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ORIGINAL ARTICLE

Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: The VERTIS FACTORIAL randomized trial

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Aim: To evaluate the efficacy and safety of ertugliflozin and sitagliptin co-administration vs the individual agents in patients with type 2 diabetes who are inadequately controlled with metformin.

Methods: In this study (Clinicaltrials.gov NCT02099110), patients with glycated haemoglobin (HbA1c) ≥7.5% and ≤11.0% (≥58 and ≤97 mmol/mol) with metformin ≥1500 mg/d (n = 1233) were randomized to ertugliflozin 5 (E5) or 15 (E15) mg/d, sitagliptin 100 mg/d (S100) or to co-administration of E5/S100 or E15/S100. The primary endpoint was change from baseline in HbA1c at Week 26.

Results: At Week 26, least squares mean HbA1c reductions from baseline were greater with E5/S100 (−1.5%) and E15/S100 (−1.5%) than with individual agents (−1.0%, −1.1% and −1.1% for E5, E15 and S100, respectively; $P < .001$ for all comparisons). HbA1c <7.0% (<53 mmol/mol) was achieved by 26.4%, 31.9%, 32.8%, 52.3% and 49.2% of patients in the E5, E15, S100, E5/S100 and E15/S100 groups, respectively. Fasting plasma glucose reductions were significantly greater with E5/S100 and E15/S100 compared with individual agents. Body weight and systolic blood pressure (SBP) significantly decreased with E5/S100 and E15/S100 vs S100 alone. Glycaemic control, body weight and SBP effects of ertugliflozin were maintained to Week 52. Genital mycotic infections were more common among ertugliflozin-treated patients compared with those treated with S100. Incidences of symptomatic hypoglycaemia and adverse events related to hypovolaemia or urinary tract infection were similar among groups.

Conclusions: In patients with uncontrolled type 2 diabetes while using metformin, co-administration of ertugliflozin and sitagliptin provided more effective glycaemic control through 52 weeks compared with the individual agents.

KEYWORDS

clinical trial, DPP-IV inhibitor, glycaemic control, phase III study, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Current guidelines recommend that a single agent be added to treatment in patients with inadequate glycaemic control with metformin monotherapy.[1] Although some patients achieve glycaemic control with dual therapy, many, especially those starting at higher HbA1c levels, may not. Further, patients who achieve glycaemic control with dual therapy may experience progressive deterioration of glycaemic control. In some cases, it may be appropriate to consider addition of a combination of two anti-hyperglycemic agents (AHAs) with complementary mechanisms of action, favourable safety profiles and without pharmacokinetic interaction, such as a sodium-glucose cotransporter 2 (SGLT2) and dipeptidyl peptidase-4 (DPP-4) inhibitors.[2] This may provide a more robust and sustained anti-hyperglycaemic effect, resulting in more patients achieving and maintaining glycaemic goals, and could become a useful alternative to the single stepwise anti-hyperglycaemic approach.

Ertugliflozin is an inhibitor of SGLT2, with high selectivity relative to SGLT1.[3,4] Ertugliflozin as monotherapy[5] or as add-on to metformin[6] or metformin and sitagliptin[7] improved glycaemic control and reduced body weight, with a safety profile consistent with that of other SGLT2 inhibitors. Sitagliptin is a DPP-4 inhibitor indicated for treatment of type 2 diabetes.[8] Sitagliptin as monotherapy,[9] or as part of dual[10] or triple[11] therapy for patients with type 2 diabetes, provides clinically meaningful reductions in blood glucose. A pooled safety analysis of data from 14 611 patients demonstrated that sitagliptin 100 mg/d was generally well tolerated in clinical studies of up to 2 years.[12]

This report presents efficacy and safety results from the Phase 3 VERTIS (eValuation of ERTugliflozin efficacy and Safety) FACTORIAL study. The primary objective was to determine whether co-administration of ertugliflozin (5 or 15 mg) with sitagliptin 100 mg provides better glycaemic benefit after 26 weeks compared with the individual agents in patients with type 2 diabetes who were inadequately controlled with metformin.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design

This was a randomized, double-blind, multicentre, 52-week factorial study (VERTIS FACTORIAL) (Protocol MK-8835-005; ClinicalTrials.gov identifier: NCT02099110) that was conducted in 2 phases: after 26 weeks (Phase A) the primary and key secondary hypotheses were assessed; after another 26 weeks (Phase B) longer term efficacy and safety were evaluated.

Eligible patients were ≥18 years of age with type 2 diabetes according to American Diabetes Association guidelines,[13] and HbA1c ≥7.5 and ≤11.0% (≥58 and ≤97 mmol/mol) with stable (≥8 weeks) metformin monotherapy ≥1500 mg/d. Patients receiving ≥1500 mg/d metformin for <8 weeks or receiving <1500 mg/d at screening entered a titration/stabilization period and were eligible after completing 8 weeks of metformin monotherapy ≥1500 mg/d.

Patients were excluded from the study if they had type 1 diabetes, a history of ketoacidosis, an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, serum creatinine ≥1.3 mg/dL (men) or ≥1.2 mg/dL (women), or history of a cardiovascular event within 3 months of screening. Patients treated with any AHA other than protocol-approved agents within 12 weeks of screening were also excluded (Methods, Appendix S1). These agents, with the exception of those used as study treatments or rescue medication, were also prohibited during the study.

