Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study

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OBJECTIVE

Evaluate the efficacy and safety of the dual sodium–glucose cotransporter 1 (SGLT1) and SGLT2 inhibitor sotagliflozin in combination with optimized insulin in type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

The inTandem1 trial, a double-blind, 52-week phase 3 trial, randomized North American adults with T1D to placebo (n = 268), sotagliflozin 200 mg (n = 263), or sotagliflozin 400 mg (n = 262) after 6 weeks of insulin optimization. The primary end point was HbA_{1c} change from baseline at 24 weeks. HbA_{1c}, weight, and safety were also assessed through 52 weeks.

RESULTS

From a mean baseline of 7.57%, placebo-adjusted HbA_{1c} reductions were 0.36% and 0.41% with sotagliflozin 200 and 400 mg, respectively, at 24 weeks and 0.25% and 0.31% at 52 weeks (all $P < 0.001$). Among patients with a baseline HbA_{1c} ≥7.0%, an HbA_{1c} <7% was achieved by 15.7%, 27.2%, and 40.3% of patients receiving placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively ($P \leq 0.003$ vs. placebo) at 24 weeks. At 52 weeks, mean treatment differences between sotagliflozin 400 mg and placebo were −1.08 mmol/L for fasting plasma glucose, −4.32 kg for weight, and −15.63% for bolus insulin dose and −11.87% for basal insulin dose (all $P < 0.001$). Diabetes Treatment Satisfaction Questionnaire scores increased significantly by 2.5 points with sotagliflozin versus placebo ($P < 0.001$) at 24 weeks. Genital mycotic infections and diarrhea occurred more frequently with sotagliflozin. Adjudicated diabetic ketoacidosis (DKA) occurred in 9 (3.4%) and 11 (4.2%) patients receiving sotagliflozin 200 and 400 mg, respectively, and in 1 (0.4%) receiving placebo. Severe hypoglycemia occurred in 17 (6.5%) patients from each sotagliflozin group and 26 (9.7%) patients receiving placebo.

CONCLUSIONS

In a 1-year T1D study, sotagliflozin combined with optimized insulin therapy was associated with sustained HbA_{1c} reduction, weight loss, lower insulin dose, fewer episodes of severe hypoglycemia, improved patient-reported outcomes, and more DKA relative to placebo (ClinicalTrials.gov, NCT02384941).

Achieving glycemic targets is difficult for patients with type 1 diabetes (T1D); hypoglycemia, wide glucose fluctuations, and weight gain represent major unresolved challenges (1–6) that threaten patient health (7,8). Mitigating these side effects is essential in T1D management. Pramlintide is approved as an insulin adjunct and may reduce weight as well as HbA_{1c}, but it requires multiple additional daily injections and is associated with an increased risk of severe hypoglycemia (1,2,9). Agents from other antihyperglycemic classes have not demonstrated sufficient benefit in T1D for manufacturers to pursue market authorization (10–13). Combining insulin with oral sodium–glucose cotransporter (SGLT) inhibitors holds promise to improve glycemic control in T1D without increasing weight or hypoglycemia, and an agent that inhibits SGLT1 further contributes to a blunting and delay of postprandial hyperglycemia (14–16). However, diabetic ketoacidosis (DKA) has emerged as the major clinical concern around SGLT inhibition in T1D (17,18). Possible contributors include decreased basal insulin, a shift to fatty acid oxidation, and increased urinary glucose excretion and volume depletion associated with SGLT2 inhibition (19,20).

Sotagliflozin (LX4211) is a novel dual inhibitor of SGLT1 and SGLT2 that decreases renal glucose reabsorption through systemic SGLT2 inhibition and delays and reduces glucose absorption in the proximal intestine through local SGLT1 inhibition, blunting and delaying postprandial hyperglycemia (21–23). Dual inhibition of SGLT1 and SGLT2 may mitigate DKA risk by reducing glucose absorption in the proximal intestine and thereby diminishing urine glucose excretion and associated water and electrolyte loss; by increasing glucagon-like peptide 1 secretion from the gut, thereby reducing glucagon; and by preserving basal insulin requirements (24–28). We report the efficacy and safety of sotagliflozin combined with insulin delivered as multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) in North American adults with T1D.

RESEARCH DESIGN AND METHODS

Design Overview

This phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted at 75 sites in the U.S. and Canada evaluated the safety and efficacy of oral sotagliflozin 200 or 400 mg combined with insulin in adult patients with inadequately controlled T1D. The study consisted of two double-blind periods: a 24-week treatment period (the primary end point assessment) followed by a 28-week double-blind extension (Fig. 1). Randomization was stratified by insulin delivery method (MDI or CSII), and week −2 HbA_{1c} values (≤8.5%, >8.5%). A subgroup of patients underwent blinded continuous glucose monitoring (CGM) with a Dexcom G4 monitor (Dexcom, San Diego, CA) during specified 1-week intervals throughout the first 24 weeks.

Starting 6 weeks before randomization, insulin therapy was optimized by adjusting basal and bolus doses to maintain fasting or preprandial blood glucose between 4.4 and 7.2 mmol/L (80 and 130 mg/dL) and 1- to 2-h postprandial glucose <10 mmol/L (<180 mg/dL). Insulin adjustment continued throughout the trial (Fig. 1).

Institutional review boards approved the protocol and consent forms. All patients provided written informed consent. An independent clinical end point committee, blinded to trial treatment, adjudicated severe hypoglycemia, DKA, major adverse cardiovascular events, drug-induced liver injury, and deaths. An independent insulin dose monitoring committee (IDMC) comprising diabetologists and certified diabetes educators blindly reviewed insulin titration decisions from the start of insulin optimization (6 weeks before baseline) through week 24 to determine whether insulin adjustments were consistent with self-monitoring of blood glucose (SMBG) patterns. An independent data monitoring committee reviewed safety. An independent statistician performed statistical analysis.

Study Population

The study included men and nonpregnant women aged ≥18 years with T1D using either MDI or CSII for insulin delivery and whose HbA_{1c} was 7.0–11.0% at screening. Patients with β-hydroxybutyrate (BHB) levels >0.6 mmol/L at screening were excluded. The Supplementary Data lists all inclusion and exclusion criteria.

