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Pharmacokinetic characteristics and clinical efficacy of a SGLT2 inhibitor plus a DPP-4 inhibitor combined therapy in type 2 diabetes

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SUMMARY

Type 2 diabetes (T2D) generally requires a combination of several pharmacological approaches to control hyperglycaemia. Combining a sodium-glucose cotransporter type 2 inhibitor (SGLT2i, known as gliflozin) and a dipeptidyl peptidase-4 inhibitor (DPP-4i, known as gliptin) appears to be an attractive strategy because of complementary modes of action. This narrative review analyzes the pharmacokinetics and clinical efficacy of different combined therapies with a SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, tofogliflozin) and a DPP-4i (linagliptin, saxagliptin, sitagliptin, teneligliptin). Drug-drug pharmacokinetic interaction studies do not show any significant changes in peak concentrations (C_{max}) and total exposure (area under the curve of plasma concentrations or AUC) of either drug when they were given orally together compared to corresponding values when each of them was absorbed alone. Some fixed-dose combinations (FDC) are already available (dapagliflozin-saxagliptin, empagliflozin-linagliptin) or in development (ertugliflozin-sitagliptin), and preliminary results showed bioequivalence of the two medications given as FDC tablets when compared with co-administration of the individual tablets. Dual therapy is more potent than either monotherapy in patients treated with diet and exercise or already treated with metformin. SGLT2i and DPP-4i could be used as initial combination or in a stepwise approach. The additional glucose-lowering effect appears to be more marked when a gliflozin is added to a gliptin than when a gliptin is added to a gliflozin. Combining the two pharmacological options is safe and does not induce hypoglycaemia.

Key-words : Combined therapy – DPP-4 inhibitor – Fixed-dose combination – SGLT2 inhibitor – Type 2 diabetes

Key points

- The combination of a sodium-glucose cotransporter type 2 inhibitor (SGLT2i), which promotes glycosuria and improves glucose tolerance independently of insulin, and a dipeptidyl peptidase-4 inhibitor (DPP-4i), an incretin-based therapy that corrects islet dysfunction, is an attractive approach for the management of type 2 diabetes.

- Both dapagliflozin plus saxagliptin and empagliflozin plus linagliptin combined therapies have been tested as separate tablets (no clinically relevant pharmacokinetic drug-drug interactions) and as fixed-dose combination (FDC: bioequivalence studies); such combined therapies are more efficacious than either monotherapy to control blood glucose, without worsening of the safety profile.

- Other combinations of a SGLT2i and a DPP-4i have been evaluated in studies that also showed the absence of drug-drug pharmacokinetic interactions and better glucose control compared to either therapy alone. An ertugliflozin-sitagliptin FDC is in current development.

- Initial SGLT2i – DPP-4i combination may be considered or one medication may be added to the other, with apparently better results when the SGLT2i was added to the DPP-4i compared with the reverse sequence. However, which glucose-lowering agent should be used in first place after metformin monotherapy failure remains an open question.

1. Introduction

Combination therapy is recommended after failure of metformin monotherapy for the management of hyperglycaemia in type 2 diabetes (T2D). Various pharmacological approaches may be added to metformin as dual therapies or combined together as triple therapies, among which sodium-glucose cotransporter type 2 inhibitors (SGLT2i) and dipeptidyl peptidase inhibitors (DPP-4i) [1, 2].

SGLT2i (also known as gliflozins), which target the kidney and promote glucosuria, belong to the newest pharmacological class of glucose-lowering agents [3]. Both their efficacy and safety have been recently reviewed [4, 5]. In T2D patients with history of cardiovascular disease, the demonstration of a remarkable reduction in cardiovascular and renal events with empagliflozin in EMPA-REG OUTCOME trial [6, 7] raised a huge interest among the medical community [8]. However, the underlying mechanisms of protection of empagliflozin remain unknown and controversial [9, 10]. SGLT2i, by specifically targeting the kidney, inhibit glucose reabsorption at the proximal tubule and thereby promote glucosuria, an effect independent of insulin. By reducing hyperglycaemia, SGLT2i dampen glucotoxicity, which indirectly results in an improvement of both beta-cell function and peripheral insulin sensitivity [11-13]. However, treatment with SGLT2i resulted in an increase in plasma glucagon concentrations, which was accompanied by a substantial increase in endogenous (hepatic) glucose production [11, 12]. Increased glucagon secretion has also been implicated in the occurrence of euglycaemic ketoacidosis episodes reported with SGLT2i [14, 15]. Thus, the addition of a DPP-4i, which inhibits glucagon and stimulates insulin secretion, may have the potential to block the increase in endogenous glucose production and thereby enhance the glucose-lowering ability of SGLT2i while reducing the risk of ketoacidosis, although this remains to be proven. Beyond a glucose-lowering effect, SGLT2i have some added value with reductions in body weight (including abdominal adiposity), blood pressure and serum uric acid, all markers considered as independent cardiovascular risk factors [3]. In EMPA-REG OUTCOME trial, empagliflozin was associated not only with a remarkable reduction in cardiovascular and all-cause mortality in T2D patients with antecedents of cardiovascular disease[6, 9] but also with a marked reduction in the incidence rate of hospitalisation for heart failure [16]. Because of their specific mode of action, some limitations exist in using SGLT2i in patients with renal impairment [17].

DPP-4i (also known as gliptins) are increasingly used in the management of T2D as an alternative or add-on therapy to other glucose-lowering agents [18]. As oral incretin-based therapy, they offer an excellent safety profile with no increased risk of hypoglycaemia, weight gain and cardiovascular events when compared to placebo [19]. DPP-4i enhance postprandial insulin secretion and suppress glucagon secretion by preventing the degradation of endogenously released incretin hormones [glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP)], two intestinal peptides whose concentrations physiologically increase after food intake. Of major interest, DPP-4i stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner, thus reducing hyperglycaemia while minimizing hypoglycaemia [18]. Furthermore, they do not induce weight gain and have proven their cardiovascular safety in several large prospective cardiovascular outcome studies [19, 20]. A higher rate of hospitalisation for heart failure with the DPP-4i saxagliptin was reported in SAVOR-TIMI 53 [21]. Because this adverse event was not observed with sitagliptin in TECOS [22], it remains controversial whether it is specific to saxagliptin, it is only a chance effect or it might be a class effect [23, 24]. What so ever, because of the marked reduction in the rate of hospitalisation for heart failure with empagliflozin in EMPA-REG OUTCOME [16], one may speculate that adding a SGLT2i to a DPP-4i would be of potential interest regarding the risk of heart failure in patients with T2D [25]. DPP-4i keep a good efficacy, together with a favourable safety profile, in patients with renal impairment, although the dosage should be reduced according to the glomerular filtration rate (for most of them except for linagliptin that is not excreted in the urine) to maintain similar total exposure as in subjects with normal renal function [26]. They may be used in patients with mild to moderate hepatic impairment but are contraindicated in patients with severe hepatic failure [27]. Detailed pharmacokinetic characteristics of available DPP-4 inhibitors have been reported in two previous papers [28, 29].

DPP-4i and SGLT2i exert their glucose-lowering effects via different and complementary mechanisms [30, 31]. When one single pharmacological class does not reach glycated haemoglobin (HbA1c) target as monotherapy or even when added to metformin, a combination of a DPP-4i and a SGLT2i could be helpful in the management of patients with T2D [32-35]. Fixed-dose combinations (FDCs) have been recently commercialized, which should facilitate therapy and improve compliance of patients with T2D [36, 37].

