



# Sotagliflozin: A Review in Type 1 Diabetes

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## Abstract

Sotagliflozin (Zynquista™) is the first dual inhibitor of sodium-glucose co-transporter-1 and -2 (SGLT1 and 2). In the phase 3, inTANDEM 1–3 trials, adjunctive use of oral sotagliflozin (200 mg or 400 mg once daily) improved glycaemic control and reduced bodyweight and insulin requirements relative to placebo over 24 weeks of treatment in adults whose type 1 diabetes (T1D) was inadequately controlled by insulin therapy. Similar benefits were seen with the drug in patients who were overweight/obese [i.e. body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup>] in inTANDEM 1 and 2 (pooled). The benefits of sotagliflozin were largely maintained over 52 weeks of treatment. Overall, use of sotagliflozin in this setting is generally well tolerated and reduces, or at least does not increase, the likelihood of hypoglycaemia; however, as with other SGLT inhibitors, sotagliflozin carries a risk of diabetic ketoacidosis (DKA). On the basis of its risk/benefit profile, sotagliflozin is indicated in the EU as an adjunct to insulin in adults with T1D with a BMI  $\geq 27$  kg/m<sup>2</sup> who have failed to achieve adequate glycaemic control despite optimal insulin therapy, thus expanding the currently limited adjunctive oral treatment options available for use in this population.

## Sotagliflozin: clinical considerations in T1D

First dual SGLT1/SGLT2 inhibitor

An oral adjunct to insulin in adults with BMI  $\geq 27$  kg/m<sup>2</sup> for whom insulin provides inadequate glycaemic control

Improves glycaemic control and reduces bodyweight and insulin requirements

Generally well tolerated; reduces, or at least does not increase, hypoglycaemia risk

Enhanced material for this Adis Drug Evaluation can be found at <https://doi.org/10.6084/m9.figshare.10303535>.

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## 1 Introduction

Type 1 diabetes (T1D) is a chronic metabolic condition in which little to no insulin is produced by the pancreas due to  $\beta$ -cell destruction [1, 2], with the resultant insulin deficiency leaving patients prone to hyperglycaemia and diabetic ketoacidosis (DKA) [3]. The elevated levels of circulating glucose that result can damage tissues, leading to complications such as foot ulceration, blindness, kidney failure, premature cardiovascular (CV) disease and death, although achieving and maintaining glucose levels as close as possible to normal can reduce the risk of these complications considerably [4]. Insulin replacement therapy is the mainstay pharmacological treatment option for T1D [4, 5] and, over the years, insulin formulations and delivery options have advanced, along with continuous glucose monitoring (CGM), to facilitate glycaemic control. However, in spite of such improvements, many patients do not achieve glycaemic targets [6] [e.g. a glycated haemoglobin (HbA<sub>1c</sub>) level  $\leq 6.5\%$  [4], although targets may be individualized [4, 5]], with some of the key barriers to the success of insulin therapy being patient fears of the associated risk of weight gain and hypoglycaemia [4]. Consequently, drugs that could be used as adjuncts to insulin to improve glycaemic control in this setting, without contributing to these limitations, have been investigated.

Sodium-glucose cotransporter (SGLT) inhibitors are oral, insulin-independent, antihyperglycaemic drugs historically used to treat type 2 diabetes (T2D), although their associated weight loss and low risk of hypoglycaemia [5] have also made them a rational target for investigation alongside insulin use in T1D. SGLTs are expressed mainly in kidney proximal tubules (SGLT2 and SGLT1) and intestinal brush-border membranes (SGLT1), with inhibition of SGLT2 reducing the renal reabsorption of glucose (thus increasing urinary glucose excretion) and inhibition of SGLT1 reducing the intestinal absorption of glucose (thus blunting post-prandial hyperglycaemia) [7, 8]. Most SGLT inhibitors selectively inhibit SGLT2 and, until recently, only one (dapagliflozin) was indicated for the adjunctive treatment of T1D. However, the SGLT inhibitor options for use in T1D have recently been expanded with sotagliflozin (Zynquista™), the first dual SGLT1/SGLT2 inhibitor. Sotagliflozin is approved in the EU as an adjunct to insulin in adults with T1D with a body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup> who have failed to achieve adequate glycaemic control despite optimal insulin therapy [7]. This article reviews data relevant to the use of sotagliflozin in this indication.

## 2 Pharmacodynamic Properties of Sotagliflozin

Sotagliflozin is an inhibitor of both SGLT1 and SGLT2, although is  $\approx 20$ -fold more selective for SGLT2 (half maximal inhibitory concentration in vitro: 36 and 1.8 nmol/L) [9]. This dual inhibitory mechanism of the drug is supported by data from a 12-week, phase 2b, dose-ranging study in patients with T1D, in which the recommended dosages of 200 mg/day or 400 mg/day used as an adjunct to stable insulin increased ( $p < 0.001$ ) urinary glucose excretion by a least-squares mean (LSM) of 57.7 g/day and 70.5 g/day relative to placebo (consistent with SGLT2 inhibition) and were associated with corresponding placebo-adjusted changes in 2-h post-prandial glucose (PPG) of  $-1.6$  mmol/L (not significant) and  $-2.8$  mmol/L ( $p = 0.013$ ) [consistent with SGLT1 inhibition] [10]. In line with these findings, a single 400 mg dose of sotagliflozin taken 0.25–5.25 h prior to a meal delayed ( $p < 0.05$  vs. placebo where reported) the rate that glucose appeared in the blood after oral administration in healthy subjects, suggesting local inhibition of intestinal SGLT1 by the drug is prolonged [11].

Consistent with natriuresis induction, sotagliflozin (as an adjunct to insulin) can alter markers of renal function and blood volume in patients with T1D [12–14]. For instance, in a pooled analysis of key phase 3 trials (inTANDEM 1 and 2; Sect. 4), estimated glomerular filtration rate (eGFR) declined slightly, albeit significantly ( $p < 0.001$ ), with sotagliflozin 200 mg/day or 400 mg/day relative to placebo after 4 weeks

of treatment (differences in mean change from baseline were  $-2.50$  mL/min/1.73 m<sup>2</sup> and  $-2.81$  mL/min/1.73 m<sup>2</sup>) and tended to return towards baseline (89–90 mL/min/1.73 m<sup>2</sup>) with continued therapy, with the difference remaining significant ( $p = 0.01$ ) at week 52 only with sotagliflozin 200 mg/day [13, 14]. The sotagliflozin regimens also generally significantly ( $p < 0.05$ ) increased haematocrit and serum albumin levels and significantly ( $p < 0.001$ ) reduced plasma levels of uric acid versus placebo during the 52-week treatment period. Urine albumin-to-creatinine ratio (UACR) was also significantly ( $p < 0.005$ ) reduced with sotagliflozin 400 mg/day versus placebo at 24 weeks in patients with albuminuria at baseline (UACR  $\geq 30$  mg/g), although the between-group difference was no longer significant at 52 weeks (post hoc subgroup analysis) [13].