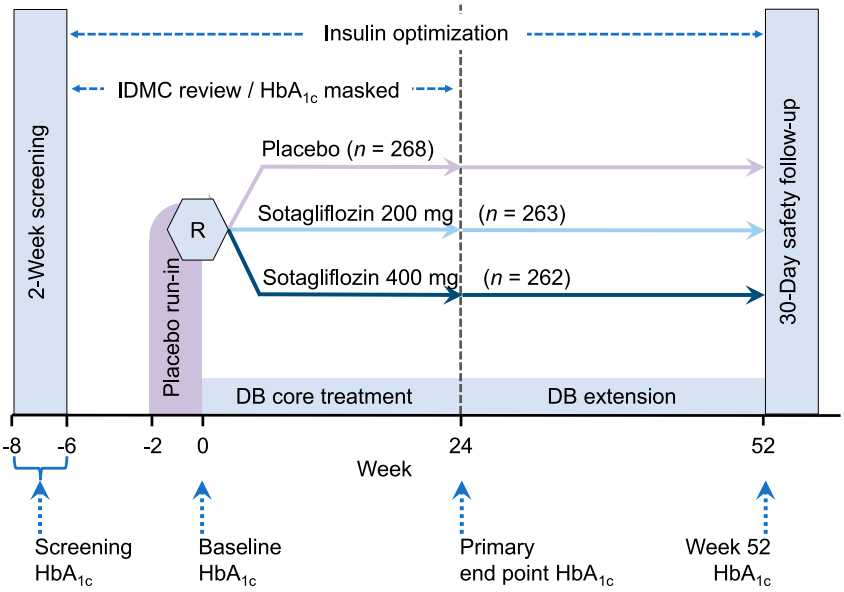

Figure 1—Study design. After a 2-week screening period, insulin therapy was optimized for 6 weeks prior to randomization (R), and optimized insulin continued until the study conclusion at week 52. After a 2-week placebo run-in, patients were randomly assigned to double-blind (DB) treatment with sotagliflozin 200 or 400 mg or placebo for 52 weeks. Insulin optimization refers to the adjustment of insulin to meet standard-of-care glycemic targets starting 6 weeks prior to randomization, which continued for the entire study. An IDMC assessed standard-of-care adherence and provided feedback to the principal investigator if deviations from standard of care were observed prior to week 24; HbA_{1c} was masked to study staff during this period. Between week 24 and 52, insulin optimization continued without input from the IDMC, and HbA_{1c} values were unmasked. Safety was monitored for 30 days after the last dose of study medication.

Interventions

Patients were randomly assigned 1:1:1 to sotagliflozin 200 mg, sotagliflozin 400 mg, or placebo administered once daily before the first meal of the day. Bolus insulin was reduced by 30% for the first meal after the first dose of study medication on day 1 only (24). Thereafter and throughout the 52-week study, investigators and/or patients adjusted insulin doses according to SMBG data to meet study targets. Based on regulatory feedback, HbA_{1c} and fasting plasma glucose (FPG) results were masked to study staff from baseline to week 24. After week 12, HbA_{1c} >11% was unmasked to allow appropriate intervention. During the 28-week extension period, HbA_{1c} and FPG were unmasked. All patients received urine ketone strips and BHB meters and strips as well as instructions on detecting and treating ketosis (Supplementary Data), urogenital hygiene, and proper hydration. Study centers received recommendations for ketosis and DKA diagnosis and management (Supplementary Data).

End Points

The primary end point was the change in HbA_{1c} from baseline to week 24. The first secondary end point was a composite consisting of the proportion of patients with HbA_{1c} <7.0% who had no episode of severe hypoglycemia and no episode of DKA at week 24. Other secondary outcomes included the change from baseline to week 24 in body weight, bolus insulin dose, FPG, and scores on the Diabetes Treatment Satisfaction Questionnaire Status (DTSQs) and the 2-item Diabetes Distress Screening Scale (DDS2) (29,30). Additional objectives included the change from baseline in systolic blood pressure (SBP) and diastolic blood pressure at week 12 in all patients and SBP in those with SBP ≥130 mmHg at baseline. HbA_{1c}, FPG, insulin dose, weight, frequency of documented hypoglycemic events (≤3.9 and ≤3.0 mmol/L [≤70 and ≤55 mg/dL], measured by SMBG), and kidney function were assessed at each study visit throughout the 52-week study. Prespecified composite end points included the proportions of patients meeting HbA_{1c} targets (<7.0% or ≥0.5% reduction) without experiencing severe hypoglycemia, DKA, or weight gain at 24 and 52 weeks. Safety and tolerability were evaluated throughout the study. DKA diagnosis was based on evidence of metabolic acidosis and other criteria (see Supplementary Data for details).

Statistical Methods

Efficacy analyses were based on the modified intent-to-treat population, which included all randomized patients who had taken at least one dose of study drug. The primary efficacy end point was the main driver used to calculate the sample size, and the latter was derived by specifying a treatment difference to detect between either dose level of sotagliflozin versus placebo of at least −0.4% and a common SD of this difference as 1.0%. The statistical testing method was planned to control the type 1 family-wise error rate both within and across the primary and secondary end points at α = 0.05. Targeting a statistical power of ≥90% to detect the stated difference and adjusting for dropouts, 250 patients per treatment group was the estimated sample size requirement. Primary efficacy end point data were analyzed using mixed-effects model for repeated measures (MMRM) statistics based on the restricted maximum likelihood method for estimation. The analysis model included fixed categorical effects of treatment, randomization strata based on use of MDI or CSII, HbA_{1c} ≤8.5% or >8.5% at week −2, and other covariates. For continuous secondary and other efficacy end points, MMRM or ANCOVA was used, with the corresponding end point and baseline value (including first-order interactions in the MMRM) in the model. For binary end points, a Cochran–Mantel–Haenszel test, stratified by the randomization stratification factors, was used. The treatment group comparisons were performed at week 24, with descriptive statistics provided for each clinic visit through week 52. Missing observations at week 24 were imputed as nonresponse. See Supplementary Data for additional details.

