



# Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct Therapy to Insulin in Type 1 Diabetes

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## OBJECTIVE

To assess the safety and efficacy of dual sodium–glucose cotransporter (SGLT) 1 and SGLT2 inhibition with sotagliflozin as adjunct therapy to insulin in type 1 diabetes.

## RESEARCH DESIGN AND METHODS

We treated 33 patients with sotagliflozin, an oral dual SGLT1 and SGLT2 inhibitor, or placebo in a randomized, double-blind trial assessing safety, insulin dose, glycemic control, and other metabolic parameters over 29 days of treatment.

## RESULTS

In the sotagliflozin-treated group, the percent reduction from baseline in the primary end point of bolus insulin dose was 32.1% ( $P = 0.007$ ), accompanied by lower mean daily glucose measured by continuous glucose monitoring (CGM) of 148.8 mg/dL (8.3 mmol/L) ( $P = 0.010$ ) and a reduction of 0.55% (5.9 mmol/mol) ( $P = 0.002$ ) in HbA<sub>1c</sub> compared with the placebo group that showed 6.4% reduction in bolus insulin dose, a mean daily glucose of 170.3 mg/dL (9.5 mmol/L), and a decrease of 0.06% (0.65 mmol/mol) in HbA<sub>1c</sub>. The percentage of time in target glucose range 70–180 mg/dL (3.9–10.0 mmol/L) increased from baseline with sotagliflozin compared with placebo, to 68.2% vs. 54.0% ( $P = 0.003$ ), while the percentage of time in hyperglycemic range >180 mg/dL (10.0 mmol/L) decreased from baseline, to 25.0% vs. 40.2% ( $P = 0.002$ ), for sotagliflozin and placebo, respectively. Body weight decreased (1.7 kg) with sotagliflozin compared with a 0.5 kg gain ( $P = 0.005$ ) in the placebo group.

## CONCLUSIONS

As adjunct to insulin, dual SGLT1 and SGLT2 inhibition with sotagliflozin improved glycemic control and the CGM profile with bolus insulin dose reduction, weight loss, and no increased hypoglycemia in type 1 diabetes.

Therapy for type 1 diabetes has advanced considerably since the historic publication of the Diabetes Control and Complications Trial (1) in 1993 with the introduction of new fast-acting and basal insulin analogs, more accurate blood glucose meters, smaller and more technically advanced insulin pumps, and the availability of continuous glucose monitoring (CGM). Despite these advances, sustained improvements in glycemic control are still associated with hypoglycemia and severe hypoglycemia (SH). The 12-month risk of SH associated with seizure or loss of consciousness was recently reported at 11.6% in adults and 9.9% in youth, rising

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to 18.6% in adults with type 1 diabetes for >40 years (2,3). The cause of death for individuals with type 1 diabetes has been examined in several longitudinal studies, indicating that between 4 and 10% of deaths can be attributed to hypoglycemia (4–7), providing a stark reminder of the risks of tight glycemic control with insulin alone. Recent data also indicate that approximately one-third of patients are worried about hypoglycemia and a similar proportion purposely maintain a hyperglycemic state seeking a “safety margin” from hypoglycemia (8). Additionally, ~30% of patients with type 1 diabetes in the U.S. are obese (9,10) and ~50% of patients have metabolic syndrome (11). There is a clear need for the development of new adjunct therapies to insulin that can improve glycemic control in this population without weight gain or an increase in the risk of hypoglycemia.

Highly selective inhibitors of sodium–glucose cotransporter (SGLT) 2, the transporter primarily responsible for renal glucose reabsorption, are approved for the treatment of type 2 diabetes (12) and under exploration in patients with type 1 diabetes (13–15). SGLT1 is the primary transporter for absorption of glucose and galactose in the intestine (16). Sotagliflozin is a novel, orally delivered, small-molecule dual inhibitor of SGLT1 and SGLT2 that was designed to reduce glucose absorption in the gastrointestinal (GI) tract via SGLT1 inhibition and renal glucose reabsorption via SGLT2 inhibition (17). SglT1 knockout mice given a meal challenge containing glucose exhibit decreased blood glucose, increased delivery of glucose to the distal small intestine and cecum, and increased GLP-1 release indicating a potential utility for inhibition of intestinal SGLT1 (18,19). Homozygous knockout mice maintained on a diet containing glucose and galactose also exhibit unformed watery stools, decreased food intake, and reduced weight, findings consistent with glucose and galactose malabsorption, a condition characterized by severe diarrhea, in infants with mutations in SGLT1 (16). With this in mind, most pharmaceutical discovery programs focused on selective SGLT2 inhibitors to avoid potential GI side effects. However, heterozygous SglT1 knockout mice also exhibit increased delivery of glucose to the distal small intestine and cecum and increased GLP-1 release after a glucose-containing meal

