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REVIEW

Spotlight on ertugliflozin and its potential in the treatment of type 2 diabetes: evidence to date

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Abstract: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the latest therapeutic strategy in the treatment of type 2 diabetes mellitus (T2DM). Using an insulin-independent mechanism (glycosuria), they reduce glucose toxicity and improve insulin sensitivity and β-cell function. The promising results obtained in clinical trials show that SGLT2 significantly improves glycemic control and provides greater cardiovascular protection, combined with a reduction in body weight and blood pressure (BP). This review focuses on ertugliflozin, a new, highly selective, and reversible SGLT2 inhibitor. Clinical trials published to date show that ertugliflozin, both as a monotherapy and as an add-on to oral antidiabetic agents, is safe and effective in reducing glycosylated hemoglobin (HbA1c), body weight, and BP in T2DM patients.

Keywords: antidiabetic drugs, glycosylated hemoglobin, glycemic control, sodium-glucose cotransporter 2 inhibitors, precision medicine, type 1 diabetes mellitus, type 2 diabetes mellitus, weight reduction

Introduction

The role of kidneys in maintaining glucose homeostasis is well known, but they have only recently become a therapeutic target in patients with type 2 diabetes mellitus (T2DM). Kidneys transfer all plasma glucose into urine within the nephron but subsequently completely reabsorb the filtered glucose through two types of sodium-glucose cotransporters (SGLTs),[1] unless plasma glucose reaches a threshold of ~180 mg/dL. Thus, under physiological conditions, no glucose is present in urine. When the concentration of plasma glucose exceeds this threshold, SGLTs become saturated and glucose in excess is excreted through urine (glycosuria), a typical sign of diabetes.[2] Hyperglycemia increases the renal threshold for glycosuria, and the kidney itself contributes to the progression of hyperglycemia by increasing glucose reabsorption in response to an elevated threshold for glycosuria and by an increase in maximum glucose reabsorptive capacity.[3]

SGLTs belong to a large family of sodium-glucose cotransporters: the sodium/glucose cotransport family SLC5.[4] Two major SGLT isoforms have been described: SGLT2, which is highly expressed in the brush border of epithelial cells in S1 and S2 segments of proximal renal tubules, and SGLT1, expressed primarily in the small intestine, the S3 segment of the proximal renal tubule, and in the myocardium.[5]

In healthy humans, under normal physiological conditions, SGLT2 is responsible for 80%–90% of renal glucose reabsorption and SGLT1 for the remaining 10%–20%.[6] These proteins carry glucose through the membranes of the proximal tubule epithelial cell in an active process that involves sodium transportation, facilitated by the sodium gradient between the tubule and the cell, which supports secondary active cotransport

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of glucose. Glucose then passively diffuses into the intercellular space, mainly via the GLUT2 (glucose transporter 2), a member of the GLUT protein family.[7]

Data from animal models of diabetes and from preclinical human studies suggest that hyperglycemia in T2DM is associated with a significantly increased expression of SGLT2 and GLUT2 proteins.[8] However, a recent paper published by Ferrannini et al reports a reduction of SGLT2 expression in diabetic patients with preserved renal function, raising the possibility that a higher expression may be limited to diseased kidneys.[9]

Despite the latter controversy, SGLT2 has become a new successful therapeutic target for the treatment of diabetes. In fact, blocking SGLT2 via selective inhibitors increases the excretion of glucose from the body (via inhibition of renal glucose reabsorption), thereby reducing hyperglycemia in T2DM. Glycosuria induced by SGLT2 inhibitors (SGLT2is) provides relief from glucose toxicity,[10,11] thus improving β-cell insulin secretion and insulin sensitivity in peripheral tissues, leading to a further reduction in plasma glucose concentration.[12] Added benefits are a significant reduction in blood pressure (BP)[13] and body weight, even though the latter is lower than expected considering the constant calorie loss through glycosuria (200 kcal/day for a daily loss of 50 g of glucose).[14]

SGLT2is (aka gliflozins) also seem to provide important cardioprotective benefits, although the mechanism is, intriguingly, still unknown.[15,16] Treatment with gliflozins induces a switch in energy source, from glucose to fat, leading to two main metabolic consequences: a reduction in glucose oxidation and an increase in free fatty acid oxidation with the stimulation of ketogenesis.[14] The latter process has given rise to the "Thrifty Substrate" hypothesis proposed by Ferrannini et al to provide a potential explanation for the clinically observed cardiovascular (CV) benefits. The selection of b-hydroxybutyrate instead of fatty acids by the heart may enhance the efficiency at the mitochondrial level and may be responsible for the improved myocardial performance.[17] Lopaschuk and Verma, on the other hand, have proposed a contrasting hypothesis: gliflozins may inhibit myocardial ketone oxidation with a consequent reduction in Acetyl-CoA. This leads to a reduction of detrimental hyper-acetylation of mitochondrial enzymes and to increased pyruvate oxidation derived from glucose. These two actions might be responsible for an improvement in mitochondrial energy production and myocardial metabolism.[18]

Besides this controversy, two recent clinical trials with empagliflozin and canagliflozin (EMPAREG and CANVAS, respectively), involving subjects with T2DM and high CV risk, have shown, to a different extent, a significant reduction in death from major adverse CV events (3-point MACE – Composite Endpoint of Major Adverse Cardiovascular Events: CV death, non-fatal myocardial infarction, or non-fatal stroke).[15,16,19] An ongoing Phase III study (currently non-recruiting) will study the CV outcomes in T2DM participants with vascular disease following ertugliflozin treatment versus placebo (ClinicalTrials.gov NCT01986881).

Given this reduction in MACE events, SGLT2is are increasingly being used to treat T2DM. However, there is still a general consensus that metformin should be used as first-line therapy for T2DM, because in addition to lowering hepatic glucose production, it has a mild effect on peripheral resistance and could also be cardioprotective, especially in obese T2DM patients in primary prevention.[20] SGLT2is are thus recommended as second- or third-line therapy for managing hyperglycemia in T2DM patients.[21,22] This topic deserves a review of its own and therefore will not be discussed further in this article.

SGLT2is are also known to induce short- and long-term reduction in BP.[23] As expected, considering their mechanism of action, SGLT2is are effective in reducing both systolic (SBP) and diastolic blood pressure (DBP), likely due to glucose-driven osmotic diuresis, as shown by increases in hematocrit and decreases in body weight.[24] Osmotic diuresis leads to the excretion of glucose and water, resulting in increased urinary output ranging from ~110 to 470 mL/day.[24]

As indicated by Mosley et al,[25] SGLTi treatment can lead to hypotension and dehydration in elderly T2DM patients (ie, 65 years and older). It is therefore critical to train these patients to recognize dehydration symptoms (eg, dizziness, lightheadedness, and fainting) and orthostatic hypotension and to prevent dehydration by drinking adequate amounts of fluids.[26]

Diuresis, however, accounts only for the short-term BP reduction induced by SGLT2is. Previous studies have observed that urine volume returns to pretreatment levels after ~12 weeks of treatment with SGLT2is, whereas BP reduction persists,[27,28] implying that diuresis is not the only mechanism involved. Other possible mechanisms, accounting particularly for long-term BP reduction, include nephron remodeling, reduction in arterial stiffness, and loss of body weight.[29] The renin–angiotensin system (RAS) plays a major role in the regulation of BP and fluid volume. Although the systemic RAS is important, the locally acting RAS, particularly that of the kidneys, is critical. There is a concern that

Table 1 SGLT2/SGLT1 selectivity of main SGLT inhibitors[33–37]

Molecule	SGLT2 (IC50 nM)	SGLT1 (IC50 nM)	SGLT2 selectivity over SGLT1
Empagliflozin	3.1	8,300	~2,500-fold
Ertugliflozin	0.87	1,960	~2,000-fold
Dapagliflozin	1.2	1,400	~1,200-fold
Canagliflozin	2.7	710	~250-fold
Sotagliflozin	1.8	36	~20-fold
Phlorizin	2,800	4,200	~1.5-fold

Abbreviations: IC50, half-maximal inhibitory concentration; SGLT, sodium-glucose cotransporter.