We previously analyzed drug-drug interactions (DDIs) with SGLT2i [38]. However, at the time of this initial publication, no studies having evaluated the combination of a SGLT2i with a DPP-4i were available. Numerous studies about this combined therapy have been published

since that time. The main aims of this narrative review are: 1) to analyze the pharmacokinetic characteristics and DDIs when a SGLT2i (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, tofogliflozin) is combined with a DPP-4i (saxagliptin, linagliptin, sitagliptin, teneligliptin); and 2) for each SGLT2i, to briefly describe the clinical efficacy of the combination with a DPP-4i in randomised controlled trials (RCTs), knowing that safety issues are reassuring and not different from the tolerance profile of each compound taken alone.

To identify relevant studies, an extensive literature search in MEDLINE was performed from January 2010 to November 2016, with the terms DPP-4i, alogliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin, SGLT2i, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, tofogliflozin, combined therapy and FDC. No language restrictions were imposed. Reference lists of original studies, other narrative reviews and previous systematic reviews were also carefully examined. Recent abstracts presented at the 2016 annual meetings of the American Diabetes Association and the European Association for the Study of Diabetes have been also scrutinized to find valuable data related to the topic of this review and not published yet as full papers. For pharmacokinetic studies, we only selected studies that analyzed the combination of a SGLT2i and a DPP-4i as separate tablets or as FDCs either in healthy volunteers or in patients with T2D. Studies devoted to only one pharmacological class, either SGLT2i [3, 39] or DPP-4i [28, 29], have been already analyzed in previous papers. For clinical studies, we only selected RCTs that reported results of a combined therapy with a SGLT2i and a DPP-4i in patients with T2D, focusing on phase 3 trials of at least 24-week duration and 100 subjects per arm (except for trials in Japanese subjects where smaller studies with 35-100 subjects per arm were also taken into account, in absence of larger studies). Numerous studies having evaluated either a SGLT2i [3, 40] or a DPP-4i [18, 41] separately have been discussed in previous papers and are not taken into account in the present review specifically devoted to SGLT2i-DPP-4i combined therapy. Finally, the web site ClinicalTrials.gov has been looked for unpublished trials. It shows numerous ongoing trials designed to better understand the complementary mode of action of SGLT2i and DPP-4i, to obtain further pharmacokinetic information regarding combined therapy (DDIs, FDC bioequivalence) and to demonstrate both the efficacy and safety of diverse combinations in T2D patients on various background therapies, mostly dapagliflozin plus saxagliptin, empagliflozin plus linagliptin, ertugliflozin plus sitagliptin and ipragliflozin plus sitagliptin. The huge number of these trials demonstrates

a major interest for such new therapeutic approach but does not permit to consider these unpublished studies in the present review, especially as no results are available yet.

2. Dapagliflozin plus saxagliptin

The potential therapeutic value of a combination therapy with saxagliptin and dapagliflozin for the treatment of T2D has been recently reviewed [42] and a FDC has been developed [43].

2.1 Pharmacokinetics

The absolute oral bioavailability of dapagliflozin and saxagliptin was determined using simultaneous intravenous ^{14}C-microdose/therapeutic oral dosing in healthy volunteers [44]. The geometric mean point estimates for dapagliflozin and saxagliptin were 78% (90% confidence interval or CI: 73, 83%) and 50% (48, 53%), respectively. The arithmetic mean half-life values for the intravenous and oral doses were similar: for dapagliflozin: 12.2±5.3 and 13.7±3.4 h; for saxagliptin 7.5±0.6 and 5.7±0.4 h, respectively. Furthermore, the plasma concentration-time terminal elimination phases for each route were parallel. Thus, this study demonstrates that the intravenous microdosing has similar pharmacokinetics to the therapeutic oral dosing [44].

The bioequivalence of saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg FDC tablets compared with co-administration of the individual tablets was evaluated in an open-label, randomised, single-dose crossover study in 72 healthy subjects [43]. Saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg FDC tablets were bioequivalent to co-administration of the individual components in healthy subjects under fasted conditions as shown by the comparison of maximum observed plasma concentrations (C_{max}) and area under the plasma concentration-time curves (AUC) (Table 1). Plasma dapagliflozin and saxagliptin concentrations decreased in a multiexponential way, and the dapagliflozin profiles were similar in case of the administration of individual components separately or as an FDC. The mean dapagliflozin terminal half-life ($t_{1/2}$) was approximately 13-16 h while the mean saxagliptin $t_{1/2}$ was approximately 5.4 to 7.3 h across all treatments. This study also found that food has no clinically meaningful effect on the overall bioavailability (total exposure) of saxagliptin/dapagliflozin FDC; nevertheless, median t_{max} for dapagliflozin was delayed from 1

to 3 h and C_{max} of dapagliflozin was reduced by ~35% to 50% under fed conditions compared with fasted conditions for the FDC tablet; in contrast, C_{max} of saxagliptin was unaffected by food [43].

A single-dose, open-label, randomised, 3-period, 3-treatment crossover DDI study was conducted to evaluate differences in the pharmacokinetic properties of saxagliptin and dapagliflozin when coadministered [45]. Forty-two healthy subjects were allocated to receive saxagliptin 5 mg alone, dapagliflozin 10 mg alone, or saxagliptin 5 mg plus dapagliflozin 10 mg coadministered, with a washout period of at least 6 days between treatments. Dapagliflozin had no effect on the pharmacokinetic properties of saxagliptin, its major active metabolite 5-OH saxagliptin, or saxagliptin total active moiety; conversely, saxagliptin had no effect on dapagliflozin pharmacokinetics, as 90% CIs for C_{max} and AUC_{inf} for all comparisons were contained entirely within the 0.80 to 1.25 equivalence intervals (Table 1). Thus no pharmacokinetic interaction could be detected when saxagliptin and dapagliflozin were coadministered [45].

2.2 Clinical efficacy

Changes in plasma glucose, insulin, and glucagon in relation to glycaemic response after a liquid meal tolerance test were analyzed during treatment with dual add-on of dapagliflozin plus saxagliptin to metformin extended release compared with dapagliflozin add-on alone or saxagliptin add-on alone in patients with T2D poorly controlled with metformin [46]. The combination of dapagliflozin plus saxagliptin provided additional reductions in glucose $AUC_{0\text{-}180\ min}$ and HbA1c, without the increase in plasma insulin seen with saxagliptin alone and without the increase in plasma glucagon seen with dapagliflozin alone [46]. The absence of plasma insulin increase with the addition of saxagliptin may probably be explained by the concomitant reduction in hyperglycaemia, mainly due to the amount of glucose lost in the urine. Several clinical studies have shown that the addition of a DPP-4 inhibitor to a background therapy with a SGLT2i results in only a modest HbA1c reduction, about half of that observed with the addition of a SGLT2i to a DPP-4i background therapy (see below and reference [30]). The fact that the DPP-4i blunts the increase in glucagon seen with the SGLT2i might contribute to reduce the risk of euglycaemic ketoacidosis reported wit SGLT2i, although this remains to be demonstrated [40].

Poorly controlled T2D adults on background metformin were randomised to dapagliflozin 10 mg/day plus saxagliptin 5 mg/day, or dapagliflozin 10 mg/day and placebo or saxagliptin 5

mg/day and placebo [47]. At week 24, greater improvements in glycaemic control were obtained with the triple therapy by the dual addition of dapagliflozin and saxagliptin than dual therapy with the addition of dapagliflozin or saxagliptin alone to background metformin monotherapy. A greater reduction in HbA1c was observed leading to a higher proportion of patients reaching an HbA1c target < 7% (53 mmol/mol) with the triple therapy (Table 2). Improvement in glucose control resulted from greater reductions in both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). The difference in blood glucose control was greater when the triple therapy was compared to the dual therapy metformin plus saxagliptin than when compared to the dual therapy metformin plus dapagliflozin. The reduction in body weight was greater with the triple therapy than with the dual therapy metformin plus saxagliptin but not with the dual therapy metformin plus dapagliflozin [47].