challenge but have normal stools, normal food intake, and normal weight gain when maintained on a diet containing glucose and galactose (18). Additionally, it has been reported that most individuals in a large family cohort of patients with galactose malabsorption at birth could tolerate a normal diet by the age of 20 years, suggesting that severe reduction in SGLT1 activity is compatible with relatively normal GI function (20). These data were consistent with a “window” for achieving glycemic efficacy with potent SGLT2 inhibition and partial SGLT1 inhibition, thereby avoiding the GI side effects of complete SGLT1 inhibition. Sotagliflozin fulfilled these criteria with 20-fold selectivity for SGLT2 over SGLT1 with SGLT2 half-maximal inhibitory concentration of 0.0018  $\mu\text{mol/L}$  and SGLT1 half-maximal inhibitory concentration of 0.036  $\mu\text{mol/L}$  (17).

Inhibiting SGLT1, the major intestinal glucose transporter, holds promise to improve glucose control by reducing postprandial glucose peaks and stimulating release of GI peptides, such as GLP-1 and polypeptide tyrosine tyrosine (PYY) (18,19,21), that assist in glycemic and appetite control (22,23). Preclinical and clinical studies conducted to date have confirmed the effects of sotagliflozin on postprandial glucose, GLP-1, and PYY (17–19,24,25). In patients with type 2 diabetes, sotagliflozin treatment lowered HbA<sub>1c</sub>, reduced body weight, and lowered blood pressure with a low risk of hypoglycemia (17,26). In a dose-ranging study in patients with type 2 diabetes inadequately controlled with metformin, HbA<sub>1c</sub> reduction nearly doubled as sotagliflozin dose increased in the absence of additional increases in urinary glucose excretion (UGE) supporting meaningful intestinal SGLT1 inhibition (26). In a recent study in patients with type 2 diabetes and moderate to severe renal impairment (estimated glomerular filtration rate 15–59 mL/min/1.73 m<sup>2</sup>), sotagliflozin produced a significant decrease in PPG excursion and an increase in GLP-1 secretion (27). This difference was preserved in the patient subgroup with more severe renal impairment despite the expected reduction of UGE suggesting that, unlike the effects of SGLT2 inhibition, the effects of intestinal SGLT1 inhibition are maintained as kidney function declines.

We hypothesized that in type 1 diabetes, sotagliflozin would improve glycemic

control while concomitantly simplifying the insulin regimen without weight gain. In contrast to selective SGLT2 inhibitors, the additional inhibition of SGLT1 by sotagliflozin was predicted to lower postprandial glycemic excursions and decrease bolus insulin, thereby lowering the potential for postprandial hypoglycemia. Here, we present the results of a randomized, multicenter, placebo-controlled, double-blind evaluation of sotagliflozin treatment in adults with inadequately controlled type 1 diabetes as adjunct therapy to usual insulin delivery method: either continuous subcutaneous insulin infusion (CSII) or multiple dose injection (MDI).

## RESEARCH DESIGN AND METHODS

### Study Design

This study was a randomized, multicenter, placebo-controlled, double-blind evaluation of sotagliflozin in adult patients with type 1 diabetes using their previous insulin delivery regimen: either CSII or MDI. The study design is presented in Fig. 1.

The study was initiated with an open-label pioneer group ( $n = 3$ ) on CSII to establish preliminary safety and to provide information on insulin dose adjustment during initiation of treatment. Subsequent to completion of treatment of the pioneer group, patients on either MDI or CSII were enrolled in the placebo-controlled portion of the study and randomly assigned 1:1, using an interactive web response system, to receive, in a double-blind fashion, either a total daily dose of 400 mg sotagliflozin or placebo taken within 15 min prior to breakfast for 29 days.

The initial 7 days (days –7 to –1) of the study were used to obtain baseline laboratory samples, to record baseline insulin doses through use of daily diaries, and to obtain at least 3 days of blinded CGM data on an outpatient basis during patients' usual insulin, dietary, and activity regimen. Days 1 and 2 of the study were conducted in an inpatient setting to allow supervision of initial insulin dose adjustments and to obtain multiple pharmacokinetic (PK) and pharmacodynamic (PD) samples. The first treatment dose (day 1) was administered before a mixed-meal tolerance test (MMTT) prior to breakfast with no bolus insulin administered. Basal insulin was continued unchanged. Subsequently, investigators adjusted the suggested dosage of short-acting insulin at each meal with guidance