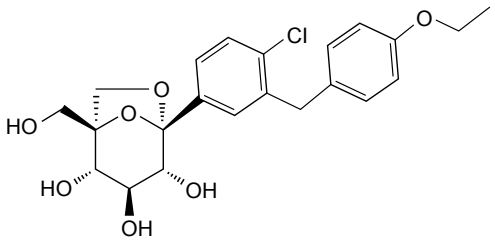

Figure 1 Molecular structure of ertugliflozin: (1S,2S,3S,4R,5S)-5-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-1-hydroxymethyl6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol (PF-04971729).

the sodium/volume loss induced by SGLT2is could activate the RAS, indeed Cherney et al[30] have reported that total angiotensinogen excretion, a marker of local RAS activity in the kidney,[31] significantly increases in type 1 diabetic patients (T1DM) treated with SGLT2is. A recent study, however, has shown that the total urinary angiotensinogen/creatinine ratio and intact angiotensinogen/creatinine ratio tended to decrease in T2DM patients treated with SGLT inhibitors.[32]

Several SGLT inhibitors have currently been approved in Europe and the USA (dapagliflozin, canagliflozin, and empagliflozin) while others are still under investigation (sotaglifozin and ertugliflozin). The main selectivity differences are summarized in Table 1.[33–37]

This review focuses on the efficacy and safety of the highly selective and reversible SGLT2i ertugliflozin.

Methods

A systematic literature search was conducted using electronic databases, including PubMed and Web of Science. Different keywords were used to identify key papers related to preclinical and human studies on ertugliflozin, including "ertugliflozin" or "PF-04971729" or "SGLT2 inhibitors" or "type 2 diabetes mellitus."

We focused our selection, prioritizing randomized controlled clinical trials with ertugliflozin and other SGLT2is. We also focused on meta-analyses and systematic reviews. Reference lists of the principal articles considered were used to find additional relevant papers. No restrictions were adopted for other study characteristics, such as numbers of subjects enrolled, endpoints, and so on.

Ertugliflozin: pharmacokinetics, metabolism, and excretion

Ertugliflozin (PF-04971729) is a novel molecule belonging to a new class of SGLT2is incorporating a unique dioxa-bicyclo [3.2.1] octane (bridged ketal) ring system (Figure 1), which has demonstrated remarkable selectivity in vitro (>2,000-fold) for SGLT2 receptors over SGLT1 and revealed a concentration-dependent glycosuria after oral administration in rats.[33]

An open-label Phase I study showed that plasma concentration peaks ~1 hour after administration of a single oral dose of [^{14}C]-Ertugliflozin 25 mg in healthy male subjects, indicating rapid oral absorption. Systemic exposure was dose proportional over the dose range of 0.5–300 mg, while elimination half-life was about 17 hours, making once-a-day dosing possible.[38]

Furthermore, ertugliflozin was found to be highly bound to plasma protein (96% in rats and dogs, 94% in humans) and binding was independent of concentration in the various species.[39]

Its primary biotransformation pathway is glucuronidation, through UDP-glucuronosyltranferase isozyme IA9, which is involved in the formation of the two main ertugliflozin metabolites: ertugliflozin-4-β-O-glucuronide and ertugliflozin-3-β-O-glucuronide (M4a and M4c). The oxidative metabolic pathway plays a lesser role, through cytochrome P450 (P450), to yield monohydroxylated metabolites (M1 and M3) and des-ethyl ertugliflozin (M2). Renal excretion of unchanged ertugliflozin is considered negligible, whereas almost half of the orally administered dose is recovered as urinary metabolites (Figure 2).[40]

Given the recent advent of fixed-dose combination drugs (FDCs), an ertugliflozin-sitagliptin FDC trial was conducted and has recently been completed. This open-label, randomized, three-period, single-dose, crossover study, in which 12 healthy adult subjects received ertugliflozin 15 mg, sitagliptin 100 mg and ertugliflozin plus sitagliptin, showed that coadministration of ertugliflozin and sitagliptin had no effect on either ertugliflozin AUC_{inf} or C_{max}; similarly, ertugliflozin did not affect sitagliptin AUC_{inf} or C_{max}. Analogous results were obtained with metformin. The absence of pharmacokinetic interaction demonstrates that ertugliflozin can be coadministered with both sitagliptin and metformin without dose adjustments.[41]

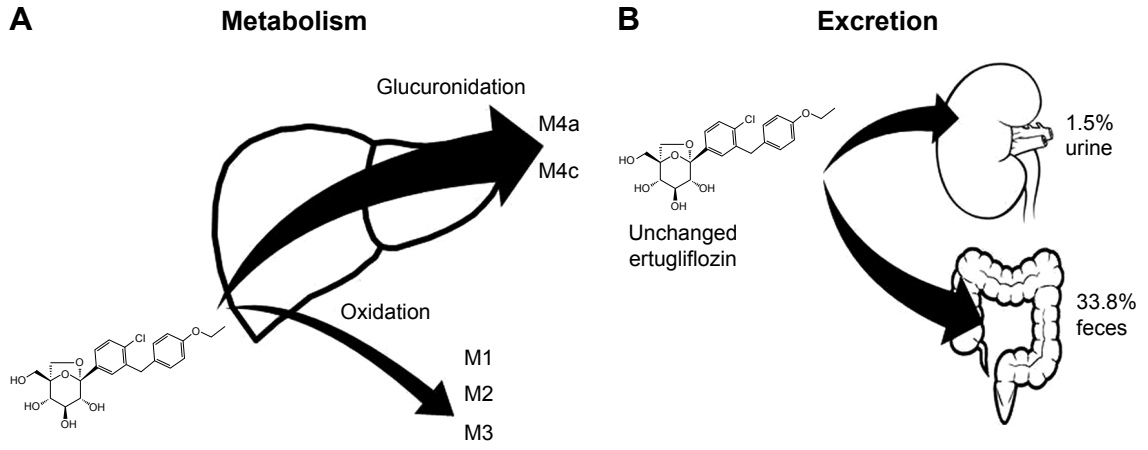

Figure 2 (**A**) Hepatic metabolism of ertugliflozin. Its primary biotransformation pathway is glucuronidation, through UDP-glucuronosyltranferase isozyme IA9, which is involved in the formation of the two main ertugliflozin metabolites: ertugliflozin-4-β-O-glucuronide and ertugliflozin-3-β-O-glucuronide (M4a and M4c). Oxidative metabolic pathway plays a lesser role, through cytochrome P450 (P450), to yield monohydroxylated metabolites (M1 and M3) and des-ethyl ertugliflozin (M2). (**B**) Excretion of unchanged ertugliflozin.