In another RCT, treatment with dapagliflozin 10 mg add-on to saxagliptin 5 mg plus metformin resulted in a greater mean HbA1c reduction from baseline to week 24 than placebo added to saxagliptin 5 mg (-0.82 vs. -0.10%, P < 0.0001) and a higher proportion of T2D patients reaching a target HbA1c < 7 % (53 mmol/mol) (38.0 vs. 12.4%, p<0.0001) (Table 3) [48]. There were statistically significantly larger reductions (all p < 0.0001) in the dapagliflozin add-on to saxagliptin plus metformin group compared with the placebo add-on to saxagliptin plus metformin group in FPG, 2-h PPG level (difference -36 mg/d; 95% CI -46.3, -24.7), and body weight (Table 3) [48].

When compared to the previous RCT, treatment with saxagliptin 5 mg add-on to dapagliflozin 10 mg plus metformin resulted in a less marked reduction in HbA1c (-0.51% versus -0.16% with placebo), but the difference remained highly significant (P < 0.0001) [49]. A larger proportion of patients achieved HbA1c <7 % (53 mmol/mol) with saxagliptin add-on (35.3%) versus placebo add-on (23.1%) to dapagliflozin plus metformin (Table 4). However, reductions in FPG and 2-h PPG were similar between treatment arms [49]. Indirect comparison with findings of the previous trial [48] may suggest that the addition of dapagliflozin on top of a dual therapy metformin plus saxagliptin results in a greater improvement in glucose control than the addition of saxagliptin on top of a dual therapy metformin plus dapagliflozin [30].

3. Empagliflozin plus linagliptin

The potential therapeutic value of a combination therapy with empagliflozin and linagliptin for the treatment of T2D has been recently reviewed [50, 51] as well as the

characteristics and potential advantages of the single-pill empagliflozin-linagliptin FDC [36, 37, 52].

3.1 Pharmacokinetics

In an open-label, randomised, multiple-dose, crossover study, sixteen healthy male subjects received empagliflozin 50 mg once daily for 5 days, both empagliflozin 50 mg once daily and linagliptin 5 mg once daily for 7 days, and linagliptin 5 mg once daily for 7 days [53]. Empagliflozin was rapidly absorbed, with a median $t_{max,ss}$ of 1 hour. Empagliflozin total exposure at steady state ($AUC_{tau,ss}$) after oral administration of empagliflozin 50 mg was similar with or without linagliptin 5 mg with respect to the standard bioequivalence acceptance range of 0.80 to 1.25. $C_{max,ss}$ was ~12% lower when empagliflozin was given with linagliptin than when given alone, with a corresponding 90% CI of 0.79 to 0.99, which was slightly outside the bioequivalence acceptance range (Table 1). However, this modest reduction in empagliflozin peak exposure when linagliptin was co-administered was not considered clinically meaningful. The median $t_{max,ss}$ was slightly longer when empagliflozin was administered with linagliptin (1.5 vs 1 h). Terminal $t_{1/2}$ values at steady state were similar when empagliflozin was given alone (8.30±11.4 h) or co-administered with linagliptin (8.44±10.7 h). Linagliptin total exposure (AUC) and peak concentration (C_{max}) were unaffected by co-administration of empagliflozin (Table 1). The median $t_{max,ss}$ for linagliptin was the same (1.5 h) with or without coadministration of empagliflozin. Consequently, these data support the co-administration of empagliflozin and linagliptin without dose adjustments [53].

An open-label, randomised, single-dose, crossover study has been completed in August 2016 (ClinicalTrials.gov Identifier: NCT02758171). The aim was to test the bioequivalence of a FDC Tablet of empagliflozin/linagliptin compared with the free combination of empagliflozin tablet and linagliptin tablet in healthy male and female subjects under fasted conditions. The results have not been published yet.

3.1.2 Clinical efficacy

A single-pill combination of empagliflozin and linagliptin was shown to produce clinical improvements in glycaemic control that were generally superior to the corresponding

improvements seen with each individual component, either empagliflozin or linagliptin alone. The findings were consistent in two RCTs of up to 52 weeks duration in patients with T2D treated with diet and exercise [54] or metformin monotherapy [55].

T2D patients not receiving glucose-lowering medications for at least 12 weeks were randomised to receive empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg for 52 weeks [54]. Reductions in HbA1c at week 24 (primary endpoint) were significantly greater for empagliflozin 25 mg/linagliptin 5 mg compared with linagliptin 5 mg ($P < 0.001$) but not compared with empagliflozin 25 mg, and were significantly greater for empagliflozin 10 mg/linagliptin 5 mg compared with linagliptin 5 mg and empagliflozin 10 mg individual components ($P < 0.001$ for both). These changes translated in different proportions of patients with baseline HbA1c $\geq$ 7% who reached HbA1c < 7% (53 mmol/mol) at week 24 (Table 2). Similar differences in favour of the dual therapy were noticed for FPG levels (Table 2). Overall, the clinical efficacy was maintained at week 52 (data not shown) [54].

To evaluate the efficacy of combinations of empagliflozin/linagliptin as second-line therapy, subjects with T2D inadequately controlled on metformin were randomised to a combination of empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg as add-on to metformin for 52 weeks [55] . At week 24 (primary endpoint), reductions in HbA1c with empagliflozin/linagliptin were superior to those with empagliflozin or linagliptin alone when added to metformin and more subjects reached HbA1c <7% (53 mmol/mol) with the triple therapy compared with each dual therapy. The same trends were observed regarding reductions in FPG levels (Table 2). The greater glucose-lowering efficacy of the triple therapy metformin/empagliflozin/linagliptin compared to each dual therapy (either metformin/empagliflozin or metformin/linagliptin) was maintained at week 52 [55].

Finally, two Phase III studies investigated the efficacy of linagliptin 5 mg versus placebo as add-on to empagliflozin 10 mg or empagliflozin 25 mg, respectively. Initially, T2D patients not well controlled with metformin received open-label empagliflozin 10 mg (study 1; n=352) or empagliflozin 25 mg (study 2; n=354) for 16 weeks [56]. Subsequently, patients with HbA1c between 7.0 and 10.5% were randomised to double-blind, double-dummy treatment with a single-pill combination of linagliptin 5 mg/empagliflozin 10 mg (n=126) or

placebo + empagliflozin 10 mg (n=130) in study 1, and a single-pill combination of linagliptin 5 mg/empagliflozin 25 mg (n=114) or placebo + empagliflozin 25 mg (n=112) in study 2. At week 24, linagliptin 5 mg significantly reduced HbA1c as add-on to empagliflozin 10 mg (from baseline placebo-subtracted reduction: -0.32 %, p=0.0103) or 25 mg (placebo-subtracted reduction : -0.47 %, p<0.001) (Table 4). Adding linagliptin 5 mg also significantly reduced FPG in both studies when compared to placebo, but not body weight. Thus linagliptin 5 mg as add-on to empagliflozin 10 mg or empagliflozin 25 mg and metformin was associated with clinically relevant improvements in glycaemic control in patients with T2D [56].