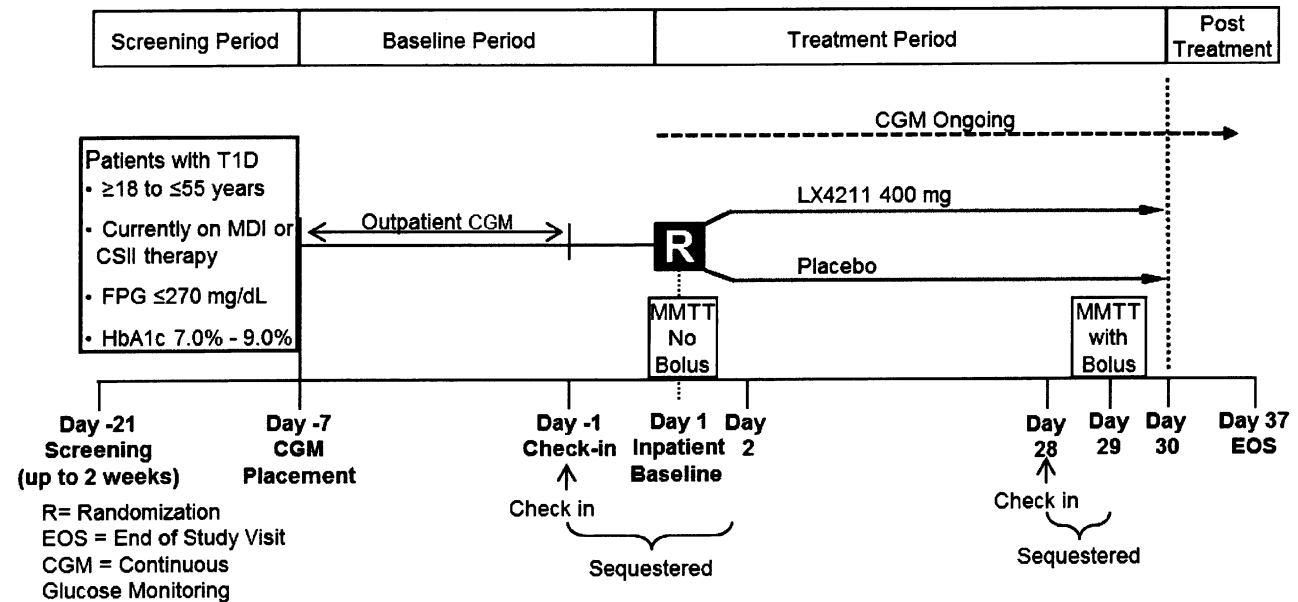


Figure 1—Study design.

from an algorithm based on treat-to-target blood glucose goals consistent with current standard of care (fasting and preprandial: 80–130 mg/dL [4.4–7.2 mmol/L], postprandial:  $<180$  mg/dL [10 mmol/L], and bedtime/overnight: 100–180 mg/dL [5.6–10 mmol/L]). On day 2, patients were discharged and insulin doses were to be adjusted as determined by the patient and investigator assessment of scheduled self-monitoring of blood glucose (SMBG). With standard American Diabetes Association dietary recommendations, patients were instructed to resume their regular routines. Blinded CGM data were collected on all patients throughout the study with the Enlite subcutaneous glucose sensor (Medtronic, Inc., Northridge, CA). On day 28, patients returned to inpatient for  $\sim 36$  h for end-of-treatment MMTT (with usual insulin dosing) and to obtain multiple PK and PD samples; patients were then discharged and followed for an additional week.

### Study Outcomes

The primary outcome of the study was the treatment effect on change from baseline of total daily bolus insulin dose during the outpatient treatment period. The secondary outcomes pertained to specifics of insulin use including change from baseline of total daily bolus insulin at each meal, total daily basal insulin, and total daily bolus plus total daily basal insulin. The secondary

outcomes pertaining to glycemic control included assessing the effect of sotagliflozin on fasting plasma glucose (FPG) and glucose excursion during the 3-h period after an MMTT as measured by area under the curves (AUCs). Secondary outcomes associated with CGM included percent time in defined ranges, 1)  $<70$  mg/dL (3.9 mmol/L) and  $\geq 70$  mg/dL (3.9 mmol/L) and  $\leq 180$  mg/dL (10.0 mmol/L) and 2)  $>180$  mg/dL (10.0 mmol/L) and  $>250$  mg/dL (13.9 mmol/L), as well as changes in mean daily interstitial glucose. Additional measures of glucose variability were included as secondary outcomes including coefficient of variation; mean SD of weekly glucose level; mean amplitude of glucose excursion (MAGE), defined as the average of all glucose excursion that exceeded 1 SD over each 24-h period, as described by Baghurst (28); low blood glucose index; and high blood glucose index (HBGI). Exploratory measures included the effect of sotagliflozin treatment on HbA<sub>1c</sub> as well as changes in GLP-1, PYY, C-peptide, and UGE over a 3-h post-breakfast MMTT.

Assessments of safety included vital signs, electrocardiograms, and laboratory parameters (chemistry, hematology, lipid profiles, and urinalysis). Safety and tolerability of sotagliflozin were assessed by collection and review of adverse events, which were followed until resolution. Adverse events of special interest in this study included urogenital infections and hypoglycemia.