As renal impairment is a common comorbidity in T2DM, the effect of renal impairment on pharmacokinetics and pharmacodynamics has been evaluated in T2DM subjects. A single oral dose of ertugliflozin 15 mg was administered to normal subjects and to subjects with varying degrees of renal impairment. As expected, systemic exposure to ertugliflozin increased by <2-fold in subjects with renal impairment compared to subjects with normal renal function, and 24-hour urinary glucose excretion decreased with declining renal function, due to decreased filtered glucose load. Ertugliflozin is therefore well tolerated in subjects with normal renal function and in T2DM subjects with renal impairment.[42]

Studies on ertugliflozin

The efficacy and safety of ertugliflozin, as monotherapy and as add-on/combination therapy with other antidiabetic drugs in patients with diabetes mellitus, is currently being established through a series of Phase II and Phase III trials, the VERTIS Studies: eValuation of ERTugliflozin effIcacy and Safety. To date, there are six completed Phase III studies, whose main characteristics are illustrated in Table 2.

Efficacy

Blood glucose control

In a Phase II study, ertugliflozin was evaluated at doses ranging from 1 to 25 mg (1, 5, 10, 25 mg) once-daily, in patients with T2DM in treatment with stable doses of metformin, compared with sitagliptin 100 mg and placebo; mean HbA1c decreased from baseline to week 12 in all ertugliflozin groups (from −0.45% to −0.72% depending on the treatment group), compared with placebo. In particular, doses of more than 5 mg/day yielded an effect on HbA1c that was numerically

Table 2 Phase III completed clinical trials

Study	No of patients	Duration (weeks)	Background therapy	Arms				
VERTIS MONO[44,45]	461	26+26	Diet and exercise	ERTU 5 mg	ERTU 15 mg	Placebo (phase A)/ metformin (phase B)		
VERTIS MET[46]	621	26+26	Metformin ≥1,500 mg die	ERTU 5 mg	ERTU 15 mg	Placebo		
VERTIS FACTORIAL[47,48]	1,233	26+26	Metformin ≥1,500 mg die	ERTU 5 mg	ERTU 15 mg	Sita 100 mg	ERTU 5 mg + SITA 100 mg	ERTU 15 mg + SITA 100 mg
VERTIS SITA[49]	291	26	Diet and exercise	ERTU 5 mg + SITA 100 mg	ERTU 15 mg + SITA 100 mg	Placebo		
VERTIS SITA2[50,51]	463	26+26	Metformin ≥1,500 mg die + Sitagliptin 100 mg die	ERTU 5 mg	ERTU 15 mg	Placebo		
VERTIS SU[52]	1,326	52	Metformin ≥1,500 mg die	ERTU 5 mg	ERTU 15 mg	Titrated glimepiride		

Abbreviations: ERTU, ertugliflozin; SITA, sitagliptin.

similar to that obtained with sitagliptin 100 mg. A greater proportion of patients treated with ertugliflozin reached HbA1c <7% at week 12 and a significant reduction from baseline in fasting plasma glucose (FPG) was also observed.[43]

The VERTIS MONO Phase III trial evaluated the efficacy and safety of ertugliflozin monotherapy in subjects with T2DM and inadequate glycemic control, despite diet and exercise (Table 2). Results from the placebo-controlled phase (phase A) of this study have been published recently.[44] Change from baseline in HbA1c at week 26 showed a significantly greater decrease in the ertugliflozin 5 mg (–0.99%; $p<0.001$) and 15 mg (–1.16%; $p<0.001$) groups, compared with placebo, which was more evident in subjects with baseline HbA1c >8%. At week 26, ertugliflozin 5 and 15 mg also achieved a significantly greater reduction in the secondary endpoints, namely, FPG and 2-hour postprandial glucose, compared with placebo (Figure 3; Table S1).[44]

Data from the active, controlled 26-week follow-up phase were recently presented at the 77th ADA scientific session. Patients previously treated with placebo had metformin added, but there were no formal comparisons for efficacy between placebo/metformin group and ertugliflozin group at week 52. There was a meaningful reduction in HbA1c from baseline, in both ertugliflozin groups (Table S1), the same benefit was observed in FPG reduction (ertugliflozin 5 mg –30.07 mg/dL; ertugliflozin 15 mg –37.55 mg/dL).[45]

Ertugliflozin efficacy has also been evaluated as add-on or combination therapy with sitagliptin and metformin. The VERTIS MET trial investigated the efficacy and safety of ertugliflozin, versus placebo, in patients with T2DM, inadequately controlled with metformin monotherapy (≥1,500 mg/day ≥8 weeks) (Table 2). At week 26, both the ertugliflozin groups showed a significant decrease in HbA1c and FPG from baseline. Specifically, ertugliflozin 5 mg, compared with placebo, caused a reduction in HbA1c of –0.7% ($p<0.001$) and of –26.69 mg/dL ($p<0.001$) in FPG, while ertugliflozin 15 mg caused a reduction of –0.88% ($p<0.001$) in HbA1c and of –38.25 mg/dL ($p<0.001$) in FPG (Figure 3; Table S1).[46]

The VERTIS FACTORIAL study investigated the efficacy and safety of coadministration of ertugliflozin 5 or 15 mg plus sitagliptin 100 mg compared with either treatment as monotherapy (Table 2). After 26 weeks, coadministration of ertugliflozin + sitagliptin was significantly more effective than either treatment alone in reducing HbA1c and FPG and increasing the number of patients achieving HbA1c <7.0%. Ertugliflozin 5 mg, ertugliflozin 15 mg, and sitagliptin 100 mg showed a reduction from baseline in HbA1c of –1.0%, –1.1%, and –1.1%, respectively (p is nonsignificant among the three groups); the addition of sitagliptin 100 mg determined a further decrease in HbA1c (ertugliflozin 5 mg + sitagliptin 100 mg –1.5%; ertugliflozin