RESULTS

Between March 2015 and February 2017, 793 patients were randomly assigned to treatment with placebo (n = 268), sotagliflozin 200 mg (n = 263), or sotagliflozin 400 mg (n = 262), and 218, 228, and 221 completed the study, respectively (Supplementary Fig. 1). Baseline characteristics were similar among groups (Supplementary Table 1). In the total cohort, 473 (59.6%) patients used CSII and 320 (40.4%) used MDI, with similar proportions in each treatment group (Supplementary Table 1).

Glycemic Control

Insulin optimization over 6 weeks improved HbA_{1c} by ∼0.65% in the three treatment groups, lowering the mean HbA_{1c} from ∼8.2% (66 mmol/mol) at screening to 7.54% (58.9 mmol/mol), 7.61% (59.7 mmol/mol), and 7.56% (59.1 mmol/mol), in the placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg groups, respectively, at randomization (baseline). At the week 24 primary end point assessment, the placebo-adjusted least squares mean (LSM) HbA_{1c} was further reduced by 0.36% (95% CI −0.45 to −0.27) and 0.41% (−0.50 to −0.32) with sotagliflozin 200 and 400 mg, respectively (both $P < 0.001$ vs. placebo). At 52 weeks, LSM differences from placebo remained significant: −0.25% (−0.37 to −0.14; $P < 0.001$) and −0.31% (−0.43 to −0.20; $P < 0.001$) (Fig. 2*A* and Supplementary Table 2). Approximately 19% of patients from each group had an HbA_{1c} <7.0% at baseline (Supplementary Table 1). Across the entire study population, 22.8%, 36.9%, and 46.9% of the placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg groups achieved an HbA_{1c} <7.0% at 24 weeks, and at 52 weeks the proportions were 20.9%, 30.0%, and 35.5%, respectively. Among patients with a baseline HbA_{1c} ≥7.0% after 6 weeks of insulin optimization, 15.7% of placebo-treated patients, 27.2% of patients receiving sotagliflozin 200 mg (P = 0.003 vs. placebo), and 40.3% of patients receiving sotagliflozin 400 mg ($P < 0.001$) achieved an HbA_{1c} <7.0% at week 24. Within this subpopulation after 52 weeks, 18.4%, 27.7%, and 35.4% of patients receiving placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively, had an HbA_{1c} <7.0%.

Placebo-adjusted differences in FPG were −0.55 mmol/L (−9.8 mg/dL) (95% CI −1.06 to −0.04 mmol/L; P = 0.034) and −0.99 mmol/L (−17.8 mg/dL) (−1.50 to −0.48; $P < 0.001$) for the 200 and 400 mg doses, respectively, at 24 weeks, and −0.68 mmol/L (−12.2 mg/dL) (−1.28 to −0.08; P = 0.028) and −1.08 mmol/L (−19.4 mg/dL) (−1.69 to −0.47; $P < 0.001$) at 52 weeks (Supplementary Table 2).

