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# A review of sotagliflozin for use in type 1 diabetes

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***Abstract*:** Type 1 diabetes is a challenging disease that is largely managed with the use of insulin. The risk of hypoglycemia, side effects of weight gain, and high glucose variability associated with insulin use have prompted researchers to explore additional therapies to treat this condition. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of medications that lower glucose in type 2 diabetes patients independent of insulin action, and have been studied for use in the type 1 diabetes population. Sotagliflozin is an SGLT2 inhibitor that demonstrates a unique binding affinity for the SGLT1 receptor. A total of three phase III clinical trials (inTandem1, inTandem2, and inTandem3) were conducted to evaluate the safety and efficacy of sotagliflozin in type 1 diabetes. A modest hemoglobin A1C reduction of 0.3–0.4% was observed, with secondary benefits of reduced glucose variability, reduced insulin dosage, and positive weight loss effects. Overall there was a reduction in the risk of severe hypoglycemia with sotagliflozin, but a higher rate of ketone formation and risk of diabetic ketoacidosis was observed, along with increased mycotic infections and volume depletion effects.

***Keywords:*** type 1 diabetes, SGLT2 inhibitors, sotagliflozin, hypoglycemia, ketones

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## Introduction

Type 1 diabetes (T1D) is a challenging disease that requires constant management, balancing insulin dosing with food intake and exercise on a daily basis. Globally there are an estimated 422 million adults living with diabetes, with approximately 10% having T1D.[1] It is estimated that approximately 1.25 million people in the US are living with T1D, including approximately 200,000 youths, with an additional 40,000 people diagnosed each year.[2] By the year 2050, an estimated 5 million people will be diagnosed with T1D in the US.[2,3] Economically, there is an estimated $14 billion spent annually in the US on T1D-associated healthcare and lost wages.[3] Currently, < 25% of patients with T1D reach the American Diabetes Association national guidelines for a goal hemoglobin A1C (A1C) of <7%.[4] In addition, data indicates there are rising numbers of T1D patients who are struggling with being overweight or obese.[5,6] Insulin treatment continues to be the standard of care for T1D, delivered by subcutaneous injection or through continuous infusion with insulin pump devices. While insulin is an essential tool for managing patient's glucose levels, it does present the risk of hypoglycemia and has been shown to present adherence barriers with treatment.[7–9] Glucose variability can be a challenge for T1D patients, many of which experience wide fluctuations in their blood glucose levels due to an improper balance between their diet and insulin dosing. These challenges have prompted researchers to explore noninsulin treatments for the type 1 diabetes population.

The sodium-glucose cotransporter 2 (SGLT2) inhibitor class of medications is an interesting option for treating T1D. There are currently four of these agents approved in the US for the treatment of type 2 diabetes (T2D), and the class has demonstrated good A1C lowering efficacy in combination with the additional benefits of blood pressure reduction and weight loss. Their therapeutic mechanism is independent of insulin action, and is not associated with hypoglycemia,

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and may target the maladaptive condition of glucose reabsorption that has been observed in T1D patients.[10] Research into these medications has demonstrated some potential cardiovascular benefits in patients with established cardiovascular disease and high coronary heart disease risk.[11–13] In addition, there are ongoing studies evaluating the use of the SGLT2 drug class in patients with renal disease, with some suggestions that these agents may provide renal protection.[12] The SGLT2 inhibitors demonstrate some variability in their activity based at least partially on the varying binding affinity between the SGLT1 and SGLT2 receptors in the body. SGLT1 proteins are expressed in the small intestines, where their role is still understudied, and the proximal tubule of the kidney, which represents approximately 10% of filtered glucose reabsorption.[14] Blocking these receptors has been shown to reduce and delay postprandial glucose excursions.[15] Inhibition of SGLT1 may lead to gastrointestinal side effects, including severe diarrhea.[16] SGLT2 proteins are located in the proximal convoluted tubule of the kidneys and are responsible for approximately 90% of filtered glucose reabsorption.[14,16]

Sotagliflozin is a new SGLT2 inhibitor that has additionally shown significant activity on the SGLT1 receptor specifically in the small intestines but not in the kidneys. It has been evaluated for the treatment of T1D. This manuscript reviews this new medication specifically in this role in the treatment of T1D.