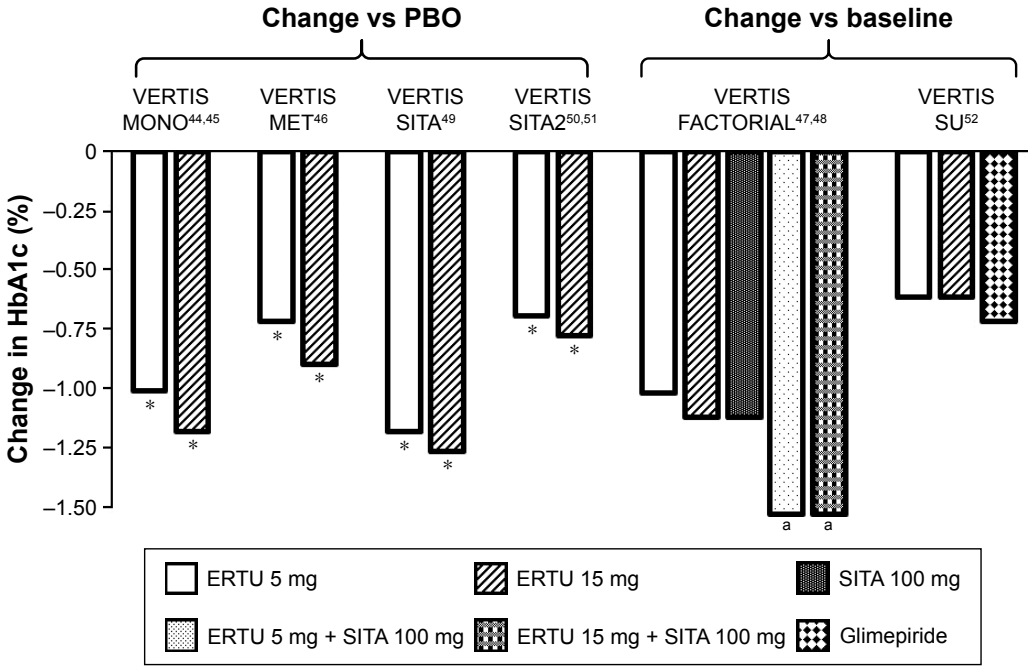

Figure 3 Mean change in HbA1c.
Notes: *$p<0.001$. [a]$p<0.004$ versus individual treatment.
Abbreviations: ERTU, ertugliflozin; HbA1c, glycosylated hemoglobin; SITA, sitagliptin; PBO, placebo.

15 mg + sitagliptin 100 mg –1.5%; $p<0.004$) (Figure 3; Table S1).

Similar results were obtained for FPG in terms of reduction from baseline (ertugliflozin 5 mg –35.7 mg/dL; ertugliflozin 15 mg –36.9 mg/dL; sitagliptin 100 mg –25.6 mg/dL; ertugliflozin 5 mg + sitagliptin 100 mg –44 mg/dL; ertugliflozin 15 mg + sitagliptin 100 mg –48.7 mg/dL). Importantly, with sitagliptin 100 mg and ertugliflozin coadministration, a greater proportion of patients achieved HbA1c <7.0% (ertugliflozin 5 mg + sitagliptin 100 mg: 52.3%; ertugliflozin 15 mg + sitagliptin 100 mg: 49.2%; ertugliflozin 5 mg: 26.4%; ertugliflozin 15 mg: 31.9%; sitagliptin 100 mg: 32.8%).[47] The treatment was continued in a double-blind 26-week extension phase, attaining an even greater decrease in HbA1c and FPG (Table S1).[48]

The VERTIS SITA trial investigated the efficacy of ertugliflozin in combination with sitagliptin in subjects with T2DM inadequately controlled with diet and exercise. Subjects were randomized 1:1:1 to take ertugliflozin 5 mg + sitagliptin 100 mg, ertugliflozin 15 mg + sitagliptin 100 mg or placebo (Table 2). As expected, after 26 weeks, the two treatment groups showed a larger reduction from baseline in HbA1c, which was significant in the pairwise comparison with placebo (ertugliflozin 5 mg + sitagliptin 100 mg –1.16%, $p<0.001$; ertugliflozin 15 mg + sitagliptin 100 mg –1.24%, $p<0.001$) (Figure 3, Table S1). There was also a meaningful reduction in FPG (ertugliflozin 5 mg + sitagliptin 100 mg: –48.3 mg/dL; ertugliflozin 15 mg + sitagliptin 100 mg: –55.4 mg/dL; placebo: –9.3 mg/dL) and 2-hour post-meal glucose PMG (ertugliflozin 5 mg + sitagliptin 100 mg: –82.8 mg/dL; ertugliflozin 15 mg + sitagliptin 100 mg: –90 mg/dL; placebo: –20.4 mg/dL). Furthermore, the respective comparison with placebo, for both FPG and 2-hour PMG, was significant ($p<0.001$). The percentage of subjects achieving HbA1c <7.0% was higher with ertugliflozin + sitagliptin compared to placebo (ertugliflozin 5 mg + sitagliptin 100 mg: 35.7%; ertugliflozin 15 mg + sitagliptin 100 mg: 31.3%; placebo: 8.3%).[49]

VERTIS SITA2, another study in the VERTIS clinical development program, assessed the safety and efficacy of adding ertugliflozin 5 or 15 mg compared with placebo to the dual combination of metformin and sitagliptin, after 26 weeks of treatment (Table 2). Blood glucose control after 26 weeks of treatment was more effective with ertugliflozin 5 and 15 mg compared with placebo. In particular, the mean change in HbA1c was greater with ertugliflozin 5 mg (–0.68%, $p<0.001$) and 15 mg (–0.76%, $p<0.001$) compared with placebo (–0.1%). The same effects were observed for FPG (5 mg –26.9 mg/dL; 25 mg –33.1 mg/dL; PBO –1.8 mg/dL) and a greater proportion of subjects treated with ertugliflozin 5 and 25 mg reached the target of HbA1c <7.0.[50] The study extension at 52 weeks has shown similar results (Table S1).[51]

The VERTIS SU trial evaluated the efficacy and safety of once-daily ertugliflozin 15 or 5 mg compared with glimepiride (initiated at 1 mg and uptitrated to a maximum of 6 or 8 mg/day) over 52 weeks, in patients with T2DM inadequately controlled with metformin. The primary endpoint was to assess non-inferiority in reducing HbA1c. Ertugliflozin 15 mg was non-inferior to glimepiride in reducing HbA1c (ertugliflozin 15 mg vs glimepiride: 0.1 [–0.0; 0.2] $p<0.001$) while non-inferiority could not be demonstrated for ertugliflozin 5 mg (0.2 [0.1; 0.3] p=ns).[52]

Body weight

As mentioned earlier, SGLT2 inhibition promotes significant energy loss through glycosuria, which causes weight loss.[53] This is evident within 4 weeks of treatment but continues for up to 102 weeks in the longer duration trials.[54,55] In particular, reduction in body-fat mass accounts for 68%–90% of the weight loss induced by SGLT2is, as reported in several clinical trials.[14,56–58]

As with other gliflozins, ertugliflozin is also effective in reducing body weight, as proven in several randomized controlled trials, probably due to caloric loss and increased diuresis.[14,59–61] After 12 weeks of ertugliflozin, at doses ranging from 1 to 25 mg, body weight decreased significantly in all treatment groups, compared with placebo and sitagliptin 100 mg.[43]

After 26 weeks of ertugliflozin monotherapy (5 and 15 mg), T2DM subjects, inadequately controlled by diet and exercise alone, achieved significant weight loss compared to placebo (ertugliflozin 5 mg –1.76 kg, $p<0.001$; ertugliflozin 15 mg –2.16 kg, $p<0.001$)[44] (Figure 4). Weight loss continued till week 52, after the active-controlled second phase of the study: at this point, the ertugliflozin 5 mg group showed a 3.23 kg decrease in body weight and the ertugliflozin 15 mg group a 3.38 kg decrease, compared with baseline values (Table S2).[45]