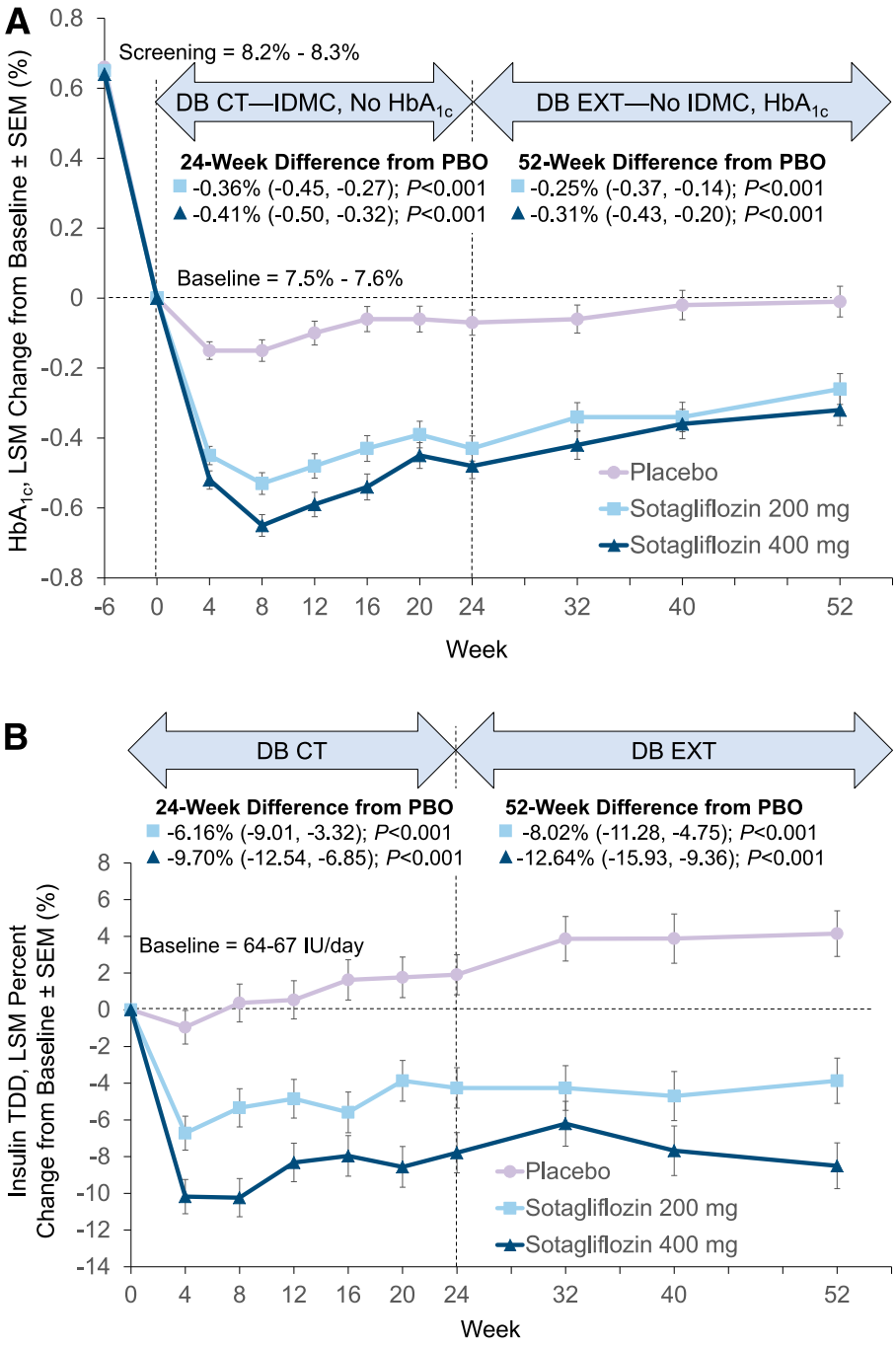

Figure 2—Primary and other selected end points. Error bars represent SEM. *A:* LSM change from baseline in HbA_{1c} over 52 weeks. Data between week −6 to week 0 depict arithmetic mean differences between screening and baseline HbA_{1c} values to illustrate effect of insulin optimization. During the 24-week double-blind (DB) core treatment (CT) period, HbA_{1c} levels were masked to study staff and an IDMC reviewed investigators' insulin titration decisions and provided feedback. During the 28-week double-blind extension (EXT), HbA_{1c} was unmasked and the IDMC did not review insulin titration. *B:* LSM percent change from baseline in total daily insulin dose (TDD) over 52 weeks. *C:* LSM change from baseline in weight over 52 weeks. PBO, placebo.

The CGM substudy assessed glycemic variability and included 136 patients (Fig. 3 and Supplementary Table 3). Baseline percent ± SD of time in range (3.9–10.0 mmol/L [70–180 mg/dL]) was 54.19% ± 12.94 and 53.18% ± 13.89 with placebo and sotagliflozin 400 mg, respectively, and time in range increased by 10.4% ± 2.89 (95% CI 4.68 to 16.12; $P < 0.001$), or 2.50 ± 0.69 h, with sotagliflozin 400 mg relative to placebo. The placebo-adjusted decrease in CGM SD was 0.37 ± 0.17 mmol/L (6.60 ± 3.06 mg/dL) (95% CI −0.70 to −0.30 mmol/L; $P = 0.033$) with the 400 mg dose.

Insulin Dose

Total daily insulin dose in the placebo group was within ~2% of baseline until week 24, after which it increased. In both sotagliflozin groups, after an initial decrease, insulin doses remained stable after week 4 (Fig. 2*B*). At 24 weeks, the LSM difference from placebo in bolus

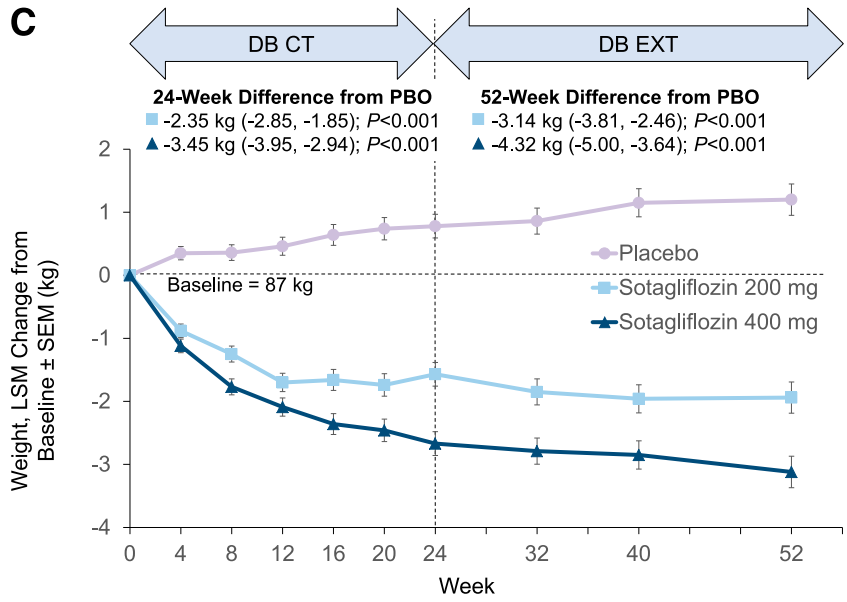

Figure 2—*Continued*.

insulin dose was −5.70% (95% CI −12.82 to 1.42; P = 0.12) with sotagliflozin 200 mg and −12.67% (−19.79 to −5.55; $P < 0.001$) with sotagliflozin 400 mg. Basal insulin dose increased with placebo while decreasing modestly with sotagliflozin (Supplementary Table 2 and Supplementary Fig. 2*A*). At 52 weeks, placebo-adjusted percent differences in bolus insulin doses were −5.53% (−14.54 to 3.48; P = 0.23) with sotagliflozin 200 mg and −15.63% (−24.67 to −6.59; $P < 0.001$) with sotagliflozin 400 mg. Absolute changes in insulin doses appear in Supplementary Table 2 and Supplementary Fig. 2*B*.

Nonglycemic End Points

At baseline, mean BMI across all three treatment groups was 29.66 ± 5.387 kg/m^2, and 44% of participants had a BMI ≥30 kg/m^2 (Supplementary Table 1). Decreases of 2.35 kg (95% CI −2.85 to −1.85) and 3.14 kg (−3.81 to −2.46) occurred in the sotagliflozin 200 mg group at 24 and 52 weeks, respectively. At week 24, the LSM difference from placebo with sotagliflozin 400 mg was −3.45 kg (−3.95 to −2.94); at week 52 the difference was −4.32 kg (−5.00 to −3.64) (all $P < 0.001$ vs. placebo) (Fig. 2*C* and Supplementary Table 2).

At week 12, sotagliflozin 200 and 400 mg were associated with placebo-adjusted mean SBP reductions of 3.5 mmHg (95% CI −5.2 to −1.8; $P < 0.001$) and 4.2 mmHg (−5.9 to −2.4; $P < 0.001$), respectively. Diastolic blood pressure also decreased by 1.8 mmHg (−2.8 to −0.7; P = 0.001) and 1.9 mmHg (−2.9 to −0.8; $P < 0.001$) with sotagliflozin 200 and 400 mg relative to placebo.