4. Canagliflozin plus a DPP-4 inhibitor

Canagliflozin is another SGLT2i commercialized both in the US and in Europe [57]. However, the only available DDI pharmacokinetic study of canagliflozin with a DPP-4i concerns teneligliptin, a DPP-4i not available in these countries but in Japan (trade name Tenelia®) [58] and Argentina (trade name Teneglucon®) [59].

4.1 Pharmacokinetics

Pharmacokinetic interactions between canagliflozin and teneligliptin were investigated in Japanese healthy adult men in an open-label, one-way crossover study using canagliflozin (200 mg/day, dose used in Japan) and teneligliptin (40 mg/day) [60]. A single dose of object drug (either canagliflozin or teneligliptin) was administered on day 1 followed by washout. After a continuous administration of precipitant drug (days 1 - 9), both drugs were concomitantly administered on day 7. No changes in exposure (AUC_{0-72h}) and peak concentrations (C_{max}) were observed for canagliflozin plus teneligliptin versus each monotherapy (Table 1). Thus, results of this single-dose study showed no pharmacokinetic interaction between canagliflozin and teneligliptin [60].

4.2 Clinical efficacy

In the ongoing prospective cardiovascular outcome trial CANVAS, 316 among the 4330 patients were taking a DPP-4i, mainly sitagliptin (75.6 %) and vildagliptin (22.5 %). The addition of canagliflozin provided significant placebo-subtracted reductions in HbA1c in those patients taking DPP-4i. At 18 weeks, the HbA1c reduction was greater with canagliflozin 300 mg (-0.75%; 95% CI -0.95, -0.54) than with canagliflozin 100 mg (-0.56%;

-0.77, -0.35) [61]. Significant placebo-subtracted reductions in body weight (-2.7 kg with canagliflozin 300 mg and -2.0 kg with canagliflozin 100 mg) and systolic blood pressure (-4.7 mm Hg with both dosages) were also noticed. Although the incidence of hypoglycaemia was numerically higher with canagliflozin versus placebo, nearly all events occurred in patients on background insulin therapy or sulphonylureas. In patients on background DPP-4i, the add-on therapy with canagliflozin improved HbA1c, body weight and systolic blood pressure, without worsening the risk of hypoglycaemia but at the expense of an increased incidence of known adverse events related to SGLT2i, especially mycotic genital infections [61].

5. SGLT2i combined with sitagliptin

Sitagliptin is the most widely used DPP-4i worldwide [62]. Thus it is not astonishing that it has been investigated in combination with almost all SGLT2i, not only those available in Europe and United States but also several others commercialized in Japan.

5.1 Dapagliflozin plus sitagliptin

5.1.1 Pharmacokinetics

A study assessed the potential for pharmacokinetic DDI between dapagliflozin and different glucose-lowering agents, among which sitagliptin, in healthy subjects [63]. In this open-label, randomised, crossover study, 18 subjects received a single-dose administration of 100 mg sitagliptin or 100 mg sitagliptin plus 20 mg dapagliflozin. Mean dapagliflozin plasma concentration versus time profile were similar with and without co-administration of sitagliptin. The prespecified criteria to conclude a lack of interaction between dapagliflozin and sitagliptin were met for C_{max} and AUC, as the 90% CIs were within the no-effect interval of 0.8–1.25 (Table 5). The t_{max} and $t_{1/2}$ for dapagliflozin were also unaffected by co-administration of sitagliptin. The median (range) t_{max} for dapagliflozin was 1.5 (1.0–4.0) h without and 1.7 (1.0–6.0) h with sitagliptin co-administration. The mean $t_{1/2}$ values for dapagliflozin were 14.3±10.1 h without and 15.9±7.1 h with sitagliptin co-administration [63]. Similarly, there were no meaningful differences in C_{max} and AUC for sitagliptin in the presence of dapagliflozin, as the 90% CIs were within the no-effect interval (Table 5). Again, the t_{max} and $t_{1/2}$ for sitagliptin were unaffected by co-administration of dapagliflozin. The median t_{max} for sitagliptin was 3.0 (0.5–5.8) h without dapagliflozin and 4.0 (1.5–8.0) h with

dapagliflozin [63]. The respective $t_{1/2}$ values for sitagliptin were 14.2±2.0 h and 14.4±2.0 h in the absence and presence of dapagliflozin.

5.1.2 Clinical efficacy

A RCT assessed the efficacy and safety of dapagliflozin 10 mg (n=225) versus placebo (n=226) as add-on therapy to sitagliptin 100 mg with or without metformin in patients with inadequately controlled T2D [64]. At 24 week add-on treatment with dapagliflozin provided additional clinical benefit with a significant reduction in HbA1c (-0.5% versus 0% with placebo) and body weight (-2.1 kg versus -0.3 kg) (Table 3). Dapagliflozin also decreased HbA1c significantly versus placebo when added to sitagliptin alone (placebo-subtracted, –0.6%; p<0.0001) or to sitagliptin plus metformin dual therapy (placebo-subtracted, –0.4%; p<0.0001). Glycaemic and body weight benefits observed at week 24 were maintained through week 48 and fewer patients receiving dapagliflozin were discontinued or rescued for failing to achieve glycaemic targets compared with placebo [64].

5.2 Canagliflozin plus sitagliptin

5.2.1 Pharmacokinetics

One study tested the pharmacokinetic interactions between canagliflozin and teneligliptin (see above) [60], but to our knowledge no study specifically investigated DDI between canagliflozin and sitagliptin.

5.2.2 Clinical efficacy

Patients with T2D inadequately controlled on metformin >/=1,500 mg/day and sitagliptin 100 mg randomly and blindly received canagliflozin 100 mg or placebo [65]. After 6 weeks, the canagliflozin dose was increased from 100 to 300 mg in 85.4% of patients. At week 26, canagliflozin (pooled 100 and 300 mg doses) demonstrated superiority in HbA1c reduction versus placebo (-0.91% vs -0.01%; P < 0.001). Canagliflozin provided significant reductions in FPG, body weight and systolic blood pressure compared with placebo (P < 0.001) (Table 3).

A 52-week open-label study performed in Japanese patients with T2D evaluated the efficacy and safety of adding canagliflozin 100 mg or 200 mg once daily (doses used in Japan) to different background glucose-lowering therapies, including DPP-4i (sitagliptin,

vildagliptin or alogliptin [66]. The baseline to end-point change in HbA1c was -1.04% with canagliflozin 100 mg (n=71) and -1.26% with canagliflozin 200 mg (n=74) in patients already treated with DPP-4i (proportion of patients receiving sitagliptin unknown) (Table 3). These reductions were almost similar or slightly greater when compared with other subgroups receiving non-DPP-4i background glucose-lowering therapies. The addition of canagliflozin to a DPP-4i was also associated with significant reductions in FPG, body weight and systolic blood pressure. As expected from the properties of the combination drugs, the incidence of hypoglycaemia was much lower in patients treated with DPP-4i than in those treated with a sulphonylurea [66].

5.3 Empagliflozin plus sitagliptin

5.3.1 Pharmacokinetics

An open label, randomised, multiple-dose (5 days), crossover study with three treatments and two treatment sequences investigated the potential DDI between empagliflozin and sitagliptin in 16 healthy male volunteers [67]. Co-administration of sitagliptin 100 mg with empagliflozin 50 mg did not have a clinically relevant effect on the $AUC_{tau,ss}$ or $C_{max,ss}$ of the analyte in plasma at steady state over a uniform dosing interval tau of empagliflozin (Table 5). Similarly, coadministration of empagliflozin 50 mg with sitagliptin 100 mg did not have a clinically meaningful effect on the $AUC_{tau,ss}$ or $C_{max,ss}$ of sitagliptin (Table 5). These results indicate that empagliflozin and sitagliptin can be co-administered without dose adjustments [67].