## Pharmacology

### *Pharmacokinetics*

Pharmacokinetic data for sotagliflozin in patients with T1D is limited. A study performed in eight healthy subjects using a single 400 mg dose of sotagliflozin reported time to maximum plasma concentration ($T_{max}$) of 1.25–4.5 h, and a half-life of 21–35 h. Exposure was affected by body weight, renal impairment, and hepatic impairment.[17] In patients with T2D, the peak concentration ($C_{max}$) after a single dose of sotagliflozin 300 mg was 105 ng/ ml for two 150 mg tablets and 135 ng/ml for six 50 mg tablets. The $T_{max}$ was 3 h. After 14 days of once daily dosing of sotagliflozin 300 mg, the mean $C_{max}$ was 27% higher than on day 1, which indicates some accumulation. In these patients with T2D and normal renal function, the half-life with once-daily dosing for 28 days was 13.5–20.7 h and steady-state was reached at day 14.[18] In patients with T2D and moderate to severe renal insufficiency, the half-life was 16.6–18.1 h, indicating that the elimination of sotagliflozin is not significantly changed by reduced kidney function. However, similar to the other SGLT2 inhibitors, sotagliflozin should probably not be used in patients with an estimated glomerular filtration rate (eGFR) of $<45$ ml/min/1.73 m$^2$ due to reductions in urinary glucose excretion and decreased glucose lowering efficacy.[19]

**Table 1.** SGLT-2: SGLT-1 selectivity of SGLT inhibitors approved and under development.[20–22]

| Generic name | SGLT2:SGLT1 selectivity |
|---|---|
| Canagliflozin | 155 |
| Dapagliflozin | 1242 |
| Empagliflozin | 2680 |
| Ertugliflozin | 2000 |
| Ipragliflozin | 254 |
| Luseogliflozin | 1770 |
| Sotagliflozin | 20 |
| Tofogliflozin | 2912 |

### *Pharmacodynamics*

Differences between the currently approved SGLT2 inhibitors include their respective selectivity profiles for SGLT2 over SGLT1. In comparison, sotagliflozin has much more of an effect on SGLT1 than other available agents (Table 1). Sotagliflozin demonstrates only a 20 times higher potency for SGLT2 over SGLT1 and is, therefore, considered to be a dual inhibitor of SGLT1 and SGLT2.[20–22]

SGLT2 accounts for 90% of glucose reabsorption in the kidney and is thought to be overexpressed in patients with diabetes. Inhibition of SGLT2 reduces glucose reabsorption in the kidney, therefore, increasing urinary glucose excretion and lowering blood glucose.[20]

SGLT1 plays a major role in glucose uptake in the small intestine. In addition, glucose uptake by intestinal SGLT1 modulates the secretion of

intestinal hormones that regulate glucose, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Diabetes increases intestinal SGLT1 expression which increases glucose uptake. Inhibition of SGLT1 delays, and perhaps reduces, glucose absorption, and enhances circulating levels of GLP-1 and GIP. Both of these mechanisms result in reductions in postprandial glucose (PPG) excursions. The SGLT1 protein is expressed in the salivary glands, liver, lung, skeletal muscle, heart, pancreatic alpha cells, and the brain, however, the significance of this is not well understood.[20,23] Pharmacodynamic data in healthy subjects and patients with T1D is limited but demonstrates that sotagliflozin delays glucose absorption by inhibiting SGLT1 and reduces renal glucose reabsorption by inhibiting SGLT2. The effect of sotagliflozin on glucose absorption was evaluated in a randomized, single dose, crossover study in 24 healthy patients. Patients received sotagliflozin 400 mg or placebo followed by an isotope tracer glucose drink within 15 min.[17] Results indicated that the rate of oral glucose appearance with sotagliflozin was significantly lower than placebo during the first 1–2 h, but was comparable over 5 h between sotagliflozin and placebo. This demonstrates a delay in glucose absorption without a change in the total amount of glucose absorbed. In addition, sotagliflozin produced higher urinary glucose excretion compared with placebo.[17]

A phase II, dose-ranging study (inTandem4) was conducted in patients with T1D.[17,24] Although it would have been helpful to conduct this study prior to initiating phase III studies, inTandem4 ran in parallel with the phase III studies. Therefore, its stated purpose was to confirm the appropriateness of doses that were concurrently being tested in phase III studies in T1D subjects. The study was conducted in 141 patients with T1D who were on either insulin pump therapy or multiple daily injections with an A1C range of 7–10% and evaluated sotagliflozin 75 mg, 200 mg, or 400 mg taken once daily before the first meal of the day *versus* placebo. Sotagliflozin increased urinary glucose excretion in a dose-dependent manner (0.3 g/day placebo, 42 g/day sotagliflozin 75 mg, 58 g/day sotagliflozin 200 mg, and 70.7 g/day sotagliflozin 400 mg, $p < 0.001$ for all *versus* placebo). After 12 weeks, sotagliflozin 400 mg was more effective than a placebo at decreasing PPG (–49 mg/dl, $p = 0.006$) but the 75 mg and 200 mg doses were not significantly different than placebo. However, sotagliflozin 200 mg and 400 mg were both more effective than placebo at lowering A1C (–0.48%, $p < 0.001$ and −0.38%, $p = 0.006$ respectively) and lowering weight (–2.4 kg, $p < 0.001$ and −2.6 kg, $p < 0.001$).[17,24]

