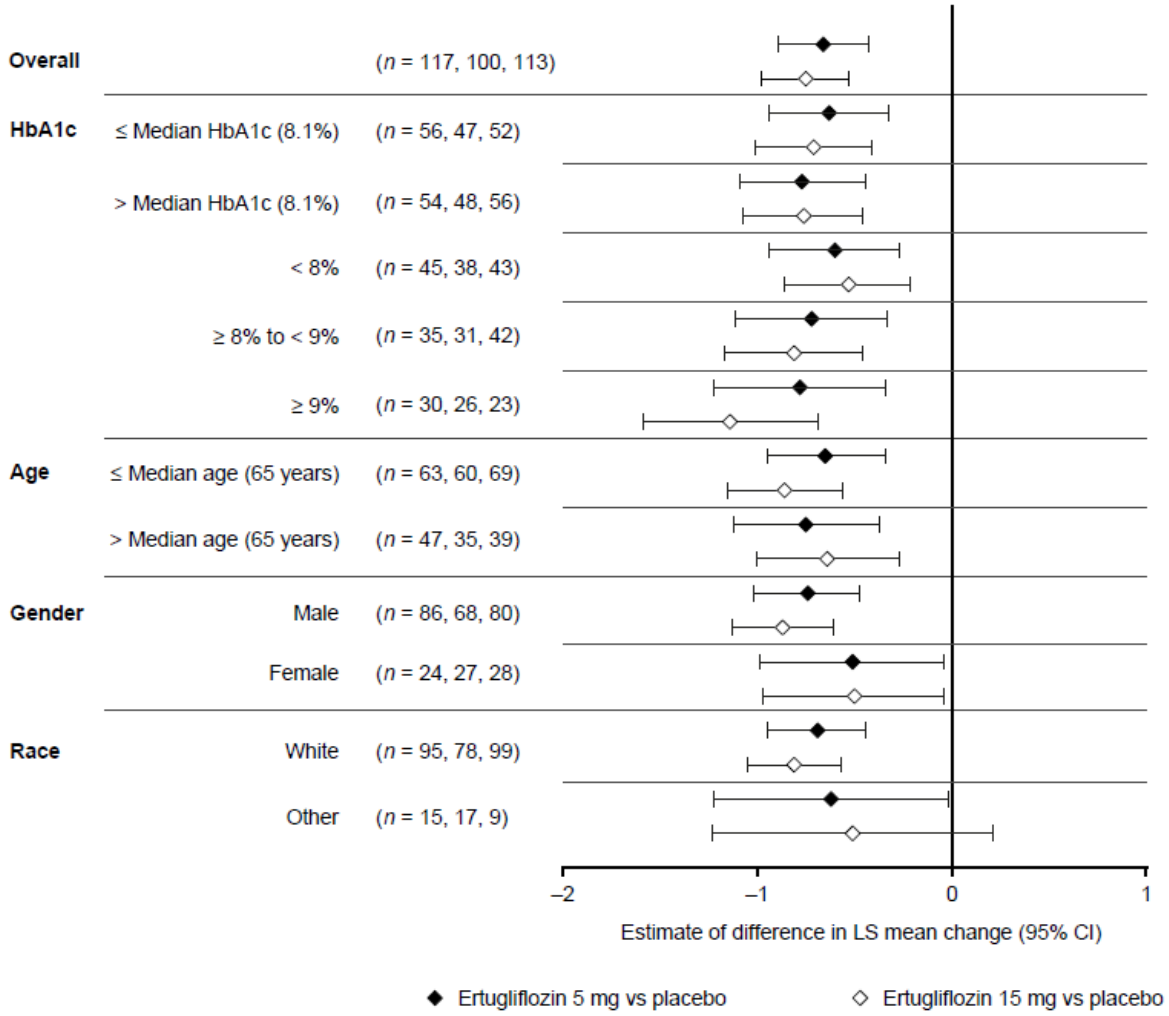
**Figure. 2 Primary and secondary efficacy outcomes**: A. LS mean change from baseline in HbA1c at Week 18; B. Proportion of patients with HbA1c <7% at Week 18; C. LS mean change from baseline in FPG at Week 18; D. LS mean change from baseline in body weight at Week 18; E. LS mean change from baseline in systolic BP at Week 18; F. LS mean change from baseline in diastolic BP at Week 18.