Sotagliflozin recipients can experience reductions in bodyweight (Sect. 4), which may be associated with changes in bone mineral density (BMD) and bone turnover [15]. BMD may decrease with sotagliflozin in patients with T1D, according to pooled DEXA data ( $n = 243$ ) from inTANDEM 1 and 2 [15]. After 52 weeks of treatment, a reduction (nominal  $p < 0.05$ ) in BMD was evident at the lumbar spine with sotagliflozin 200 mg/day or 400 mg/day (LSM difference vs. placebo:  $-1.27\%$  and  $-2.53\%$ ) and at the total hip with sotagliflozin 400 mg/day ( $-1.18\%$ ). Numerical increases in bone turnover biomarkers (C-terminal telopeptide of type 1 collagen; type 1 procollagen N-terminal propeptide) were also seen with sotagliflozin versus placebo over this period. Fracture data are discussed in Sect. 5.3.

## 3 Pharmacokinetic Properties of Sotagliflozin

Sotagliflozin appears to display dose-proportional pharmacokinetics across dosages of 200 mg and 400 mg once daily, and  $\geq 71\%$  of a single dose is estimated to be absorbed [7]. Maximum plasma concentrations ( $C_{\max}$ ) of sotagliflozin are reached in a median of 2.5–4 h after multiple doses of 400 mg or 800 mg. Exposure to sotagliflozin was increased when taken with a high-caloric breakfast versus in the fasted state (e.g.  $C_{\max}$  increased  $\approx 2.5$ -fold); sotagliflozin should be taken before the first meal of the day (Sect. 6). Sotagliflozin displays high plasma protein binding independent of concentration in vitro, as does its major human metabolite 3-*O*-glucuronide (M19) [ $\approx 2\%$  of the drug is unbound], with clinical studies confirming these findings [7]. Sotagliflozin has a very high volume of distribution after oral administration of a single 400 mg dose (mean 9392 L) [7], indicating extensive distribution into tissues.

Metabolism of sotagliflozin is extensive and occurs predominantly via glucuronidation (by UGT1A9 mainly, and UGT1A1 and UGT2B7 to a lesser degree) but also oxidation

(by CYP3A4) [7]. Sotagliflozin is excreted via the urine (57% of a dose) and faeces (37%), with M19 and unchanged parent drug being the predominant moieties excreted via these respective routes. According to a population pharmacokinetic analysis that largely assessed patients with T1D, sotagliflozin has an apparent total body clearance of 239 L/h. The mean terminal half-life of the drug is 21–35 h and the corresponding value for M19 is 19–26 h [7].

Sotagliflozin is not recommended for use in patients with moderate or severe hepatic impairment, as exposure to the drug in these populations is increased; however, sotagliflozin can be used without dosage adjustment in mild hepatic impairment [7]. Renal impairment also increases sotagliflozin exposure [7]. Treatment with sotagliflozin should not be started in patients whose eGFR is  $< 60$  mL/min/1.73 m<sup>2</sup> and should be discontinued if eGFR persistently declines below 45 mL/min/1.73 m<sup>2</sup>. Sotagliflozin has not been studied in T1D patients with severe renal impairment, end-stage renal disease or on dialysis, and should therefore not be used in these populations. Renal function should be assessed before initiating sotagliflozin (or a concomitant drug that may reduce renal function) and periodically thereafter [7].

The dosage of sotagliflozin does not need to be adjusted on the basis of age [7]. However, sotagliflozin should not be initiated in patients aged  $\geq 75$  years (as therapeutic experience is limited) and its use in patients aged  $\geq 65$  years must take into account their renal function and increased volume depletion risk. Bodyweight, gender and race have no clinically meaningful impact on sotagliflozin pharmacokinetics [7].

### 3.1 Drug Interactions

In vitro, sotagliflozin is not an inhibitor of CYP1A2, 2C9, 2C19, 2D6 or 3A4 or an inducer of CYP1A2, 2B6 or 3A4, whereas M19 inhibits CYP2D6 and 3A4 and also induces the latter [7]. Induction of CYP1A2, 2B6 and 2C9 by sotagliflozin also cannot be ruled out and, consequently, if sotagliflozin is coadministered with drugs that are substrates of these enzymes, efficacy should be monitored for any potential decreases. In addition, some transporter proteins are inhibited by sotagliflozin (p-gp and BCRP) or M19 (MRP2, OAT3 and OATP1B1/B3) in vitro [7].

Exposure to sotagliflozin is reduced upon coadministration with rifampicin (a UGT and CYP enzyme inducer) and, as a result, frequent monitoring of glucose levels should be considered if sotagliflozin is to be coadministered with this drug or other enzyme inducers (e.g. phenytoin, phenobarbital, ritonavir) [7].

Sotagliflozin increases exposure to digoxin through p-gp inhibition; thus, appropriate monitoring is advised if these medications are taken concomitantly [7]. Although coadministering sotagliflozin with the known OAT3, OATP and

BCRP substrate rosuvastatin did not increase rosuvastatin exposure to any clinically relevant extent, the possibility that sotagliflozin may cause more extensive increases in exposure to other sensitive substrates of these transporters (e.g. benzylpenicillin, bosentan, fexofenadine, furosemide, methotrexate, paclitaxel) cannot be ruled out; thus, if using sotagliflozin in combination with such substrates, additional safety monitoring may be required [7].

## 4 Therapeutic Efficacy of Sotagliflozin

The clinical efficacy of oral sotagliflozin as an adjunct to insulin in adults with T1D inadequately controlled with their current insulin therapy was evaluated in five 12- to 52-week, placebo-controlled, phase 2/2b [10, 16] or 3 [17–19] trials of randomized, double-blind design. This section focuses on the phase 3 trials, known as inTANDEM 1 (conducted in USA and Canada) [17], inTANDEM 2 (EU and Israel) [18] and inTANDEM 3 (global) [19] [in which 793, 782 and 1405 patients were randomized, respectively] [17–19], except where data are limited. Pooled and meta-analysis data are also discussed.

To participate in inTANDEM 1 [17], 2 [18] or 3 [19], patients had to be aged  $\geq 18$  years (to  $\leq 75$  years [17, 18]), have had T1D for  $\geq 1$  year, have an HbA<sub>1C</sub> level at screening of 7.0–11.0% and be receiving insulin/insulin analogue(s) via continuous subcutaneous insulin infusion (CSII) or multiple daily injection (MDI) [17–19]. inTANDEM 1 and 2 specified that the method of insulin delivery must not have changed in the last 3 months [17, 18], whereas inTANDEM 3 specified that the basal insulin dose must not have been modified in the last  $\geq 2$  weeks [19]. Patients with an eGFR  $< 45$  mL/min/1.73 m<sup>2</sup> were among those excluded from the trials [17–19].