### Study Oversight

The human research committees and/or institutional review boards of participating investigative sites approved the protocols, and all patients provided written informed consent.

### Statistical Analysis

The intent-to-treat population was comprised of all randomized patients in the placebo controlled expansion group. Analyses using this population served as the primary population for statistical analyses and reporting. The PK population included all patients who received at least one dose of study drug and had sufficient, valid PK samples to estimate key parameters for at least one of the days of sampling. Pharmacokinetic summaries were based on the PK population. The safety population included all patients who were randomized and received  $\geq 1$  dose of study drug.

## RESULTS

### Patients

A total of 36 patients were enrolled in the study between 8 February and 20 November 2013, with 3 patients in the open-label pioneer group and 33 patients in the randomized, placebo-controlled, double-blind cohort. Results for the pioneer group were used to evaluate safety and inform the insulin-adjustment paradigm for the double-blind portion of the study. Baseline characteristics of the patients are shown in Table 1. Patient disposition is summarized in Supplementary Fig. 2.

**Table 1—Demographic characteristics (intent-to-treat population)**

Patient characteristics	Placebo (N = 17)	Sotagliflozin (N = 16)
Age (years), median (range)	34.0 (21, 57)	45.5 (21, 55)
Sex, n (%)		
Female	9 (53)	8 (50)
Male	8 (47)	8 (50)
Race, n (%)		
White/Caucasian	14 (82)	16 (100)
Asian	2 (12)	0
Other	1 (6)	0
Weight (kg), median (range)	72.7 (55.3, 104.6)	74.2 (55.6, 107.9)
BMI (kg/m <sup>2</sup> ), mean (SD)	26.2 (3.0)	27.1 (3.1)
Duration of diabetes (years), median (range)	18.5 (4.7, 40.8)	16.8 (3.4, 42.9)
HbA <sub>1c</sub> (%), mean (SD)	7.98 (0.51)	7.94 (0.55)
HbA <sub>1c</sub> (mmol/mol), mean (SD)	62.83 (5.66)	63.38 (6.04)
FPG (mmol/L), mean (SD)	8.89 (3.96)	9.45 (3.45)
Seated systolic BP (mmHg), mean (SD)	119.8 (7.0)	118.1 (9.2)
Serum sodium (mmol/L), mean (SD)	138.24 (3.75)	137.63 (2.45)
Serum creatinine (μmol/L), mean (SD)	76.11 (9.86)	76.94 (11.82)
Serum BUN (mmol/L), mean (SD)	4.68 (0.99)	4.96 (1.02)
Hematocrit, mean (SD)	41.94 (4.87)	41.63 (4.86)
Insulin therapy, n (%)		
MDI	5 (29)	6 (38)
CSII	12 (71)	10 (63)
Total daily insulin (IU/kg), mean	0.60	0.60
Daily insulin, ratio of bolus/total	0.45	0.49

BP, blood pressure.

## Outcomes

### Bolus Insulin

The percent change from baseline in total daily bolus insulin use was  $-32.0\%$  in the sotagliflozin group and  $-6.4\%$  in the placebo group ( $P = 0.007$ ) (Tables 2 and 3). Given that sotagliflozin was administered once daily before breakfast, a prespecified subgroup analysis of bolus insulin use before major meals was conducted to detect differences throughout the day. Reductions of bolus insulin from baseline before each meal were noted in patients treated with sotagliflozin compared with placebo:  $-28.4\%$  vs.  $13.6\%$  at breakfast ( $P = 0.046$ ),  $-25.9\%$  vs.  $7.1\%$  at lunch ( $P = 0.08$ ), and  $-23.8\%$  vs.  $39.3\%$  at dinner ( $P = 0.052$ ) (Table 3). The effects of sotagliflozin on bolus insulin requirements were similar whether patients were on MDI or CSII.

### Basal Insulin and Total Daily Insulin

The use of basal insulin was similar between the groups, and the change from baseline for both groups was minimal. There was a numerical decrease from baseline of  $2.4\%$  for the sotagliflozin group compared with a numerical increase from baseline of  $0.2\%$  in the placebo group ( $P = 0.53$ , Tables 2 and 3).

Total daily insulin was lower for the sotagliflozin group, with a reduction from baseline of  $15.3\%$  ( $P = 0.002$ ) and a reduction of  $0.7\%$  for the placebo group ( $P = 0.029$ , difference between groups) (Tables 2 and 3).