5.3.2 Clinical efficacy

In EMPA-REG OUTCOME, 11.3 % of patients receiving empagliflozin were on a background therapy containing a DPP-4i (529 out of a total of 4687 subjects) [6]. However, the proportion of patients receiving sitagliptin was not mentioned and no specific subanalysis was performed in this subgroup of T2D patients.

5.4 Ipragliflozin plus sitagliptin

5.4.1 Pharmacokinetics

The clinical pharmacokinetics and pharmacodynamics of the novel SGLT2i ipragliflozin, which has gained approval for clinical use in T2D in Japan, have been reviewed [68]. To investigate the effect of ipragliflozin on the pharmacokinetics of sitagliptin and vice versa, ipragliflozin 150 mg and sitagliptin 100 mg were administered alone or in combination in two cohorts of 32 healthy subjects [69]. Multiple doses of ipragliflozin did not change the AUC_{inf} and C_{max} of a single dose of sitagliptin : geometric mean ratio (GMR) and 90% CI for AUC_{inf} and C_{max}, with and without ipragliflozin, were within the predefined range of 80-125 % (Table 5). Similarly, multiple doses of sitagliptin did not change the pharmacokinetics of a single dose of ipragliflozin (Table 5). Thus, no dose-adjustments are likely to be required when ipragliflozin is given in combination with sitagliptin in patients with T2D [69].

5.4.2 Clinical efficacy

Ongoing phase 3 studies are assessing the safety and efficacy of either the addition of ipragliflozin once daily to sitagliptin background therapy (ClinicalTrials.gov Identifier: NCT02577003) or the addition of sitagliptin once daily to ipragliflozin background therapy (ClinicalTrials.gov Identifier: NCT02577016) in Japanese participants with T2D and inadequate glycaemic control on lifestyle and pharmacological monotherapy. The primary hypothesis for these studies is that the addition of a second active drug compared with placebo provides greater reduction in HbA1c as assessed by change from baseline at Week 24, as it has been already shown for the combinations saxagliptin-dapagliflozin [47] and linagliptin-empagliflozin [54, 55].

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5.5 Tofogliflozin plus sitagliptin

5.5.1 Pharmacokinetics

Tofogliflozin (Apleway®, Deberza®) has been developed by Chugai Pharmaceutical for the treatment of T2D, and a marketing authorization application was filed in Japan in 2013 by licensees Sanofi K.K. and Kowa. Tofogliflozin has received its first global approval for this indication in Japan as either monotherapy or in combination with other antihyperglycaemic agents [70].

The effects of sitagliptin 100 mg on the pharmacokinetics and pharmacodynamics of tofogliflozin 40 mg, and the effects of tofogliflozin 40 mg on the pharmacokinetics of sitagliptin 100 mg were investigated in 18 healthy male volunteers [71]. A single dose tofogliflozin had no or little effect on peak concentrations (C_{max}) and exposure (AUC) of

sitagliptin and a single dose of sitagliptin had no or little effect on C_{max} and AUC of tofogliflozin (Table 5) [71].

5.5.2 Clinical efficacy

To evaluate the long-term efficacy of tofogliflozin, Japanese patients with T2D not well controlled with an another oral monotherapy were randomly assigned to receive tofogliflozin 20 or 40 mg once daily orally in an open-label trial lasting 52 weeks [72]. In the subgroup on a background therapy with a DPP-4i (including sitagliptin), a significant reduction in HbA1c was noticed at 52 weeks: -0.78 ± 0.88 % with the dose of 20 mg (n=32) and -0.93 ± 0.86 % with the dose of 40 mg (n=60) (both P< 0.0001) (Table 3). In the meantime, body weight was reduced by -2.69 ± 2.81 kg and -2.50 ± 1.86 k, respectively (P< 0.0001). Tofogliflozin also reduced waist circumference and lowered systolic/diastolic blood pressure [72].

5.6 Luseogliflozin plus sitagliptin

5.6.1 Pharmacokinetics

Luseogliflozin (Lusefi(®) is an orally SGLT2i developed by Taisho Pharmaceutical for the treatment of patients with T2D in Japan [73]. A dedicated study investigated potential DDI between 5 mg luseogliflozin and 50 mg sitagliptin (dose used in Japan) in 12 healthy Japanese males [74]. When administered in combination with sitagliptin, the GMRs and 90% CIs for C_{max}, $AUC_{0–24h}$, and AUC_{inf} of luseogliflozin were within the reference range (Table 5). Similarly, when sitagliptin was administered with luseogliflozin, the GMRs and 90% CIs for C_{max}, $AUC_{0–24h}$, and AUC_{inf} of sitagliptin were within the reference range for bioequivalence (Table 5).

5.6.2 Clinical efficacy

An open-label trial investigated the efficacy of luseogliflozin added to existing oral antidiabetic drugs, among which DPP-4i, in Japanese patients with T2D inadequately controlled with monotherapy [75]. At week 52, luseogliflozin 2.5 mg added to a DPP-4i (including sitagliptin) in 103 patients resulted in a significant reduction in HbA1c (-0.52%, P<0.001), without increasing the risk of hypoglycaemia. Similarly, the decrease in FPG and body weight from baseline at week 52 in the subgroup on background therapy with DPP-4i averaged –18.5 mg/dL and –1.96 kg, respectively (P < 0.001 for both) (Table 3) [75].

5.7 Ertugliflozin plus sitagliptin

5.7.1 Pharmacokinetics

Ertugliflozin is a new orally active SGLT2i that is currently in co-development by Pfizer and Merck. The disposition of ertugliflozin (PF-04971729) was studied after a single 25 mg oral dose of [^{14}C]-ertugliflozin given to healthy subjects [76]. The absorption of ertugliflozin was rapid with a T_{max} averaging 1.0 hour. The total administered radioactivity excreted in feces and urine was 40.9% and 50.2%, respectively. Unchanged ertugliflozin collectively accounted for approximately 35% of the dose, suggestive of moderate metabolic elimination. The principal biotransformation pathway involved glucuronidation whereas a minor metabolic fate involved oxidation by cytochrome P450. Overall, these data showed that the drug is well absorbed and eliminated largely via glucuronidation [76].

In an open-label, randomised, three-period, single-dose, crossover study, 12 fasted healthy subjects received ertugliflozin 15 mg, sitagliptin 100 mg and ertugliflozin plus sitagliptin[77]. Ertugliflozin did not have any impact on AUC_{inf} or C_{max} of sitagliptin as the 90% CIs for the GMRs were within 80 and 125%. Similarly, co-administration of sitagliptin with ertugliflozin had no effect on either AUC_{inf} or C_{max} of ertugliflozin based on bioequivalence boundaries (Table 5). The lack of pharmacokinetic interaction demonstrates that ertugliflozin can be co-administered with sitagliptin without any need for dose adjustment [77].

5.7.2 Clinical efficacy

In a large RCT whose preliminary results were recently presented as congress abstracts [78, 79], 1,233 T2D patients who were inadequately controlled on metformin alone (≥1500 mg/day) were randomised to one of five treatment groups in a 1:1:1:1:1 ratio: co-administration of ertugliflozin 5 mg with sitagliptin 100 mg; co-administration of ertugliflozin 15 mg with sitagliptin 100 mg; ertugliflozin 5 mg; ertugliflozin 15 mg; or sitagliptin 100 mg (VERTIS Factorial trial : ClinicalTrials.gov Identifier: NCT02099110). the co-administration of ertugliflozin and sitagliptin improved blood glucose control, assessed by a significantly greater reduction in HbA1c at 26 weeks (primary endpoint) and the secondary endpoint of achieving an HbA1c goal of < 7.0 % (53 mmol/mol) (Table 2). Furthermore, the study also showed that the combined therapy was significantly more effective than ertugliflozin or sitagliptin alone in reducing FPG, and significantly more effective in reducing body weight and systolic blood pressure compared to sitagliptin alone (but not ertugliflozin alone), all being secondary endpoints [78, 79].