Insulin therapy was optimized to maintain a fasting or preprandial blood glucose level of 4.4–7.2 mmol/L [17–19] and a 1- to 2-h [17, 18] or 2-h or peak [19] PPG level of  $< 10$  mmol/L throughout the three studies, with inTANDEM 1 and 2 also including a 6-week insulin optimization period before randomization (i.e. baseline) [17, 18]. In inTANDEM 1 and 2, insulin titration decisions were assessed by an independent insulin dose monitoring committee (IDMC) up to week 24, with HbA<sub>1C</sub> levels masked to study staff during this period; between weeks 24 and 52, HbA<sub>1C</sub> levels were unmasked and the IDMC had no further input in insulin optimization [17, 18]. In inTANDEM 3, insulin dosage adjustments were performed by the investigators [19].

At baseline across the three trials, patients had a mean age of 41–46 years, a mean T1D duration of 18–24 years, a mean BMI of 28–30 kg/m<sup>2</sup>, a mean systolic BP (SBP)/diastolic BP (DBP) of 120–123/76–77 mmHg and were predominantly White (88–96%) [17–19]. Patients were receiving a daily

total insulin dose of  $\approx 0.7$  IU/kg, with a majority receiving their insulin therapy via injection in inTANDEM 2 (74.3%) [18] and 3 (60.4%) [19] and via CSII in inTANDEM 1 (59.6%) [17].

## 4.1 InTANDEM 1 and 2

### 4.1.1 Glycaemic Parameters

Adding sotagliflozin 200 mg or 400 mg once daily to an optimized insulin regimen in adults whose T1D had been inadequately controlled by insulin therapy improved glycaemic control over 24 weeks in inTANDEM 1 [17] and 2 [18]. At 24 weeks, each sotagliflozin dosage had significantly reduced HbA<sub>1C</sub> (primary endpoint) and fasting plasma glucose (FPG) levels relative to the addition of placebo (Table 1). Moreover, up to 2.3-fold more sotagliflozin 200 mg/day or 400 mg/day than placebo recipients had achieved a target HbA<sub>1C</sub> level of < 7% (37% and 47% vs. 23% [17]; 33% and 34% vs. 15% [18]). The HbA<sub>1C</sub>-lowering benefits of sotagliflozin were seen regardless of patient age (at baseline or diagnosis), sex, race, T1D duration, geographical region, method of insulin delivery or baseline HbA<sub>1C</sub>, BMI or eGFR [7]. Moreover, the improvements in glycaemic control with the drug versus placebo were generally maintained over 52 weeks of treatment (Table 1) [17, 18]. The glycaemic benefits of sotagliflozin in inTANDEM 1 and 2 were supported by the findings of a pooled analysis of the two trials ( $n = 1575$ ) [20, 21].

CGM data from inTANDEM 1 ( $n = 136$ ) [17] and inTANDEM 2 ( $n = 142$ ) [18] showed that sotagliflozin may also improve glycaemic variability. At 24 weeks, significant ( $p < 0.05$ ) reductions were seen relative to placebo in both the mean amplitude of glycaemic excursions and CGM standard deviation with sotagliflozin 400 mg/day in inTANDEM 1 [17] and 2 [18] and with sotagliflozin 200 mg/day in inTANDEM 2 [18]; neither measure improved significantly versus placebo with sotagliflozin 200 mg/day in inTANDEM 1 [17]. Consistent with these findings, recipients of sotagliflozin 400 mg/day (inTANDEM 1 and 2) and 200 mg/day (inTANDEM 2) spent significantly ( $p < 0.05$ ) more time with glucose values in the target range of 3.9–10.0 mmol/L than placebo recipients [17, 18].

In a prespecified pooled analysis of CGM data from the two studies ( $n = 278$ ), sotagliflozin 200 mg/day or 400 mg/day for 24 weeks significantly ( $p < 0.05$ ) increased the percentage of time patients spent with glucose levels in the target range by a mean of 5.4% and 11.7% versus placebo (primary endpoint) [estimated to represent an extra 1.3 h/day and 2.8 h/day], without increasing the time they spent with levels below target (i.e. < 3.9 mmol/L) [22]. Indeed, another analysis of the pooled CGM data ( $n = 265$ ) [23] found that the sotagliflozin regimens significantly reduced the

hyperglycaemia risk (as measured by the high blood glucose index) [ $p < 0.0001$  vs. placebo at 4, 12 and/or 24 weeks] without significantly impacting the hypoglycaemia risk (as measured by the low blood glucose index).

### 4.1.2 Bodyweight and Insulin Doses

Adding sotagliflozin 200 mg or 400 mg once daily to an optimized insulin regimen significantly reduced bodyweight over 24 weeks relative to adding placebo in inTANDEM 1 and 2, with weight loss being sustained with each sotagliflozin regimen over 52 weeks of treatment (Table 1) [17, 18]. Insulin requirements also declined with the drug, with recipients of sotagliflozin 200 mg/day or 400 mg/day having significant ( $p \leq 0.002$ ) reductions in their total daily insulin dose compared with placebo recipients, both at week 24 (difference vs. placebo:  $-9.0\%$  and  $-12.5\%$  in inTANDEM 1 [17] and  $-8.2\%$  and  $-9.5\%$  in inTANDEM 2 [18]) and at week 52 ( $-11.3\%$  and  $-15.9\%$  [17] and  $-6.3\%$  and  $-8.2\%$  [18]). These reductions in total daily dose generally appeared to be driven by changes in bolus insulin dose requirements (Table 1) [17, 18]. Pooled data from the trials supported these insulin [20] and bodyweight [21] findings, with pooled DEXA data indicating that most (73–86%) of the bodyweight lost by sotagliflozin recipients is accounted for by losses in body fat [24].

