Supplementary Materials

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Supplementary Methods

Statistical Analysis

The primary efficacy endpoint was the change from baseline in A1C at Week 26 in the overall cohort. Key secondary efficacy endpoints, analyzed in the Stage 3A CKD cohort at Week 26, were changes from baseline in A1C, body weight, systolic blood pressure (SBP), and FPG, and the proportion of patients with A1C <7.0%. Other efficacy endpoints were change from baseline in diastolic blood pressure (DBP), time to glycemic rescue, and proportion of patients who received glycemic rescue therapy in the Stage 3A CKD cohort, and changes from baseline in A1C, FPG, body weight, SBP and DBP in the Stage 3B CKD cohort.

The primary and key secondary efficacy endpoints were to be assessed using an ordered testing procedure at Week 26. For the primary efficacy endpoint, ertugliflozin 15 mg was to be tested versus placebo first, followed by ertugliflozin 5 mg versus placebo. The following order was to be used for the secondary endpoints: body weight (ertugliflozin 15 mg vs placebo), SBP (ertugliflozin 15 mg vs placebo), body weight (ertugliflozin 5 mg vs placebo), SBP (ertugliflozin 5 mg vs placebo), FPG

(ertugliflozin 15 mg followed by ertugliflozin 5 mg, both vs placebo), proportion of patients with A1C <7.0% (ertugliflozin 15 mg followed by ertugliflozin 5 mg, both vs placebo). Each test was to be performed at the two-sided 0.05 level, and continued until a *p*-value ≥0.05 was obtained. Because the *p*-value for the first test in this sequence was ≥0.05, no further hypothesis testing was performed, although *p*-values have been provided for descriptive purposes. No hypothesis testing for efficacy endpoints was planned at Week 52.

Supplementary Table 1. Proportion of patients with available metformin assay results

Number of patients, *n/N* (%)	**Week 6**	**Week 12**	**Week 18**	**Week 26**[a]
Overall cohort				
Placebo	125/151 (82.8)	135/146 (92.5)	128/140 (91.4)	74/122 (60.7)
Ertugliflozin 5 mg	137/155 (88.4)	136/150 (90.7)	130/142 (91.5)	88/128 (68.8)
Ertugliflozin 15 mg	125/148 (84.5)	133/142 (93.7)	130/138 (94.2)	86/132 (65.2)
Stage 3A CKD cohort				
Placebo	84/96 (87.5)	84/91 (92.3)	81/87 (93.1)	45/76 (59.2)
Ertugliflozin 5 mg	94/103 (91.3)	95/101 (94.1)	89/97 (91.8)	59/90 (65.6)
Ertugliflozin 15 mg	80/92 (87.0)	83/89 (93.3)	82/87 (94.3)	58/85 (68.2)
Stage 3B CKD cohort				
Placebo	41/55 (74.5)	51/55 (92.7)	47/53 (88.7)	29/46 (63.0)
Ertugliflozin 5 mg	43/52 (82.7)	41/49 (83.7)	41/45 (91.1)	29/38 (76.3)
Ertugliflozin 15 mg	45/56 (80.4)	50/53 (94.3)	48/51 (94.1)	28/47 (59.6)

n, number of patients with metformin assay results at the stated time point; *N*, number of patients in the full analysis set for A1C who were not rescued at or before the stated time point.

[a]Week 26 samples were available only for patients who agreed to provide a biomarker sample, and therefore fewer patients had metformin assays for that time point.

A1C, glycated hemoglobin; CKD, chronic kidney disease.