In the VERTIS MET trial, the addition of ertugliflozin 5 and 15 mg to at least 1,500 mg of metformin determined significant weight loss, compared to placebo (Figure 4).[46]

Coadministration of ertugliflozin 5 and 15 mg and sitagliptin 100 mg led to an effective decrease in body weight (ertugliflozin 5 mg + sitagliptin 100 mg: –2.5 kg, $p<0.001$; ertugliflozin 15 mg + sitagliptin 100 mg: –2.9 kg, $p<0.001$),

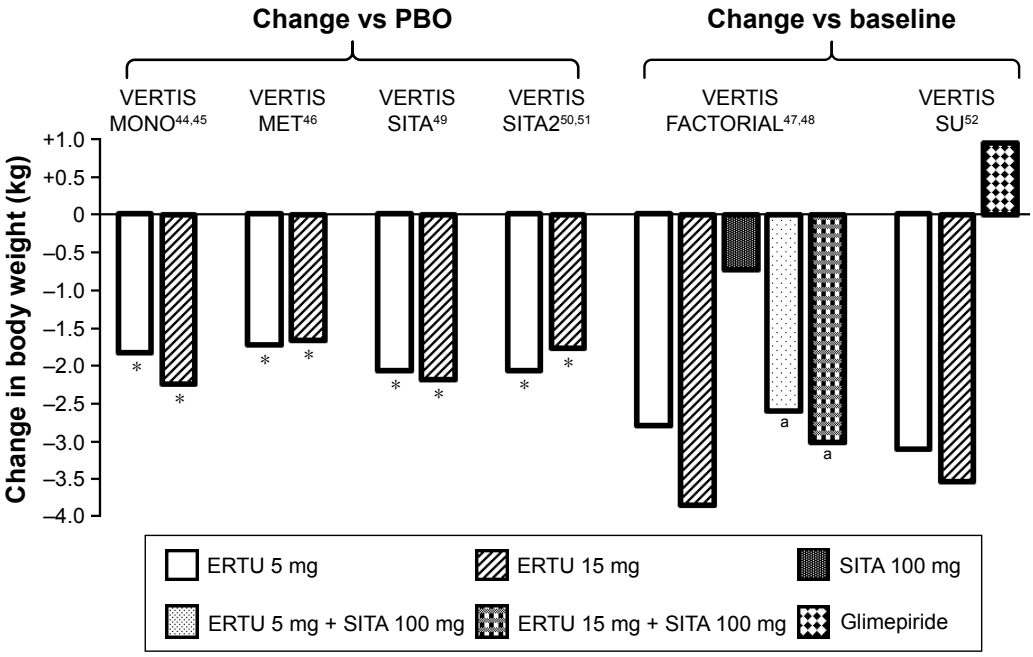

Figure 4 Mean change in body weight.
Notes: *$p<0.001$. [a]$p<0.005$ versus SITA.
Abbreviations: ERTU, ertugliflozin; SITA, sitagliptin; PBO, placebo.

compared to sitagliptin alone, which was not significant if compared to ertugliflozin 5 and 15 mg alone (sitagliptin 100 mg: –0.7 kg; ertugliflozin 5 mg: –2.7 kg; ertugliflozin 15 mg: –3.7 kg).[47]

A similar body weight reduction for each group was reached at week 52 (Table S2).[48]

The VERTIS SITA trial showed that ertugliflozin 5 mg or ertugliflozin 15 mg with sitagliptin combination therapy was effective in inducing weight loss, compared to placebo (ertugliflozin 5 mg + sitagliptin 100 mg: –2.0 kg, $p<0.001$; ertugliflozin 15 mg + sitagliptin 100 mg: –3 kg, $p<0.001$) after 26 weeks of treatment (Figure 4).[49]

Furthermore, the addition of ertugliflozin 5 or 15 mg to metformin 1,500 mg and sitagliptin 100 mg determined considerable body weight reduction, compared with placebo (ertugliflozin 5 mg: –2 kg, $p<0.001$; ertugliflozin 15 mg: –1.7 kg, $p<0.001$), which persisted at week 52 (Figure 4; Table S2).[50,51]

As expected, in the VERTIS SU trial, both ertugliflozin 5 and 15 mg induced a greater weight loss compared to glimepiride (ertugliflozin 5 mg vs glimepiride: –3.9 kg [–4.4; –3.4] nominal $p<0.001$; ertugliflozin 15 mg vs glimepiride: –4.3 kg [–4.8; –3.8] $p<0.001$).[52]

Blood pressure

As previously explained, SGLT2is play an important role in lowering both SBP and DBP. A Phase II dose-ranging study showed a decrease in SBP from baseline (placebo-corrected least squares mean) as early as week 4 with ertugliflozin 5 mg (–2.59 mmHg; $p=0.087$) and 10 mg (–2.86 mmHg; $p=0.068$), which continued to be observed at week 12 with ertugliflozin 5–25 mg/day (5 mg: –3.48 mmHg, $p=0.056$; 10 mg: –2.88 mmHg, $p=0.096$; 25 mg: –3.37 mmHg, $p=0.064$).[43]

In the first-phase VERTIS MONO trial, the ertugliflozin 15 mg versus placebo comparison for SBP was not significant, so the pre-specified hypothesis testing sequence was halted and testing of ertugliflozin 5 mg versus placebo for SBP and for both ertugliflozin groups versus placebo for DBP was not performed.[44] At week 52, however, a meaningful reduction was observed in SBP (ertugliflozin 5 mg: –3.27 mmHg; ertugliflozin 15 mg: –2.24 mmHg) rather than DBP (ertugliflozin 5 mg: –0.73 mmHg; ertugliflozin 15 mg: 0.18 mmHg).[45]

However, results from other Phase III studies have shown significant reductions in SBP when ertugliflozin was added to metformin or metformin and sitagliptin (VERTIS FACTORIAL, VERTIS SITA, and VERTIS SITA2); therefore, like other SGLT2is, ertugliflozin is effective in reducing BP.

In the VERTIS SU trial, both 5 and 15 mg ertugliflozin groups showed a greater reduction in SBP compared to glimepiride (ertugliflozin 5 mg vs glimepiride: –3.2 mmHg [–4.7; –1.7] nominal $p<0.001$; ertugliflozin 15 mg vs glimepiride: –4.8 mmHg [–6.3; –3.3] nominal $p<0.001$).[52]

Safety and tolerability

Adverse events

SGLT2is seem to obtain clinical benefits without significant side effects or are at least well tolerated.[62] The most commonly reported side effects are genital fungal infections (GFIs) and rare urinary tract infections (UTIs) triggered by the glycosuria.[63]

In a Phase II dose-ranging study, in T2DM patients inadequately controlled with metformin, ertugliflozin was generally well tolerated over the 12-week treatment period.[43] Serious adverse events (cellulitis, syncope, and acute myocardial infarction) have been recorded in pre-randomization and post-randomization phases of the study, even though none were considered treatment related. The most commonly reported adverse events (AEs) across all treatment groups were upper respiratory tract infections, diarrhea, UTIs, and GFIs. The latter two occurred in seven of the 328 subjects (two in placebo, two in ertugliflozin 1 mg, three in ertugliflozin 10 mg group) and nine of the 328 randomized patients (one in placebo, one in ertugliflozin 5 mg, three in ertugliflozin 10 mg, and four in ertugliflozin 25 mg). No subjects receiving sitagliptin had signs/symptoms of UTI or GFI. Ten participants experienced hypoglycemia AEs during the study; five during the metformin run-in period and five during the treatment period (three in ertugliflozin 5 mg; one in 10 mg; one in 25 mg). None of these required external assistance. General frequency of AEs symptomatic of volume depletion (eg, dehydration, hypotension, and hypovolemia) was rare; four subjects reported dizziness (possible volume depletion AE).