### 4.1.3 Other Outcomes

Sotagliflozin 200 mg or 400 mg once daily significantly ( $p \leq 0.02$ ) reduced SBP and DBP relative to placebo over 12 and 52 weeks of therapy in inTANDEM 1, with the LSM difference versus placebo in the change from baseline ranging from  $-2.8$  to  $-4.4$  mmHg for SBP and  $-1.4$  to  $-2.3$  mmHg for DBP [17]. The BP-lowering benefits of sotagliflozin were less clear in inTANDEM 2, particularly in terms of DBP [for which the only significant ( $p = 0.04$ ) LSM difference vs. placebo was with 200 mg/day at week 52;  $-1.3$  mmHg] [18]. However, pooled analyses [13, 25] of the studies demonstrated significant ( $p < 0.05$  vs. placebo) reductions in SBP and DBP with both sotagliflozin dosages at 12–52 weeks, supporting the inTANDEM 1 findings. The pooled data also indicated that sotagliflozin had significant ( $p < 0.05$  vs. placebo) benefit on SBP regardless of baseline SBP (< or  $\geq 130$  mmHg) [prespecified analysis], on DBP in patients with a baseline DBP of  $\geq 80$  mmHg (post hoc analysis) [13] and on various markers of arterial stiffness/vascular resistance (post hoc analysis) [25].

In addition, a variety of composite endpoints assessed in inTANDEM 1 and 2 indicated net clinical benefit with sotagliflozin. For instance, significantly ( $p \leq 0.002$ ) more sotagliflozin (200 mg/day or 400 mg/day) than placebo recipients achieved an HbA<sub>1C</sub> level of < 7.0% at week 24

**Table 1 Efficacy of oral sotagliflozin as a once-daily adjunct to insulin therapy in adults with inadequately controlled T1D in phase 3 trials, including a pooled analysis of obese/overweight patients**

Regimen (mg/day) [no. of evaluable pts <sup>a</sup> ]	Wk of eval	HbA <sub>1c</sub> (%) Change from BL [BL]	Fasting plasma glucose (mmol/L)		Bodyweight (kg)		Daily basal insulin dose (IU)		Daily bolus insulin dose (IU)		
			Diff vs. PL in change	Change from BL [BL]	Diff vs. PL in change	Change from BL [BL]	Diff vs. PL in change	% change from BL [BL]	Diff vs. PL in change	% change from BL [BL]	
<b>InTANDEM 1 [17]</b>											
SOT 200 [245]	24	-0.43 <sup>b</sup> [7.6]	-0.36 <sup>***</sup>	-0.34 [8.6]	-0.55*	-1.6 [87.0]	-2.4 <sup>***</sup>	-1.7 [34.8]	-5.5 <sup>***</sup>	-1.8 [30.3]	-5.7
SOT 400 [242]		-0.48 <sup>b</sup> [7.6]	-0.41 <sup>***</sup>	-0.78 [8.2]	-0.99 <sup>***</sup>	-2.7 [86.5]	-3.5 <sup>***</sup>	-5.4 [33.4]	-9.1 <sup>***</sup>	-8.8 [30.8]	-12.7 <sup>***</sup>
PL [246]		-0.07 <sup>b</sup> [7.5]		+0.21 [8.5]		+0.8 [87.3]		+3.8 [35.1]		+3.9 [31.7]	
SOT 200 [233]	52	-0.26 [7.6]	-0.25 <sup>***</sup>	-0.18 [8.6]	-0.68*	-1.9 [87.0]	-3.1 <sup>***</sup>	-1.7 [34.8]	-7.7 <sup>***</sup>	+1.5 [30.3]	-5.5
SOT 400 [224]		-0.32 [7.6]	-0.31 <sup>***</sup>	-0.58 [8.2]	-1.08 <sup>***</sup>	-3.1 [86.5]	-4.3 <sup>***</sup>	-5.9 [33.4]	-11.9 <sup>***</sup>	-8.6 [30.8]	-15.6 <sup>***</sup>
PL [219]		-0.01 [7.5]		+0.50 [8.5]		+1.2 [87.3]		+6.0 [35.1]		+7.0 [31.7]	
<b>InTANDEM 2 [18]</b>											
SOT 200 [239]	24	-0.39 [7.7]	-0.37 <sup>****b</sup>	-0.71 [9.1]	-1.20 <sup>***</sup>	-1.9 [81.9]	-2.0 <sup>***</sup>	-4.2 [29.2]	-5.8 <sup>**</sup>	-7.0 [31.1]	-12.9 <sup>***</sup>
SOT 400 [241]		-0.37 [7.7]	-0.35 <sup>****b</sup>	-0.93 [9.2]	-1.42 <sup>***</sup>	-2.5 [82.0]	-2.6 <sup>***</sup>	-3.0 [29.5]	-4.7*	-10.5 [31.9]	-16.4 <sup>***</sup>
PL [239]		-0.02 [7.8]		+0.49 [8.9]		+0.1 [81.1]		+1.7 [29.8]		+5.9 [32.1]	
SOT 200 [227]	52	-0.18 [7.7]	-0.21 <sup>**</sup>	-0.15 [9.1]	-0.27	-1.9 [81.9]	-2.2 <sup>***</sup>	-3.5 [29.2]	-6.7 <sup>**</sup>	-3.5 [31.1]	-7.7
SOT 400 [230]		-0.28 [7.7]	-0.32 <sup>***</sup>	-0.75 [9.2]	-0.87 <sup>**</sup>	-2.6 [82.0]	-2.9 <sup>***</sup>	-3.5 [29.5]	-6.7 <sup>**</sup>	-7.9 [31.9]	-12.2 <sup>**</sup>
PL [229]		+0.04 [7.8]		+0.13 [8.9]		+0.3 [81.1]		+3.2 [29.8]		+4.2 [32.1]	
<b>InTANDEM 3 [19]</b>											
SOT 400 [699]	24	-0.79 [8.3]	-0.46 <sup>***</sup>	-0.79 [9.2]	-1.29 <sup>***</sup>	-2.2 [82.4]	-3.0 <sup>***</sup>	-3.1 [29.5]	-9.9 <sup>***</sup>	-5.7 [27.3]	-12.3 <sup>***</sup>
PL [703]		-0.33 [8.2]		+0.49 [9.1]		+0.8 [81.6]		+6.8 [29.6]		+6.6 [28.7]	
Pooled inTANDEM 1 & 2 data in pts with body mass index $\geq 27$ kg/m <sup>2</sup> [28]											
SOT 200 [305]	24	-0.43 [7.7]	-0.39 <sup>***</sup>			-1.93 [94.7]	-2.3 <sup>***</sup>				
SOT 400 [313]		-0.50 [7.6]	-0.45 <sup>***</sup>			-2.98 [93.7]	-3.3 <sup>***</sup>				
PL [298]		-0.04 [7.6]				+0.34 [94.2]					

BL values are means and changes from BL are least-squares means

BL baseline, Diff difference, eval evaluation, HbA<sub>1c</sub> glycosylated haemoglobin, PL placebo, pts patients, SOT sotagliflozin, wk week

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$

<sup>a</sup>Evaluate for HbA<sub>1c</sub>: no. of pts evaluable differed for other endpoints in inTANDEMI (241–245 at wk 24; 216–233 at wk 52) and inTANDEM2 (237–241; 226–233) and for basal insulin dose in inTANDEM 3 (698 SOT and 701 PL)

<sup>b</sup>Primary endpoint

without experiencing severe hypoglycaemia or DKA (33% and 44% vs. 22% in inTANDEM 1 [17]; 31% and 32% vs. 15% in inTANDEM 2 [18]), with this benefit maintained at week 52 [17, 18].