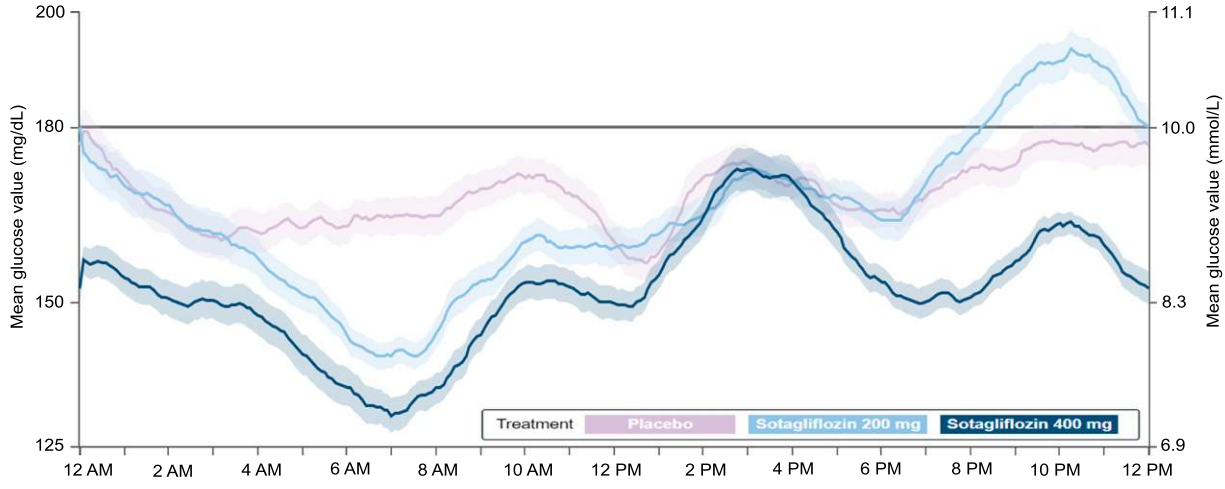

Figure 3—Sotagliflozin inTandem1 interstitial glucose. 24-h CGM tracing consisting of interstitial glucose readings collected every 5 min. Solid lines represent mean values from each treatment group (light purple, placebo [n = 45]; light blue, sotagliflozin 200 mg [n = 44]; dark blue, sotagliflozin 400 mg [n = 47]); shaded areas represent ± 1 SEM. The figure shows data collected from midnight. Actual start time for 24-h readings may vary for each subject. Top of target CGM range = 10.0 mmol/L (180 mg/dL).

Among those with SBP ≥130 mmHg at baseline, sotagliflozin 200 and 400 mg reduced SBP by 5.4 mmHg (−9.9 to −1.0; $P = 0.017$) and 6.6 mmHg (−10.9 to −2.3; $P = 0.003$) relative to placebo.

In the sotagliflozin 200 and 400 mg arms, estimated glomerular filtration rate initially decreased by 3 and 4 mL/min/1.73 m^2, respectively, then increased, remaining ~2 mL/min/1.73 m^2 below baseline between weeks 24 and 52 (Supplementary Fig. 3 and Supplementary Table 2). The reductions in estimated glomerular filtration rate were reversed 1 week after discontinuation of sotagliflozin (Supplementary Table 2).

At the week 52 visit, mean total cholesterol increased by 0.1 mmol/L in the placebo group and by 0.2 and 0.3 mmol/L in the sotagliflozin 200 and 400 mg groups, respectively. Mean LDL cholesterol increased by 0.1, 0.1, and 0.2 mmol/L with placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively. Other lipid changes were small and not considered clinically meaningful.

Composite End Points

More patients receiving sotagliflozin than placebo achieved composite end points including an HbA_{1c} <7.0% plus no severe hypoglycemia, DKA, or weight gain (Supplementary Fig. 4). The proportion achieving an HbA_{1c} <7.0% without experiencing any severe hypoglycemia or DKA at 24 weeks was 21.64% with placebo, 33.46% with sotagliflozin 200 mg, and 43.51% with sotagliflozin 400 mg (Supplementary Fig. 5). The differences from placebo were statistically significant and remained significant at 52 weeks (sotagliflozin 200 mg: 7.21% [95% CI −0.27 to 14.68; $P = 0.049$]; sotagliflozin 400 mg: 13.41% [5.67 to 21.15; $P < 0.001$]). Throughout the study, the difference in proportions of placebo- and sotagliflozin-treated patients who achieved an HbA_{1c} <7.0% and experienced either severe hypoglycemia (≤3.0%) or DKA (≤1.5%) was not statistically significant (Supplementary Fig. 5). Similar proportions of patients in the sotagliflozin treatment groups achieved an HbA_{1c} reduction ≥0.5% without severe hypoglycemia or DKA (Supplementary Fig. 5).

The proportion of patients who achieved an HbA_{1c} <7.0% without weight gain at 24 weeks was 8.58% with placebo, 30.42% with sotagliflozin 200 mg, and 43.51% with sotagliflozin 400 mg (Supplementary Fig. 6 and Supplementary Table 4), with treatment differences from placebo of 21.84% (95% CI 14.97 to 28.71; $P < 0.001$) and 34.93% (27.68 to 42.18; $P < 0.001$) for sotagliflozin 200 and 400 mg, respectively. Significantly more patients who achieved an HbA_{1c} <7.0% lost >5% of body weight while taking sotagliflozin 200 mg (difference from placebo, 5.34% [1.89 to 8.78; $P < 0.001$]) or 400 mg (12.61% [7.99 to 17.24; $P < 0.001$]), and few sotagliflozin-treated patients gained weight (Supplementary Fig. 6 and Supplementary Table 4). At 52 weeks, the proportions of patients losing or not gaining weight remained significantly larger in the sotagliflozin groups, and similar patterns were observed among those with an HbA_{1c} reduction ≥0.5% at 24 and 52 weeks (Supplementary Fig. 6 and Supplementary Table 4).