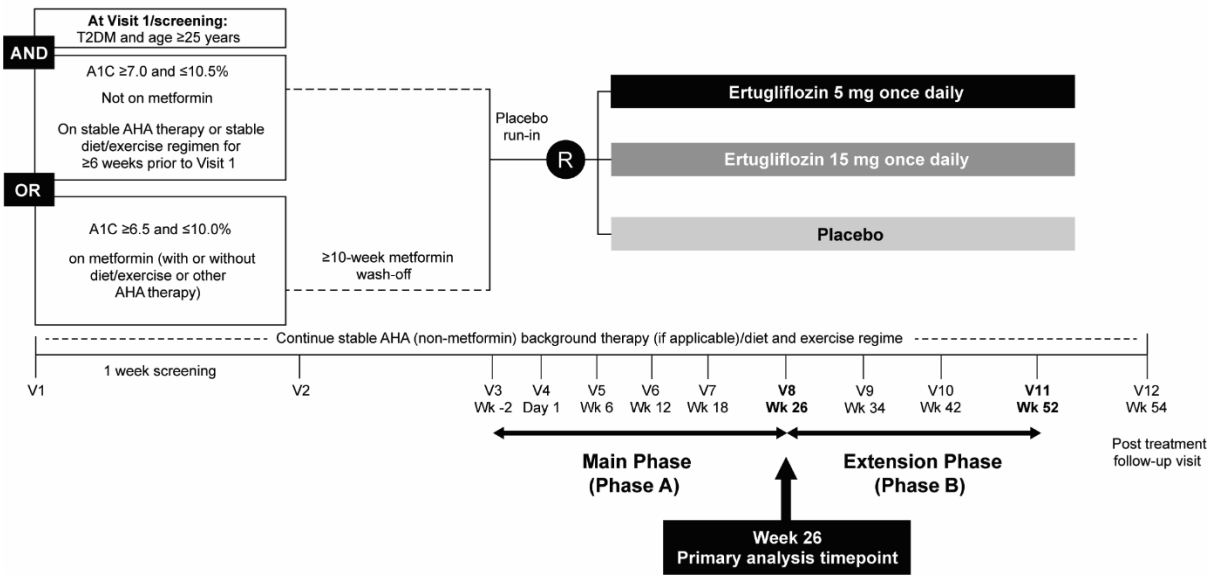
Supplementary Table 2. Cumulative proportion of patients with positive metformin assay results

Number of patients, *n* (%)	**Week 6**	**Week 12**	**Week 18**	**Week 26**
Overall cohort				
Placebo (*n* = 154)	16 (10.4)	20 (13.0)	24 (15.6)	26 (16.9)
Ertugliflozin 5 mg (*n* = 158)	14 (8.9)	22 (13.9)	23 (14.6)	24 (15.2)
Ertugliflozin 15 mg (*n* = 155)	18 (11.6)	23 (14.8)	26 (16.8)	28 (18.1)
Stage 3A CKD cohort				
Placebo (*n* = 99)	12 (12.1)	15 (15.2)	19 (19.2)	20 (20.2)
Ertugliflozin 5 mg (*n* = 105)	9 (8.6)	16 (15.2)	16 (15.2)	16 (15.2)
Ertugliflozin 15 mg (*n* = 97)	16 (16.5)	18 (18.6)	21 (21.6)	22 (22.7)
Stage 3B CKD cohort				
Placebo (*n* = 55)	4 (7.3)	5 (9.1)	5 (9.1)	6 (10.9)
Ertugliflozin 5 mg (*n* = 53)	5 (9.4)	6 (11.3)	7 (13.2)	8 (15.1)
Ertugliflozin 15 mg (*n* = 58)	2 (3.4)	5 (8.6)	5 (8.6)	6 (10.3)

n, number of patients with a positive metformin assay result (i.e., above the limit of quantification) at or before the stated time point; *N*, number of patients in the full analysis set for A1C.

A1C, glycated hemoglobin; CKD, chronic kidney disease.