In a double-blind, randomised Phase 3 trial, T2D patients with HbA1c 7.0 - 10.5% on stable metformin ≥1500 mg/day and sitagliptin 100 mg/day were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo (VERTIS SITA2 trial : Clinical Trial Registration Number: NCT02036515; congress abstract only) [80]. After 26 weeks, ertugliflozin 5 and 15 mg were significantly more effective than placebo in reducing HbA1c, FPG, body weight and systolic blood pressure, and a significantly greater proportion of subjects were at the target of HbA1c < 7.0 % (Table 3).

6. Conclusion

The combination of a SGLT2i and a DPP-4i is an attractive therapeutic strategy because the complementary modes of action of the two medications contribute to improve blood glucose control in patients with T2D, without deteriorating the safety/tolerance profile of each compound. DDI studies between different DPP-4i and SGLT2i showed no significant changes in total exposure and C_{max} as well as in other classical PK parameters (t_{max} and $t_{1/2}$). Clinical trials showed that the combination of a SGLT2i and a DPP-4i is effective and safe in patients with T2D treated with diet alone or metformin. FDC formulations combining saxagliptin plus dapagliflozin and linagliptin plus empagliflozin are already commercialized and others combinations are currently investigated for the management of T2D. In absence of head-to-head trials comparing different DPP-4i-SGLT2i combinations, it is currently impossible to decide if one combination is superior to another one for the management of T2D. Although the precise positioning of a DPP-4i-SGLT2i combination should be better delineated by further studies, this approach appears to be a new option for the management of patients with T2D, with a good efficacy/safety ratio. However, because of the higher cost of this combination, careful pharmaco-economic evaluation would be of major interest.

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Table 1 : Results of pharmacokinetic interactions in studies combining a SGLT2i (commercialized in EUROPE and US) with a DPP-4i (except sitagliptin ;: see table 4) : dapagliflozin plus saxagliptin, empagliflozin plus linagliptin and canagliflozin plus teneligliptin. Data are adjusted geometric mean ratios (GMR) (90% confidence interval).

Single dose, Bioequivalence study [43]	n	Dapagliflozin		Saxagliptin	
		C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}
Dapagliflozin 5 mg/ Saxagliptin 2.5 mg FDC vs Dapagliflozin 5 mg plus Saxagliptin 2.5 mg (separated tablets)	36	1.093 (1.013-1.178)	1.006 (0.982-1.030)	1.047 (0.967-1.133)	1.040 (1.006-1.075)
Dapagliflozin 10 mg/ Saxagliptin 5 mg FDC vs Dapagliflozin 10 mg plus Saxagliptin 5 mg (separated tablets)	35	0.946 (0.878-1.019)	1.036 (1.010-1.062)	1.059 (0.993-1.129)	1.007 (0.973-1.042)
Single dose, DDI study [45]	n	Dapagliflozin		Saxagliptin	

		C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}
Dapagliflozin 10 mg + saxagliptin 5 mg vs saxagliptin 5 mg alone	42	NA	NA	0.927 (0.883–0.972)	0.991 (0.960–1.022)
Dapagliflozin 10 mg + saxagliptin 5 mg vs Dapagliflozin 10 mg alone	42	0.943 (0.867–1.026)	0.990 (0.966–1.014)	NA	NA
Multiple dose, DDI study (5-7 days) [53]	n	Empagliflozin		Linagliptin	
		$C_{max,ss}$	$AUC_{tau,ss}$	$C_{max,ss}$	$AUC_{tau,ss}$
Empagliflozin 50 mg/ Linagliptin 5 mg vs Linagliptin 5 mg alone	16	NA	NA	1.01 (0.87-1.19)	1.03 (0.96-1.11)
Empagliflozin 50 mg/ Linagliptin 5 vs Empagliflozin 50 mg alone	16	0.88 (0.79-0.99)	1.02 (0.97-1.07)	NA	NA
Single dose, DDI study [60]	n	Canagliflozin		Teneligliptin	
		C_{max}	AUC_{0-72h}	C_{max}	AUC_{0-72h}

Canagliflozin 200 mg/ Teneligliptin 40 mg vs Teneligliptin 40 mg alone	19	NA	NA	0.983 (0.940-1.028)	0.976 (0.903-1.056)
Canagliflozin 200 mg/ Teneligliptin 40 mg vs Canagliflozin 200 mg alone	25	0.982 (0.880-1.095)	0.982 (0.955-1.011)	NA	NA

AUC : area under the plasma concentration-time curve

C_{max} : maximum observed plasma concentration

DDI : drug-drug interaction

FDC : fixed dose combination

NA : not applicable

Table 2: Results of clinical trials comparing the efficacy of a SGLT2i-DPP-4i combination with either monotherapy in patients with type 2 diabetes.

Reference	Background therapy/ trial duration weeks	Treatment/ Patients	ΔBW (vs baseline) kg	ΔBW (vs mono-therapy) kg	ΔFPG (vs baseline) mg/dl	ΔFPG (vs mono-therapy mg/dl	Baseline HbA1c %	ΔHbA1c (vs baseline) %	ΔHbA1c (vs mono-therapy) %	% patients HbA1c < 7%	Patients reaching HbA1c < 7% (vs mono-therapy) OR
Rosenstock et al 2015 [47]	Metformin/ 24 weeks	Dapa 10 mg + Saxa 5 mg N = 179	-2.1	+ 0.3 (NA) P=NT [a] -2.1 (-2.7 to -1.4) P=NT [b]	-38 ± 2.8	-6 (-13.8 to 1.7) P=NT [a] -24 (-31.6 to -15.9) P=NT [b]	8.92 ± 1.18	-1.47 ± 0.08	-0.27 (-0.48 to -0.37) p=0.0166 [a] -0.59 (-0.81 to -0.37) p<0.0001 [b]	41	1.9 (NA) p=NA [a] 2.3 (NA) p=NA [b]
		Dapa 10 mg N = 179	-2.4		-32 ± 2.8		8.87 ± 1.16	-1.20 ± 0.08		22	
		Saxa 5 mg N = 176	0		-14 ± 2.9		9.03 ± 1.05	-0.88 ± 0.08		18	

Lewin et al 2015 [54]	Diet + exercise/ 24 weeks	Empa 25 mg + Lina 5 mg N = 134	-2.0	0.1 (-0.9 to 1.1) p=0.801 [a] -1.2 (-2.2 to -0.2) p=0.018 [b]	-29.6	-5.3 (-12.7 to 2.1) p=0.161 [a] -23.6 (-31.1 to -16.2) p<0.001 [b]	7.99 ± 0.95	-1.08 ± 0.06	-0.14 (-0.33 to 0.06) p=0.179 [a] -0.41 (-0.61 to -0.22) p<0.001 [b]	55.4	1.9 (1.1 to 3.3) p=0.022 [a] 3.1 (1.8 to 5.3) p<0.001 [b]
		Empa 10 mg + Lina 5 mg N = 135	-2.7	-0.5 (-1.5 to 0.5) p=0.362 [a] -2.0 (-3.0 to -1.0) p<0.001 [b]	-28.2	-5.6 (-13.3 to 1.6) p=0.125 [a] -22.3 (-29.7 to -14.9) p<0.001 [b]	8.04 ± 0.96	-1.24 ± 0.06	-0.41 (-0.61 to -0.31) p<0.001 [a] -0.57 (-0.76 to -0.37) p<0.001 [b]	62.3	3.0 (1.7 to 5.2) p<0.001 [a] 4.3 (2.5 to 7.5) P<0.001 [b]
		Empa 25 mg N = 133	-2.1		-24.2		7.99 ± 0.97	-0.95 ± 0.06		41.5	
		Empa 10 mg	-2.3		-22.4		8.05 ± 1.03	-0.83 ± 0.06		38.8	