At 24 weeks, a composite outcome of HbA_{1c} <7.0%, no weight gain, no severe hypoglycemia, and no DKA was achieved by 7.84%, 27.76%, and 40.84% of patients receiving placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively. Differences from placebo were 19.92% (95% CI 13.25 to 26.59; $P < 0.001$) and 33.00% (25.86 to 40.15; $P < 0.001$) in the sotagliflozin 200 and 400 mg groups, respectively. Similar treatment differences were maintained at 52 weeks (Supplementary Fig. 6 and Supplementary Table 4).

Patient-Reported Outcomes

Treatment satisfaction measured by the DTSQs remained stable in the placebo group while increasing in both sotagliflozin groups. At week 24, the LSM difference between placebo and sotagliflozin 200 mg was 2.5 (95% CI 1.7 to 3.3) and between placebo and sotagliflozin 400 mg was 2.5 (1.8 to 3.3), changes that were statistically significant and clinically meaningful ($P < 0.001$) (Supplementary Table 2 and Supplementary Fig. 7). Diabetes distress was measured with the DDS2 throughout the study and decreased significantly in both sotagliflozin groups while increasing with placebo (Supplementary Table 2 and Supplementary Fig. 8). At week 24, sotagliflozin-treated patient scores on the DDS2 decreased by 0.7 (−0.9 to −0.4; $P < 0.001$) and 0.8 (−1.0 to −0.5; $P < 0.001$) with the 200 and 400 mg doses, respectively, relative to placebo. At week 52, LSM differences from placebo were −0.4 (−0.7 to −0.2; $P = 0.003$) and −0.5 (−0.8 to −0.2; $P < 0.001$) for sotagliflozin 200 and 400 mg, respectively.

Hypoglycemia

Over 52 weeks, fewer patients receiving sotagliflozin 200 mg than those receiving placebo reported documented hypoglycemia ≤3.9 mmol/L (≤70 mg/dL) or ≤3.0 mmol/L (≤55 mg/dL), and the frequency of documented hypoglycemia was similar between the placebo and sotagliflozin 400 mg groups (Table 1 and Supplementary Table 2). Documented hypoglycemia ≤3.9 mmol/L occurred at frequencies of 96.1, 84.1, and 90.0 events per person-year in the placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg groups, respectively, with relative rates of 0.88 (95% CI 0.77 to 0.99; $P = 0.040$) for sotagliflozin 200 mg and 0.93 (0.82 to 1.06; $P = 0.28$) for sotagliflozin 400 mg versus placebo. The proportion of patients with SMBG ≤3.0 mmol/L from week 51 to 52 was 23.5%, 15.1%, and 13.9% on placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively, with a relative risk for sotagliflozin 200 and 400 mg versus placebo of 0.64 (0.44 to 0.93; $P = 0.017$) and 0.59 (0.40 to 0.87; $P = 0.007$), respectively.

Over 52 weeks, 17 (6.5%) patients from each sotagliflozin group and 26 (9.7%) placebo-treated patients experienced ≥1 positively adjudicated severe hypoglycemia event (Table 1). Two patients receiving placebo and one receiving sotagliflozin 200 mg discontinued due to severe hypoglycemia.

DKA and Acidosis-Related Adverse Events

Out of 82 patients reporting a serious or nonserious acidosis-related event (Supplementary Table 5), 21 had ≥1 positively adjudicated DKA event: 1 (0.4%; a CSII user) in the placebo group, 9 (3.4%; 8 CSII users) in the sotagliflozin 200 mg group, and 11 (4.2%; 7 CSII users) in the sotagliflozin 400 mg group. In 14 out of 21 DKA events, patients had blood glucose >250 mg/dL (Supplementary Table 5). Positively adjudicated DKA led to discontinuations by four patients in each sotagliflozin group (Table 1).

Table 1—Summary of adverse events and events of special interest, overall treatment period (baseline to 52 weeks)

	Placebo (*n* = 268)	Sotagliflozin 200 mg (*n* = 263)	Sotagliflozin 400 mg (*n* = 262)
Any adverse event	216 (80.6)	215 (81.7)	209 (79.8)
Serious adverse event	20 (7.5)	27 (10.3)	29 (11.1)
Severe adverse event	7 (2.6)	12 (4.6)	12 (4.6)
Death	1 (0.4)*	0	0
Positively adjudicated adverse events			
≥1 severe hypoglycemia event†	26 (9.7)	17 (6.5)	17 (6.5)
≥1 severe nocturnal hypoglycemia event†**	10 (3.7)	10 (3.8)	2 (0.8)
≥1 DKA event	1 (0.4)	9 (3.4)	11 (4.2)
≥1 DKA event among CSII users	1/160 (0.6)	8/156 (5.1)	7/157 (4.5)
≥1 DKA event among MDI users	0/108	1/107 (0.9)	4/105 (3.8)
Major adverse cardiovascular events			
Myocardial infarction or hospitalization for unstable angina	3 (1.1)	4 (1.5)	0
Stroke	1 (0.4)	0	1 (0.4)
Heart failure hospitalization	0	0	0
Coronary revascularization	2 (0.7)	2 (0.8)	0
Drug-induced liver injury	0	0	2 (0.8)
Events of special interest			
Any	266 (99.3)	260 (98.9)	259 (98.9)
Genital mycotic infection	9 (3.4)	24 (9.1)	34 (13.0)
Diarrhea‡	18 (6.7)	22 (8.4)	27 (10.3)
Urinary tract infection	19 (7.1)	26 (9.9)	11 (4.2)
Bone fracture	10 (3.7)	9 (3.4)	5 (1.9)
Renal event§	5 (1.9)	7 (2.7)	4 (1.5)
Volume depletion||	4 (1.5)	8 (3.0)	4 (1.5)
Malignancies of special interest¶	0	2 (0.8)	2 (0.8)
Amputation	0	0	1 (0.4)
Pancreatitis	0	0	0
Venous thrombotic event	0	0	0
Any documented hypoglycemia# (SMBG ≤3.9 mmol/L [≤70 mg/dL])	266 (99.3)	260 (98.9)	258 (98.5)
Any nocturnal documented hypoglycemia**	247 (92.2)	239 (90.9)	238 (90.8)
Any SMBG value ≤3.0 mmol/L (≤55 mg/dL)	248 (92.5)	250 (95.1)	244 (93.1)
Any adverse event leading to discontinuation	11 (4.1)	13 (4.9)	17 (6.5)
Any event of special interest leading to discontinuation††	7 (2.6)	8 (3.0)	12 (4.6)
Aortic valve incompetence	1 (0.4)	0	0
Diarrhea	1 (0.4)	0	1 (0.4)
Hepatitis	0	0	1 (0.4)
Urinary tract infection	0	1 (0.4)	0
Cystitis glandularis	1 (0.4)	0	0
Vulvovaginal events‡‡	1 (0.4)	0	2 (0.8)
Blood creatinine increased	0	0	1 (0.4)
Hepatic enzymes increased	0	1 (0.4)	1 (0.4)
DKA (positively adjudicated)	0	4 (1.5)	4 (1.5)
Acetonemia§§	0	1 (0.4)	1 (0.4)
Hypoglycemia	3 (1.1)	1 (0.4)	0
Severe hypoglycemia (positively adjudicated)	2 (0.7)	1 (0.4)	0