The ertugliflozin safety profile is therefore similar to that of other SGLT2is.[64] In conclusion, ertugliflozin was well tolerated in this population, with the majority of AEs being of mild or moderate intensity.

In a Phase III study (VERTIS MONO), the total incidence of AEs in ertugliflozin and placebo groups was similar (Table 3). Both the doses of ertugliflozin (5 and 15 mg) were generally safe and well tolerated during the study period (26 weeks). Genital mycotic infections in women occurred in 11 (16.4%) and 14 (22.6%) participants in the ertugliflozin 5 and 15 mg groups, respectively, compared with four participants (5.6%) in the placebo group (p=0.043 and p=0.005 for ertugliflozin 5 and 15 mg, respectively, compared with placebo).

In men, genital mycotic infections occurred in three (3.4%) and five (5.6%) participants in the ertugliflozin 5 and 15 mg groups, respectively, compared with 1 (1.2%) in the placebo group. There were no serious genital mycotic

Table 3 Phase III completed clinical trials: adverse events

Study	Arms	Adverse events				
		GFI (women)	GFI (men)	UTI	Symptomatic hypoglycemia	Hypovolemia
VERTIS MONO[44,45] (after 52 weeks)	PBO/MET (n=153)	7 (9.9)	1 (1.2)	21 (13.7)	7 (4.6)	7 (4.6)
	ERTU 5 mg (n=156)	18 (26.9)[a]	3 (3.4)	17 (10.9)	2 (1.3)	3 (1.9)
	ERTU 15 mg (n=152)	18 (29)[b]	7 (7.8)[c]	10 (6.6)[d]	4 (2.6)	3 (2.0)
VERTIS MET[46]	PBO (n=209)	1 (0.9)	0 (0.0)	2 (1.0)	4 (1.9)	1 (0.5)
	ERTU 5 mg (n=207)	6 (5.5)	3 (3.1)	6 (2.9)	7 (3.4)	1 (0.5)
	ERTU 15 mg (n=205)	7 (6.3)[e]	3 (3.2)	7 (3.4)	7 (3.4)	2 (1.0)
VERTIS FACTORIAL[47,48,*]	ERTU 5 mg (n=250)	–	–	–	2.4	1.6
	ERTU 15 mg (n=248)	–	–	–	–	0.8
	SITA 100 mg (n=247)	–	–	–	–	0
	ERTU 5 mg + SITA 100 mg (n=243)	–	–	–	–	0
	ERTU 15 mg + SITA 100 mg (n=244)	–	–	–	4.9	0
VERTIS SITA[49,**]	PBO (n=97)	2 (5.0)	0 (0.0)	5 (5.2)	1 (1.0)	1 (1.0)
	ERTU 5 mg + SITA 100 mg (n=98)	2 (4.9)	3 (5.3)	8 (8.2)	3 (3.1)	2 (2.0)
	ERTU 15 mg + SITA 100 mg (n=96)	3 (7.0)	1 (1.9)	3 (3.1)	3 (3.1)	2 (2.1)
VERTIS SITA2[50,51] (after 26 weeks)	PBO (n=153)	1.9	0	2	2.6	0.7
	ERTU 5 mg (n=156)	8	4.9	2.6	3.2	0.6
	ERTU 15 mg (n=153)	12.7	3.7	4.6	0.7	0
VERTIS SU[52]	ERTU 5 mg (n=448)	17 (7.7)	10 (4.4)	30 (6.7)	14 (3.1)	5 (1.3)
	ERTU 15 mg (n=440)	25 (10.0)	4 (2.1)	28 (6.4)	23 (5.2)	3 (0.7)
	Titrated glimepiride (n=437)	3 (1.4)	0 (0)	30 (6.9)	84 (19.2)	3 (0.7)

Notes: [a]p=0.010 vs PBO/MET; [b]p=0.005 vs PBO/MET; [c]p=0.042 vs PBO/MET; [d]p=0.039 PBO/MET; [e]incidence significantly higher (p=0.032) versus PBO. *Empty cells = incomplete data and/or see text. **All p-values for the comparison between ERTU 5/SITA 100 vs PBO and ERTU 15/ SITA 100 vs PBO are ≥0.05.
Abbreviations: ERTU, ertugliflozin; SITA, sitagliptin; MET, metformin; PBO, placebo; GFI, genital fungal infection; UTI, urinary tract infection.

infection AEs. In general, genital mycotic infections in women had a significantly higher incidence with ertugliflozin than in the placebo group. The incidence of genital mycotic infections was also higher in men in the ertugliflozin groups compared with placebo groups, but this difference was not significant.

The incidence of UTI in the ertugliflozin 5 and 15 mg groups was 7.1% and 3.9%, respectively, compared with 8.5% for placebo. One UTI AE led to discontinuation of the study medication in a man in the placebo group. There were no serious UTI AEs. The incidence of hypovolemia in the ertugliflozin 5 and 15 mg groups was 1.3% and 2.0%, respectively, compared with 3.9% in the placebo group.

Events associated with symptomatic hypoglycemia and documented hypoglycemia were unusual in both the ertugliflozin and placebo groups. The percentage of participants with symptomatic hypoglycemia AEs were placebo, 1.3%; ertugliflozin 5 mg, 1.3%; and ertugliflozin 15 mg, 2.6%. Documented hypoglycemia, which included symptomatic and asymptomatic hypoglycemia, occurred in one participant (0.7%) in the placebo group and four participants (2.6%) in each of the ertugliflozin 5 and 15 mg groups. Two participants in the ertugliflozin 15 mg group experienced a severe hypoglycemia AE; one episode required non-professional assistance and one required professional assistance (Table 3).[44]

An increased incidence of genital mycotic infections was reported in the Phase III VERTIS MET study. Adverse events in women increased in the ertugliflozin 5 mg group and were markedly higher in the ertugliflozin 15 mg group compared to placebo (p=0.032). The incidence in men was higher in both ertugliflozin groups versus placebo. The incidence of UTIs and symptomatic hypoglycemia AEs was greater in both ertugliflozin groups versus placebo. The incidence of hypovolemia was low and similar across all treatment groups. In conclusion, ertugliflozin was largely well tolerated but was correlated with a higher incidence of genital mycotic infections compared with placebo (Table 3).[46]

In the VERTIS FACTORIAL double-blind Phase III trial, the incidence of adverse events was identical across groups, except for higher rates of genital mycotic infections in groups treated with ertugliflozin vs sitagliptin alone (females, 4.9%–7.6% vs 1.1%; males, 2.4%–4.7% vs 0%, respectively).