## Clinical evidence

Three double-blind, randomized controlled trials (inTandem1–3) have been published that evaluate the safety and efficacy of sotagliflozin in adult patients with T1D.[25–27] The inTandem trials enrolled a total of approximately 3000 patients from around the world with a diagnosis of T1D that were managed with either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) with an A1C of between 7% and 11% at the screening. Average A1C levels at the screening were 8.2%, 8.4%, and 8.2% for inTandem trials 1–3, respectively. All three trials utilized insulin optimization dosing to target and maintain a fasting plasma glucose (FPG) between 80 and 130 mg/day and 2 h postprandial glucose <180 mg/day. Patients were excluded from all trials if β-hydroxybutyrate (BHB) was >0.6 mmol/l at screening, if severe hypoglycemia or diabetic ketoacidosis (DKA) was present in the previous month, or if patients had an eGFR <45 ml/min/1.73 m$^2$. A summary of baseline patient characteristics for the inTandem trials can be found in Table 2.

### *Sotagliflozin added to optimized insulin regimens*

The inTandem1 and inTandem2 studies were nearly identical in their design with the only difference being that inTandem1 was conducted in North America[25] and inTandem2 was conducted in Europe and Israel.[26] Both studies were 52 weeks in duration and compared the effects of either sotagliflozin 200 mg or 400 mg to placebo when added to an optimized insulin regimen. Insulin optimization began 6 weeks prior to randomization and continued through to the end of the trial. An independent insulin dose monitoring committee (IDMC) was utilized to blindly review insulin titration decisions during the first 24 weeks of the trial in order to ensure insulin adjustments were consistent with self-monitoring blood glucose patterns. The primary endpoint was changed in A1C from baseline to 24 weeks.

**Table 2.** Summary of study design and baseline patient characteristics of inTandem studies evaluating sotagliflozin in type 1 diabetes.

| Study | Design | Baseline patient characteristics | Run-in time prior to randomization | Baseline glucose and insulin dose at randomization | Study arms |
|---|---|---|---|---|---|
| Buse *et al.* (inTandem1)[23] North America | Double-blind; 52 weeks (24w core, 28w long term extension); *n* = 793 | Mean age 46 years; 52% female; 92% white; BMI 29.7 kg/m$^2$; DM duration 24.4 years; 40.4% used MDI | Insulin optimization for 6 weeks with a 2 week placebo run-in | A1C 7.6%<br>FPG 152 mg/dl<br>TDD: 64–67 IU/ day | Placebo<br>Sotagliflozin 200 mg daily<br>Sotagliflozin 400 mg daily |
| Danne *et al.* (inTandem2)[24] European Union and Israel | Double-blind; 52 weeks (24w core, 28w long term extension); *n* = 782 | Mean age 41 years; 48% female; 96% white; BMI 27.8 kg/m$^2$; DM duration 18.4 years; 74.3% used MDI | Insulin optimization for 6 weeks with a 2-week placebo run-in | A1C 7.8%<br>FPG 163 mg/dl<br>TDD: 60–62 IU/day | Placebo<br>Sotagliflozin 200 mg daily<br>Sotagliflozin 400 mg daily |
| Garg *et al.* (inTandem3)[25] 19 countries | Double-blind; 24 weeks; *n* = 1402 | Mean age 43 years; 50% female; 88% white; BMI 28 kg/m$^2$; DM duration 20 years; 60.4% used MDI | Single-blind placebo run-in for 2 weeks | A1C 8.2%<br>FPG 164 mg/dl<br>TDD: 57–58 IU/day | Placebo<br>Sotagliflozin 400 mg daily |

A1C, hemoglobin A1C; BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; MDI, multiple daily injections; TDD, total daily dose.