Data are *n* or *n* (%) and include patients who received at least one dose of a study drug and include events that occurred up to 30 days after the last dose of double-blind study treatment. *Death due to endocarditis, judged not related to study drug. †Severe hypoglycemia was defined as any event that required assistance from another person or during which the patient lost consciousness or had a seizure. Hypoglycemia events include all those that occurred between first and last dose of study drug during the 52-week double-blind treatment period. ‡Diarrhea was mostly mild to moderate and transient. §Renal events are listed in Supplementary Data. ||Volume depletion events are listed in Supplementary Data. ¶Included two breast cancer cases, one thyroid cancer, and one melanoma. #Documented hypoglycemia was defined as a blood glucose level of ≤3.9 mmol/L (≤70 mg/dL) with or without hypoglycemia symptoms. In the sotagliflozin development program, hypoglycemia is considered an event of special interest, with a specialized case report form. Because analysis for hypoglycemia was based on data recorded in the case report form, investigators were asked to not submit hypoglycemic events on the adverse event case report form unless the episode met criteria for a serious adverse event. **Nocturnal hypoglycemia was defined as positively adjudicated severe hypoglycemia or investigator-reported documented hypoglycemia (blood glucose level of ≤3.9 mmol/L [≤70 mg/dL] with or without hypoglycemia symptoms) that occurred between midnight and 5:59 A.M., regardless of whether the patient was awake during the event. ††All events of special interest leading to discontinuation were investigator reported except for DKA and severe hypoglycemia, which were positively adjudicated. ‡‡Vulvovaginal mycotic infection, vulvovaginits, and vulvovaginal pruritus. §§Both cases of acetonemia were negatively adjudicated for DKA.

Mean BHB levels increased by ~0.1 mmol/L from baseline in both sotagliflozin groups (Supplementary Fig. 9). Over 52 weeks, a BHB ≥0.6 mmol/L occurred in 15.7%, 44.1%, and 45.8% of patients in the placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg groups, respectively.

Other Safety Outcomes

As shown in Table 1, during 52 weeks of double-blind treatment, the frequency of overall adverse events was similar among the treatment groups: 216 (80.6%), 215 (81.7%), and 209 (79.8%) with placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively. The total number of events of special interest occurred at similar rates: 266 (99.3%), 260 (98.9%), and 259 (98.9%) with placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively. Sotagliflozin-treated patients reported more serious adverse events (placebo: 20 [7.5%]; 200 mg: 27 [10.3%]; 400 mg: 29 [11.1%]), and severe adverse events occurred in 7 (2.6%) placebo-treated patients and 12 patients from each sotagliflozin group (4.6%). One death due to endocarditis occurred in the placebo group. In the sotagliflozin groups, 13 (4.9%; 200 mg) and 17 (6.5%; 400 mg) patients discontinued due to an adverse event, compared with 11 (4.1%) taking placebo.

Adverse events were mostly mild to moderate in severity. The most common events of special interest were genital mycotic infections (consistent with SGLT2 inhibition) and diarrhea (consistent with SGLT1 inhibition) (Table 1). Among sotagliflozin-treated patients, 24 (9.1%; 200 mg) and 34 (13.0%; 400 mg) reported a genital mycotic infection, compared with 9 (3.4%) receiving placebo. Three patients discontinued due to vulvovaginal events (one receiving placebo and two receiving sotagliflozin 400 mg). Diarrhea occurred in 18 (6.7%), 22 (8.4%), and 27 (10.3%), patients receiving placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively, and led to one discontinuation each in the placebo and sotagliflozin 400 mg groups. Bone fractures occurred in 10 (3.7%), 9 (3.4%), and 5 (1.9%) patients taking placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively. There was one transmetatarsal amputation that was considered to be not related to the study drug in a patient taking sotagliflozin 400 mg who had a previous history of foot and toe amputations. Four patients (two from each sotagliflozin group) reported malignancies (two breast, one thyroid, and one melanoma); none were considered drug-related.

CONCLUSIONS

This study demonstrated the efficacy of sotagliflozin in reducing HbA_{1c} and improving patient outcomes beyond HbA_{1c} (31). Sotagliflozin 400 mg was associated with lower insulin doses, FPG, weight, and SBP as well as improved glycemic variability with less hypoglycemia. Sotagliflozin 200 mg did not reduce bolus insulin doses; however, reductions in total insulin dose, FPG, and weight were associated with P values <0.05. The incidence of severe hypoglycemia was lower with sotagliflozin than placebo. DKA was increased with sotagliflozin treatment, yet significantly more people taking sotagliflozin 200 or 400 mg than those receiving placebo had an HbA_{1c} <7.0% without experiencing severe hypoglycemia, DKA, or weight gain at 24 and 52 weeks. Those receiving sotagliflozin also reported statistically significant improvements in treatment satisfaction and diabetes distress.