[a] Since the ERTU 15 mg vs PBO comparison for SBP was not significant at the P = .05 level, the prespecified hypothesis testing sequence stopped and the testing of ERTU 5 mg vs PBO for SBP and ERTU 15 and 5 mg vs PBO for DBP were not performed.

BP, blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LS, least squares; SE, standard error of the mean.

**Figure. 3** Estimate of PBO-adjusted change from baseline in HbA1c at Week 18 by subgroup category (FAS population, excluding rescue approach). Point estimate and 95% CIs are shown. The median age (65 years) and median HbA1c (8.1%) were derived from the overall patient population of the main study.




Values in parentheses are *n*'s for PBO, ERTU 5 mg and 15 mg groups, respectively.

ERTU, ertugliflozin; FAS, full analysis set; HbA1c, glycated haemoglobin; LS, least squares; PBO, placebo.

**Table 1**. Patient demographics and baseline characteristics (all patients treated)

| ENDO 2021 VERTIS CV Sub-study Met SU First Draft | PBO (n=117) | ERTU 5 mg (n=100) | ERTU 15 mg (n=113) | Total (n=330) |
|---|---|---|---|---|
| Gender, *n* (%) | | | | |
| Male | 91 (77.8) | 72 (72.0) | 84 (74.3) | 247 (74.8) |
| Age, years | 63.7 (8.9) | 62.7 (8.0) | 63.2 (8.3) | 63.2 (8.4) |
| Race | | | | |
| White | 102 (87.2) | 82 (82.0) | 104 (92.0) | 288 (87.3) |
| Black/African American | 2 (1.7) | 3 (3.0) | 3 (2.7) | 8 (2.4) |
| Asian | 10 (8.5) | 9 (9.0) | 3 (2.7) | 22 (6.7) |
| Other[a] | 3 (2.6) | 6 (6.0) | 3 (2.7) | 12 (3.6) |
| Ethnicity, n (%) | | | | |
| Hispanic or Latino | 13 (11.1) | 9 (9.0) | 14 (12.4) | 36 (10.9) |
| Not Hispanic or Latino | 104 (88.9) | 91 (91.0) | 99 (87.6) | 294 (89.1) |
| Region, n (%) | | | | |
| North America | 30 (25.6) | 18 (18.0) | 18 (15.9) | 66 (20.0) |
| South America | 7 (6.0) | 8 (8.0) | 13 (11.5) | 28 (8.5) |
| Europe | 62 (53.0) | 60 (60.0) | 72 (63.7) | 194 (58.8) |
| Asia | 7 (6.0) | 7 (7.0) | 1 (0.9) | 15 (4.5) |
| South Africa | 10 (8.5) | 7 (7.0) | 7 (6.2) | 24 (7.3) |
| Australia/New Zealand | 1 (0.9) | 0 (0.0) | 2 (1.8) | 3 (0.9) |
| Duration of T2DM, years | 11.6 (7.5) | 11.6 (7.5) | 11.1 (7.2) | 11.4 (7.4) |
| Weight, kg | 90.4 (17.5) | 91.9 (20.4) | 92.8 (17.2) | 91.7 (18.3) |
| BMI, kg/m$^2$ | 31.0 (5.1) | 32.0 (5.5) | 32.3 (5.0) | 31.7 (5.2) |
| HbA1c, % | 8.3 (1.0) | 8.4 (1.0) | 8.3 (1.0) | 8.3 (1.0) |
| mmol/mol | 66.9 (10.9) | 68.2 (10.5) | 67.2 (10.5) | 67.4 (10.6) |
| FPG, mg/dL | 177.3 (45.6) | 183.5 (49.6) | 174.0 (52.8) | 178.0 (49.3) |
| mmol/L | 9.8 (2.5) | 10.2 (2.8) | 9.7 (2.9) | 9.9 (2.7) |
| SBP, mmHg | 135.0 (14.0) | 133.6 (13.9) | 133.9 (15.2) | - |
| DBP, mmHg | 77.7 (8.3) | 78.0 (7.7) | 76.7 (9.0) | - |
| eGFR, mL/min/1.73m$^2$ | 85.5 (17.7) | 84.8 (18.0) | 80.2 (17.4) | 83.5 (17.8) |
| Background glucose-lowering | | | | |

Data presented as mean (SD) unless otherwise stated.