### Glucose Levels by CGM

Over the outpatient treatment period, sotagliflozin therapy resulted in a lower mean daily glucose as measured by CGM (Supplementary Fig. 1) of  $148.8$  mg/dL ( $8.3$  mmol/L) compared with a placebo value of  $170.3$  mg/dL ( $9.5$  mmol/L) ( $P = 0.010$ ) (Table 3). In addition, patients in the sotagliflozin treatment group spent a greater percentage of time in the target glycemic range defined as  $\geq 70$  mg/dL ( $3.9$  mmol/L) and  $\leq 180$  mg/dL ( $10.0$  mmol/L) compared with placebo ( $68.2\%$  vs.  $54.0\%$ ,  $P = 0.003$ ) (Table 3 and Supplementary Fig. 1), while percentage of time spent in the hyperglycemic range,  $> 180$  mg/dL ( $10.0$  mmol/L), was lower compared with placebo ( $25.0\%$  vs.  $40.2\%$ ,  $P = 0.002$ ) (Table 3 and Supplementary Fig. 1), as was percentage of time spent  $> 250$  mg/dL ( $13.9$  mmol/L) ( $6.7\%$  vs.  $14.1\%$ ,  $P < 0.008$ ) (Table 3). The sotagliflozin and placebo groups exhibited a

similar percentage of time spent in the hypoglycemic ranges of  $< 70$  mg/dL ( $3.9$  mmol/L) ( $6.7\%$  vs.  $5.8\%$ ,  $P = 0.80$ ) (Table 3 and Supplementary Fig. 1).

After meals, sotagliflozin treatment produced favorable effects on postprandial glycemic excursions as assessed by CGM during a 3-h period. In the sotagliflozin group, mean change from baseline at breakfast was  $-16.7$  mg/dL ( $-0.93$  mmol/L) vs.  $-4.2$  mg/dL ( $-0.23$  mmol/L) ( $P = 0.034$ ) (Supplementary Table 2). The changes from baseline at lunch and dinner were numerically lower for sotagliflozin than placebo but did not reach statistical significance.

Notably, there was less glucose variability on sotagliflozin treatment as measured by MAGE, calculated as  $120.8$  mg/dL ( $6.7$  mmol/L) for the sotagliflozin treatment group, compared with  $145.5$  mg/dL ( $8.1$  mmol/L) for placebo ( $P = 0.041$ ) (Table 3). CGM SD was also lower on sotagliflozin treatment, calculated as  $50.0$  for the sotagliflozin treatment group compared with  $58.8$  for placebo ( $P = 0.022$ ) (Table 3). Consistent with the percentage of time spent in hyperglycemic ranges, the mean HBGI was reduced from baseline in the sotagliflozin group compared with an increase in the placebo group ( $P = 0.006$ ) (Table 3).

### HbA<sub>1c</sub>

There was a significant decrease in HbA<sub>1c</sub> of  $0.55\%$  ( $5.9$  mmol/mol) from baseline after 29 days of treatment with sotagliflozin compared with  $0.06\%$  ( $0.65$  mmol/mol) for the placebo group ( $P = 0.002$ ) (Table 2). The effects of sotagliflozin on HbA<sub>1c</sub> were similar whether patients were on MDI or CSII.

### Hypoglycemia

Total hypoglycemic events defined as SMBG  $\leq 70$  mg/dL ( $3.9$  mmol/L) in the placebo group numbered 354. Of these, 185 (52%) were symptomatic and 117 (33%) were asymptomatic. In the sotagliflozin treatment group, the total number of events was 304. Of these, 162 events (53%) were symptomatic and 80 events (26%) were asymptomatic. There were no SH events in either group. Hypoglycemic events per patient per day (PPD), defined as SMBG  $\leq 70$  mg/dL ( $3.9$  mmol/L), declined significantly from baseline during treatment in both groups, and in both groups hypoglycemia PPD was  $0.4$  (Table 2). Hypoglycemic events PPD, by blinded CGM (defined as  $\geq 10$  continuous minutes of glucose readings  $< 70$  mg/dL