The glycemic and weight reductions, as well as composite end points including achievement of HbA_{1c} targets without severe hypoglycemia, DKA, or weight gain, were comparable to observations from the other inTandem trials. In the 24-week, global inTandem3 study, sotagliflozin 400 mg yielded significant placebo-adjusted reductions in HbA_{1c}, weight, insulin dose, and blood pressure with reduced hypoglycemia and a low incidence of DKA in patients with T1D (14). In inTandem3, insulin doses were not optimized prior to baseline, a key difference from the current study. The inTandem2 trial was conducted for 52 weeks in Europe with the same design as this study and had similar overall findings, including an even more pronounced improvement in glycemic variability (32). SGLT1 inhibition blunts and delays postprandial glucose absorption. In this and the other inTandem studies, the unique benefit of this mechanism is supported by a lower requirement for bolus insulin, with associated reductions in glycemic variability and hypoglycemia relative to placebo.

Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT-1) is a phase 3 trial evaluating the use of dapagliflozin in T1D. Baseline HbA_{1c} was 8.5% (higher than the inTandem1 baseline HbA_{1c}) after an 8-week lead-in period in which insulin treatment was titrated to individual glucose targets without optimizing it, and placebo-adjusted HbA_{1c} reductions were 0.4% to 0.5% (15). Patients with HbA_{1c} <7.5% at baseline were excluded. In the current study, 19% of patients had HbA_{1c} <7.0% at randomization, and after 6 weeks of insulin optimization, total mean ± SD baseline HbA_{1c} was 7.6% ± 0.7. The further HbA_{1c} decrease at 24 weeks was 0.4%. Sotagliflozin 400 mg was also associated with significantly improved measures of glycemic variability, as have been reported with dapagliflozin and canagliflozin (15,33). These improvements were achieved with decreases in total insulin doses that were driven by bolus insulin doses at 24 weeks.

There are multiple pathophysiological mechanisms by which SGLT2 inhibition might increase ketosis, including basal insulin reductions, glucagon increases, and increased urinary glucose excretion, all of which lead to a shift from glucose to fat as source of energy and therefore increase rates of lipolysis in adipose tissue and ketogenesis in the liver, which would increase circulating ketone body levels (19,20). The rate of DKA in this study was higher with sotagliflozin than placebo but still within the range reported in the general T1D population (2). The majority of patients resumed therapy after temporary discontinuation of sotagliflozin due to a DKA event. When using similar adjudication categories, the DKA rates were consistent between DEPICT-1 and this study (34). A contributing factor may have been CSII use, which can increase DKA risk through operational or mechanical failures (35,36). CSII users comprised 60% of the total study population and 75% of patients reporting DKA in the sotagliflozin groups (and the single placebo-treated patient reporting DKA). A preponderance of DKA among CSII users is consistent with other studies of SGLT inhibitors in T1D (14,15). In this and the other inTandem studies, sotagliflozin was associated with mildly increased mean BHB levels of ~0.1 mmol/L (the smallest increment detectable by point-of-care BHB meters). Increased

efforts to mitigate DKA, including protocol revisions, "Dear Dr." letters, site training, and improved educational materials (patient wallet cards; Supplementary Data), were distributed after U.S. and European regulatory authorities issued safety communications about the risk of DKA with SGLT2 inhibitors in 2015. This enhanced risk mitigation strategy reduced the severity of ketosis for several patients. Further work needs to be done to elucidate the risk factors for DKA and identify the characteristics of patients who would be at higher risk. When SGLT inhibitors are administered, monitoring for ketosis, particularly during metabolically stressful situations, is required. SGLT inhibitors should be discontinued before scheduled surgical procedures, and patients and clinicians should remain in close consultation regarding other forms of behavioral and physiological stress (37).

This study population had a mean baseline BMI of 30 kg/m^2 and nearly half were obese, consistent with the general adult population with T1D (2,3,38). Sotagliflozin provided a dose-dependent decrease in weight of 3–4 kg (4–5%) relative to placebo, and the magnitude of weight reductions increased throughout the year-long study, demonstrating that sotagliflozin maintained weight loss even in patients receiving intensified insulin therapy.

Sotagliflozin treatment improved diabetes distress and treatment satisfaction in this study and inTandem2 (32). Decreases in weight and/or insulin doses may be linked to these improvements, as suggested by studies reporting improved treatment satisfaction with canagliflozin and pramlintide used as adjunctive therapy for T1D (33,39).

Generalization of these results is limited by protocol details including the population recruited (HbA_{1c} 7–11%), the supervised insulin optimization efforts during lead-in and for 52 weeks after randomization, more frequent SMBG and ketone testing than in clinical practice, and the expertise and attention of the investigators and study staff. A regulatory request that HbA_{1c} and FPG be masked until after the primary end point assessment at week 24 also does not reflect clinical practice. The patient education and ketone monitoring called for in the protocol (see details in Supplementary Data) mitigated DKA risk, such that the incidence in the placebo-treated arm was 0.4%. This level of DKA mitigation may be difficult to achieve in clinical practice.

In conclusion, the addition of sotagliflozin to intensified insulin therapy for 1 year in patients with T1D reduced HbA_{1c} and improved clinical outcomes beyond HbA_{1c}, including weight reduction, increased time in range, and a lower incidence of severe hypoglycemia. To date, advances in T1D management have been largely limited to insulin formulation and delivery innovations (1,5,6). Although SGLT inhibition is associated with DKA, this risk is manageable with proper education and mitigation plans. The beneficial effects on HbA_{1c}, glycemic variability, and weight with less hypoglycemia outweigh this risk and support the combination of SGLT inhibitors with insulin as a therapeutic approach for T1D (14–16,24,33,40). After 1 year, substantially greater proportions of patients receiving sotagliflozin versus placebo achieved HbA_{1c} targets without experiencing severe hypoglycemia, DKA, or weight gain and had improvements in treatment satisfaction. We conclude that sotagliflozin is effective in subjects with T1D and has an acceptable risk-benefit profile.

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