Improved Time in Range and Glycemic Variability With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: A Pooled Analysis of 24-Week Continuous Glucose Monitoring Data From the inTandem Program

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OBJECTIVE

To evaluate effects of the dual sodium–glucose cotransporter (SGLT) 1 and SGLT2 inhibitor sotagliflozin in combination with insulin on glucose time in range (TIR) and glucose excursions, postprandial glucose (PPG), and other glycemic metrics in adults with type 1 diabetes using masked continuous glucose monitoring (CGM).

RESEARCH DESIGN AND METHODS

Data sets from the inTandem1 (clinical trial reg. no. NCT02384941) and inTandem2 (clinical trial reg. no. NCT02421510) double-blind randomized trials evaluating sotagliflozin versus placebo in adults with type 1 diabetes treated with optimized insulin were pooled for analyses of masked CGM data from a subset of participants in each trial. The pooled cohort included patients randomized to receive placebo (n = 93), sotagliflozin 200 mg (n = 89), or sotagliflozin 400 mg (n = 96). The primary outcome was change from baseline to week 24 in glucose TIR (3.9–10.0 mmol/L [70–180 mg/dL]). Secondary end points included time below and above the target range and 2-h PPG level assessed after a standardized mixed meal.

RESULTS

Mean percentage of glucose TIR/percentage time spent at <3.9 mmol/L (<70 mg/dL) during week 24 was 51.6%/5.9%, 57.8%/5.5%, and 64.2%/5.5% with placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively, which corresponded to a placebo-adjusted change from a baseline of +5.4%/−0.3% (P = 0.026; +1.3/−0.1 h/day) for sotagliflozin 200 mg and +11.7%/−0.1% (P < 0.001; +2.8/−0.02 h/day) for sotagliflozin 400 mg. Placebo-adjusted PPG reductions were 1.9 ± 0.7 mmol/L (35 ± 13 mg/dL; P = 0.004) and 2.8 ± 0.7 mmol/L (50 ± 13 mg/dL; P < 0.001) with sotagliflozin 200 and 400 mg, respectively.

CONCLUSIONS

Combined with optimized insulin in type 1 diabetes, sotagliflozin significantly increased glucose TIR without increasing time spent at <3.9 mmol/L and reduced PPG, thereby improving glycemic control.

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Managing type 1 diabetes is a challenge for even skilled, experienced patients and clinicians. Although insulin therapy is lifesaving for patients with type 1 diabetes, and intensive glycemic control reduces the complications of diabetes (1), it exposes patients to hypoglycemia and weight gain. Moreover, many patients have difficulty controlling glucose fluctuations, which can occur on a minute-by-minute basis. Because HbA_{1c} does not reflect short-term variations in blood glucose, daily exposure to hypoglycemia and hyperglycemia, or the impact of blood glucose variations on patients' quality of life, the international Type 1 Diabetes Outcomes Program recently recommended an additional set of type 1 diabetes outcomes measures beyond HbA_{1c} level. These include glucose time in range (TIR), hypoglycemia, hyperglycemia, and the incidence of diabetic ketoacidosis (DKA) (2). Further refining glycemic outcomes beyond HbA_{1c}, an international consensus group recently recommended 15 key metrics for continuous glucose monitoring (CGM) analyses and reporting, with particular emphasis on percentage of TIR at 3.9–10.0 mmol/L (70–180 mg/dL) and a means of alerting patients when glucose exceeds or is below this range (3).

The challenges of managing type 1 diabetes have prompted interest in insulin adjuncts, with the goal of improving glycemic control without increasing hypoglycemia or weight gain (4,5). To date, only pramlintide has been approved as an adjunct to insulin for the treatment of type 1 diabetes, but this agent requires prandial injections and is associated with an increased risk of severe hypoglycemia, nausea, and vomiting (4,6). Studies of incretin mimetics (i.e., dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists) and metformin have shown few if any benefits (7–10), but sodium–glucose cotransporter (SGLT) inhibitors have shown promise in combination with insulin for type 1 diabetes management (11–16).

Sotagliflozin (LX4211) is a novel dual inhibitor of SGLT1 and SGLT2 that decreases renal glucose reabsorption through systemic SGLT2 inhibition. In addition, SGLT1 inhibition reduces glucose absorption in the proximal gastrointestinal tract, causing a blunting and delay of postprandial glucose (PPG) (17–19). The resulting lower peak PPG should reduce time above the goal blood glucose range and increase the time within that range (i.e., TIR), resulting in less glycemic variability. The inTandem phase 3 program consists of three completed international, randomized, double-blind, placebo-controlled trials of sotagliflozin combined with insulin for the treatment of type 1 diabetes (11–13). In each, sotagliflozin significantly reduced HbA_{1c}, fasting plasma glucose, body weight, and blood pressure (in patients with SBP $\geq$130 mmHg) and increased the proportion of patients achieving HbA_{1c} $<$7.0% and those achieving composite outcomes consisting of HbA_{1c} $<$7.0% without severe hypoglycemia or DKA or HbA_{1c} reductions $\geq$0.5% without severe hypoglycemia or DKA.

The inTandem1 and inTandem2 trials had identical trial designs in which insulin therapy was optimized for all patients starting 6 weeks before the initiation of oral therapy to identify incremental effects of sotagliflozin that could not be achieved by merely increasing insulin doses (12,13). These trials included a randomly selected subgroup of patients who underwent masked CGM to assess the effect of sotagliflozin on TIR and glycemic variability as well as the assessment of 2-h PPG to evaluate postmeal glucose excursions. Here, we describe the results of pooled analyses of data from the CGM substudies from inTandem1 and inTandem2.

RESEARCH DESIGN AND METHODS

Design Overview

Prespecified pooled analyses were conducted using 24-week CGM substudy data from two phase 3, 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials of oral sotagliflozin 200 or 400 mg once daily in combination with optimized insulin in adults with type 1 diabetes who had inadequate glycemic control on insulin alone. The trials were conducted in the U.S. and Canada (inTandem1 [clinical trial reg. no. NCT02384941, ClinicalTrials.gov]) and Europe and Israel (inTandem2 [clinical trial reg. no. NCT02421510, ClinicalTrials.gov]); trial design details have been previously reported (12,13).