After 24 weeks of treatment, the placebo-adjusted least squares mean (LSM) A1C for inTandem1 participants had decreased by 0.36% (95% CI −0.45 to −0.27) and 0.41% (95% CI −0.50 to −0.32) with sotagliflozin 200 mg and 400 mg, respectively (both $p < 0.001$) (Table 3). While this benefit in A1C reduction remained significant at 52 weeks compared with the placebo, it was less pronounced. A1C reduction peaked after the first 8 weeks of treatment then steadily decreased over the next 44 weeks. Very similar results were reported for the inTandem2 trial where the placebo-adjusted LSM A1C after 24 weeks had decreased by 0.37% (95% CI −0.48 to −0.25) and 0.35% (95% CI −0.47 to −0.24) for sotagliflozin 200 mg and 400 mg, respectively. Again, the benefit in A1C reduction remained significant at 52 weeks, but was less pronounced, with the greatest A1C reductions seen after 8 weeks of treatment. In both trials, higher numbers of patients in both sotagliflozin groups achieved A1C targets of <7% compared with placebo. Of those patients in inTandem1 with a baseline A1C ⩾7.0% after insulin optimization, 15.7%, 27.2%, and 40.3% of patients achieved an A1C of <7.0% after 24 weeks of treatment in the placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg groups, respectively (both $p < 0.005$). Of those patients in inTandem2 with a baseline A1C ⩾7.0% after insulin optimization, 6.1%, 24.6%, and 26.3% of patients achieved an A1C of <7.0% after 24 weeks of treatment in the placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg groups, respectively (both $p < 0.001$).

Compared with placebo, average FPG decreased significantly for the 200 mg and 400 mg doses at 24 weeks and was sustained at 52 weeks for inTandem1. For inTandem2, average FPG decreased significantly for both doses at 24 weeks but was not sustained at 52 weeks, with the change in FPG for the 200 mg group no longer being significant. Both studies showed significant reductions in weight ranging from 1.98 kg to 3.45 kg for the 200 mg and 400 mg doses at 24 weeks with further dose-dependent weight reductions seen at 52 weeks. Participants in inTandem1 with a baseline SBP ⩾130 mm Hg saw significant reductions in SBP at 24 weeks with placebo-adjusted LSM decreases of 5.4 mm Hg and 6.6 mm Hg for the 200 mg and 400 mg groups, respectively, which were more substantial than those with a baseline SBP <130 mm Hg. However, these results were no longer significant compared with placebo at

**Table 3.** Efficacy endpoints across randomized controlled trials of sotagliflozin in type 1 diabetes.

| Study | Study arms | Change in A1C (%) from baseline to 24 weeks | Change in A1C (%) from baseline until end of study (difference from placebo) | | Net benefit+ (%) from baseline until end of study (difference from placebo) | | Change in weight (kg) from baseline until end study (difference from placebo) | | Percent change in TDD of insulin from baseline until end of study (difference from placebo) | | Change in FPG (mg/dl) from baseline until end of study (difference from placebo) | | Change in SBP (mm Hg) from baseline until end of study (difference from placebo) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Buse *et al.* (inTandem1)[23] North America | | | 24w | 52w | 24w | 52w | 24w | 52w | 24w | 52w | 24w | 52w | 24w | 52w |
| | Placebo | −0.07* | – | – | – | – | – | – | – | – | – | – | – | – |
| | Sotagliflozin 200 mg | −0.43*Δ | −0.36* | −0.25* | 12* | 13.4* | −2.35* | −3.14* | −6.16* | −8.02* | −9.8* | −12.2* | −3.5* | −2.8* |
| | Sotagliflozin 400 mg | −0.48*Δ | −0.41* | −0.31* | 22* | 7.2* | −3.45* | −4.32* | −9.70* | −12.64* | −17.8* | −19.4* | −4.2* | −4.4* |
| Danne *et al.* (inTandem2)[24] European Union and Israel | | | 24w | 52w | 24w | 52w | 24w | 52w | 24w | 52w | 24w | 52w | 24w | 52w |
| | Placebo | −0.02 | – | – | – | – | – | – | – | – | – | – | – | – |
| | Sotagliflozin 200 mg | −0.39*Δ | −0.37* | −0.21* | 16.3* | 11.3* | −1.98* | −2.18* | −8.23* | −6.26* | −21.6* | −4.9 | −0.4 | −3.0* |
| | Sotagliflozin 400 mg | −0.37*Δ | −0.35* | −0.32* | 17.2* | 12.3* | −2.58* | −2.92* | −9.47* | −8.17* | −25.7* | −15.8* | −2.8* | −2.8* |
| Garg *et al.* (inTandem3)[25] 19 countries | Placebo | −0.33* | – | | – | | – | | – | | – | | – | |
| | Sotagliflozin 400 mg | −0.79* | −0.46* | | 13.4*Δ | | −2.98* | | −9.71* | | −23.2* | | −3.5*++ | |

*Statistically significant.
ΔPrimary endpoint.
+Proportion of patients with A1C <7% without any episode of SH or DKA.
++Difference between groups at 16 weeks (not evaluated at 24 weeks).
DKA, diabetic ketoacidosis; FPG, fasting plasma glucose; SH, severe hypoglycemia; TDD: total daily dose.