**4.1.3.1 Patient-Reported Outcomes** Treatment satisfaction (as measured by Diabetes Treatment Satisfaction Questionnaire Status scores) was significantly ( $p < 0.001$ ) improved with the addition of once-daily sotagliflozin 200 mg or 400 mg relative to placebo at 24 weeks (the one timepoint evaluated) in inTANDEM 1 [17], inTANDEM 2 [18] and a post hoc analysis of pooled data from the two trials [26]. Each sotagliflozin dosage was also associated with a significant ( $p \leq 0.025$ ) reduction in diabetes distress (as assessed by the 2-item Diabetes Distress Screening Scale score) versus placebo at 24 weeks, with this benefit generally being maintained over 52 weeks' therapy [17, 18] (the exception being sotagliflozin 200 mg/day in inTANDEM 2 for which the difference vs. placebo was no longer statistically significant [18]).

Exit interview data from inTANDEM 1 and 2 further highlight how symptom improvements may improve the lives and satisfaction of patients with T1D [27]. Before trial entry, all 41 of the patients interviewed found maintaining their blood glucose levels within range difficult. During inTANDEM 1 or 2, the symptom improvements most commonly reported by sotagliflozin recipients included fewer hyperglycaemic events, increased blood glucose stability, lower HbA<sub>1C</sub> levels and reduced/improved insulin use [21–24 of 27 (78–89%) recipients vs. 5–7 of 14 (36–50%) placebo recipients]. Among patients who reported improvements in their symptoms, most (97%) reported that the improvements had impacted their lives positively (most commonly their mood/emotions, physical functioning and self-esteem). Moreover, satisfaction (assessed on a 7-point scale; 0 = very dissatisfied to 6 = very satisfied) was numerically higher during than before trial participation in patients who received sotagliflozin (5.5 vs. 3.9), whereas the opposite was true for those who received placebo (3.7 vs. 4.3). Improvements in satisfaction were related to improvements in symptoms and well-being [27].

## 4.2 inTANDEM 3

In adults whose T1D was inadequately controlled by insulin therapy, adding sotagliflozin 400 mg once daily to the existing insulin regimen (i.e. without an optimization run-in period) provided net clinical benefit, with significantly ( $p < 0.001$ ) more recipients of the drug than of placebo achieving an HbA<sub>1C</sub> level of  $< 7.0\%$  at 24 weeks without experiencing severe hypoglycaemia or DKA (28.6% vs. 15.2%; primary endpoint) [19]. This benefit was observed regardless of insulin delivery method. Sotagliflozin

significantly reduced HbA<sub>1C</sub> and FPG levels (Table 1), bodyweight (Table 1) and insulin requirements, as indicated by the mean daily total insulin dose (placebo-adjusted reduction of  $-9.7\%$ ;  $p < 0.001$ ) and the daily dose of both basal and bolus insulin (Table 1), relative to placebo. There were also significant ( $p < 0.001$ ) reductions in SBP and DBP with sotagliflozin compared with placebo at week 16 (LSM between-group differences for change from baseline were  $-3.8$  mmHg and  $-1.3$  mmHg) [19].

## 4.3 In Patients with a BMI $\geq 27$ kg/m<sup>2</sup>

In a post hoc analysis of pooled data from inTANDEM 1 and 2, sotagliflozin was an effective adjunct to insulin in overweight or obese patients (i.e. BMI  $\geq 27$  kg/m<sup>2</sup>) with T1D [28]. The addition of sotagliflozin 200 mg or 400 mg once daily, compared with adding placebo, significantly reduced both HbA<sub>1C</sub> levels and bodyweight over 24 weeks of treatment (Table 1) and also significantly ( $p < 0.01$ ) increased the percentage of time that patients ( $n = 58$ – $65$  evaluated) spent with glucose levels in range during this period (LSM changes were  $+6.3\%$  and  $+13.1\%$  vs.  $-1.92\%$  with placebo, from mean baseline values of 50–56%). SBP was also significantly ( $p = 0.005$ ) reduced with sotagliflozin 400 mg/day, but not 200 mg/day, relative to placebo (LSM changes were  $-4.0$  mmHg and  $-2.9$  mmHg vs.  $-1.6$  mmHg, from mean baseline values of 124–125 mmHg). Notably, the benefits seen with sotagliflozin in this patient population generally appeared to be of greater magnitude than those seen in patients with a BMI  $< 27$  kg/m<sup>2</sup> [28].

## 4.4 Other Trials and Analyses

When the efficacy of sotagliflozin was assessed in patients with renal impairment in a pooled analysis of inTANDEM 1, 2 and 3, HbA<sub>1C</sub> level reductions with the drug were comparable between patients with an eGFR  $\geq 60$  to  $< 90$  mL/min/1.73 m<sup>2</sup> ( $n = 841$ ) and those with an eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>; patients whose eGFR was  $< 60$  mL/min/1.73 m<sup>2</sup> ( $n = 79$ ) had numerical reductions in HbA<sub>1C</sub> (no further details reported) [7].

A meta-analysis of randomized controlled trials supports the clinical benefit of sotagliflozin 200 mg/day or 400 mg/day in patients with T1D, with the drug improving ( $p \leq 0.05$ ) both glycaemic (e.g. HbA<sub>1C</sub>, FPG, 2-h PPG) and non-glycaemic (bodyweight, daily insulin doses, SBP, DBP) outcomes relative to placebo [12]. Data were from three to six studies of 4–52 weeks' duration (among which were inTANDEM 1, 2 and 3); the number of sotagliflozin 200 mg/day or 400 mg/day recipients or placebo recipients that were evaluated was not specified [12].

A small, randomized, phase 2 study (inTANDEM 5) assessed the efficacy of adjunctive sotagliflozin in young

adults (aged 18–30 years) with T1D poorly controlled by insulin therapy ( $\text{HbA}_{1\text{C}} \geq 9.0\%$ ) [16]. LSM changes from baseline in  $\text{HbA}_{1\text{C}}$  levels after 12 weeks of therapy (primary endpoint) did not significantly differ between the overall sotagliflozin 400 mg once daily ( $n = 43$ ) and placebo ( $n = 42$ ) groups ( $-1.33\%$  vs.  $-0.99\%$ ; baseline values were  $9.9\%$  and  $9.7\%$ ), although significantly favoured sotagliflozin among patients whose  $\text{HbA}_{1\text{C}}$  was  $\geq 9.0\%$  and  $\leq 10.0\%$  at screening (LSM difference vs. placebo  $-0.75\%$ ;  $p = 0.006$ ) [prespecified subgroup analysis]. Benefit was also evident with sotagliflozin versus placebo in the overall patient population with regard to 2-h PPG (LSM between-group difference  $-3.1$  mmol/L) and bodyweight (LSM between-group difference  $-2.4$  kg) [descriptive  $p \leq 0.001$  for each comparison] [16].