[a] Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Multiple.

For entry into study, the minimum daily dose of metformin was ≥ 1500 mg, and the following for specific SUs: gliclazide (immediate-release) ≥ 160 mg; gliclazide (modified-release) ≥ 60 mg; glimepiride ≥ 4 mg; glipizide ≥10 mg; glyburide (glibenclamide) ≥ 10 mg; micronized glyburide ≥ 6 mg. Calculations of median dose and distribution of doses for gliclazide and glyburide make no adjustment for any potential formulation differences.

[b] n=48 for PBO, 48 for ERTU 5 mg and 44 for ERTU 15 mg.

[c] n=36 for PBO, 29 for ERTU 5 mg and 50 for ERTU 15 mg.

[d] n=18 for PBO, 12 for ERTU 5 mg and 8 for ERTU 15 mg.

[e] n=15 for PBO, 11 for ERTU 5 mg and 11 for ERTU 15 mg.

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ERTU, ertugliflozin; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; PBO, placebo; SBP, systolic blood pressure; SU, sulfonylurea; T2DM, type 2 diabetes mellitus.

**Table 2**. Summary of AEs (all patients treated)

| Event | PBO (n=117) | ERTU 5 mg (n=100) | ERTU 15 mg (n=113) |
|---|---|---|---|
| ≥ 1 AE | 55 (47.0) | 48 (48.0) | 62 (54.9) |
| ≥ 1 SAE | 6 (5.1) | 7 (7.0) | 8 (7.1) |
| Treatment discontinuation due to AE | 2 (1.7) | 0 (0.0) | 3 (2.7) |
| AE leading to death[a] | 0 (0.0) | 0 (0.0) | 1 (0.9) |

Data are number (%) of patients with AE. Patients with multiple occurrences of an AE are counted once.

[a] One patient in the ERTU 15 mg group died from multiple organ dysfunction syndrome on Day 89; the patient was a 66-year-old, white male with history of myocardial infarction and atrial fibrillation and background acenocoumarol use.

AE, adverse event; ERTU, ertugliflozin; PBO, placebo; SAE, serious adverse event.

**Table 3**. Summary of adverse events of special interest (all patients treated)

| Event | PBO (n=117) | ERTU 5 mg (n=100) | ERTU 15 mg (n=113) |
|---|---|---|---|
| Prespecified AEs of interest | | | |
| GMI (women)[a] | 1 (3.8) | 0 (0.0) | 3 (10.3) |
| GMI (men)[b] | 0 (0.0) | 3 (4.2) | 4 (4.8) |
| UTI | 4 (3.4) | 2 (2.0) | 4 (3.5) |
| Symptomatic hypoglycemia[c] | 9 (7.7) | 11 (11.0) | 14 (12.4) |
| Hypovolemia | 0 (0.0) | 0 (0.0) | 1 (0.9) |
| Other AEs of interest | | | |
| Documented hypoglycemia[d] | 17 (14.5) | 20 (20.0) | 30 (26.5) |
| Severe hypoglycemia[e] | 1 (0.9) | 2 (2.0) | 2 (1.8) |

Data are number (%) of patients with AE. AE adverse event, GMI genital mycotic infection, SAE serious adverse event, UTI urinary tract infection.

[a] n=26 for PBO, 28 for ERTU 5 mg, and 29 for ERTU 15 mg.

[b] n=91 for PBO, 72 for ERTU 5 mg, and 84 for ERTU 15 mg.

[c] Event with clinical symptoms reported by the investigator as hypoglycemia (biochemical documentation not required).

[d] Episodes with a glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L) with or without symptoms.

[e] Episodes of hypoglycemia requiring medical or non-medical assistance.

AE adverse event, ERTU ertugliflozin, GMI genital mycotic infection, PBO placebo, UTI urinary tract infection.

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A.G.P., R.F., and D.E.L. are employees of Pfizer and own stock and/or stock options in Pfizer Inc., New York, NY, USA. J.L. and I.G. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD) and may own stock in Merck & Co., Inc., Kenilworth, NJ, USA. M.J.B.

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