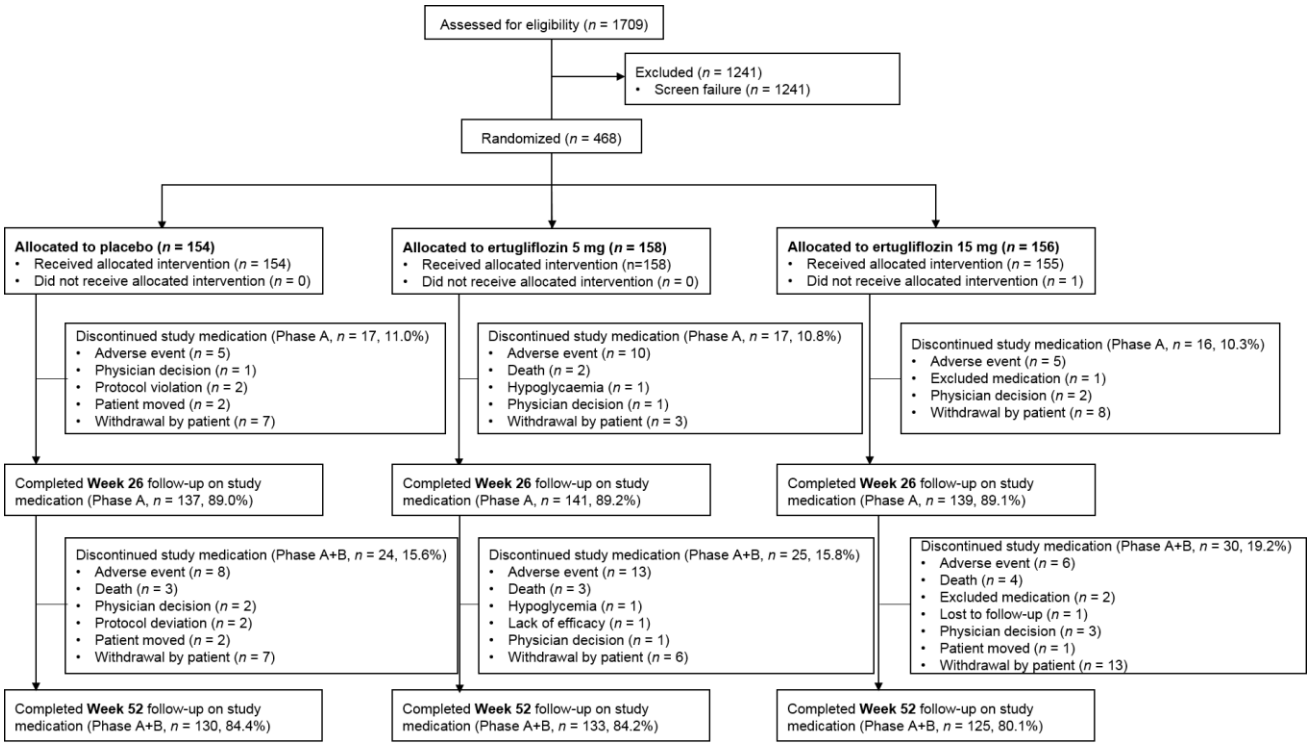
Supplementary Figure 1. Study design



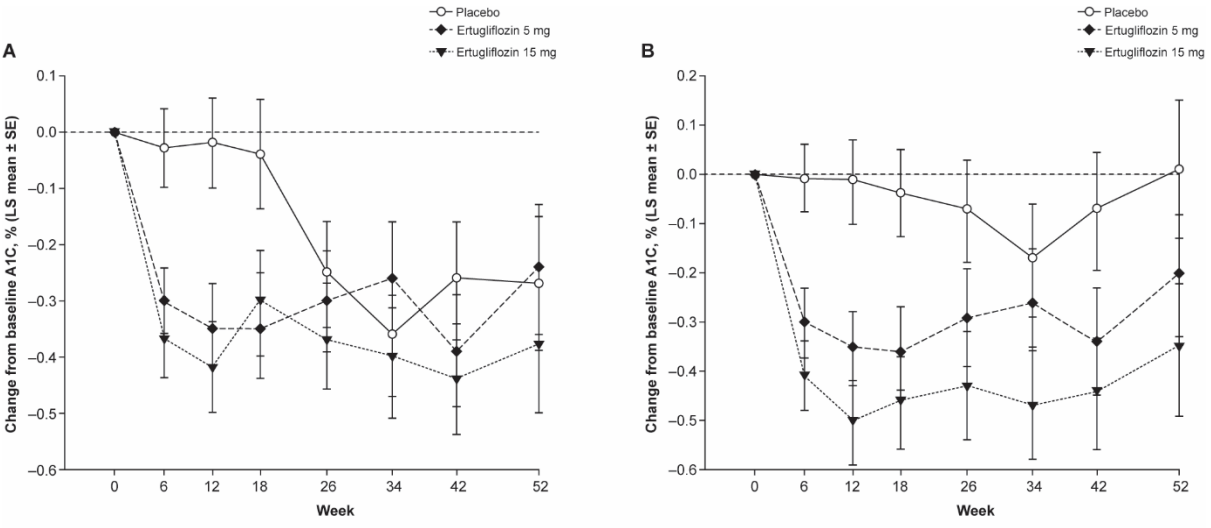
The duration of the trial was up to 67 weeks (with 12 clinic visits) for each patient. This included a 1-week Screening Period (Visit 1 to Visit 2); a variable period (Visit 2 to Visit 3) of at least 3 weeks (allowing assessment for stable renal function in patients on stable therapy with a non-metformin AHA [monotherapy or combination therapy] or diet/exercise alone at Visit 1) or at least 10 weeks (allowing assessment for stable renal function and metformin wash-off for patients on metformin at Visit 1); a 2-week single-blind placebo run-in period (Visit 3 to Visit 4); a 52-week double-blind treatment period (including a 26-week Main Phase [Phase A; Visit 4 to Visit 8] followed by a 26-week Extension Phase [Phase B; Visit 8 to Visit 11]); and a post-treatment visit 14 days after the last dose of blinded study medication to assess renal function and key safety parameters.

A1C, glycated hemoglobin; AHA, antihyperglycemic agent; R, randomization; T2DM, type 2 diabetes mellitus; V, visit, Wk, week.