Randomization was implemented centrally, using an interactive voice response system/integrated web response system. Eligible patients were randomized equally (using a computer-generated schedule) among 5 treatment groups: ertugliflozin 5 mg (E5), ertugliflozin 15 mg (E15), sitagliptin 100 mg (S100), and the co-administrations E5/S100 and E15/S100. Oral sitagliptin and ertugliflozin were administered as separate tablets once daily, at approximately the same time each morning, without regard to food intake. Ertugliflozin and sitagliptin were packaged identically relative to their matching placebos to maintain blinding. Patients, investigators, contract research personnel (Covance) and the sponsor were blinded to group assignments. The sponsor was unblinded at Week 26 to permit authoring of the Phase A clinical study report. Patients and personnel associated with the conduct of the study at Covance and study sites remained blinded until after completion of Phase B.

Patients received glycaemic rescue therapy with open-label glimepiride (or insulin glargine if glimepiride was not considered appropriate by the investigator) if they met rescue criteria (Methods, Appendix S1). Rescued patients remained blinded.

A subset of patients participated in a mixed-meal tolerance test (MMTT) that was performed at Day 1 and Week 26 (Methods, Appendix S1). Randomization was stratified by participation in the MMTT (yes/no).

The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. All participating patients provided written informed consent prior to participating in study-related activities. The protocol and statistical analysis plan were developed by the sponsors in consultation with an external Scientific Advisory Committee.

2.2 | Endpoints

The primary efficacy endpoint was change from baseline in HbA1c at Week 26. Key secondary efficacy endpoints, also evaluated at Week 26, were: change from baseline in fasting plasma glucose (FPG), body weight and systolic blood pressure (SBP); proportion of patients with HbA1c <7.0% (<53 mmol/mol); and, for the MMTT subset only, change from baseline in β-cell responsivity static component (Φ_s).

Safety endpoints included the number (%) of patients with adverse events (AEs), AEs of special interest (symptomatic hypoglycaemia and AEs associated with genital mycotic infection [gender-specific], urinary tract infection and hypovolaemia) (Methods, Appendix S1).

Patients who experienced symptoms consistent with hypoglycaemia or had blood glucose values ≤70 mg/dL (3.9 mmol/L), regardless

of symptoms, were to complete an entry in a hypoglycaemia assessment log (definitions of hypoglycaemia are given in Methods, Appendix S1).

2.3 | Statistical analysis

The primary study hypotheses were that, after 26 weeks of treatment, co-administration of E5/S100 or E15/S100 in addition to metformin provides a greater reduction from baseline in HbA1c than addition of either individual agent. No hypothesis testing was conducted at Week 52.

A sample size of 250 per group (equivalent to a sample size of 220 per group, accounting for information loss as a result of missing data and the correlation among repeated measures) was estimated to provide ~94% power to detect a difference in HbA1c of 0.4% for each pairwise comparison at a given ertugliflozin dose level, assuming a standard deviation (SD) of 1.2% based on a 2-sided test at a 5% α-level.

Efficacy analyses included all randomized, treated patients who had ≥1 measurement of the efficacy outcome. Observations obtained after initiation of glycaemic rescue therapy were treated as missing in all efficacy analyses. For glycaemic endpoints, the efficacy of E5/S100 and E15/S100 was compared with that of the corresponding dose of ertugliflozin alone and S100 alone. For body weight and SBP endpoints, E5/S100 and E15/S100 were compared only with S100.

A longitudinal data analysis (LDA) model[14] was used to evaluate continuous endpoints, with fixed effects for treatment, baseline eGFR, time (categorical) and interaction of time by treatment, with a constraint that the true mean at baseline is common to all groups, which is valid because of randomization. Missing data were handled implicitly by the model. Logistic regression was used to evaluate the proportion of patients with HbA1c <7.0% (<53 mmol/mol), fitted with terms for treatment, baseline eGFR and baseline HbA1c, with missing data imputed via multiple imputation using the LDA model described above.

An ordered testing procedure was used to control for the type 1 error rate at 0.05 significance (2-sided) (Table S1, Appendix S1). Consistency of treatment effect was assessed across different subgroups including baseline HbA1c categories (Appendix S1). For Week 52 efficacy endpoints, statistical testing was not performed; however, 95% confidence intervals (CIs) are provided for between-group comparisons.

Safety analyses included all randomized, treated patients. All safety analyses at Week 26, except the analysis of serious AEs (SAEs) and discontinuations because of AEs, excluded data acquired following initiation of glycaemic rescue. All safety analyses at Week 52, with the exception of those related to hypoglycaemia, included post rescue observations. *P* values for between-group differences in prespecified AEs were computed using the Miettinen and Nurminen method.[15] Changes in lipid parameters (high-density lipoprotein cholesterol [HDL-C] and low-density lipoprotein cholesterol [LDL-C]) were assessed by an LDA model similar to that used for the primary endpoint. Changes from baseline in eGFR were summarized descriptively. Further details of the study methods are provided in the study protocol in Appendix S2.

3 | RESULTS

This study was conducted in 21 countries across 242 trial centres. The countries and investigators are in Appendix S1. The trial started on April 29, 2014; the last patient completed Phase A on November 11, 2015 and Phase B on May 26, 2016.

3.1 | Patients

A total of 1233 patients were randomized and 1232 treated patients were included in the primary endpoint analysis. Across the groups, ≥89.5% of patients completed 26 weeks with the study drug (Figure S1, Appendix S1). Baseline characteristics were generally similar among groups (Table 1). Overall, patients had a mean baseline HbA1c of 8.5% to 8.6% (69.4 to 70.2 mmol/mol) and a mean eGFR of 91.9 to 92.8 mL/min/1.73 m^2.