Participants in the CGM substudy of each trial underwent masked CGM with a Dexcom G4 monitor (Dexcom, Inc., San Diego, CA) during specified 1-week intervals throughout the first 24 weeks: week $-$1 to baseline, week 3–4, week 11–12, and week 23–24. Because it was possible that the CGM substudies of each trial would not meet their individual enrollment targets (n = 70/arm), the inTandem1 and inTandem2 protocols were modified before data were unmasked to include prespecified pooled analyses of CGM data. At baseline and week 24, CGM substudy participants had 2-h plasma PPG assessments after ingesting a standardized mixed liquid nutrition drink with bolus insulin matched to the carbohydrate content of the meal (Supplementary Data) (20,21).

The institutional review boards for each study center or the local ethics committees approved the protocol, consent form, and associated documents. All patients provided written informed consent. An independent statistician performed statistical analyses.

Study Population

The inTandem program included men and nonpregnant women $\geq$18 years of age who had type 1 diabetes treated with insulin delivered via multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) whose HbA_{1c} was between 7.0% and 11.0% at screening. Full details have been published previously (12,13).

Interventions

After a 6-week insulin optimization phase, patients were randomly assigned in a 1:1:1 ratio to placebo, sotagliflozin 200 mg, or sotagliflozin 400 mg, given as two tablets administered orally once daily. Insulin optimization continued throughout the trial for all patients. Regardless of the HbA_{1c} level achieved at the end of the optimization period, all patients were randomly assigned to treatment. Study personnel adjusted basal and bolus insulin 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 PPG $<$10 mmol/L ($<$180 mg/dL) based on self-monitored blood glucose (SMBG) patterns (12,13).

End Points

The primary efficacy end point was the change from baseline to week 24 (week 23–24 period) in percentage of TIR of 3.9–10.0 mmol/L (70–180 mg/dL).

Secondary end points included percentage time and area under the curve (AUC) outside the target range. These correspond to hyperglycemia (>10.0 mmol/L [>180 mg/dL]), hypoglycemia (<3.9 mmol/L [<70 mg/dL]), and the change from baseline to week 24 in AUC values above or below different thresholds (>10.0 or >13.9 mmol/L [>180 or >250 mg/dL]; <3.0 or <3.9 mmol/L [<55 or <70 mg/dL]) by time of day (full 24-h day, diurnal period [0600 to 2359 h], nocturnal period [0000 to 0559 h]) and the change from baseline in 2-h PPG (measured as plasma glucose) after a standardized mixed meal at week 24. To provide context on the risk of hypoglycemia, CGM TIR is expressed similarly to blood pressure, as percentage of TIR (3.9–10.0 mmol/L [70–180 mg/dL])/percentage time <3.9 mmol/L (<70 mg/dL). Glycemic variability was assessed with CGM data including the SD of glucose, mean daily glucose, mean amplitude of glycemic excursions (MAGE), and coefficient of variation (CV) as previously defined (22,23). Hypoglycemia by CGM was defined as at least 10 min of continuous CGM readings below the thresholds of 3.9 mmol/L (70 mg/dL) or 3.0 mmol/L (55 mg/dL).

Statistical Methods

Analyses of CGM data were based on the modified intent-to-treat subpopulation participating in the CGM substudy of each trial, which included all randomized CGM patients who had taken at least one dose of study drug. Three to 7 days worth of valid CGM recordings were required for a visit to be used for analysis; a visit consisted of a weekly session of recordings. For any day within a visit to be eligible, ≥80% of the data points had to have been nonmissing. Gaps in the CGM recording for those days included in a visit were imputed using a linear interpolation approach (24) of the planned 7 days. Because mealtime bolus insulin administration directly influences PPG, and to perform analyses under ideal design conditions to best evaluate any effects related to study treatment, the PPG analyses were based on the per-protocol population, which included all modified intent-to-treat patients who completed 24 weeks of treatment without significant protocol deviations, took bolus insulin and the study drug at the designated time at the standardized mixed meal, and completed all required mixed meal test procedures.

Continuous, longitudinal end point data were analyzed using the mixed-effects model for repeated measures method based on the restricted maximum likelihood method for estimation with several prespecified fixed effects, including first-order interactions with time, and the corresponding end point as the dependent variable in the model. ANCOVA was used for analyses of measures taken at a single time point post-baseline. For binary end points, the Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors, was used. The treatment group comparisons were performed at week 24. Missing observations at week 24 were imputed as nonresponse in the Cochran-Mantel-Haenszel analysis.

RESULTS

The pooled cohort included 278 adults (136 from inTandem1 and 142 from inTandem2) randomly assigned to receive placebo (n = 93), sotagliflozin 200 mg (n = 89), or sotagliflozin 400 mg (n = 96). Baseline characteristics were similar between groups (Table 1). In the total pooled analysis, 143 (51.4%) patients used MDI and 135 (48.6%) used CSII (Table 1).

Of the pooled cohort, sufficiently complete CGM data for analyses were available for 61 of 93 patients (66%) receiving placebo; 63 of 89 patients (71%) receiving sotagliflozin 200 mg; and 72 of 96 patients (75%) receiving sotagliflozin 400 mg. The mean percentage of TIR/percentage time spent <3.9 mmol/L (<70 mg/dL) during week 24 was 51.6%/5.9%, 57.8%/5.5%, and 64.2%/5.5% with placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively. Placebo-adjusted differences from baseline to week 24 in percentage of TIR were 5.4% ± 2.4% (95% CI 0.6–10.1; P = 0.026) and 11.7% ± 2.3% (95% CI 7.1–16.3; $P < 0.001$) with sotagliflozin 200 and 400 mg, respectively (Table 2), which was estimated to be an additional TIR of 1.3 h/day with sotagliflozin 200 mg and 2.8 h/day with sotagliflozin 400 mg (Fig. 1). Placebo-subtracted changes from baseline to week 24 in the percentage time spent >10.0 mmol/L (>180 mg/dL) were −5.0% ± 2.6% (95% CI −10.2 to 0.1; P = 0.055) and −11.8% ± 2.5% (95% CI −16.7 to −6.8; $P < 0.001$) in the sotagliflozin 200 and 400 mg groups, translating to −1.2 h/day and −2.8 h/day, respectively. Patients receiving sotagliflozin 200 and 400 mg spent less time at >13.9 mmol/L (>250 mg/dL) relative to placebo; differences were −3.7% ± 1.8% (95% CI −7.3 to −0.1; P = 0.045) and −7.7% ± 1.8% (95% CI −11.2 to −4.2; $P < 0.001$), or 0.9 and 1.9 fewer hours, respectively. No significant differences were observed in the percentage of time spent at <3.9 mmol/L (<70 mg/dL) or <3.0 mmol/L (<55 mg/dL) for either dose level of sotagliflozin compared with placebo (Table 2). Average week 24 ambulatory glucose profiles for each study group are shown in Supplementary Fig. 1.