**Table 4.** Adverse events across randomized controlled trials of sotagliflozin in type 1 diabetes.

| Study | Study arms | Severe hypoglycemia (%) | DKA (%) | Amputations (%) | Bone density/ fractures (%) | Genital mycotic infections (%) | UTI (%) | Volume depletion (%) | Diarrhea (%) |
|---|---|---|---|---|---|---|---|---|---|
| Buse *et al.* (inTandem1)[1] North America | Placebo | 9.7 | 0.4 | 0 | 3.7 | 3.4 | 7.1 | 1.5 | 6.7 |
| | Sotagliflozin 200 mg | 6.5 | 3.4 | 0 | 3.4 | 9.1 | 9.9 | 3 | 8.4 |
| | Sotagliflozin 400 mg | 6.5 | 4.2 | 0.4 | 1.9 | 13 | 4.2 | 1.5 | 10.3 |
| Danne *et al.* (inTandem2)[2] EU and Israel | Placebo | 5 | 0 | 0 | 3.1 | 2.3 | 5 | 0.4 | 3.5 |
| | Sotagliflozin 200 mg | 5 | 2.3 | 0.4 | 2.3 | 9.2 | 4.2 | 2.3 | 4.6 |
| | Sotagliflozin 400 mg | 2.3 | 3.4 | 0 | 1.9 | 11.0 | 6.8 | 0.8 | 7.2 |
| Garg *et al.* (inTandem3)[3] 19 countries | Placebo | 2.4 | 0.6 | 0 | 0.7 | 2.1 | 3.8 | 0.3 | 2.3 |
| | Sotagliflozin 400 mg | 3.0 | 3.0 | 0 | 0.6 | 6.4 | 3.6 | 1.9 | 4.1 |

DKA, diabetic ketoacidosis; UTI, urinary tract infection.

52 weeks and inTandem2 only showed a significant SBP decrease in these patients for the 400 mg dose.

Patient satisfaction for both studies was evaluated using the Diabetes Treatment Satisfaction Questionnaire where an increase in score indicates greater treatment satisfaction. For inTandem 1, at week 24, the LSM difference from placebo was 2.5 points for the 200 mg and 400 mg groups (both $p < 0.001$) with very similar results of 2.0 and 1.7 points for the 200 mg and 400 mg groups (both $p < 0.001$), respectively, in inTandem2. Similarly, the two-item Diabetes Distress Screening Scale showed that distress decreased significantly in the sotagliflozin-treated groups while showing no change or increasing in the placebo groups.

Major adverse events across the inTandem phase III trials are outlined in Table 4. Hypoglycemia events seen in the sotagliflozin trials are discussed in a separate section below. Both inTandem1 and 2 trials showed an increased risk for DKA at the 200 mg and 400 mg doses. During the 52 weeks, inTandem1 reported 21 participants with ⩾1 DKA event (22 events in total) with only 1 of those in the placebo group, 9 participants (8 CSII users) in the 200 mg group, and 11 participants (7 CSII users) in the 400 mg group leading to 4 patients in each treatment group discontinuing sotagliflozin. During the 52 weeks, inTandem2 reported 15 participants with ⩾1 DKA event with 6 of these in the 200 mg group (1 CSII user), 5 in the 400 mg group (5 CSII users), and none in the placebo group leading to 4 participants in the 400 mg group discontinuing therapy. Each trial reported that baseline BHB levels increased by an average of approximately 0.1 mmol/l in each sotagliflozin group compared with placebo which did not change from baseline. InTandem2 reported that 87% of DKA events were associated with a potential contributory factor including infection, concomitant illness, missed insulin dose, or insulin pump interruption. No such data was reported for inTandem1.

### *Sotagliflozin added to stable insulin therapy*

The inTandem3 study was conducted at 133 centers worldwide and compared the effects of sotagliflozin 400 mg *versus* placebo when added onto stable insulin therapy for a total of 24 weeks.[27] There was a 2 week, single-blind, run-in period

where all participants received a placebo before being randomized 1:1 to receive either sotagliflozin 400 mg or placebo. The inTandem3 study did not utilize an IDMC as used in the first two studies.

Patients in the sotagliflozin group demonstrated an overall drop in A1C from a baseline of 0.79%, compared with 0.33% in the placebo group (Table 3). Significantly more patients met the primary endpoint of A1C <7% with no episodes of severe hypoglycemia or DKA (28.6% *versus* 15.2%; a difference of 13.4%, $p < 0.001$) at 24 weeks. A subgroup analysis showed that it made no difference whether the participants were using CSII or MDI. There were significantly more participants in the sotagliflozin group with an A1C ⩾7% at 24 weeks with at least one episode of DKA *versus* those in the placebo group (2.6% *versus* 0.6%; a difference of 2%, $p = 0.003$). Of those participants achieving a reduction in A1C of ⩾0.5%, significantly more people in the sotagliflozin group experienced DKA compared with placebo (1.43% *versus* 0.14%; difference 1.29%, $p = 0.006$).