3.2 | Efficacy

At Week 26, significantly greater reductions in HbA1c were observed in both co-administration treatment groups compared with individual agents ($P < .001$ for all comparisons) (Table 2). Reductions in HbA1c were observed in all groups at the first post-baseline visit at Week 6 (Figure 1A). Larger reductions in HbA1c were observed in patients with higher baseline HbA1c levels (Table S2, Appendix S1). Greater HbA1c lowering for the co-administrations compared with individual agents was observed across subgroups of age, sex, race or ethnicity (Table S2, Appendix S1).

At Week 26, HbA1c <7.0% (<53 mmol/mol) was achieved by 26.4%, 31.9%, 32.8%, 52.3% and 49.2% of patients in the E5, E15, S100, E5/S100 and E15/S100 groups, respectively. The odds of having HbA1c <7.0% (<53 mmol/mol) at Week 26 were significantly greater in the co-administration groups compared with groups receiving individual agents (Table 2). At Week 26, the co-administrations provided significantly greater reductions in FPG compared with individual agents (Table 2).

At Week 26, significantly greater reductions in body weight and SBP were observed for E5/S100 and E15/S100 vs S100 (all $P \leq .005$) (Table 2, Figure 1B). At Week 26, diastolic blood pressure, which was not included in the ordered testing procedure, decreased from baseline by a similar extent in all groups (Table S3, Appendix S1). Effects on glycaemic control, body weight and SBP were maintained through Week 52 and were generally similar to results at Week 26 (Table 2; Figure 1A and B).

At Week 26, greater reductions in 2-hour post-prandial glucose and total glucose $AUC_{0\text{-}3hr}$ were observed during the MMTT in both co-administration groups compared with the individual-agent groups (Table S4, Appendix S1). The β-cell responsivity static component (Φ_s), a measure of the stimulatory effect of glucose on insulin secretion at steady state,[16] and HOMA-β increased relative to baseline in all groups (Table S4, Appendix S1). There were no meaningful changes from baseline in insulin or C-peptide in any group (data not shown).

The proportion of patients receiving rescue medication was low across groups; fewer patients in the E5/S100 (2.5%) and E15/S100

TABLE 1 Baseline characteristics

	E5 (n = 250)	E15 (n = 248)	S100 (n = 247)	E5/S100 (n = 243)	E15/S100 (n = 244)
Male, n (%)	127 (50.8)	134 (54.0)	154 (62.3)	123 (50.6)	126 (51.6)
Age, years	55.1 (10.1)	55.3 (9.5)	54.8 (10.7)	55.2 (10.4)	55.1 (9.8)
Duration of type 2 diabetes mellitus, years	7.1 (5.4)	7.3 (5.4)	6.2 (5.2)	7.0 (5.6)	6.9 (5.2)
Race, n (%)					
American Indian or Alaska Native	7 (2.8)	4 (1.6)	4 (1.6)	2 (0.8)	4 (1.6)
Asian	22 (8.8)	22 (8.9)	29 (11.7)	22 (9.1)	36 (14.8)
Black or African American	7 (2.8)	6 (2.4)	11 (4.5)	12 (4.9)	10 (4.1)
Multiple	8 (3.2)	11 (4.4)	9 (3.6)	10 (4.1)	6 (2.5)
Native Hawaiian or other Pacific Islander	0	0	1 (0.4)	0	0
White	206 (82.4)	205 (82.7)	193 (78.1)	197 (81.1)	188 (77.0)
Region, n (%)					
North America	76 (30.4)	77 (31.0)	73 (29.6)	74 (30.5)	75 (30.7)
South America	43 (17.2)	42 (16.9)	39 (15.8)	44 (18.1)	42 (17.2)
Europe	104 (41.6)	105 (42.3)	102 (41.3)	104 (42.8)	95 (38.9)
Asia	23 (9.2)	21 (8.5)	25 (10.1)	18 (7.4)	29 (11.9)
Australia/New Zealand	4 (1.6)	3 (1.2)	8 (3.2)	3 (1.2)	3 (1.2)
Body weight, kg	88.6 (22.2)	88.0 (20.3)	89.8 (23.5)	89.5 (20.8)	87.5 (20.5)
BMI, kg/m^2	31.8 (6.2)	31.5 (5.8)	31.7 (6.5)	32.5 (6.7)	31.8 (6.5)
HbA1c, %	8.6 (1.0)	8.6 (1.0)	8.5 (1.0)	8.6 (1.0)	8.6 (1.0)
HbA1c, mmol/mol	70.2 (11.4)	70.2 (11.0)	69.4 (11.3)	70.0 (10.8)	70.1 (10.6)
Fasting plasma glucose, mg/dL	184.1 (52.2)	179.5 (45.7)	177.4 (46.6)	183.8 (44.3)	177.2 (49.4)
Systolic blood pressure, mmHg	129.7 (12.5)	128.9 (12.5)	128.3 (12.2)	130.2 (12.6)	129.1 (13.3)
Estimated glomerular filtration rate, mL/min/1.73 m^2	91.9 (20.6)	92.8 (21.4)	92.6 (18.2)	91.9 (20.4)	92.6 (19.2)

Abbreviations: BMI, body mass index; E5, ertugliflozin 5 mg; E15, ertugliflozin 15 mg; HbA1c, glycated haemoglobin; S100, sitagliptin 100 mg. Data are given as mean (standard deviation) unless otherwise specified.