UTI rates were higher with ertugliflozin alone (but not ertugliflozin + sitagliptin) vs sitagliptin alone (range: 3.2% [SITA] to 5.6% [ERTU 15 mg]). The incidence of symptomatic hypoglycemia was 2.4%, in the group treated with ertugliflozin 5 mg and 4.9% in the group treated with ertugliflozin 15 mg + sitagliptin. Hypovolemia AE rates were 1.6% and 0.8% in ertugliflozin 5 and 15 mg groups, respectively, and 0% in all other groups (Table 3).[47]

After 52 weeks, the percentage of genital mycotic infections in the treatment groups with ertugliflozin + sitagliptin was similar to that observed in the treatment group with ertugliflozin alone and significantly higher than that observed in the group treated with sitagliptin alone ($p<0.05$, except ertugliflozin 5 mg + sitagliptin in females).

Incidence of symptomatic hypoglycemia did not differ across groups but was higher in the group treated with ertugliflozin 15 mg + sitagliptin. Incidence of UTIs and hypovolemia was comparable across groups.[48]

In the Phase III VERTIS SITA trial, the incidence of AEs was not meaningfully different across groups (all p-values for the comparison between Ertu 5/Sita 100 vs placebo and Ertu 15/Sita 100 versus placebo are $\geq$0.05); no deaths were recorded during the study (Table 3).[49]

In the VERTIS SITA2 Phase III trial, after 26 weeks, the incidence of AEs was comparable among treatment groups, but a higher rate of genital mycotic infections was recorded with ertugliflozin 5 and 15 mg (males: 4.9% and 3.7% vs no events with placebo; females: 8.0% and 12.7% vs 1.9% with placebo).

Incidence of UTI was similar in placebo and ertugliflozin 5 mg groups (2.0% and 2.6%) but higher in the ertugliflozin 15 mg group (4.6%).

Among groups, rates were similar for symptomatic hypoglycemia (placebo 2.6%; ertugliflozin 5 mg, 3.2%; ertugliflozin 15 mg, 0.7%) and hypovolemia AEs (placebo 0.7%; ertugliflozin 5 mg, 0.6%; ertugliflozin 15 mg, no events) (Table 3).[50]

After 52 weeks, rates of genital mycotic infections were higher in ertugliflozin treatment groups compared to placebo (males: ertugliflozin 5 mg 4.9%, ertugliflozin 15 mg 3.7%, placebo 0%; females: ertugliflozin 5 mg 12.0%, ertugliflozin 15 mg 14.1%, placebo 1.9%; all $p<0.05$ vs placebo except ertugliflozin 15 mg males). The incidence of UTIs, symptomatic hypoglycemia and hypovolemia AEs did not differ significantly among groups.[51]

In the VERTIS SU trial, after 52 weeks, compared to glimepiride, the ertugliflozin 5 and 15 mg treatment groups showed higher rates of genital mycotic infections (males: ertugliflozin 5 mg 10 [4.4], ertugliflozin 15 mg 4 [82.1], glimepiride 0 [0]), while no significant difference in UTIs and hypovolemia were observed among the three groups (Table 3). As expected, both ertugliflozin groups showed less symptomatic hypoglycemia than the glimepiride group

(ertugliflozin 5 mg 14 [3.1]; ertugliflozin 15 mg 23 [5.2]; glimepiride 84 [19.2]).[52]

Laboratory variables

To date, few data have been collected on changes in low-density lipoprotein – high-density lipoprotein (LDL-HDL) cholesterol during treatment with SGLT2s. Previous studies observed a slight increment in LDL and HDL cholesterol, even though the mechanism remains unknown.[3,64]

In the VERTIS MONO Phase III study, mean baseline LDL cholesterol was ~100 mg/dL in all treatment groups. At week 26, the LS mean placebo-adjusted percent change in LDL cholesterol from baseline was 4.05% (95% CI −2.82, 10.92) and 8.69% (95% CI 1.75, 15.63) for ertugliflozin 5 and 15 mg, respectively. Mean baseline HDL cholesterol level was ~45 mg/dL for each treatment group. At week 26, the LS mean placebo-adjusted percent change in HDL cholesterol from baseline was 4.70% (95% CI 0.71, 8.69) and 8.57% (95% CI 4.55, 12.59) for ertugliflozin 5 and 15 mg groups, respectively.[44]

In the Phase III VERTIS MET study, at week 26, in both treatment groups with ertugliflozin 5 mg or 15 mg, eGFR values were similar at baseline (mean [SD] change from baseline, mL/min/1.73 m^2: placebo 1.0 [10.7], ertugliflozin 5 mg 0.3 [12.0], ertugliflozin 15 mg 0.2 [14.8]). The placebo adjusted difference in LS mean (95% CI) percent change from baseline to week 26 in LDL-C was 2.0 (−6.0, 10.0) for ertugliflozin 5 mg and 2.6 (−5.5, 10.7) for ertugliflozin 15 mg. Respective values for HDL-C were 4.5 (1.4, 7.6) and 4.4 (1.3, 7.5).[46]

Conclusion

Ertugliflozin represents another valid SGLT2i for the treatment of T2DM. As with other gliflozins, its insulin-independent mechanism is effective in reducing HbA1c, BP, and body weight, both as monotherapy and in combination with other glucose-lowering agents. Individual variations in response to SGLT2is have been reported, partially attributable to genetic variations.[65] T2DM is a heterogeneous disease, and response to an antidiabetic medication, such as an SGLT2i, could vary considerably among individuals; therefore, identification of pharmacogenetic biomarkers to predict therapeutic response might be important to maximize benefits and minimize side effects in personalized medicine.[66]

As expected, the clinical benefits of ertugliflozin are obtained without significant side effects. Currently, clinical trials investigating the safety and efficacy of ertugliflozin in treating T1DM are still lacking. Despite the thrilling results obtained in SGLT2i clinical trials, in terms of not only glycemic control but also CV protection, one conundrum still awaits solution: will gliflozins change the natural history of diabetes? To date, not surprisingly, sequential add-on therapy results with ertugliflozin have shown a significant improvement in glucose metabolism. We still lack data from studies on head to head comparison of SGLT2i molecules, which might help to choose the right medication case by case. However, the possibility of having ertugliflozin in combination therapy with sitagliptin, the most prescribed DPP-4 inhibitor, is an undeniable advantage. In future, one challenge might be to study their effects as combined initial therapy in newly diagnosed T2DM, having durability as a primary outcome, that is, the ability to maintain adequate glucose control without the (usual) need to add further treatment. Gliflozins, in combination with a DPP-4 inhibitor and metformin, as initial therapy, could modify the natural history of diabetes and slow down its progression.[67]

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Author contributions

All authors participated in the conception and drafting of the manuscript and reviewed it for intellectual content. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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Supplementary materials