		N = 132									
		Lina 5 mg N = 133	-0.8		-5.9		8.05 ± 0.89	-0.67 ± 0.06		32.3	
DeFronzo et al 2015 [55]	Metformin/24 weeks	Empa 25 mg + Lina 5 mg N = 134	-3.0	0.2 (-0.7 to 1.0) p=0.660 [a] -2.3 (-3.2 to -1.4) p<0.001 [b]	-35.3	-16.4 (-23.4 to -9.5) p<0.001 [a] -22.2 (-29.3 to -15.1) p<0.001 [b]	7.9 ± 0.79	-1.19 ± 0.06	-0.58 (-0.75 to -0.41) p<0.001 [a] -0.50 (-0.67 to -0.32) p<0.001 [b]	61.8	4.2 (2.3 to 7.6) p<0.001 [a] 3.5 (1.9 to 6.4) p<0.001 [b]
		Empa 10 mg + Lina 5 mg N = 135	-2.6	-0.1 (-0.7 to 1.0) p=0.876 [a] -1.9 (-2.6 to -1.1) p<0.001 [b]	-32.2	-11.3 (-18.3 to -4.4) P=0.002 [a] -19.1 (-26.2 to -12.0) p<0.001 [b]	7.95 ± 0.80	-1.08 ± 0.06	-0.42 (-0.59 to -0.25) p<0.001 [a] - 0.39 (-0.56 to – 0.21) p<0.001 [b]	57.8	4.5 (2.5 to 8.2) p<0.001 [a] 2.8 (1.6 to 5.0) p<0.001 [b]
		Empa 25 mg	-3.2		-18.8		8.02 ± 0.83	-0.62 ± 0.06		32.6	

		N = 140									
		Empa 10 mg N = 137	-2.5		-20.8		8.00 ± 0.93	-0.66 ± 0.06		28.0	
		Lina 5 mg N = 128	-0.7		-13.1		8.02 ± 0.90	-0.70 ± 0.06		36.1	
Eldor et al 2016 [78] and Pratley et al 2016 [79]	Metformin/26 weeks	Ertu 15 mg + Sita 100 mg N = 244	-2.9	+0.8 (NA) p=NS [a] -2.2 (NA) p<0.001 [b]	-48.7	-11.8 (NA) p<0.001 [a] -23.1 (NA) p<0.001 [b]	8.6 ± NA	-1.5 ± NA	-0.4 (NA) p<0.001 [a] -0.4 (NA) p<0.001 [b]	49.2	1.5 (NA) p<0.001 [a] 1.5 (NA) p<0.001 [b]
		Ertu 5 mg + Sita 100 mg N = 243	-2.5	+ 0.2 (NA) p=NS [a] -1.8 (NA) p<0.001 [b]	-44.0	-8.3 (NA) p<0.001 [a] -18.4 (NA) p<0.001 [b]	8.6 ± NA	-1.5 ± NA	-0.5 (NA) p<0.001 [a] -0.4 (NA) p<0.001 [b]	52.3 p<0.001 [b]	2.0 (NA) p<0.001 [a] 1.6 (NA) p<0.001 [b]
		Ertu 15 mg N = 248	-3.7		-36.9		8.6 ± NA	-1.1 ± NA		31.9	

		Ertu 5 mg N = 250	-2.7		-35.7		8.6 ± NA	-1.0 ± NA		26.4	
		Sita 100 mg N = 247	-0.7		-25.6		8.5 ± NA	-1.1 ± NA		32.8	

a : versus SGLT2i alone (at corresponding dosage)

b: versus DPP-4i alone

NA : not available

NS : not significant

NT : not tested

OR : odds ratio

Delta : change

BW : body weight

FPG : fasting plasma glucose

HbA1c : glycated haemoglobin

Table 3: Results of clinical trials investigating the addition of a SGLT2i versus a placebo on a metformin-DPP-4i background therapy or the addition of a SGLT2i (open label) on a DPP-4i background therapy in patients with type 2 diabetes.

Reference	Background therapy/ trial duration	Treatment/ patients	ΔBW (vs baseline) kg	ΔBW (vs placebo) kg	ΔFPG (vs baseline) mg/dl	ΔFPG (vs placebo) mg/dl	Baseline HbA1c %	ΔHbA1c (vs baseline) %	ΔHbA1c (vs placebo) %	% patients HbA1c < 7%	patients reaching HbA1c < 7% % /OR
Mathieu et al 2015 [48]	Metformin + Saxagliptin 5 mg/ 24 weeks	Dapa 10 mg N=160	-1.9	-1.5 (-2.12 to -0.89) p<0.0001	-33	- 28 (-35.4 to -19.6) p<0.0001	8.17 ± 0.98	-0.82 ± 0.07	-0.71 (-0.91 to -0.53) p<0.0001	38.0 p<0.0001	OR = 3.1 (NA) p<0.0001
		Placebo N=160	-0.4		-5		8.24 ± 0.96	-0.10 ± 0.07		12.4	
Jabbour et al 2014 [64]	Sitagliptin 100 mg (± metformin)/ 24 weeks	Dapa 10 mg N=223	-2.1 (-2.5 to -1.8)	-1.9 (-2.4 to -1.4) p<0.0001	-24.1 (-28.7 to -19.5)	-27.9 (-34.5 to -21.4) p<0.0001	7.9 ± 0.8	-0.5 (-0.6 to -0.4)	-0.5 (-0.6 to -0.3) p<0.0001	27.8 (22.2 to 33.4)	OR = 1.6 (NA)
		Placebo	-0.3 (-0.6		+3.8 (-0.8 to +		8.0 ± 0.8	0 (-0.1 to		17.9	

		N=224	to + 0.1)		8.4)			+ 0.1)		(13.3 to 22.5)	
Rodbard et al 2016 [65]	Metformin + Sitagliptin 100 mg/ 26 weeks	Cana 100-300 mg N=107	-3.1±NA	-1.6 (-2.4 to -0.7) p<0.001	-29.8±NA	-27.2 (-40.4 to -14.0) p<0.001	8.5 ± 0.9	-0.91 ±NA p<0.001	-0.89 (-1.19 to -0.59) p<0.001	32.3	4.5 (1.9 to 10.9) P=0.001
		Placebo N=106	-1.6		-2.6		8.4 ± 0.8	-0.01 ±NA		12.2	
Lauring et al 2016 [80]	Metformin + Sitagliptin 100 mg/ 26 weeks	Ertu 15 mg N=153	-3.0 (-3.5 to -2.6)	-1.7 (-2.3 to -1.1) P<0.001	-1.8 (-2.1 to -1.5)	-1.7 (-2.2 to -1.3) P<0.001	8.0 0.8	-0.86 (-0.99 to -0.72)	-0.76 (-0.95 to -0.58) P<0.001	39.9	OR=2.3 (NA)
		Ertu 5 mg N=156	-3.3 (-3.8 to -2.9)	-2.0 (-2.6 to -1.4) P<0.001	-1.5 (-1.8 to -1.0)	-1.4 (-1.8 to -1.0) P<0.001	8.1 0.9	-0.78 (-0.91 to -0.65)	-0.68 (-0.87 to -0.50) P<0.001	32.1	OR=1.9 (NA)