(0.0%) groups received glycaemic rescue therapy by Week 26 compared with patients in the E5 (6.4%), E15 (2.8%) and S100 (6.5%) groups. At Week 52, 11.1% and 10.7% of patients had received rescue medication in the E5/S100 and E15/S100 groups, respectively, compared with 18.4%, 21.0% and 27.9% of patients in the E5, E15 and S100 groups, respectively.

3.3 | Safety

During both Phase A and Phase A + B, overall incidences of AEs, SAEs and discontinuations following AEs were not meaningfully different across groups (Table 3). Incidences of drug-related AEs were higher in the co-administration groups compared with the S100 group. The most commonly reported drug-related AEs in patients receiving any ertugliflozin treatment were genital mycotic infections; compared with S100, the differences were statistically significant for E15/S100 in women and E5/S100 and E15/S100 in men during Phase A + B. During Phase A + B, 5 patients discontinued study medication because of a genital mycotic infection: 2 patients in the E5 group (both with balanoposthitis), 2 patients in the E15 group (1 with vulvovaginal candidiasis and 1 with vulvovaginal mycotic infection) and 1 patient in the E15/S100 group (with genital candidiasis). No genital mycotic infections were SAEs.

There were 2 deaths during the study. A patient in the E15 group died following an ischaemic stroke on Day 318. This patient, who had a history of smoking, diabetic neuropathy, diabetic angiopathy of the lower extremities, retinopathy and hypertension also underwent a toe amputation on Day 166, following a diagnosis of gangrene on Day 155. A patient in the E15/S100 group died of pancreatic carcinoma 31 days after discontinuation of study medication.

During both Phase A and Phases A + B, incidences of urinary tract infections, hypovolaemia-related AEs and symptomatic hypoglycaemia were similar in all groups (Table 3). Documented hypoglycaemia occurred during Phase A in 5.6%, 5.2%, 3.6%, 5.3% and 9.0% of patients, and during Phases A + B in 6.8%, 6.5%, 5.7%, 7.0% and 11.5% of patients in the E5, E15, S100, E5/S100 and E15/S100 groups, respectively (Table S5, Appendix S1). Two patients, both in the E15 group, had an AE of severe hypoglycaemia. One reported a single episode with a markedly depressed level of consciousness and a finger stick glucose value of 61 mg/dL (3.4 mmol/L). The other reported 7 episodes that required medical assistance, with finger stick glucose values between 61 and 70 mg/dL (3.4 and 3.9 mmol/L).

Treatment with ertugliflozin, as individual agent or co-administered with sitagliptin, resulted in early reductions from baseline in mean eGFR, with marginally greater reductions in the combination treatment groups compared with individual agents. These decreases were modest, were considered not clinically meaningful, and were followed by a return to (or near return to) baseline in all groups, with the exception of the E15/S100 group,