The AUC >10.0 mmol/L (>180 mg/dL) decreased significantly in both sotagliflozin groups by 0.5 ± 0.2 mmol/L (8.4 ± 4.2 mg/dL) × minutes/1,000 (95% CI −0.9 to −0.01; P = 0.045) with 200 mg and 1.0 ± 0.2 mmol/L (17.7 ± 4.1 mg/dL) × minutes/1,000 (95% CI −1.4 to −0.5; $P < 0.001$) with 400 mg relative to placebo (Table 2), a finding supported by CGM tracings of mean 24-h glucose excursions (Fig. 2). Severe hyperglycemia as measured by AUC >13.9 mmol/L (>250 mg/dL) decreased by 0.4 ± 0.1 mmol/L (6.9 ± 2.1 mg/dL) × minutes/1,000 (95% CI −0.6 to −0.2; P = 0.001) with sotagliflozin 400 mg but was not significantly different with sotagliflozin 200 mg (Table 2). Differences from placebo for hypoglycemic AUC values were not statistically significant (Table 2): <3.9 mmol/L (<70 mg/dL), −0.006 ± 0.01 mmol/L (−0.1 ± 0.2 mg/dL) for both sotagliflozin 200 and 400 mg; <3.0 mmol/L (<55 mg/dL), −0.0006 ± 0.006 mmol/L (−0.01 ± 0.1 mg/dL) for sotagliflozin 200 mg and −0.002 ± 0.006 mmol/L (−0.03 ± 0.1 mg/dL) for sotagliflozin 400 mg. The decline in mean glucose value from 12:00 to 6:00 A.M. in patients treated with sotagliflozin shown in Fig. 2 was not associated with a significant increase in nocturnal hypoglycemia.

After a standardized mixed meal (Supplementary Data), the 2-h plasma PPG concentration decreased by 1.9 ± 0.7 mmol/L (35 ± 13 mg/dL) (95% CI −3.4 to −0.5; P = 0.009) with sotagliflozin 200 mg and by 2.8 ± 0.7 mmol/L (50 ± 13 mg/dL) (95% CI −4.2 to −1.3; $P < 0.001$) with sotagliflozin 400 mg relative to placebo.

Table 1—Baseline characteristics

Characteristic	Placebo (*n* = 93)	Sotagliflozin 200 mg (*n* = 89)	Sotagliflozin 400 mg (*n* = 96)	Total (*N* = 278)
inTandem1 participants, *n* (%)	45 (48)	44 (49)	47 (49)	136 (49)
inTandem2 participants, *n* (%)	48 (52)	45 (51)	49 (51)	142 (51)
Age (years)	43.5 (14.2)	44.2 (13.2)	45.1 (12.1)	44.3 (13.2)
Female sex, *n* (%)	52 (55.9)	47 (52.8)	48 (50.0)	147 (52.9)
Race or ethnic group, *n* (%)*				
White	89 (95.7)	86 (96.6)	92 (95.8)	267 (96.0)
Black	2 (2.2)	0	2 (2.1)	4 (1.4)
Asian	1 (1.1)	0	0	1 (0.4)
Other	1 (1.1)	3 (3.4)	2 (2.1)	6 (2.2)
Hispanic/Latino ethnicity	5 (5.4)	4 (4.5)	7 (7.3)	16 (5.8)
HbA_{1c} (%)	7.6 (0.7)	7.6 (0.6)	7.6 (0.7)	7.6 (0.7)
HbA_{1c} (mmol/mol)	59.5 (7.2)	59.4 (7.0)	59.1 (8.1)	59.3 (7.4)
Diabetes duration (years)	24.6 (12.8)	22.2 (12.3)	23.4 (12.0)	23.4 (12.4)
Weight (kg)	85.5 (17.9)	86.4 (16.6)	86.1 (16.9)	86.0 (17.1)
BMI (kg/m^2)	29.4 (5.5)	29.5 (4.8)	29.7 (4.9)	29.5 (5.0)
BMI $\geq$30 kg/m^2, *n* (%)	41 (44.1)	41 (46.1)	46 (47.9)	128 (46.0)
Total daily insulin dose (IU/kg)	0.8 (0.3)	0.7 (0.2)	0.8 (0.3)	0.7 (0.3)
Daily insulin dose (IU/day)				
Total	65.8 (34.6)	60.3 (24.7)	65.7 (33.0)	64.0 (31.2)
Basal	34.6 (15.9)	31.3 (14.0)	33.8 (15.0)	33.3 (15.0)
Bolus and corrections	31.2 (22.0)	28.9 (15.3)	31.9 (21.9)	30.7 (20.0)
Insulin therapy, *n* (%)				
MDI	44 (47.3)	43 (48.3)	48 (50.0)	135 (48.6)
CSII	49 (52.7)	46 (51.7)	48 (50.0)	143 (51.4)

Data are mean (SD) unless otherwise indicated. *Determined according to patient self-report.