A1C was significantly reduced from baseline in the treatment group compared with placebo (–0.79% *versus* −0.33%; difference −0.46%, $p < 0.001$) with greater reductions seen in those with higher baseline A1C (for A1C >9%, treatment difference of −0.50%). In the treatment group the total insulin dose, basal insulin dose, and bolus insulin dose were all significantly decreased by −5.25 units, −2.60 units, and −2.84 units, respectively (all $p$ values <0.001).

Serious adverse events were higher in the sotagliflozin group compared with placebo (6.9% *versus* 3.3%) leading to more adverse event withdrawals from the treatment group (6.3% *versus* 2.3%). Hypoglycemia is discussed in the following. Acidosis-related adverse events were higher in the sotagliflozin group compared with the placebo group (8.6% *versus* 2.4%), as was the rate of DKA episodes (3% *versus* 0.6%). The rate of DKA was higher in the sotagliflozin group regardless of whether CSII or MDI was used, those using CSII had a higher rate of DKA (4.4% *versus* 0.7% for CSII; 2.1% *versus* 0.5% for MDI).

### *Meta-analysis data*

A meta-analysis of sotagliflozin's randomized controlled trials specifically focused on sotagliflozin's safety and efficacy was published in April 2019.[28] A total of six trials with over 3200 patients were included for analysis. In addition to the three phase III trials previously discussed, the authors also included the phase II dose-ranging trial (inTandem4)[24] along with two additional smaller trials published in abstract form.[29,30] Overall the reported A1C reduction with the use of sotagliflozin in T1D subjects was −0.34% (95% CI −0.41% to −0.27%). FPG was reduced by an average of −16.98 mg/dl, with 2 h postprandial glucose reductions averaging −39.2 mg/dl. The authors estimated an average daily insulin reduction of approximately 9% and a weight loss average of −3.54% with sotagliflozin treatment. The relative risk (RR) for ketoacidosis was averaged at 3.93 (1.94–7.96), with the RR of genital mycotic infections higher by an average of 3.12 and increased volume depletion events at a RR of 2.19. The author's conclusions were that sotagliflozin improved both glycemic and nonglycemic outcomes with the risk of increased ketoacidosis, which they stated could be minimized by appropriate patient selection and a decrease in the overall basal insulin dose.[28]

### *Continuous glucose monitoring data*

Although A1C is the gold standard for assessing glucose control, there are limitations to using A1C as the sole marker of effective glucose control. A1C does not capture glucose variability or day-to-day disease control. Other indices including continuous glucose monitoring (CGM) and time in range may better capture the patient experience. In addition, time in range has been associated with the risk of microvascular complications.[31,32]

A CGM substudy was completed using pooled data from inTandem1 and inTandem2.[33] Participants in the CGM substudy ($n = 278$; 93 placebos, 89 sotagliflozin 200 mg, and 96 sotagliflozin 400 mg) were monitored using blinded CGM during prespecified periods (week −1 to baseline, week 3–4, week 11–12, and week 23–24). The major outcomes of the study were time within the target glucose range (70–180 mg/dl), time above (>180 mg/dl), and time below (<70 mg/dl).

From baseline to week 24, sotagliflozin 200 mg increased the time within the target glucose range by 1 h 17 min compared with placebo ($p = 0.026$) and sotagliflozin 400 mg increased the time within

the target glucose range by 2 h 49 min compared with placebo ($p < 0.001$). FPG decreased by 15.7 mg/dl and 21.4 mg/dl with sotagliflozin 200 mg and 400 mg respectively compared with placebo. Postprandial glucose decreased by 35 mg/dl and 50 mg/dl with sotagliflozin 200 mg and 400 mg respectively compared with placebo ($p = 0.009$ and $<0.001$ respectively). There was a decrease of more than 1 h/day of time spent with glucose >180 mg/dl with sotagliflozin 200 mg compared with placebo and nearly 3 h with sotagliflozin 400 mg. There was a numeric decrease in hypoglycemia (events/patient/day) and percentage of time spent/ day with glucose <55 mg/dl with sotagliflozin compared with placebo.[33]