## 5 Tolerability of Sotagliflozin

Oral sotagliflozin was generally well tolerated when used for up to 52 weeks as an adjunct to insulin therapy in adults with T1D in the phase 3 trials discussed in Sect. 4, with a pooled analysis of inTANDEM 1 and 2 (the studies with the longest treatment duration) being the focus of discussion here [15]. In this pooled analysis, adverse events (AEs) that were considered treatment-related (i.e. TRAEs) occurred in numerically more sotagliflozin 200 mg/day or 400 mg/day than placebo recipients ( $31.9\%$  and  $36.8\%$  vs.  $20.2\%$ ), although were not often severe ( $3.6\%$  and  $4.2\%$  vs.  $2.1\%$  of patients), serious ( $3.4\%$  and  $4.4\%$  vs.  $1.9\%$ ) or the cause of study drug discontinuation ( $3.6\%$  and  $5.9\%$  vs.  $2.3\%$ ) [15]. The most common treatment-emergent AEs with sotagliflozin that occurred (with one or each of the dosages) at an incidence numerically greater than with placebo included viral upper respiratory tract infection, diarrhoea, urinary tract infection, DKA (all reports), blood ketone body increased and vulvovaginal mycotic infection ( $2.9$ – $14.9\%$  of sotagliflozin 200 mg/day or 400 mg/day recipients vs.  $0.6$ – $13.1\%$  of placebo recipients) [15]. See Sects. 5.2 and 5.3 for further discussion of DKA (positively-adjudicated cases) and genital mycotic infections.

### 5.1 Hypoglycaemia

When used as an adjunct to insulin over 52 weeks in the pooled analysis of inTANDEM 1 and 2, sotagliflozin 200 mg/day or 400 mg/day significantly ( $p < 0.01$ ) reduced the risk of documented hypoglycaemia at a blood glucose threshold of  $\leq 3.1$  mmol/L compared with placebo [ $14.9$  and  $15.0$  vs.  $19.0$  events per patient-year (PY)] [7]. Rates of documented hypoglycaemia events at a blood glucose threshold of  $\leq 3.9$  mmol/L in the respective groups were  $81.3$  and  $83.7$  versus  $95.6$  per PY [7]. Moreover, positively-adjudicated

severe hypoglycaemia events (i.e. requiring assistance or associated with seizure/loss of consciousness) occurred in  $5.7\%$  and  $4.4\%$  of sotagliflozin 200 mg/day or 400 mg/day recipients versus  $7.4\%$  of placebo recipients, with the latter comparison representing a significant ( $p = 0.04$ )  $41\%$  reduction in risk [7]; the exposure-adjusted incidence rates (EAIRs) per PY in the respective groups were  $0.14$  and  $0.07$  vs.  $0.11$  [15].

Furthermore, in an exploratory post hoc analysis of pooled data from these trials that evaluated hypoglycaemia as a function of  $\text{HbA}_{1\text{C}}$ , at 52 weeks, sotagliflozin 200 mg/day or 400 mg/day ( $n = 460$  and  $454$ ) was associated with a significantly ( $p < 0.05$ ) lower incidence than placebo ( $n = 448$ ) of hypoglycaemia events defined as blood glucose  $\geq 3$  to  $< 3.9$  mmol/L ( $45$  and  $46$  vs.  $58$  adjusted events per PY), blood glucose  $< 3$  mmol/L ( $12$  and  $11$  vs.  $16$  adjusted events per PY) or positively-adjudicated severe hypoglycaemia events (see earlier definition) [ $2.6\%$  and  $2.2\%$  vs.  $6.3\%$  of patients] [29]. Meta-analysis data (Sect. 4.4) also demonstrated a significant ( $p \leq 0.007$ ) reduction in the rate of hypoglycaemia (blood glucose  $\leq 3.9$  mmol/L) with sotagliflozin 200 mg/day or 400 mg/day versus placebo in patients with T1D, although the corresponding between-group differences in severe hypoglycaemia events (see earlier definition) were not statistically significant [12].

Similarly, over 52 weeks' treatment among inTANDEM 1 and 2 participants with a baseline BMI  $\geq 27$  kg/m<sup>2</sup> ( $n = 916$ ; pooled post hoc data), sotagliflozin 200 mg/day or 400 mg/day was associated with a significantly ( $p < 0.02$ ) lower rate of documented hypoglycaemia events (blood glucose  $\leq 3.1$  mmol/L) than placebo ( $13.8$  and  $14.6$  vs.  $17.99$ ) [28]. Although the EAIRs of positively-adjudicated severe hypoglycaemia with the sotagliflozin regimens were almost half that of placebo ( $46.5$  and  $41.1$  vs.  $81.0$  per 1000 PY), the relative reductions in risk did not reach statistical significance based on 95% confidence intervals. In patients with a baseline BMI  $< 27$  kg/m<sup>2</sup> ( $n = 659$ ), the documented hypoglycaemia event rate over 52 weeks was  $16.7$  with sotagliflozin 200 mg/day,  $16.99$  with sotagliflozin 400 mg/day and  $20.3$  with placebo, and the respective positively-adjudicated severe hypoglycaemia EAIRs were  $84.8$ ,  $59.5$  and  $83.9$  per 1000 PY; the difference in documented hypoglycaemia between sotagliflozin 200 mg/day and placebo was significant ( $p = 0.049$ ) [28].

### 5.2 Diabetic Ketoacidosis

Over 52 weeks of treatment, the incidence of positively-adjudicated DKA was numerically higher with sotagliflozin 200 mg/day or 400 mg/day than with placebo in the overall pooled analysis ( $2.9\%$  and  $3.8\%$  vs.  $0.2\%$ ); the EAIR in the respective groups was  $3.1$ ,  $4.2$  and  $0.2$  per 100 PYs [15]. DKA was serious in all cases and led to some

patients interrupting the study [10 of 15 (67%) sotagliflozin 200 mg/day, 9 of 20 (45%) sotagliflozin 400 mg/day and 1 of 1 (100%) placebo recipients] or discontinuing it [4 of 15 (27%), 8 of 20 (40%) and none of 1 (0%) patients, respectively]. The median time to DKA onset was markedly shorter with sotagliflozin 400 mg/day than 200 mg/day (134 vs. 214 days) [15]. Data from the meta-analysis were consistent with these findings, with the DKA incidence being significantly ( $p < 0.001$ ) greater than placebo with sotagliflozin 400 mg/day (risk ratio 4.41; 95% CI 1.92–10.12) but not 200 mg/day (risk ratio 3.65; 95% CI 0.83–15.94) [12]. Potential DKA risk factors included prior DKA, > 20% reduction in insulin dose, CSII use, high baseline levels of the ketone body beta-hydroxybutyrate (BHB) or greater BHB level increases [15], and there were inverse correlations between DKA and both the initial HbA<sub>1C</sub> level and the degree by which the basal insulin dose was reduced [12].