The placebo-adjusted mean daily glucose concentration decreased by 0.4 ± 0.3 mmol/L (7.9 ± 4.7 mg/dL) (95% CI −1.0 to 0.1; $P = 0.09$) with sotagliflozin 200 mg and by 1.1 ± 0.3 mmol/L (18.9 ± 4.6 mg/dL) (95% CI −1.6 to −0.6; $P < 0.001$) with the sotagliflozin 400 mg dose. The MAGE also was reduced by 0.7 ± 0.3 mmol/L (12.7 ± 5.5 mg/dL) (95% CI −1.3 to −0.1; $P = 0.022$) and 1.2 ± 0.3 mmol/L (22.1 ± 5.4 mg/dL) (95% CI −1.9 to −0.7; $P < 0.001$) with sotagliflozin 200 and 400 mg, respectively, relative to placebo. The SD for glucose decreased in both treatment groups by 0.3 ± 0.1 mmol/L (4.6 ± 2.3 mg/dL) (95% CI −0.5 to −0.01; $P = 0.042$) and 0.4 ± 0.1 mmol/L (6.8 ± 2.2 mg/dL) (95% CI −0.6 to −0.1; $P = 0.002$) with sotagliflozin 200 and 400 mg, respectively, relative to placebo. The CV did not differ between the sotagliflozin and placebo groups.

The Supplementary Data include week 24 CGM data for individual but representative patients from each treatment group whose baseline HbA_{1c} values were close to 6.5%, 7.0%, and 8.0%. At the baseline HbA_{1c} threshold of 6.5% (Supplementary Fig. 2), sotagliflozin 200 and 400 mg were associated with dose-dependent decreases in the percentage of time at >10.0 mmol/L (180 mg/dL). At the higher HbA_{1c} thresholds of 7.0% (Supplementary Fig. 3) and 8.0% (Supplementary Fig. 4), patients exhibited dose-dependent increases in the percentage of TIR, decreases in the percentage of time at >10.0 mmol/L, and decreases in the percentage of time at <3.9 mmol/L (70 mg/dL).

Compared with placebo, hypoglycemia by CGM (in number of events per patient per day) did not differ with sotagliflozin 200 or 400 mg at either hypoglycemic threshold (<3.0 mmol/L [55 mg/dL] and <3.9 mmol/L [<70 mg/dL]) (Table 2) (all $P > 0.05$). Similarly, no significant differences were observed in the percentage of time spent below hypoglycemic thresholds during nocturnal periods or for diurnal hypoglycemia (Table 2).

CONCLUSIONS

In pooled analyses of masked CGM data from two phase 3 trials involving adults with type 1 diabetes treated with optimized insulin therapy, dual inhibition of SGLT1 and SGLT2 with sotagliflozin significantly increased the percentage of the TIR 3.9–10.0 mmol/L (70–180 mg/dL), reduced the percentage of time spent at >10.0 and >13.9 mmol/L (180 and 250 mg/dL), and reduced PPG and glycemic variability. These findings were predicted as a result of the blunting and delay of glucose absorption due to SGLT1 inhibition, resulting in lower peak PPG (and less time spent above the goal glucose range) and more time spent in the goal glucose range, with a net result of less glycemic variability. These outcomes demonstrate that sotagliflozin-produced efficacy beyond HbA_{1c} was achieved without an increase in percentage time below target range or increased hypoglycemia risk. With the exception of artificial pancreas studies, this has not been observed with insulin therapy alone (25).

High-dose (400 mg) sotagliflozin was associated with significant improvements in all CGM metrics recently recommended by an international CGM consensus group (3) except for CV, which was not statistically different between treatment groups (Table 2). Changes with high-dose sotagliflozin were consistently larger than those observed with

Table 2—Changes in CGM values and 2-h PPG at week 24*

	Placebo (n = 93)	Sotagliflozin 200 mg (n = 89)	Sotagliflozin 400 mg (n = 96)
Time in target range, 3.9–10.0 mmol/L (70–180 mg/dL)			
Percentage time 3.9–10.0 mmol/L (70–180 mg/dL)†			
Patients, *n*	61	63	72
Mean baseline ± SD	52.3 ± 13.8	52.2 ± 15.3	50.7 ± 14.8
Mean week 24 ± SD	51.6 ± 14.7	57.8 ± 15.9	64.2 ± 14.0
Change from baseline, LSM ± SE (95% CI; *P* value)	−1.3 ± 1.8 (−4.8 to 2.3; 0.49)	4.1 ± 1.8 (0.5–7.6; 0.024)	10.5 ± 1.7 (7.1–13.8; <0.001)
Difference from placebo ± SE (95% CI; *P* value)		5.4 ± 2.4 (0.6–10.1; 0.026)	11.7 ± 2.3 (7.1–16.3; <0.001)
Difference from placebo in hours per day corresponding to percentage time per day ± SE†		1.3 ± 0.6	2.8 ± 0.6
Time in hyperglycemic range			
Percentage time >10.0 mmol/L (>180 mg/dL)†			
Patients, *n*	61	63	72
Mean baseline ± SD	41.9 ± 15.4	41.9 ± 16.7	44.0 ± 17.1
Mean week 24 ± SD	42.6 ± 16.9	36.7 ± 16.8	30.3 ± 14.5
Change from baseline, LSM ± SE (95% CI; *P* value)	1.2 ± 2.0 (−2.7 to 5.1; 0.54)	−3.8 ± 2.0 (−7.7 to 0.1; 0.055)	−10.5 ± 1.9 (−14.2 to −6.8; <0.001)
Difference from placebo ± SE (95% CI; *P* value)		−5.0 ± 2.6 (−10.2 to 0.1; 0.055)	−11.8 ± 2.5 (−16.7 to −6.8; <0.001)
Difference from placebo in hours per day corresponding to percentage time per day ± SE‡		−1.2 ± 0.6	−2.8 ± 0.6
Percentage time >13.9 mmol/L (>250 mg/dL)†			
Patients, *n*	61	63	72
Mean baseline ± SD	17.9 ± 12.4	18.6 ± 13.0	17.6 ± 12.2
Mean week 24 ± SD	17.4 ± 12.6	13.3 ± 12.7	8.6 ± 8.2
Change from baseline, LSM ± SE (95% CI; *P* value)	0.2 ± 1.4 (−2.5 to 2.9; 0.90)	−3.5 ± 1.4 (−6.2 to −0.8; 0.012)	−7.5 ± 1.3 (−10.0 to −5.0; <0.001)
Difference from placebo ± SE (95% CI; *P* value)		−3.7 ± 1.8 (−7.3 to −0.1; 0.045)	−7.7 ± 1.8 (−11.2 to −4.2; <0.001)
Difference from placebo in hours per day corresponding to percentage time per day ± SE‡		−0.9 ± 0.4	−1.9 ± 0.4
Time in hypoglycemic ranges			
Percentage time <3.9 mmol/L (<70 mg/dL)†			
Patients, *n*	61	63	72
Mean baseline ± SD	5.8 ± 5.3	5.9 ± 5.6	5.4 ± 6.1
Mean week 24 ± SD	5.9 ± 5.2	5.5 ± 5.6	5.5 ± 5.2
Change from baseline, LSM ± SE (95% CI; *P* value)	0.1 ± 0.7 (−1.2 to 1.4; 0.84)	−0.2 ± 0.7 (−1.5 to 1.1; 0.76)	0.1 ± 0.6 (−1.2 to 1.3; 0.92)
Difference from placebo ± SE (95% CI; *P* value)		−0.3 ± 0.9 (−2.0 to 1.4; 0.70)	−0.1 ± 0.8 (−1.7 to 1.6; 0.93)
Difference from placebo in hours per day corresponding to percentage time per day ± SE‡		−0.1 ± 0.2	−0.02 ± 0.2
Percentage time <3.9 mmol/L (<70 mg/dL) during nocturnal period (0000–0559 h)			
Patients, *n*	71	68	75
Mean baseline ± SD	8.2 ± 11.0	7.4 ± 9.8	7.6 ± 10.5
Change from baseline, LSM ± SE (95% CI; *P* value)	−1.4 ± 1.2 (−3.8 to 1.0; 0.25)	−0.6 ± 1.3 (−3.0 to 1.9; 0.66)	1.0 ± 1.2 (−1.4 to 3.3; 0.43)