**Table 2—Overall summary of results**

	Placebo (N = 17)	Sotagliflozin (N = 16)	P
<b>Efficacy</b>			
HbA <sub>1c</sub> change from baseline (%)	−0.06	−0.55*	<b>0.002</b>
FPG change from baseline assessed at day 29 (mg/dL)	39.0	−18.6	0.15
Daily bolus insulin change from baseline assessed at days 3–27 (%)	−6.4	−32.0*	<b>0.007</b>
Daily basal insulin change from baseline assessed at days 3–27 (%)	0.2	−2.4	0.53
Total daily insulin change from baseline assessed at days 3–27 (%)	−0.7	−15.3*	<b>0.029</b>
Mean body weight change from baseline assessed at day 29 (kg)	0.5	−1.7*	<b>0.005</b>
Postmeal urinary glucose (g/3 h) at day 29†	9.2	29.1	<b>0.025</b>
Postmeal plasma glucose AUC (mg · h/dL over 3 h) at day 29†	761	595	<b>0.005</b>
PYY postmeal AUC change from baseline assessed at day 29 (pmol/L · h over 3 h)	−0.7	6.0*	<b>0.018</b>
Seated systolic blood pressure change from baseline assessed at day 29 (mmHg)	−3.9	−4.9	0.45
<b>Safety</b>			
Patients with any TEAE (%)	12 (71)	14 (88)	N/A
Patients with SAE (both with DKA‡)	0	2	N/A
Hypoglycemic events (SMBG ≤70 mg/dL, baseline–day 36)	354	304	N/A
Documented symptomatic hypoglycemia (SMBG ≤70 mg/dL, baseline–day 36)	185	162	N/A
Asymptomatic hypoglycemia (SMBG ≤70 mg/dL, baseline–day 36)	117	80	N/A
SH	0	0	N/A
Hypoglycemia (SMBG ≤70 mg/dL, PPD) change from baseline at days 3–27	−0.4*	−0.7*	0.77
Hypoglycemia (CGM ≥10 continuous min <70 mg/dL, PPD) change from baseline assessed at days 3–27	−0.15	−0.09	0.75
<b>Laboratory values associated with volume status</b>			
Serum sodium (mmol/L), change from baseline at day 29 (day 36)	−1.00 (−0.53)	−0.50 (1.50)	N/A
Serum creatinine (μmol/L), change from baseline at day 29 (day 36)	−0.53 (1.53)	2.63 (0.63)	N/A
Serum BUN (mmol/L), change from baseline at day 29 (day 36)	0.41 (0.11)	1.02 (−0.41)	N/A
Hematocrit, change from baseline at day 29 (day 36)	−1.4 (0)	2.1 (1.5)	N/A

For laboratory values, change from baseline was assessed at day 29, the last day of therapy, and day 36, 1 week off therapy, unless otherwise specified. N/A, not applicable; SAE, serious adverse event. \* $P < 0.05$ , change from baseline. †Day 1 is not a true “baseline”; therefore,  $P$  values are calculated from two-sample  $t$  tests using the observed means. ‡Both were assessed as due to insulin pump and deemed not drug related. Bold values are statistically significant.

(3.9 mol/L), declined numerically during treatment in both groups.

#### **Body Weight, PYY, Urinary Glucose, and Other Outcomes**

Mean body weight decreased with sotagliflozin treatment compared with an increase in the placebo group (−1.7 kg vs. 0.5 kg) ( $P = 0.005$ ) (Table 2). Change from baseline AUC after a meal challenge for PYY was increased by 6.0 pmol/L · h over 3 h in the sotagliflozin group and decreased by 0.7 pmol/L · h over 3 h with placebo ( $P = 0.018$ ) (Table 2).

An MMTT performed on the last treatment day of the study showed a lower serum glucose 3-h AUC in the sotagliflozin group compared with placebo (595 mg · h/dL vs. 761 mg · h/dL, respectively,  $P = 0.009$ ) (Table 2). The mean 3-h UGE was higher in the sotagliflozin group compared with placebo (29.1 g/3 h vs. 9.2 g/3 h, respectively,  $P = 0.025$ ) (Table 2). Systolic blood pressure decreased in both groups, with a decline of 4.9 mmHg in the sotagliflozin-treated group and a decline of 3.9 with placebo ( $P = 0.45$ ) (Table 2). Laboratory values associated with volume

status (serum sodium, serum creatinine, serum BUN [blood urea nitrogen], and hematocrit) were assessed at baseline, the last day of therapy (day 29), and 1 week after last dose of study medication (day 36). In the sotagliflozin group, there were numeric increases in most values, which returned toward baseline at day 36, consistent with reversible perfusion and volume effects. There were no meaningful changes in other exploratory end points including stimulated C-peptide, C-reactive protein, triglycerides, and uric acid (data not shown).

#### **Adverse Events**

Fourteen (88%) patients on sotagliflozin reported adverse events compared with 12 (71%) patients on placebo. No adverse events led to discontinuation from the study. The most frequently reported treatment-emergent adverse events (TEAEs) in the sotagliflozin group by MedDRA System Organ Class were GI disorders, eight sotagliflozin patients (50%) compared with three placebo patients (18%), with the most notable imbalance being three reports of nausea

on sotagliflozin versus one on placebo. Treatment differences in incidence of TEAEs were not statistically tested. TEAEs are summarized in Supplementary Table 1.

Two serious adverse events of diabetic ketoacidosis were reported in two patients using insulin infusion pumps and treated with sotagliflozin. Both cases of DKA were assessed by the investigators as pump related and were not related to the study drug. Details of the events are provided in Supplementary Table 1.