Table S1 Glycemic efficacy of ertugliflozin: data from Phase III clinical trials

Study	Arms	Mean change from baseline HbA1c %				HbA1c difference vs PBO			
		To end of main study		To end of extension		To end of main study		To end of extension	
		LS mean	(95% CI)	LS mean	(95% CI)	LS mean	(95% CI)	LS mean	(95% CI)
VERTIS MONO[1,2]	PBO (n=153)	0.2	(0.02–0.37)	–	–	–	–	–	–
	ERTU 5 mg (n=155)	−0.79	(−0.95, −0.63)	−0.74	(−0.89, −0.58)	−0.99*	(−1.22, −0.76)	–	–
	ERTU 15 mg (n=155)	−0.96	(−1.12, −0.80)	−0.89	(−1.05, −0.74)	−1.16*	(−1.39, −0.93)	–	–
VERTIS MET[3]	PBO (n=209)	–	–	–	–	–	–	–	–
	ERTU 5 mg (n=207)	–	–	–	–	−0.70*	(−0.87, −0.53)	–	–
	ERTU 15 mg (n=205)	–	–	–	–	−0.88*	(−1.05, −0.71)	–	–
VERTIS FACTORIAL[4,5]	ERTU 5 mg (n=250)	−1.0	(−1.1, −0.9)	−0.96	(−1.10, −0.82)	–	–	–	–
	ERTU 15 mg (n=248)	−1.1	(−1.2, −1.0)	−0.93	(−1.07, −0.79)	–	–	–	–
	SITA 100 mg (n=247)	−1.1	(−1.2, −0.9)	−0.82	(−0.97, −0.68)	–	–	–	–
	ERTU 5 mg + SITA 100 mg (n=243)	−1.5[a]	(−1.6, −1.4)	−1.36	(−1.50, −1.22)	–	–	–	–
	ERTU 15 mg + SITA 100 mg (n=244)	−1.5[a]	(−1.6, −1.4)	−1.39	(−1.53, −1.25)	–	–	–	–
VERTIS SITA[6]	PBO (n=96)	−0.44	(−0.69, −0.19)	–	–	–	–	–	–
	ERTU 5 mg + SITA 100 mg (n=98)	−1.60	(−1.82, −1.39)	–	–	−1.16*	(−1.49, −0.84)	–	–
	ERTU 15 mg + SITA 100 mg (n=96)	−1.68	(−1.90, −1.46)	–	–	−1.24*	(−1.57, −0.91)	–	–
VERTIS SITA 2[7,8]	PBO (n=153)	−0.1	(−0.23, 0.04)	0.02	(−0.15, 0.19)	–	–	–	–
	ERTU 5 mg (n=156)	−0.78	(−0.91, −0.65)	−0.75	(−0.90, −0.59)	−0.68*	(−0.87, −0.50)	−0.76	(−0.98, −0.54)
	ERTU 15 mg (n=155)	−0.86	(−0.99, −0.72)	−0.81	(−0.97, −0.66)	−0.76*	(−0.95, −0.58)	−0.83	(−1.05, −0.61)
		Mean change from baseline HbA1c %				HbA1c difference vs glimepiride			
VERTIS SU[9]	ERTU 5 mg (n=448)	−0.6	NA			0.2	(0.1, 0.3)		
	ERTU 15 mg (n=440)	−0.6	NA			0.1	(−0.0, 0.2)*		
	Titrated glimepiride (n=437)	−0.7	NA						

Notes: *$p<0.001$. [a]$p<0.004$ versus individual treatment.
Abbreviations: ERTU, ertugliflozin; SITA, sitagliptin; PBO, placebo; HbA1c, glycated hemoglobin.

Table S2 Mean change in body weight

Study	Arms	Mean change from baseline (kg)				Weight difference vs PBO (kg)			
		To end of main study		To end of extension		To end of main study		To end of extension	
		LS mean	(95% CI)	LS mean	(95% CI)	LS mean	(95% CI)	LS mean	(95% CI)
VERTIS MONO[1,2]	PBO (n=153)	–	–	–	–	–	–	–	–
	ERTU 5 mg (n=155)	–	–	−3.23	(−3.91, −2.55)	−1.76*	(−2.57, −0.95)	–	–
	ERTU 15 mg (n=155)	–	–	−3.38	(−4.06, −2.71)	−2.16*	(−2.98, −1.34)	–	–
VERTIS MET[3]	PBO (n=209)	–	–	–	–	–	–	–	–
	ERTU 5 mg (n=207)	–	–	–	–	−1.67*	(−2.24, −1.11)	–	–
	ERTU 15 mg (n=205)	–	–	–	–	−1.60*	(−2.16, −1.03)	–	–
VERTIS FACTORIAL[4,5]	ERTU 5 mg (n=250)	−2.7	(−3.1, −2.3)	−2.4	(−2.9, −1.8)	–	–	–	–
	ERTU 15 mg (n=248)	−3.7	(−4.2, −3.3)	−3.2	(−3.8, −2.7)	–	–	–	–
	SITA 100 mg (n=247)	−0.7	(−1.1, −0.2)	−0.1	(−0.7, 0.5)	–	–	–	–
	ERTU 5 mg + SITA 100 mg (n=243)	−2.5[a]	(−3.0, −2.1)	−2.4	(−3.0, −1.8)	–	–	–	–
	ERTU 15 mg + SITA 100 mg (n=244)	−2.9[a]	(−3.4, −2.5)	−2.8	(−3.4, −2.2)	–	–	–	–
VERTIS SITA[6]	PBO (n=96)	−0.9	(−1.7, −0.2)	–	–	–	–	–	–
	ERTU 5 mg + SITA 100 mg (n=98)	−2.9	(−3.6, −2.3)	–	–	−2.0*	(−3.0, −1.0)	–	–
	ERTU 15 mg + SITA 100 mg (n=96)	−3.0	(−3.7, −2.4)	–	–	−2.1*	(−3.1, −1.1)	–	–
VERTIS SITA 2[7,8]	PBO (n=153)	−1.3	(−1.8, −0.9)	−1.0	(−1.7, −0.3)	–	–	–	
	ERTU 5 mg (n=156)	−3.3	(−3.8, −2.9)	−3.5	(−4.1, −2.9)	−2.0*	(−2.6, −1.4)	−2.5	(−3.4, −1.6)
	ERTU 15 mg (n=155)	−3.0	(−3.5, −2.6)	−2.8	(−3.4, −2.2)	−1.7*	(−2.3, −1.1)	−1.9	(−2.8, −1.0)
		Mean change from baseline (kg)				Weight difference vs glimepiride (kg)			
VERTIS SU[9]	ERTU 5 mg (n=448)	−3.0				−3.9	(−4.4, −3.4)*		
	ERTU 15 mg (n=440)	−3.4				−4.3	(−4.8, −3.8)[b]		
	Titrated glimepiride (n=437)	0.9							

Notes: *$p<0.001$; [a]$p<0.005$ vs SITA; [b]nominal $p<0.001$ (non-inferiority for HbA1c not demonstrated for ERTU 5 vs glimepiride and the multiplicity strategy did not permit testing of any further secondary hypotheses).
Abbreviations: ERTU, ertugliflozin; SITA, sitagliptin; PBO, placebo.

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