Continued on p. 924

Table 2—Continued

	Placebo (n = 93)	Sotagliflozin 200 mg (n = 89)	Sotagliflozin 400 mg (n = 96)
Difference from placebo ± SE (95% CI; *P* value)		0.9 ± 1.6 (−2.3 to 4.1; 0.59)	2.4 ± 1.6 (−0.7 to 5.5; 0.13)
Difference from placebo in hours per day corresponding to percentage time per day ± SE‡		0.2 ± 0.4	0.6 ± 0.4
Percentage time <3.9 mmol/L (<70 mg/dL) during diurnal period (0600–2359 h)			
Patients, *n*	61	63	71
Mean baseline ± SD	5.3 ± 5.1	5.6 ± 5.4	4.6 ± 5.1
Change from baseline, LSM ± SE (95% CI; *P* value)	0.6 ± 0.6 (−0.6 to 1.8; 0.35)	−0.07 ± 0.6 (−1.3 to 1.1; 0.91)	0.2 ± 0.6 (−1.0 to 1.3; 0.79)
Difference from placebo ± SE (95% CI; *P* value)		−0.6 ± 0.8 (−2.2 to 0.9; 0.42)	−0.4 ± 0.8 (−1.9 to 1.1; 0.59)
Difference from placebo in hours per day corresponding to percentage time per day ± SE‡		−0.1 ± 0.2	−0.1 ± 0.2
Percentage time <3.0 mmol/L (<55 mg/dL)†			
Patients, *n*	61	63	72
Mean baseline ± SD	2.4 ± 3.0	2.4 ± 3.7	2.3 ± 4.0
Mean week 24 ± SD	2.4 ± 3.2	2.1 ± 3.1	1.8 ± 2.6
Change from baseline, LSM ± SE (95% CI; *P* value)	−0.1 ± 0.4 (−0.8 to 0.7; 0.88)	−0.2 ± 0.4 (−1.0 to 0.5; 0.57)	−0.5 ± 0.4 (−1.2 to 0.2; 0.16)
Difference from placebo ± SE (95% CI; *P* value)		−0.2 ± 0.5 (−1.1 to 0.8; 0.75)	−0.4 ± 0.5 (−1.4 to 0.5; 0.36)
Difference from placebo in hours per day corresponding to percentage time per day ± SE‡		−0.04 ± 0.1	−0.1 ± 0.1
Percentage time <3.0 mmol/L (<55 mg/dL) during nocturnal period (00:00–05:59 h)			
Patients, *n*	71	68	75
Mean baseline ± SD	4.3 ± 7.3	3.3 ± 6.8	4.0 ± 7.3
Change from baseline, LSM ± SE (95% CI; *P* value)	−0.8 ± 0.8 (−2.4 to 0.8; 0.35)	−0.6 ± 0.8 (−2.3 to 1.0; 0.44)	−0.2 ± 0.8 (−1.8 to 1.3; 0.78)
Difference from placebo ± SE (95% CI; *P* value)		0.1 ± 1.1 (−2.0 to 2.2; 0.91)	0.5 ± 1.0 (−1.5 to 2.6; 0.61)
Difference from placebo in hours per day corresponding to percentage time per day ± SE‡		0.02 ± 0.3	0.1 ± 0.3
Percentage time <3.0 mmol/L (<55 mg/dL) during diurnal period (0600–2359 h)			
Patients, *n*	61	63	71
Mean baseline ± SD	1.9 ± 2.6	2.1 ± 3.5	1.7 ± 3.0
Change from baseline, LSM ± SE (95% CI; *P* value)	0.3 ± 0.3 (−0.3 to 0.9; 0.38)	−0.1 ± 0.3 (−0.8 to 0.5; 0.71)	−0.3 ± 0.3 (−0.9 to 0.3; 0.37)
Difference from placebo ± SE (95% CI; *P* value)		−0.4 ± 0.4 (−1.2 to 0.4; 0.33)	−0.6 ± 0.4 (−1.4 to 0.2; 0.17)
Difference from placebo in hours per day corresponding to percentage time per day ± SE‡		−0.1 ± 0.1	−0.1 ± 0.1
Glycemic instability†			
AUC >10.0 mmol/L (>180 mg/dL), mmol/L (mg/dL) × minutes/1,000			
Patients, *n*	61	63	72
Mean baseline ± SD	2.4 ± 1.5 (43.6 ± 27.8)	2.5 ± 1.7 (45.1 ± 30.2)	2.4 ± 1.5 (44.0 ± 27.7)
Change from baseline, LSM ± SE (95% CI; *P* value)	0.1 ± 0.2 (1.3 ± 3.2) (−0.3 to 0.4 [−4.9 to 7.5]; 0.68)	−0.4 ± 0.2 (−7.1 ± 3.2) (−0.7 to −0.1 [−13.3 to −0.9]; 0.024)	−0.9 ± 0.2 (−16.4 ± 3.0) (−1.2 to −0.6 [−22.2 to −10.6]; <0.001)