TABLE 2 Key efficacy endpoints at Week 26 and Week 52

		E5 (n = 250)	E15 (n = 248)	S100 (n = 247)	E5/S100 (n = 243)	E15/S100 (n = 244)
HbA1c, %	Baseline, mean (SD)	8.6 (1.0)	8.6 (1.0)	8.5 (1.0)	8.6 (1.0)	8.6 (1.0)
	Week 26, mean (SD)	7.4 (0.9)	7.4 (1.0)	7.3 (1.1)	7.0 (1.0)	7.0 (0.9)
	Change from baseline at Week 26	−1.0 (−1.1, −0.9)	−1.1 (−1.2, −1.0)	−1.1 (−1.2, −0.9)	−1.5 (−1.6, −1.4)	−1.5 (−1.6, −1.4)
	Difference vs ertugliflozin	—	—	—	−0.5 (−0.6, −0.3)[a]	−0.4 (−0.6, −0.3)[a]
	Difference vs sitagliptin	—	—	—	−0.4 (−0.6, −0.3)[a]	−0.5 (−0.6, −0.3)[a]
	Change from baseline at Week 52	−1.0 (−1.1, −0.8)	−0.9 (−1.1, −0.8)	−0.8 (−1.0, −0.7)	−1.4 (−1.5, −1.2)	−1.4 (−1.5, −1.3)
	Difference vs ertugliflozin	—	—	—	−0.4 (−0.6, −0.2)	−0.5 (−0.7, −0.3)
	Difference vs sitagliptin	—	—	—	−0.5 (−0.7, −0.3)	−0.6 (−0.8, −0.4)
HbA1c, mmol/mol	Baseline, mean (SD)	70.2 (11.4)	70.2 (11.0)	69.4 (11.3)	70.0 (10.8)	70.1 (10.6)
	Change from baseline at Week 26	−11.2 (−12.5, −9.9)	−11.8 (−13.1, −10.5)	−11.5 (−12.8, −10.2)	−16.2 (−17.6, −14.9)	−16.6 (−17.9, −15.3)
	Difference vs ertugliflozin	—	—	—	−5.1 (−6.9, −3.2)[a]	−4.8 (−6.6, −3.0)[a]
	Difference vs sitagliptin	—	—	—	−4.7 (−6.6, −2.9)[a]	−5.1 (−6.9, −3.3)[a]
	Change from baseline at Week 52	−10.5 (−12.0, −9.0)	−10.2 (−11.7, −8.6)	−9.0 (−10.6, −7.4)	−14.9 (−16.4, −13.3)	−15.2 (−16.7, −13.7)
	Difference vs ertugliflozin	—	—	—	−4.4 (−6.5, −2.3)	−5.0 (−7.2, −2.9)
	Difference vs sitagliptin	—	—	—	−5.9 (−8.0, −3.7)	−6.2 (−8.4, −4.1)
Patients with HbA1c <7.0% (<53 mmol/mol)	n (%) at Week 26	66 (26.4)	79 (31.9)	81 (32.8)	127 (52.3)	120 (49.2)
	Odds ratio vs ertugliflozin (95% CI)	—	—	—	4.1 (2.7, 6.4)[a]	2.5 (1.7, 3.8)[a]
	Odds ratio vs sitagliptin (95% CI)	—	—	—	3.0 (1.9, 4.5)[a]	2.6 (1.7, 3.9)[a]
	n (%) at Week 52	64 (25.6)	56 (22.6)	66 (26.7)	99 (40.7)	97 (39.8)
	Odds ratio vs ertugliflozin (95% CI)	—	—	—	3.0 (1.9, 4.8)	2. 7 (1.7, 4.2)
	Odds ratio vs sitagliptin (95% CI)	—	—	—	2.4 (1.6, 3.6)	2.2 (1.5, 3.4)
Fasting plasma glucose, mg/dL	Baseline, mean (SD)	184.1 (52.2)	179.5 (45.7)	177.4 (46.6)	183.8 (44.3)	177.2 (49.4)
	Change from baseline at Week 26	−35.7 (−40.0, −31.4)	−36.9 (−41.2, −32.6)	−25.6 (−29.9, −21.2)	−44.0 (−48.3, −39.6)	−48.7 (−53.0, −44.4)
	Difference vs ertugliflozin	—	—	—	−8.2 (−13.8, −2.7)[b]	−11.8 (−17.3, −6.2)[a]
	Difference vs sitagliptin	—	—	—	−18.4 (−24.0, −12.8)[a]	−23.1 (−28.8, −17.5)[a]
	Change from baseline at Week 52	−28.7 (−33.7, −23.6)	−30.8 (−36.1, −25.5)	−15.2 (−20.6, −9.8)	−39.3 (−44.3, −34.2)	−41.8 (−46.8, −36.8)
	Difference vs ertugliflozin	—	—	—	−10.6 (−17.3, −3.9)	−11.0 (−17.8, −4.1)
	Difference vs sitagliptin	—	—	—	−24.1 (−31.0, −17.1)	−26.6 (−33.6, −19.7)
Body weight, kg	Baseline, mean (SD)	88.6 (22.2)	88.0 (20.3)	89.8 (23.5)	89.5 (20.8)	87.5 (20.5)
	Change from baseline at Week 26	−2.7 (−3.1, −2.2)	−3.7 (−4.2, −3.3)	−0.7 (−1.1, −0.2)	−2.5 (−3.0, −2.1)	−2.9 (−3.4, −2.5)
	Difference vs sitagliptin	—	—	—	−1.8 (−2.5, −1.2)[a]	−2.3 (−2.9, −1.6)[a]
	Change from baseline at Week 52	−2.4 (−2.9, −1.8)	−3.2 (−3.8, −2.7)	−0.1 (−0.7, 0.5)	−2.4 (−3.0, −1.8)	−2.8 (−3.4, −2.2)
	Difference vs sitagliptin	—	—	—	−2.3 (−3.1, −1.5)	−2.7 (−3.5, −1.9)

(*Continues*)

TABLE 2 (Continued)

		E5 (n = 250)	E15 (n = 248)	S100 (n = 247)	E5/S100 (n = 243)	E15/S100 (n = 244)
Systolic blood pressure, mmHg	Baseline, mean (SD)	129.7 (12.4)	128.9 (12.5)	128.3 (12.2)	130.2 (12.6)	129.1 (13.3)
	Change from baseline at Week 26	−3.9 (−5.3, −2.5)	−3.7 (−5.1, −2.3)	−0.7 (−2.1, 0.8)	−3.4 (−4.8, −2.0)	−3.7 (−5.1, −2.3)
	Difference vs sitagliptin	—	—	—	−2.8 (−4.7, −0.8)[c]	−3.0 (−4.9, −1.1)[d]
	Change from baseline at Week 52	−2.7 (−4.2, −1.2)	−1.6 (−3.1, 0.0)	−0.2 (−1.8, 1.5)	−2.3 (−3.8, −0.8)	−2.2 (−3.7, −0.7)
	Difference vs sitagliptin	—	—	—	−2.1 (−4.3, 0.0)	−2.0 (−4.2, 0.2)

Abbreviations: CI, confidence interval; E5, ertugliflozin 5 mg; E15, ertugliflozin 15 mg; HbA1c, glycated haemoglobin; S100, sitagliptin 100 mg. Data are given as least squares mean (95% CI) except where stated. n values indicate randomized patients who received at least 1 dose of study medication and had at least 1 assessment. [a]$P < .001$; [b]$P = .004$; [c]$P = .005$; [d]$P = .002$. Statistical testing was not performed at Week 52.

in which a modest decrease from baseline remained through Week 52 (Figure S2, Appendix S1). There were no notable between-group differences in the proportion of patients who had at least 1 eGFR value or a last on-treatment eGFR value >30% or >50% above baseline.