Among inTANDEM 1 and 2 participants with a baseline BMI  $\geq 27$  kg/m<sup>2</sup>, the EAIR of DKA per 1000 PYs at 52 weeks was 28.6 and 37.6 with sotagliflozin 200 mg/day or 400 mg/day versus 3.7 with placebo [risk difference: 24.9 (95% CI 3.8–46.1) and 33.9 (95% CI 10.6–57.3)]; corresponding rates among patients with a baseline BMI < 27 kg/m<sup>2</sup> were 34.9 and 48.7 versus 0 in the respective groups [risk difference: 34.9 (95% CI 9.1–60.8) and 48.7 (95% CI 16.9–80.5)] [28].

Various DKA risk minimization measures are recommended for sotagliflozin. Sotagliflozin should not be initiated in patients with an increased DKA risk (e.g. low insulin needs; recurrent/recent history of DKA) [7]. Prior to starting sotagliflozin or increasing its dosage, patients must have normal ketone levels, be able to self-monitor glucose and ketone levels and have measured their blood/urinary ketone levels several times in the 1–2 weeks before sotagliflozin initiation. Patients must also be familiar with what impacts their ketone levels and be informed of DKA (risk/risk factors/signs/symptoms), how/when to monitor ketone levels and what to do if ketosis/DKA is suspected [7]. Sotagliflozin should be discontinued if DKA is suspected/diagnosed, and DKA then treated as per standard of care; sotagliflozin should only be restarted if the DKA cause is identified and resolved [7].

### 5.3 Other Adverse Events of Special Interest

Recipients of sotagliflozin may experience genital mycotic infections, particularly if they are female. In the overall pooled analysis, genital mycotic infections occurred with numerically greater incidence with sotagliflozin 200 mg/day or 400 mg/day than with placebo both in female patients (15% and 17% vs. 5%) [e.g. vulvovaginal mycotic infection] and male patients (3% and 6% vs. 1%) [e.g. balanoposthitis]. Events were mostly mild/moderate in females and all mild/moderate in males, and none were serious in either of the sexes [7, 15]. Similarly, in the meta-analysis,

sotagliflozin 200 mg/day or 400 mg/day significantly ( $p \leq 0.003$ ) increased the risk of genital infections versus placebo, with the risk ratios being 3.20 (95% CI 1.50–6.82) and 3.16 (95% CI 2.04–4.88) for the respective comparisons [12]. However, where specified, genital mycotic infections were not often the cause of treatment discontinuation ( $\leq 1.2\%$  of females and  $\leq 0.4\%$  of males across sotagliflozin and placebo groups) [7, 15]. Monitoring for, and treating, genital mycotic infections appropriately is recommended [7].

Among patients treated with SGLT2 inhibitors, there have been post-marketing reports of necrotizing fasciitis of the perineum, a serious, albeit rare, infection (also referred to as Fournier's gangrene) that can be life-threatening and may be preceded by uro-genital infection or perineal abscess [7]. Sotagliflozin recipients should seek medical attention if they have malaise or fever, together with genital/perineal tenderness, pain, erythema or swelling. Those suspected of having necrotizing fasciitis of the perineum should discontinue sotagliflozin and be treated appropriately [7].

By increasing urinary glucose excretion, sotagliflozin may induce osmotic diuresis and, consequently, intravascular volume contraction/depletion [7]. Volume depletion-related AEs (e.g. dehydration, postural dizziness, hypotension) were uncommon among sotagliflozin 200 mg/day or 400 mg/day recipients in the overall pooled analysis (< 3.0% vs. 1.0% of placebo recipients) [15], with the likelihood not significantly differing from placebo in the meta-analysis [risk ratios were 2.09 (95% CI 0.66–6.64) and 2.38 (95% CI 0.97–5.82) for 200 mg/day and 400 mg/day] [12]. However, the risk of symptomatic hypotension with sotagliflozin is greater in patients who are elderly, renally impaired, taking diuretics or have low SBP [7]. Volume contraction should be evaluated and, if necessary, volume status corrected, prior to starting sotagliflozin. Monitoring for hypotension signs/symptoms is recommended during treatment, as is volume status/electrolyte monitoring in patients with conditions that may cause fluid loss; sotagliflozin may be interrupted temporarily until fluid loss is corrected [7].

Various other AEs of special interest were also uncommon with sotagliflozin. In the pooled analysis of inTANDEM 1 and 2, dosages of 200 mg/day or 400 mg/day were associated with a low incidence of renal-related AEs (1.5% and 1.3% vs. 1.5% with placebo) and fractures (2.9% and 1.9% vs. 3.4%; 52-week DEXA subgroup data) [15]. There was also a low incidence of malignancies of special interest (0.1–0.3% across sotagliflozin 200 mg/day or 400 mg/day and placebo recipients) and lower limb amputations (one each with sotagliflozin 200 mg/day or 400 mg/day, both of the toe) with the drug in T1D trials (pooled); the incidence rate of adjudicated major adverse CV events per 1000 PY in a pooled analysis of T1D or T2D phase 2/3 trials ( $n = 3571$ ) was 9.97 and 4.95 with sotagliflozin 200 mg/day or 400 mg/day versus 8.65 with placebo [15]. As another SGLT2 inhibitor (canagliflozin) has been associated with lower limb

amputations (in long-term clinical trials in T2D patients with high cardiovascular risk [30]), sotagliflozin recipients should be counselled on preventative routine foot care [7].

## 6 Dosage and Administration of Sotagliflozin

Sotagliflozin is indicated in the EU as an adjunct to insulin therapy to improve glycaemic control in adults with T1D with a BMI  $\geq 27$  kg/m<sup>2</sup> who have failed to achieve adequate glycaemic control despite optimal insulin therapy [7]. Sotagliflozin should be initiated at a dosage of 200 mg once daily, with this increased to 400 mg once daily after  $\geq 3$  months of treatment if further glycaemic control is required and 200 mg once daily is being tolerated; sotagliflozin should be taken before the first meal of the day. Insulin dosages may require adjustment either when initiating sotagliflozin (consider 20% reduction of first bolus insulin dose) or throughout sotagliflozin therapy (individualize bolus and basal insulin doses on the basis of blood glucose levels) to avoid hypoglycaemia, although such adjustments should be made with caution to avoid ketosis/DKA. Other DKA mitigation strategies should also be implemented (Sect. 5.2) [7]. Consult local prescribing information for further details pertaining to DKA mitigation, drug interactions, use in special patient populations, contraindications and other warnings and precautions.