Continued on p. 925

Table 2—Continued

	Placebo (*n* = 93)	Sotagliflozin 200 mg (*n* = 89)	Sotagliflozin 400 mg (*n* = 96)
Difference from placebo ± SE (95% CI; *P* value)		−0.5 ± 0.2 (−8.4 ± 4.2) (−0.9 to −0.01 [−16.7 to −0.2]; 0.045)	−1.0 ± 0.2 (−17.7 ± 4.1) (−1.4 to −0.5 [−25.7 to −9.7]; <0.001)
AUC >13.9 mmol/L (>250 mg/dL), mmol/L (mg/dL) × minutes/1,000			
Patients, *n*	61	63	72
Mean baseline ± SD	0.8 ± 0.8 (14.7 ± 14.5)	0.9 ± 0.9 (16.0 ± 16.3)	0.8 ± 0.8 (14.0 ± 14.5)
Change from baseline, LSM ± SE (95% CI; *P* value)	0.03 ± 0.1 (0.6 ± 1.7) (−0.1 to 0.2 [−2.7 to 3.8]; 0.73)	−0.2 ± 0.1 (−3.0 ± 1.6) (−0.3 to 0.01 [−6.3 to 0.2]; 0.07)	−0.4 ± 0.1 (−6.3 ± 1.5) (−0.5 to −0.2 [−9.4 to −3.3]; <0.001)
Difference from placebo ± SE (95% CI; *P* value)		−0.2 ± 0.1 (−3.6 ± 2.2) (−0.4 to 0.04 [−7.9 to 0.7]; 0.10)	−0.4 ± 0.1 (−6.9 ± 2.1) (−0.6 to −0.1 [−11.1 to −2.7]; 0.001)
AUC <3.9 (<70 mg/dL), mmol/L (mg/dL) × minutes/1,000			
Patients, *n*	61	63	72
Mean baseline ± SD	0.1 ± 0.1 (1.2 ± 1.4)	0.1 ± 0.1 (1.2 ± 1.6)	0.1 ± 0.1 (1.1 ± 1.7)
Change from baseline, LSM ± SE (95% CI; *P* value)	−0.002 ± 0.01 (−0.04 ± 0.2) (−0.02 to 0.02 [−0.4 to 0.3]; 0.81)	−0.006 ± 0.01 (−0.1 ± 0.2) (−0.02 to 0.01 [−0.4 to 0.2]; 0.57)	−0.01 ± 0.01 (−0.2 ± 0.2) (−0.03 to 0.01 [−0.4 to 0.2]; 0.35)
Difference from placebo ± SE (95% CI; *P* value)		−0.006 ± 0.01 (−0.1 ± 0.2) (−0.03 to 0.02 [−0.5 to 0.4]; 0.81)	−0.006 ± 0.01 (−0.1 ± 0.2) (−0.03 to 0.02 [−0.5 to 0.3]; 0.61)
AUC <3.0 mmol/L (<55 mg/dL), mmol/L (mg/dL) × minutes/1,000			
Patients, *n*	61	63	72
Mean baseline ± SD	0.02 ± 0.03 (0.3 ± 0.5)	0.02 ± 0.04 (0.3 ± 0.7)	0.02 ± 0.04 (0.3 ± 0.7)
Change from baseline, LSM ± SE (95% CI; *P* value)	−0.006 ± 0.006 (−0.1 ± 0.1) (−0.01 to 0.006 [−0.2 to 0.1]; 0.33)	−0.006 ± 0.006 (−0.1 ± 0.1) (−0.01 to 0.006 [−0.2 to 0.1]; 0.26)	−0.006 ± 0.006 (−0.1 ± 0.1) (−0.01 to 0.001 [−0.2 to 0.02]; 0.10)
Difference from placebo ± SE (95% CI; *P* value)		−0.0006 ± 0.006 (−0.01 ± 0.1) (−0.01 to 0.01 [−0.2 to 0.1]; 0.91)	−0.002 ± 0.006 (−0.03 ± 0.1) (−0.01 to 0.006 [−0.2 to 0.1]; 0.66)
PPG			
2-h PPG, mmol/L (mg/dL)§			
Patients, *n* (per-protocol population)	57	59	62
Mean baseline ± SD	12.9 ± 5.1 (232 ± 93)	12.3 ± 5.4 (221 ± 96)	11.4 ± 5.1 (205 ± 91)
Change from baseline, LSM ± SE (95% CI; *P* value)	−0.2 ± 0.6 (−3.6 ± 10.4) (−1.3 to 0.9 [−24.2 to 16.9]; 0.73)	−2.1 ± 0.6 (−38.3 ± 10.5) (−3.3 to −1.0 [−59.0 to −17.6]; <0.001)	−3.0 ± 0.6 (−53.3 ± 10.1) (−4.1 to −1.9 [−73.2 to −33.4]; <0.001)
Difference from placebo ± SE (95% CI; *P* value)		−1.9 ± 0.7 (−34.6 ± 13.2) (−3.4 to −0.5 [−60.6 to −8.6]; 0.009)	−2.8 ± 0.7 (−49.7 ± 13.1) (−4.2 to −1.3 [−75.5 to −23.9]; <0.001)
Glycemic variability			
CV, %†			
No. patients	61	63	72
Mean baseline ± SD	37.7 ± 5.9	37.9 ± 7.3	35.8 ± 7.4
Change from baseline, LSM ± SE (95% CI; *P* value)	−1.0 ± 0.9 (−2.7 to 0.8; 0.27)	−2.5 ± 0.9 (−4.2 to −0.7; 0.005)	−2.0 ± 0.8 (−3.7 to −0.4; 0.016)
Difference from placebo ± SE (95% CI; *P* value)		−1.5 ± 1.2 (−3.8 to 0.8; 0.20)	−1.0 ± 1.1 (−3.3 to 1.2; 0.36)