During Phase A + B, there was 1 confirmed case of diabetic ketoacidosis in the E15/S100 group. Three patients had confirmed fracture events: 1 patient in the E5 group (cranium; cause not available), 1 in the E15 group (hand and rib fracture following a fall) and 1 in the E5/S100 group (phalanges fracture after hand struck by door).

At Week 52, mean increases from baseline in LDL-C (9.9%, 9.5%, 10.9%, 10.9% and 10.1%) and HDL-C (6.3%, 7.2%, 0.8%, 6.3% and 9.2%) and median reductions from baseline in triglycerides (5.8%, 5.3%, 3.5%, 5.7% and 2.3%) were observed in each group (E5, E15, S100, E5/S100 and E15/S100, respectively) (Table S6, Appendix S1).

Small mean increases from baseline in haemoglobin were observed at Week 12 (first observation) in the 4 ertugliflozin-treated groups, and continued through Week 52. At Week 52, mean changes in haemoglobin (0.34, 0.40, −0.33, 0.52 and 0.60 g/dL) and in haematocrit (2.0%, 2.1%, −0.2%, 2.4% and 2.8%) were observed in all groups (E5, E15, S100, E5/S100 and E15/S100, respectively).

4 | DISCUSSION

In this study of patients with type 2 diabetes and inadequate glycaemic control with metformin, co-administration of ertugliflozin (5 or 15 mg) with sitagliptin (100 mg) provided significantly greater improvements in measures of glycaemic control compared with addition of either a corresponding dose of ertugliflozin or sitagliptin after 26 weeks. A reduction in HbA1c of ~1% was observed by Week 6 (the first post-randomization visit) in the co-administration groups, suggesting that this approach may allow poorly controlled patients to improve HbA1c values relatively quickly. The effects of ertugliflozin and sitagliptin (as individual agents or when co-administered) on glycaemic control were maintained through 52 weeks.

Despite mean baseline HbA1c values of 8.5% to 8.6% (69.4 to 70.2 mmol/mol), ~50% of patients achieved the target HbA1c of <7.0% (<53 mmol/mol) after 26 weeks of treatment with ertugliflozin + sitagliptin, compared with ~30% of patients treated with the individual agents. Likewise, after 52 weeks of treatment, ~40% of patients achieved the goal with ertugliflozin + sitagliptin therapy compared with ~25% of those using individual agents. The HbA1c benefit of adding ertugliflozin + sitagliptin co-administration therapy over the individual agents was consistent across baseline HbA1c sub-categories. These findings suggest that patients who are poorly controlled with metformin alone can obtain greater glycaemic control from direct advancement to co-administration therapy with 2 additional AHAs.

The effects of ertugliflozin on body weight observed in this study are consistent with those observed in other Phase 3 studies of ertugliflozin[5–7] and other SGLT2 inhibitors.[17] In the present

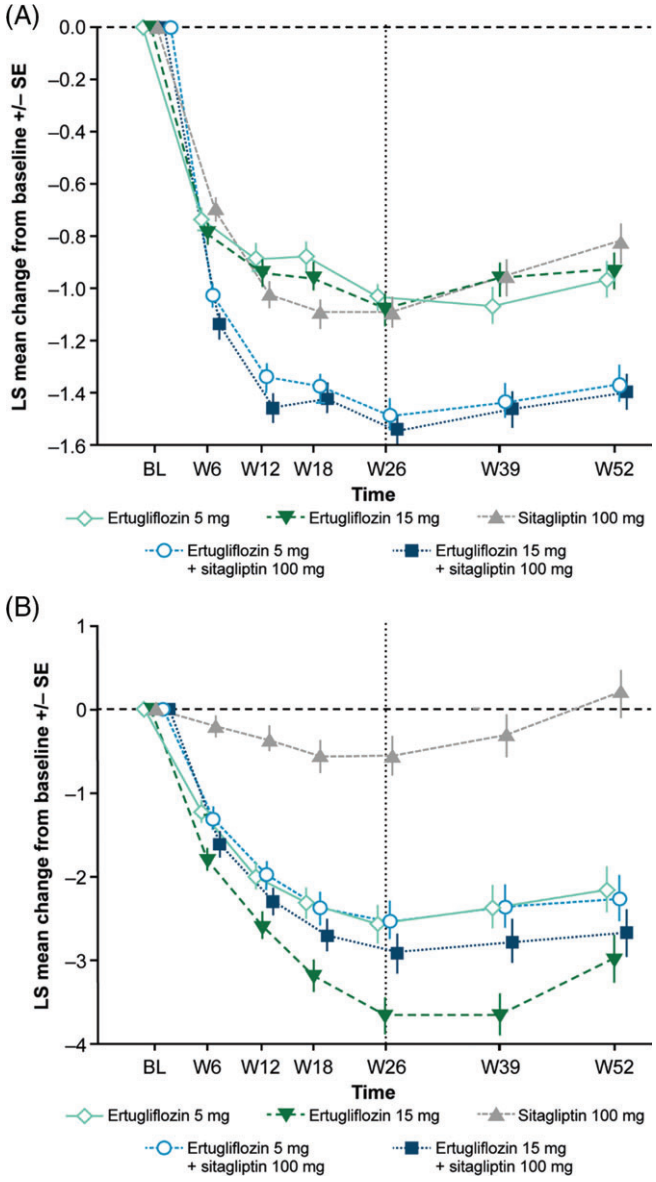

FIGURE 1 Change over time in (A), glycated haemoglobin (HbA1c) (%) and (B), body weight (kg). LS, least squares; SE, standard error

study, meaningful differences in the glycaemic efficacy of ertugliflozin 5 or 15 mg, alone or in combination with sitagliptin, were not observed. Co-administration studies may not be the ideal studies in which to discern differences between ertugliflozin doses. Two ertugliflozin doses were selected for Phase 3 studies, as dose-response modeling indicated that ertugliflozin 5 and 15 mg would provide 80% and 90% of maximal efficacy.[4,18] Although not powered to detect between-dose differences, in a monotherapy study, an add-on to metformin study, and an add-on to metformin + sitagliptin study, the 15 mg dose provided 0.2%,[5] 0.2%[6] and 0.1%[7] greater reductions in HbA1c compared with the 5 mg dose, suggesting that the higher dose is generally associated with greater SGLT2 inhibition and efficacy.