### *Hypoglycemia*

The incidence, prevalence, and severity of hypoglycemia across the sotagliflozin studies were carefully tracked and analyzed. Pooled data from a meta-analysis of the six placebo-controlled studies, including all four of the inTandem studies, noted that sotagliflozin treatment was associated with lower rates of hypoglycemic events compared with placebo (–9.09 events/patient year, 95% CI −13.82 to −4.36, $p < 0.001$).[28] In addition, this meta-analysis noted a lower risk of severe hypoglycemia with sotagliflozin treatment of 31% compared with placebo (RR 0.69, 95% CI 0.49–0.98, $p = 0.04$). This is consistent with the European product labeling for sotagliflozin, where pooled data from the two 52 week trials showed a decreased incidence of severe hypoglycemia, along with lower documented rates of both overall and nocturnal hypoglycemic events in the sotagliflozin treatment groups compared with insulin alone.[34] Of note, the definitions for hypoglycemia (<70 mg/dl, <55 mg/dl for moderate) and severe hypoglycemia (low blood sugar requiring assistance from another person or resulting in loss of consciousness or seizure) were consistent across the trials and followed national guideline recommendations.

## Discussion

Sotagliflozin was among the first in the SGLT2 inhibitor class to apply for approval in the EU and the US for the treatment of T1D. It is unique in its dual inhibition of SGLT1 and SGLT2, having a stronger affinity for the SGLT1 receptors than any of the medications currently available for treating T2D in the US. Whether this higher SGLT1 affinity translates to additional benefits in the treatment of diabetes or unwanted side effects remains to be seen, but theoretical models and initial clinical trials suggest that additional PPG control could be achieved by this medication. In addition, it may help to set sotagliflozin apart from other medications in the SGLT2 inhibitor class, many of which are currently being evaluated for potential use in the T1D population.

The treatment of T1D with an SGLT2 inhibitor offers benefits and risks to this population. Increasing the excretion of glucose through the urine, independent of insulin action, offers a beneficial mechanism for reducing the overall glucose load in the body while potentially lowering insulin requirements. The data suggest that treatment with sotagliflozin successfully lowered A1C by approximately 0.3–0.4% compared with the placebo. This is a relatively modest reduction, which may not on its own outweigh the potential risks of SGLT2 therapy. There are a number of secondary benefits to consider, however, including improved glucose variability, improved PPG lowering, and positive effects on weight. Because insulin has been implicated in increasing weight, mitigating weight gain could be beneficial.[35,36] Data from a small safety and efficacy study performed with 33 patients over 29 days in 2015 demonstrated that higher doses of sotagliflozin were associated with greater reductions in patient's insulin doses, and a 2–3 kg average weight reduction at 24 weeks.[29] A1C reduction, in contrast, appeared to plateau at a dose of approximately 200 mg/day. While 400 mg/day dosing did demonstrate higher numbers of patients achieving an A1C of <7%, this was balanced by a higher prevalence in adverse events with a higher dosage, including the risks for DKA. In general, it is felt that further evidence is required to justify doses exceeding 200 mg in this patient population. The lower rates of severe hypoglycemia seen in the sotagliflozin-treated groups compared with patients using insulin alone, in combination with overall lower hypoglycemic events in this population (approximately nine events per patient year) suggest another potential secondary benefit to the T1D patients.

The safety profile of sotagliflozin showed similar adverse events as seen with the SGLT2 inhibitors in the T2D population, with genital mycotic infections occurring at significantly higher rates than placebo. Urinary tract infections (UTIs) were also observed, but at a low rate, with some trials

showing no difference from placebo. Diarrhea and volume depletion were documented side effects in the sotagliflozin-treated groups, occurring more frequently than placebo. Of note, a substantial incidence of ketone formation was shown to occur in the sotagliflozin treatment groups, and this was a major concern cited by the Food and Drug Administration's (FDA) subcommittee reviewing the new drug application.[17] Across pooled data for sotagliflozin, there were a total of 71 investigator-reported metabolic acidosis or DKA events in 69 subjects (6.6%) using active drugs, compared with 7 subjects (1.3%) in the placebo groups.[17] Evaluation of these reports led to the confirmation of DKA in 35 treated subjects (3.3%) and 1 placebo subject (0.2%). A total of 12 of the 35 subjects discontinued the study drug due to DKA events.[17] The previously mentioned phase II 2015 safety and efficacy sotagliflozin study with 33 patients showed an 8-fold increased risk of DKA with sotagliflozin treatment, with a number needed to harm of 26 patient years.[29] This early study did not have any mitigation strategies in place for patients that could reduce the risk of DKA. In contrast, another phase II 12 week trial conducted in 87 young adults aged between 18 and 30 years old with T1D utilized ketone monitoring and maintained close correspondence with participants who became ill.[30] In this trial, there were no episodes of DKA seen in the treatment group and one in the placebo.[30] It is possible that ketone formation, and the risk of DKA, were major considerations in the FDA's submission of a complete response letter for sotagliflozin in March 2019, stating that the drug was not approved as of that time, even after it had been approved by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). Further data demonstrating that DKA-mitigating strategies can successfully reduce or avoid these risks are required.