Continued on p. 926

Table 2—Continued

	Placebo (n = 93)	Sotagliflozin 200 mg (n = 89)	Sotagliflozin 400 mg (n = 96)
SD, mmol/L (mg/dL)†			
Patients, *n*	61	63	72
Mean baseline ± SD	3.6 ± 0.8 (65 ± 15)	3.7 ± 0.8 (66 ± 14)	3.4 ± 0.8 (62 ± 14)
Change from baseline, LSM ± SE (95% CI; *P* value)	−0.1 ± 0.1 (−1.5 ± 1.7) (−0.3 to 0.1 [−4.8 to 1.9]; 0.40)	−0.3 ± 0.1 (−6.0 ± 1.7) (−0.5 to −0.2 [−9.4 to −2.7]; <0.001)	−0.5 ± 0.1 (−8.2 ± 1.6) (−0.6 to −0.3 [−11.4 to −5.1]; <0.001)
Difference from placebo ± SE (95% CI; *P* value)		−0.3 ± 0.1 (−4.6 ± 2.3) (−0.5 to −0.01 [−9.0 to −0.2]; 0.042)	−0.4 ± 0.1 (−6.8 ± 2.2) (−0.6 to −0.1 [−11.1 to −2.5]; 0.002)
Mean daily glucose, mmol/L (mg/dL)			
Patients, *n*	61	63	72
Mean baseline ± SD	9.7 ± 1.7 (175 ± 31)	9.8 ± 1.8 (176 ± 33)	9.9 ± 1.8 (178 ± 32)
Change from baseline, LSM ± SE (95% CI; *P* value)	0.1 ± 0.2 (2.0 ± 3.6) (−0.3 to 0.5 [−5.0 to 9.1]; 0.57)	−0.3 ± 0.2 (−5.9 ± 3.6) (−0.7 to 0.1 [−12.9 to 1.1]; 0.10)	−0.9 ± 0.2 (−16.9 ± 3.4) (−1.3 to −0.6 [−23.5 to −10.3]; <0.001)
Difference from placebo ± SE (95% CI; *P* value)		−0.4 ± 0.3 (−7.9 ± 4.7) (−1.0 to 0.1 [−17.2 to 1.3]; 0.09)	−1.1 ± 0.3 (−18.9 ± 4.6) (−1.6 to −0.6 [−27.9 to −9.9]; <0.001)
MAGE, mmol/L (mg/dL)			
Patients, *n*	61	63	72
Mean baseline ± SD	9.2 ± 2.0 (166 ± 35)	9.1 ± 1.9 (163 ± 34)	8.8 ± 2.0 (158 ± 36)
Change from baseline, LSM ± SE (95% CI; *P* value)	−0.2 ± 0.2 (−3.0 ± 4.2) (−0.6 to 0.3 [−11.3 to 5.4]; 0.48)	−0.9 ± 0.2 (−15.7 ± 4.2) (−1.3 to −0.4 [−24.0 to −7.4]; <0.001)	−1.4 ± 0.2 (−25.1 ± 3.9) (−1.8 to −1.0 [−32.8 to −17.3]; <0.001)
Difference from placebo ± SE (95% CI; *P* value)		−0.7 ± 0.3 (−12.7 ± 5.5) (−1.3 to −0.1 [−23.6 to −1.8]; 0.022)	−1.2 ± 0.3 (−22.1 ± 5.4) (−1.9 to −0.7 [−32.7 to −11.5]; <0.001)
CGM hypoglycemic events			
Hypoglycemic events per patient per day, <3.9 mmol/L (<70 mg/dL)‖			
Patients, *n*	61	63	72
Mean baseline ± SD	1.1 ± 0.8	1.1 ± 0.7	0.9 ± 0.7
Change from baseline, LSM ± SE (95% CI; *P* value)	0.03 ± 0.1 (−0.2 to 0.2; 0.73)	−0.2 ± 0.1 (−0.4 to 0.03; 0.11)	−0.002 ± 0.1 (−0.2 to 0.2; 0.98)
Difference from placebo ± SE (95% CI; *P* value)		−0.2 ± 0.1 (−0.5 to 0.1; 0.15)	−0.04 ± 0.1 (−0.3 to 0.2; 0.78)
Hypoglycemic events per patient per day, <3.0 mmol/L (<55 mg/dL)‖			
Patients, *n*	61	63	72
Mean baseline ± SD	0.5 ± 0.5	0.4 ± 0.5	0.4 ± 0.4
Change from baseline, LSM ± SE (95% CI; *P* value)	0.1 ± 0.1 (−0.03 to 0.2; 0.14)	0.003 ± 0.1 (−0.1 to 0.1; 0.96)	−0.04 ± 0.1 (−0.2 to 0.1; 0.44)
Difference from placebo ± SE (95% CI; *P* value)		−0.1 ± 0.1 (−0.3 to 0.1; 0.28)	−0.1 ± 0.1 (−0.3 to 0.02; 0.09)

LSM, least squares mean. *Conducted in a subgroup of patients who underwent blinded CGM with a Dexcom G4 monitor (Dexcom Inc.) during specified 1-week intervals throughout the first 24 weeks. †Included in 2017 international consensus on use of CGM (3). The consensus group identified hypoglycemia cutoffs as follows: level 1, <3.9–3.0 mmol/L (<70–54 mg/dL); level 2, <3.0 mmol/L (<54 mg/dL). ‡Assuming 100% daily CGM data were available for analysis, 1.0% of daily CGM time = 0.24 h. §To assess the change in PPG under standardized conditions, the per-protocol population was selected; 2-h plasma PPG values were obtained after a standardized mixed meal. ‖A CGM hypoglycemic event was defined by CGM sensor values of at least 10 continuous minutes below the thresholds of 3.9 mmol/L (70 mg/dL) or 3.0 mmol/L (55 mg/dL).