The degree of additivity between ertugliflozin and sitagliptin when co-administered was as predicted by the quantitative model of Polidori et al.,[19] who systematically examined the additivity of AHAs across 8 studies in which simultaneous initiation of combination therapy was compared with the individual agents. The analysis included data from 4 AHA classes (metformin, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors). In all cases, efficacy in the combination arms was less than the sum of the efficacy of the individual treatment arms. On average, additivity was ~78% across the studies, which is in good agreement with the additivity observed in our study. Polidori et al. note that AHA efficacy is influenced by baseline HbA1c; therefore, when initiating 2 agents, 1 agent can be considered to lower the baseline HbA1c for the other. When Polidori et al. incorporated this effective reduction in baseline HbA_{1c} caused by the first agent into their model, it was found to accurately predict the observed efficacy of combination therapy.

The difference in HbA1c reduction for ertugliflozin + sitagliptin co-administration, compared with either individual agent (~0.5%), is generally consistent with that observed in a previous study comparing empagliflozin and linagliptin co-administration with either individual agent.[20] In a study of dapagliflozin and saxagliptin, the combination provided 0.3% and 0.6% greater reduction in HbA1c vs dapagliflozin or saxagliptin alone, respectively.[21] HbA1c entry criteria may explain the differences in HbA1c reductions from baseline after SGLT2/DPP-4 inhibitor treatment that was observed between these studies. Mean baseline HbA1c values in the current study (8.5%–8.6% [69–70 mmol/mol]) fall between those in the studies discussed above (7.9%-8.0% [63-64 mmol/mol][20] and 8.9%–9.0% [73–74 mmol/mol][21]).

The ertugliflozin + sitagliptin safety profile was consistent with that of the individual agents[5–7,17] with no evident unique safety issues. There was no meaningful difference in the incidence of urinary tract infections among groups. Hypovolaemia and symptomatic hypoglycaemia AEs were infrequent. The incidence of documented hypoglycaemia was low in all groups, with no clinically meaningful differences between the ertugliflozin + sitagliptin co-administration groups and the individual-agent groups, a finding consistent with previous studies of SGLT2 and DPP-4 inhibitors.[12,20–23] An increased incidence of genital mycotic infections is expected with SGLT2 inhibitors because of the increased renal excretion of glucose with these agents; indeed, a higher incidence of genital mycotic infections was observed in the ertugliflozin-containing groups compared with sitagliptin groups, and a similar incidence was observed between groups receiving ertugliflozin as an individual agent or receiving it co-administered with sitagliptin.

Transient, reversible decreases in renal function, probably haemodynamic in nature, have been associated with SGLT2 inhibitors and there have been post-marketing reports of infrequent events of acute renal injury.[24] However, long-term data from the empagliflozin and canagliflozin cardiovascular outcome studies (EMPA-REG and CANVAS) showed that the progression of kidney disease was slowed with empagliflozin or canagliflozin treatment.[25,26] In the sitagliptin cardiovascular safety study (TECOS), a small reduction in eGFR was observed early on, which was not progressive over time; the mean change from baseline in eGFR was −4.0 mL/min/1.73 m^2 in the sitagliptin group vs −2.8 mL/min/1.73 m^2 in the placebo group at 48 weeks.[27]

Consistent with observations concerning other SGLT2 inhibitors,[17,28] in the current study LDL-C levels increased slightly in

TABLE 3 Safety summary and prespecified adverse events (AEs)