## 7 Place of Sotagliflozin in the Management of Type 1 Diabetes

Patients with T1D require lifelong insulin therapy [31], with recommended regimens including MDIs of prandial and basal insulin [4, 5] and (for patients with disabling hypoglycaemia or high HbA<sub>1C</sub> on MDIs [4]) CSII [4, 5]. Although life-saving [32], insulin therapy is not without its challenges, being associated with weight gain [5], hypoglycaemia [5] and high glycaemic variability [33], and many patients finding it difficult to achieve and maintain glycaemic targets [6, 34]. With this in mind, various non-insulin based agents have been evaluated as adjuncts to insulin in T1D [35]. However, to date, only two have been approved for use in this setting in the EU [dapagliflozin (at low dose) and sotagliflozin], both of which are SGLT inhibitors, a class of oral agents that act independently of insulin and have minimal glucose-lowering properties in the presence of euglycaemia [36, 37].

The most recently approved of these two agents is sotagliflozin, which differs from other available SGLT inhibitors in being the first to inhibit both SGLT1 and SGLT2 (rather than selectively inhibiting SGLT2). Approval of sotagliflozin (Sect. 6) was based largely on the findings of the 24- to 52-week phase 3 inTANDEM 1–3 clinical trials, in which

the drug, when added to a background insulin regimen in adults with T1D, improved glycaemic control and reduced bodyweight and total daily insulin requirements, regardless of whether the background insulin regimen was (Sect. 4.1) or was not (Sect. 4.2) optimized before randomization. Notably, the reductions in total daily insulin requirements generally seemed to be driven by a lessened need for bolus insulin (Sects. 4.1 and 4.2), which is consistent with the drug's partial inhibition of SGLT1, with consequent blunting/delaying of PPG absorption (Sect. 2). Sotagliflozin can also improve BP, as well as glycaemic stability and the time spent with glucose in the target range (Sect. 4), with these glycaemic effects being increasingly popular aims in T1D management as CGM devices become more widely available [33].

Adjunctive use of sotagliflozin for up to 52 weeks in this setting is generally well tolerated (Sect. 5). Overall, its addition to insulin therapy reduces, or at least does not increase, the incidence of hypoglycaemia (Sect. 5.1), although an increased risk of DKA has been seen with the drug (Sect. 5.2). As DKA risk minimization measures (Sect. 5.2) do not eliminate the risk, the European Medicines Agency consider sotagliflozin to have a negative risk/benefit balance for patients with T1D overall [15]. However, in T1D patients who are overweight/obese (BMI  $\geq 27$  kg/m<sup>2</sup>), the benefits of sotagliflozin (which likewise include glycaemic control, bodyweight and BP improvements; Sect. 4.3) are considered to outweigh its risks (Sect. 5.2), particularly given the importance of bodyweight and BP reductions in overweight patients and their greater insulin needs (higher insulin doses have lower DKA risk) [15]. Consequently, sotagliflozin is indicated for use in adults with T1D with a BMI  $\geq 27$  kg/m<sup>2</sup> who have failed to achieve adequate glycaemic control despite optimal insulin therapy (Sect. 6), with use of dapagliflozin in T1D being likewise limited to patients with a BMI  $\geq 27$  kg/m<sup>2</sup> for similar reasons [38, 39].

Despite the increased risk of DKA with adjunctive SGLT inhibitor use, most (93%) patients with T1D who evaluated the risk-benefit profile of sotagliflozin in a recent blinded online survey reported they would consider taking the drug as an adjunctive therapy [40]. This finding may reflect sotagliflozin's potential to address some of the greatest unmet needs of the patients, among which were treatment simplification, maintaining/improving HbA<sub>1C</sub> levels, reducing mental effort and increasing the time with in-range glucose levels [40]. Notably, another online survey indicated that, among the treatment choices provided, most patients with T1D preferred the benefit/risk profile of low-dose SGLT inhibitor therapy, with DKA risk being considered the most important drug characteristic [41]. Indeed, mitigating DKA is an important aspect of using SGLT inhibitors in T1D, with this being highlighted by recent international consensus recommendations on DKA risk management in this setting [42].

As the proportion of obese/overweight patients with T1D is increasing [35], so is the number of individuals for whom

adjunctive SGLT inhibitor therapy may be suitable. In terms of choosing between sotagliflozin and dapagliflozin, both have the convenience of once-daily oral administration, and comparative data from an indirect network meta-analysis suggest their efficacy and tolerability profiles are generally similar [43]. However, direct head-to-head data would be of interest to confirm the relative efficacy/tolerability of these agents and to determine whether the extra mechanism of lowering glucose associated with dual SGLT1 and SGLT2 inhibition (Sect. 1) provides any clinical benefit over more selective inhibition of SGLT2. Pharmacoeconomic data for sotagliflozin would also be of interest, as would longer-term clinical experience with adjunctive SGLT inhibitor use in T1D, particularly as it is not yet known whether such regimens may provide CV benefit in this setting (as has been seen with some SGLT inhibitors in T2D [5, 44]).

Diabetes is a complex and demanding disease for patients to manage, causing emotional distress in up to almost half of patients [5]. Adding sotagliflozin to insulin therapy reduced diabetes distress and improved treatment satisfaction in key T1D trials (Sect. 4.1.3.1); whether this may improve patient quality of life and adherence remains to be determined. However, most patients interviewed after participating in inTANDEM 1 or 2 felt that the symptom improvements they experienced positively impacted their lives (Sect. 4.1.3.1).

In conclusion, sotagliflozin, as an adjunct to insulin in patients with T1D with BMI  $\geq 27$  kg/m<sup>2</sup> who have failed to achieve adequate glycaemic control despite optimal insulin therapy, is effective and generally well tolerated and thus a welcome addition to the currently limited adjunctive oral treatment options available for use in this population.

#### Data Selection Sotagliflozin: 143 records identified

Duplicates removed	38
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	20
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	41
<b>Cited efficacy/tolerability articles</b>	19
<b>Cited articles not efficacy/tolerability</b>	25
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Sotagliflozin, Zynquista, LX-4211, SAR-439,954, LP-802034, Type 1 Diabetes Mellitus. Records were limited to those in English language. Searches last updated 11 November 2019.	

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