#### **CONCLUSIONS**

We evaluated dual inhibition of SGLT1 and SGLT2 using sotagliflozin as adjunct to insulin in inadequately controlled type 1 diabetes in a double-blind, placebo-controlled trial over 29 days. During the study period, patients continued their usual insulin delivery regimens while attempting to achieve American Diabetes Association–recommended glucose targets goals and maintaining their usual activity levels and diet. Treatment with 400 mg sotagliflozin given once daily before breakfast resulted in significant reductions in bolus insulin

**Table 3—Summary of CGM and CGM-derived results and prespecified insulin dose analysis**

	Placebo (N = 17)			Sotagliflozin (N = 16)			P
	Baseline	Treatment	Change from baseline value [%]	Baseline	Treatment	Change from baseline value [%]	
CGM mean daily glucose (mg/dL)	160.6 (25.9)	170.3 (24.0)	5.9 [NC]	163.6 (38.7)	148.8 (18.0)*	−14.0 [NC]	<b>0.010</b>
CGM hypoglycemia events/patient/day (≥10 continuous min <70 mg/dL)	1.09 (1.01)	0.90 (0.47)	−0.2 [NC]	1.06 (0.59)	0.95 (0.41)	−0.1 [NC]	0.75
CGM % time in ranges (mg/dL)							
<70	8.5 (9.5)	5.8 (4.7)	−2.3 [NC]	7.9 (7.3)	6.7 (5.0)	−1.5 [NC]	0.80
70–180	55.9 (12.1)	54.0 (12.0)	−0.2 [NC]	56.4 (15.6)	68.2 (12.1)*	11.6 [NC]	<b>0.003</b>
>180	35.6 (14.4)	40.2 (13.7)	2.5 [NC]	35.7 (18.3)	25.0 (11.2)*	−10.1 [NC]	<b>0.002</b>
>250	12.0 (9.3)	14.1 (7.9)	1.1 [NC]	15.3 (14.8)	6.7 (6.6)*	−7.9 [NC]	<b>0.008</b>
CGM variability measures							
SD (mg/dL)	57.2 (13.9)	58.8 (9.6)	1.2 [NC]	60.5 (16.5)	50.0 (12.2)*	−8.9 [NC]	<b>0.022</b>
Coefficient of variation	35.6 (8.8)	35.4 (5.2)	0.3 [NC]	37.4 (5.2)	33.7 (6.0)	−2.9 [NC]	0.41
MAGE	135.5 (34.9)	145.5 (25.6)	7.5 [NC]	145.5 (39.5)	120.8 (30.5)*	−20.0 [NC]	<b>0.041</b>
HBGI	8.7 (3.7)	9.7 (3.7)	0.5 [NC]	9.2 (6.5)	6.2 (3.1)*	−2.9 [NC]	<b>0.006</b>
LBGI	2.2 (2.2)	1.5 (1.1)*	−0.6 [NC]	1.9 (1.5)	1.8 (1.2)	−0.2 [NC]	0.61
Insulin dose data							
Total daily bolus (primary)	20.9 (14.0)	18.8 (11.2)	−2.1 [−6.4]	23.0 (11.6)	15.4 (9.2)	−7.3 [−32.0]	<b>0.007</b>
Total daily basal	26.1 (9.4)	25.9 (9.3)	−0.2 [0.2]	27.1 (7.1)	26.6 (8.7)	−0.5 [−2.4]	0.53
Total daily (basal + bolus)	45.9 (17.5)	44.4 (15.5)	−1.5 [−0.7]	47.0 (17.9)	37.6 (15.3)	−7.6 [−15.3]	<b>0.029</b>
Breakfast bolus	4.8 (4.1)	4.4 (2.9)	— [13.6]	5.6 (3.6)	3.4 (2.0)	— [−28.4]	<b>0.046</b>
Lunch bolus	5.6 (4.8)	5.0 (3.9)	— [7.1]	6.4 (3.9)	4.4 (2.7)	— [−25.9]	0.08
Dinner bolus	6.2 (5.7)	5.8 (4.2)	— [39.3]	7.2 (4.1)	5.3 (3.4)	— [−23.8]	0.052

Data are mean (SD) unless otherwise indicated. Arithmetic change from baseline is shown; P values are from least squares mean analyses of change from baseline scores (absolute and % change). The baseline analysis period consists of days −6 to −2, and the treatment analysis period consists of days 3–27. LBGI, low blood glucose index; NC, not calculated. \*P < 0.05, change from baseline. Bold values are statistically significant.

dose while improving glycemic control by multiple measures including lower mean daily glucose, a higher percentage of time spent in target range, less time spent in hyperglycemic ranges, and lower HbA<sub>1c</sub>.