		E5 (n = 250)	E15 (n = 248)	S100 (n = 247)	E5/S100 (n = 243)	E15/S100 (n = 244)
One or more AEs	Week 26 (ER)	128 (51.2)	107 (43.1)	103 (41.7)	111 (45.7)	114 (46.7)
	Week 52 (IR)	155 (62.0)	143 (57.7)	142 (57.5)	143 (58.8)	136 (55.7)
AEs related to study drug[a]	Week 26 (ER)	42 (16.8)	30 (12.1)	12 (4.9)	27 (11.1)	39 (16.0)
	Week 52 (IR)	49 (19.6)	40 (16.1)	21 (8.5)	36 (14.8)	50 (20.5)
Serious AEs	Week 26 (IR)	8 (3.2)	3 (1.2)	4 (1.6)	6 (2.5)	4 (1.6)
	Week 52 (IR)	12 (4.8)	5 (2.0)	8 (3.2)	9 (3.7)	12 (4.9)
Deaths	Week 26 (IR)	0	0	0	0	0
	Week 52 (IR)	0	1 (0.4)	0	0	1 (0.4)[b]
Discontinuations following an AE	Week 26 (IR)	6 (2.4)	3 (1.2)	1 (0.4)	3 (1.2)	7 (2.9)
	Week 52 (IR)	8 (3.2)	8 (3.2)	7 (2.8)	8 (3.3)	9 (3.7)
Prespecified AEs						
Genital mycotic infection (female)	Week 26 (ER)	6 (4.9)	8 (7.0)	1 (1.1)	6 (5.0)	9 (7.6)[c]
	Week 52 (IR)	6 (4.9)	8 (7.0)	2 (2.2)	9 (7.5)	11 (9.3)[c]
Genital mycotic infection (male)	Week 26 (ER)	6 (4.7)	5 (3.7)	0	5 (4.1)[c]	3 (2.4)
	Week 52 (IR)	8 (6.3)	7 (5.2)	0	5 (4.1)[c]	5 (4.0)[c]
Urinary tract infection	Week 26 (ER)	13 (5.2)	14 (5.6)	8 (3.2)	8 (3.3)	9 (3.7)
	Week 52 (IR)	22 (8.8)	21 (8.5)	13 (5.3)	17 (7.0)	12 (4.9)
Symptomatic hypoglycaemia[d]	Week 26 (ER)	6 (2.4)	6 (2.4)	6 (2.4)	6 (2.5)	12 (4.9)
	Week 52 (ER)	7 (2.8)	8 (3.2)	7 (2.8)	7 (2.9)	15 (6.1)
Hypovolaemia	Week 26 (ER)	4 (1.6)	2 (0.8)	0	0	0
	Week 52 (IR)	7 (2.8)	4 (1.6)	1 (0.4)	0[e]	2 (0.8)

Abbreviations: AE, adverse event; E5, ertugliflozin 5 mg; E15, ertugliflozin 15 mg; ER, analysis excludes events occurring after rescue medication; HbA1c, glycated haemoglobin; IR, analysis includes events occurring after rescue medication; S100, sitagliptin 100 mg. Data are given as n (%).

[a] Determined by the investigator to be related to the study drug.

[b] Death in the E15/S100 group occurred off-treatment during the post-study follow-up period.

[c] $P < .05$ vs S100.

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

[e] $P < .05$ vs E5.

all groups, possibly explained by reduced LDL-C catabolism.[28] Small decreases in triglycerides have been observed with other SGLT2 inhibitors,[17] while, in the current study, triglyceride levels were reduced in the co-administration groups compared with the individual-agent groups. This difference may be related to improved glycaemic control in the co-administration groups. Observed small changes in haemoglobin and haematocrit were not considered clinically meaningful.

Study limitations include the relatively short-term duration (52 weeks); additional studies are needed to assess long-term benefits of initial combination therapy compared with sequential addition of anti-hyperglycaemic agents.

To summarize, in patients with type 2 diabetes who are inadequately controlled with metformin, co-administration of ertugliflozin and sitagliptin provided effective and sustained glycaemic control over 52 weeks compared with corresponding doses of ertugliflozin or sitagliptin, and reduced body weight and SBP over 52 weeks compared with sitagliptin. Ertugliflozin demonstrated a safety profile consistent with that of the SGLT2 inhibitor class over 52 weeks of treatment.

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Conflict of interest

R. E. P. is a consultant (fees paid to institution) for AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., GlaxoSmithKline, Hanmi Pharmaceutical Co., Ltd, Janssen Pharmaceuticals, Inc., Ligand Pharmaceuticals, Inc., Lilly, Merck & Co., Inc., Kenilworth, New Jersey, Novo Nordisk Inc. and Takeda; has received research support from Merck & Co., Inc., Kenilworth, New Jersey, Sanofi-Aventis US, LLC, Takeda, Lilly and Novo Nordisk Inc.; is on speaker's bureaus (fees paid to institution) for AstraZeneca and Novo Nordisk Inc.; and reports other funding from Novo Nordisk Inc. A. R., G. G., S. B. H., S. S., J. J, S. S. E. and B. L. are employees of Merck Sharp & Dohme Corp., a

subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, and may own stock and/or hold stock options in the company. R. E. was an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey at the time the study was conducted. Y. Q. is an employee of MSD R & D (China) Co., Ltd., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey and may own stock and/or hold stock options in the company. S. G. T. and J. P. M. are employees and shareholders of Pfizer Inc.

Author contributions

R. E. P. contributed to the analysis and interpretation of data, and acted as coordinating investigator. R. E. contributed to the concept and study design, and acquisition, analysis and interpretation of data. A. R. contributed to the acquisition and interpretation of data. G. G. contributed to the concept and study design, analysis and interpretation of data, and provided statistical expertise. S. B. H. contributed to the analysis and interpretation of data and provided statistical expertise. Y. Q. contributed to the analysis and interpretation of data and provided statistical expertise. S. S. contributed to the concept and study design and interpretation of data. J. J. contributed to the concept and study design and interpretation of data. S. G. T. contributed to the concept and study design, analysis and interpretation of data, and drafting the manuscript. J. P. M. contributed to the concept and study design and interpretation of data, and provided statistical expertise. S. S. E. contributed to the concept and study design and interpretation of data. B. L. contributed to the concept and study design, acquisition of data, analysis and interpretation of data, and drafting the manuscript. In addition, R. E., A. R., S. S. E., G. G., S. B. H., J. J., B. L., Y. Q., S. S., S. G. T. and J. P. M. contributed to drafting the clinical study report. The authors are responsible for the work described in this paper. All authors reviewed and edited the manuscript for important intellectual content and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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