It is worth considering whether sotagliflozin offers unique benefits for T1D patients not seen with other SGLT2 inhibitors that are already FDA approved for the treatment of T2D. There is some published data available for other SGLT2 inhibitors in the context of T1D treatment. A 2015 article evaluated the effects of canagliflozin or placebo in 351 T1D patients over 18 weeks, with a primary endpoint of successfully achieving an A1C reduction of $\geqslant$0.4% with no increase in body weight.[36] Success rates for this endpoint were 36.9% with the 100 mg treatment group and 41.4% in the 300 mg treatment group, compared with 14.5% in the placebo group ($p < 0.001$), and both treatment groups demonstrated a reduction in insulin dose, body weight, and A1C when compared with placebo. Rates of hypoglycemia were low across all three groups, but both canagliflozin groups showed an increase in ketone-related adverse events [$n = 6$ (5.1%) in the 100 mg group and $n = 11$ (9.4%) in the 300 mg group, compared with 0 in the placebo] and DKA serious enough that it required hospitalization [$n = 5$ (4.3%) and $n = 7$ (6%) respectively, compared with 0 in the placebo group].[37] A similar study evaluated dapagliflozin 5 mg and 10 mg and placebo in 833 T1D patients over 24 weeks, with a primary endpoint of change in A1C from baseline.[37] Efficacy data from 778 of these patients demonstrated a mean A1C reduction of −0.42% in the 5 mg dapagliflozin group and −0.45% in the 10 mg dapagliflozin group, compared with placebo ($p < 0.0001$). Hypoglycemic episodes were similar across groups, with ketone-related events occurring in five patients (2%) in the 5 mg group and eight patients (3%) in the 10 mg group, compared with two patients (1%) in the placebo group. DKA leading to study discontinuation occurred in one patient (5 mg) and five patients (10 mg) compared with 0 in the placebo group.[38] Collectively, these data are similar to the results shown with sotagliflozin, suggesting modest A1C reductions with no worsening hypoglycemia, balanced by an increased risk of DKA. There was nothing of note in the sotagliflozin trials that clearly set them apart from the other SGLT2 inhibitor agents, suggesting that efficacy results may be viewed as a class effect. In addition, dapagliflozin is approved for the treatment in T1D in Europe but similarly received a complete response letter from the FDA in 2019 rejecting its approval for the T1D population at that time.

With regard to sotagliflozin's use in the treatment of T1D, there are some key counseling points that clinicians should bear in mind. Taking into consideration the ketone formation data and risk of DKA, patients should be counseled to recognize the signs and symptoms of diabetic ketoacidosis and should be willing to monitor ketone levels. Type 1 patients using sotagliflozin should stop the drug prior to any scheduled surgical procedures, and should have open communication with their providers about any behavioral or physiologic stress that may increase the risk of DKA. Because this drug class does have a diuresis effect,

patients should be encouraged to increase their water intake regularly and stay hydrated. The volume depletion and diarrhea side effects could worsen both fluid balance and predispose patients to DKA, further reiterating the importance of adequate hydration. Patients who would potentially be good candidates for sotagliflozin therapy are those who are experiencing frequent hypoglycemia, are engaged and willing to work to optimize their insulin therapy and are open to communicating with their providers. Patients with a high risk of DKA or a history of previous DKA episodes would probably not be good candidates for sotagliflozin therapy. Those patients who have difficulties with the self-management aspect of the disease or who have difficulties following a treatment plan would likewise not be ideal candidates for this treatment. In addition, patients who are on a high protein, low carbohydrate ketogenic diet would have a higher risk of ketone formation, and should not be considered for SGLT2 therapy while following these diet plans.

## Conclusion

Sotagliflozin has demonstrated efficacy in reducing A1C levels in the T1D population, with secondary benefits of decreasing insulin utilization, weight loss, lower risk of severe hypoglycemia, and decreased FPG. These benefits, however, must be weighed against an increased risk of ketone formation and diabetic ketoacidosis. Currently, sotagliflozin is available for the treatment of T1D in Europe but is not approved for use in the US at this time.

## Authors' note

Conceived/designed collaboratively across all 3 authors. WN-Analyzed the data. WN Wrote the first draft of the manuscript, Collaborative 1st draft, split into sections, all 3 authors contributed. All three authors contributed to the writing of the manuscript. Agree with manuscript results and conclusions-All 3 authors contributed. Jointly developed the structure and arguments for the paper-All 3 authors contributed. WN-Made critical revisions and approved final version. Revised by WN and JT. All authors reviewed and approved of the final manuscript.

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