		Placebo N=153	-1.3 (-1.8 to -0.9)		-0.1 (-0.4 to 0.2)		8.0 0.8	-0.10 (-0.23 to 0.04)		17.0	
Inagaki et al 2015 [66]	Any DPP-4i/ 52 weeks	Cana 100 mg N=71	-4.00 ± 3.63 (P<0.001)	No placebo	-37.5 ± 29.7 (P<0.001)	No placebo	8.19 ± 0.85	-1.04 ± 0.76 (P<0.001)	No placebo	50.7	No placebo
		Cana 200 mg N=74	-4.37 ± 4.35 (P<0.001)	No placebo	-41.0 ± 29.0 (P<0.001)	No placebo	8.33 ± 0.89	-1.26 ± 0.69 (P<0.001)	No placebo	48.6	No placebo
Tanizawa et al 2014 [72]	Any DPP-4i/ 52 weeks	Tofo 20 mg N=35	-2.69 ± 2.81 (P< 0.0001).	No placebo	NA	No placebo	8.38 ± 0.95	-0.78 ± 0.88 (P< 0.0001)	No placebo	NA	No placebo
		Tofo 40 mg N=68	-2.50 ± 1.86 (P< 0.0001)	No placebo	NA	No placebo	8.19 ± 0.89	-0.93 ± 0.86 (P< 0.0001)	No placebo	NA	No placebo

Seino et al 2015 [75]	Any DPP-4i/ 52 weeks	Luseo 2,5 mg N=103	-1.96 ± NA (P<0.001)	No placebo	-18.5 ± NA (P<0.001)	No placebo	7.88 ± 0.78	-0.52% (P<0.001)	No placebo	NA	No placebo

NA : not available

Delta : change from baseline

BW : body weight

FPG : fasting plasma glucose

HbA1c : glycated haemoglobin

OR : odds ratio

Table 4: Results of clinical trials investigating the addition of a DPP4i versus a placebo on a metformin-SGLT2 background therapy in patients with type 2 diabetes.

Reference	Background therapy/ trial duration	Treatment/ patients	ΔBW (vs baseline) kg	ΔBW (vs placebo) kg	ΔFPG (vs baseline) mg/dl	ΔFPG (vs placebo) mg/dl	Baseline HbA1c %	ΔHbA1c(vs baseline) %	ΔHbA1c(vs placebo) %	% patients HbA1c < 7%	patients reaching HbA1c < 7% % /OR
Matthaei et al 2015 [49]	Metformin + Dapa 10 mg/24 weeks	Saxa 5 mg N=153	-0.53 (NA)	-0.02 (NA) NT	-9.0 (-14.3 to -3.9)	-4 (-11.0 to -3.6) NT	7.97 0.83	-0.51 (-0.63 to -0.39)	-0.35 (-0.52 to -0.18) P<0.0001	35.3 (28.2 to 42.4)	1.5 (NA) P=NT
		Placebo N=162	-0.51 (NA)		-5.0 (-10.4 to -0.2)		7.86 0.93	-0.16 (-0.28 to -0.04)		23.1 (16.9 to 29.3)	
Tinahones et al 2016 [56]	Metformin + Empa 10 mg/ 24 weeks	Lina 5 mg N=126	NA	0.6 (-0.1 to 1.3) P=0.095	NA	-12.6 (-21.6 to -3.6) P=0.0103	8.04 ± 0.96	-0.53 ± NA	-0.32 (-0.52 to -0.13) P=0.001	25.9 (NA)	OR = 4.0 (1.8 to 8.9) p<0.001
		Placebo	NA		NA		8.03 ± 0.85	-0.21 ± NA		10.9 (NA)	

		N=130									
Tinahones et al 2016 [56]	Metformin + Empa 25 mg/ 24 weeks	Lina 5 mg N = 114	NA	0.1 (-0.6 to 0.8) P=0.8008	NA	-7.2 (-16.2 to -0.0) P=0.0452	7.82 ± 0.71	-0.58 (NA)	-0.47 (-0.66 to -0.28) p<0.001	36.0 (NA)	OR = 4.4 (2.1 to 9.4) P<0.001
		Placebo N=112	NA		NA		7.88 ± 0.90	-0.10 (NA)		15.0 (NA)	

NA : not available

NT : not tested

Delta : change from baseline

BW : body weight

FPG : fasting plasma glucose

HbA1c : glycated haemoglobin

OR : odds ratio

Table 5 : Results of pharmacokinetic interactions in studies combining a SGLT2i (dapagliflozin, empagliflozin, ipragliflozin, tofogliflozin and ertugliflozin; no such specific study for canagliflozin) with sitagliptin, the most widely prescribed DPP-4i used as reference. Data are adjusted geometric mean ratios (90% confidence interval).

Single dose Kasichayanula et al 2011 [63]	n	Dapagliflozin		Sitagliptin	
		C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}
Dapagliflozin 20 mg Sitagliptin 100 mg	18	0.96 (0.88–1.05)	1.08 (1.03–1.13)	0.89 (0.81–0.97)	1.01 (0.98–1.04)
Multiple dose Brand et al 2012[67]	n	Empagliflozin		Sitagliptin	
		$C_{max,ss}$	$AUC_{0-t,ss}$	$C_{max,ss}$	$AUC_{0-t,ss}$
Empagliflozin 50 mg Sitagliptin 100 mg	16	1.076 (0.97-1.194)	1.104 (1.039-1.173)	1.085 (1.007-1.169)	1.031 (0.989-1.073)
Multiple dose/single dose Smulders et al 2012 [69]	n	Ipragliflozin		Sitagliptin	
		C_{max}	AUC_{inf}	C_{max}	AUC_{inf}
Ipragliflozin 150 mg	32	0.965	0.950	0.924	1.001

Sitagliptin 100 mg		(0.904–1.031)	(0.934–0.966)	(0.828–1.031)	(0.969–1.035)
Single dose Kasahara et al 2016 [71]	n	Tofogliflozin		Sitagliptin	
		C_{max}	AUC_{inf}	C_{max}	AUC_{inf}
Tofogliflozin 40 mg Sitagliptin 100 mg	18	0.956 (0.860–1.06)	1.02 (0.998–1.05)	0.877 (0.783–0.982)	1.03 (1.00–1.05)
Single dose Sasaki et al 2015 [74]	n	Luseogliflozin		Sitagliptin	
		C_{max}	AUC_{inf}	C_{max}	AUC_{inf}
Luseogliflozin 5 mg Sitagliptin 50 mg	12	0.967 (0.914, 1.02)	0.986 (0.948, 1.03)	0.983 (0.922, 1.05)	1.03 (1.01, 1.05)
Single dose Kumar et al 2016 [77]	n	Ertugliflozin		Sitagliptin	
		C_{max}	AUC_{inf}	C_{max}	AUC_{inf}
Ertugliflozin 15 mg Sitagliptin 100 mg	12	0.982 (0.912-1.057)	1.023 (0.997-1.049)	1.017 (0.917-1.128)	1.017 (0.984-1.050)

AUC : area under the plasma concentration-time curve

C_{max} : maximum observed plasma concentration

FDC : fixed dose combination

NA : not applicable

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