Sotagliflozin also produced significant pre- and postmeal improvements in glucose levels by CGM. Improvement in postprandial glucose was also demonstrated by favorable effects during the MMTT, where compared with placebo, sotagliflozin produced a statistically significant decrease in 3-h plasma glucose AUC at the end of treatment. The primary effect of SGLT1 inhibition is reduction in postprandial glucose (19,29–31) and, of note, occurred with significantly lower bolus insulin used by patients on sotagliflozin. This contrasts with trials of empagliflozin and dapagliflozin, selective SGLT2 inhibitors, in type 1 diabetes that did not show any significant reductions in bolus insulin use (15,32,33). Further work is required to clarify the extent to which this discrepancy is driven by the SGLT1 inhibition of sotagliflozin versus differences in trial design. Importantly, the favorable effects on daily glycemic control and insulin use

were accompanied by a 0.55% reduction of HbA<sub>1c</sub> after 29 days of treatment with sotagliflozin. In an 8-week open-label study in patients with type 1 diabetes, empagliflozin produced a 0.4% reduction in HbA<sub>1c</sub> (32).

The reduction in bolus insulin use could contribute to a lower risk for postprandial hypoglycemia, and it is interesting to note that hypoglycemic events PPD were numerically lower than baseline for both treatment groups when measured by either SMBG or blinded CGM. Based on these findings, sotagliflozin provided clinically meaningful improvement in glycemic control without increased hypoglycemic events. Patients treated with sotagliflozin also demonstrated significant improvements in measures of glycemic variability based on 24-h CGM analysis during the treatment period. These measures included the 24-h SD, 24-h glucose interquartile range, HBGI (a predictor for hyperglycemia), mean daily sensor glucose, and MAGE.

Patients treated with sotagliflozin demonstrated weight loss (−1.7 kg) compared with a weight gain (0.5 kg) for the placebo group. The systolic

blood pressure decrease in the sotagliflozin group (−4.9 mmHg) was similar to the placebo group (−3.9 mmHg). Consistent with the SGLT1 inhibitory effects of sotagliflozin, postprandial GI hormone PYY was significantly increased and sotagliflozin's SGLT2 inhibitor effect was reflected by increased UGE. These parameters provide confirmation of sotagliflozin's dual mechanism of action of SGLT1 inhibition in the GI tract and SGLT2 inhibition in the kidney.

Four patients in the sotagliflozin group reported an AE of nausea compared with one patient in the placebo group, an effect possibly associated with increased GLP-1 activity. One case occurred 3 days after cessation of treatment. The three cases that occurred during treatment were early in onset, mild in intensity, and of short duration (2 days or less). No patient on sotagliflozin reported any genitourinary infections, while one patient on placebo reported cystitis in the posttreatment follow-up period. There were no cases of SH reported, and numerically less hypoglycemic events PPD in the sotagliflozin-treated group compared with placebo. Two patients in the sotagliflozin group reported an event

of DKA, which was attributed (by the investigators) to insulin pump therapy. Both cases were associated with high laboratory blood glucose readings ( $>350$  mg/dL [ $19.4$  mmol/L]) at presentation, a finding expected in DKA. Nonetheless, given the serious nature of such events, DKA will be closely monitored in all future type 1 diabetes trials. Notably, two cases of DKA were reported in patients with type 1 diabetes receiving the selective SGLT2 inhibitor empagliflozin, but in both cases the patients presented with blood glucose levels lower than typically associated with DKA (14,32).

This initial study of sotagliflozin in type 1 diabetes had several limitations. With the known effects of sotagliflozin on reducing glucose absorption, bolus insulin administration was closely monitored in an inpatient setting during the first 48 h of the study, and guidance for insulin dosing upon first dosing with sotagliflozin was conservative with an emphasis on patient safety in an effort to lower the theoretical risk for episodes of SH. This could have introduced bias in the results favoring a reduction of bolus insulin use compared with basal over the outpatient treatment period. Finally, highly significant reductions in insulin doses achieved in some patients may have led certain participants or caregivers to believe they were effectively unblinded during the study, introducing behavioral biases that could have impacted the results given the small numbers of patients enrolled in this study.

Although insulin provides a lifesaving therapy for individuals with type 1 diabetes, the challenges and burden of managing the disease with insulin therapy alone remain daunting. As work continues to develop disease-modifying treatments such as the artificial pancreas,  $\beta$ -cell transplantation, and immunomodulatory therapy to protect  $\beta$ -cells, efforts must also be made to identify adjunct therapies that could be used in combination with insulin to improve glycemic control, lower the burden of disease, and improve quality of life. After 29 days' treatment, sotagliflozin, a next-generation dual SGLT1 and SGLT2 inhibitor, significantly reduced  $HbA_{1c}$  levels, daily bolus and total daily insulin dose, postprandial blood glucose, and body weight, with no increase in hypoglycemia risk. In addition, sotagliflozin significantly improved time spent in the glucose range as measured

by the following CGM glucose indices: mean daily glucose; percent time spent between 70 and 180 mg/dL,  $>180$  mg/dL, and  $>250$  mg/dL; and glucose variability (mean SD, MAGE, and HBGI). Sotagliflozin as an adjunctive treatment to insulin improved both glucose control and glycemic variability. Larger studies of a longer duration are needed to confirm these findings.

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