Supplementary Figure 2. Patient disposition

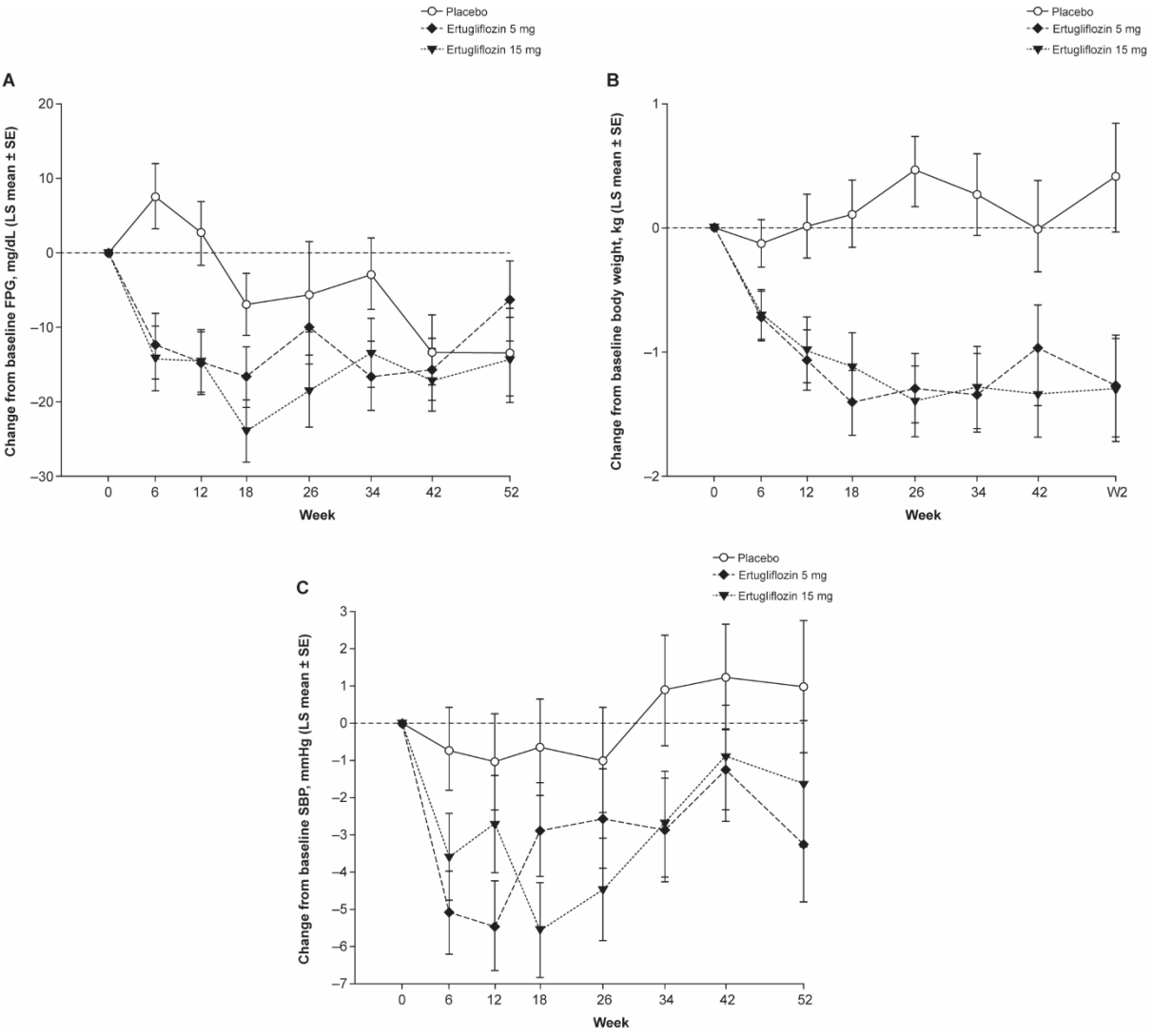


Supplementary Figure 3. Change over time in glycated hemoglobin up to 52 weeks in (A) Stage 3A chronic kidney disease (CKD) cohort (estimated glomerular filtration rate [eGFR] ≥45 to <60 mL/min/1.73 m^2); (B) Stage 3A CKD cohort excluding metformin users (post-hoc analysis)



LS, least squares; SE, standard error.

Supplementary Figure 4. Change over time in the Stage 3A chronic kidney disease cohort (estimated glomerular filtration rate [eGFR] ≥45 to 60 mL/min/1.73 m^2) for up to 52 weeks in (A) fasting plasma glucose; (B) body weight; (C) systolic blood pressure



LS, least squares; SE, standard error.