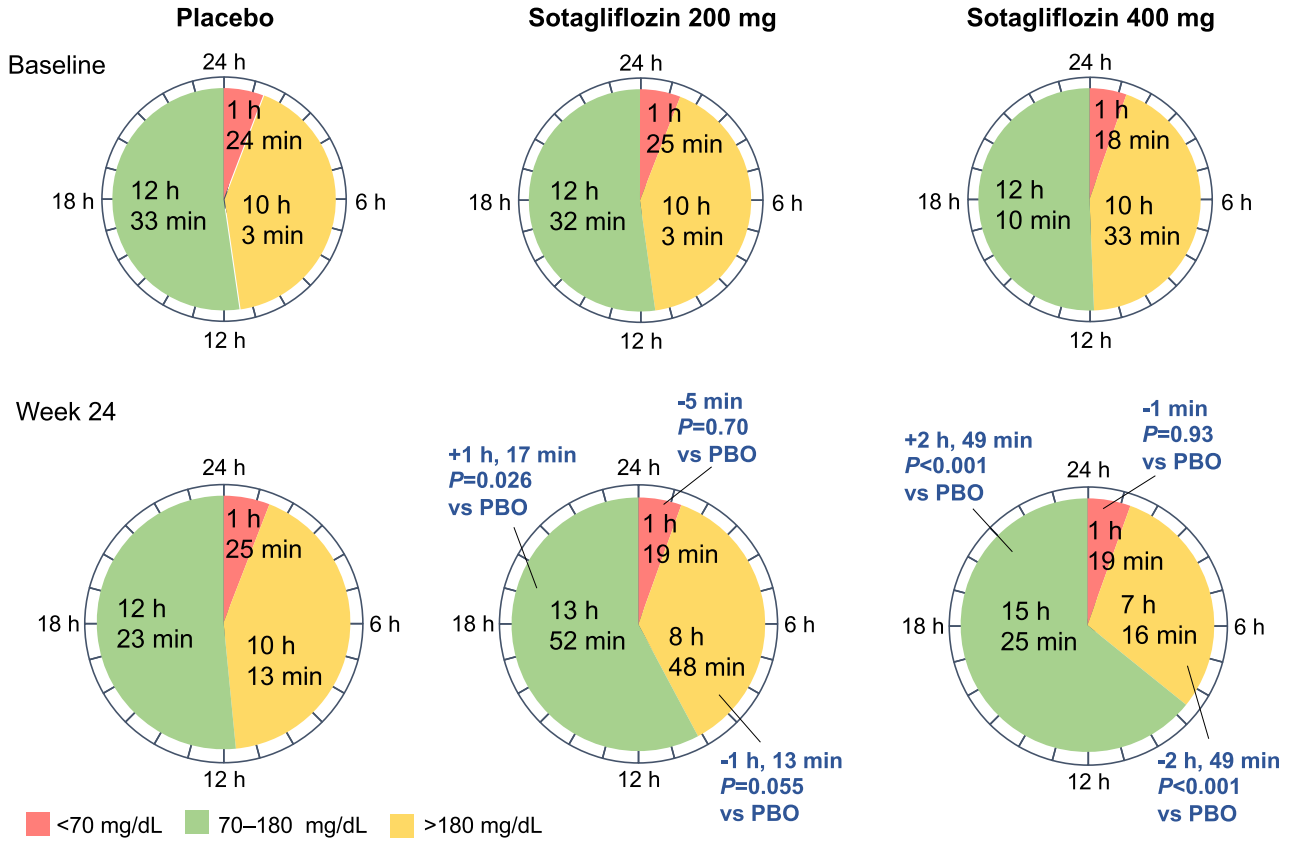

Figure 1—Time spent in glycemic ranges of <3.9, 3.9–10.0, and >10.0 mmol/L (<70, 70–180, and >180 mg/dL) among patients monitored with blinded CGM. Time values were calculated by multiplying values for the percentage of time spent in specified ranges (Table 2) by 0.24 (assumes 100% data capture) to determine the number of hours, and the resulting right-of-decimal values by 60 to determine the number of minutes (e.g., the baseline percentage of TIR of 3.9–10.0 mmol/L in the placebo group was 52.3% × 0.24 = 12.552 h; 0.552 × 60 = 33 min). PBO, placebo.

low-dose sotagliflozin (200 mg). These observations are consistent with dose-dependent decreases in weight and blood pressure reported from inTandem1 and inTandem2 (12,13). In the main studies, the higher dose of sotagliflozin was also associated with more DKA and mechanism of action–related adverse events including diarrhea (SGLT1 inhibition) and genital mycotic infection (SGLT2 inhibition) (12,13). The evaluation of week 24 versus baseline CGM data for individual patients at various baseline HbA_{1c} thresholds further demonstrated dose-related increases in TIR and decreases in time spent with glucose at <3.9 or >10.0 mmol/L, suggesting that sotagliflozin may provide a higher quality of HbA_{1c} at the HbA_{1c} thresholds studied, in a dose-dependent manner (26).

An international CGM consensus group identified <3.0 and >13.9 mmol/L (<54 and >250 mg/dL) as action thresholds for patients to avoid serious health consequences from hypoglycemia or hyperglycemia (the hyperglycemia action threshold was established in patients not treated with SGLT inhibitors) (3). The time spent below the <3.0 mmol/L threshold was not increased, and the time spent at >13.9 mmol/L significantly decreased by nearly an hour per day with sotagliflozin 200 mg and nearly 2 h with the 400 mg dose. Furthermore, a CGM AUC >13.9 mmol/L decreased significantly with high-dose sotagliflozin treatment. Time spent at >10.0 mmol/L (>180 mg/dL) decreased significantly with both dose levels by more than an hour with the lower dose and by nearly 3 h with the higher dose.

HbA_{1c} is typically measured at 3-month intervals, and SMBG profiles are often insufficient to allow treatment intensification without an increased risk for hypoglycemia. The present analyses of CGM data during combination therapy with sotagliflozin and insulin show how sotagliflozin has the potential to simultaneously improve glycemia and reduce the risk for hypoglycemia, thereby increasing the TIR. CGM profiles of patients treated with sotagliflozin and placebo with similar baseline HbA_{1c} values show a distinct improvement in the amplitude of glycemic excursions. Erratic swings of glucose levels out of the target range have been associated with patient-related outcomes such as perceived poor health and functioning or increased anxiety or absenteeism (27–29). In a study comparing basal-bolus to premixed insulin therapy, improved glycemic variability was associated with improved patient-reported outcomes (30). Likewise, the improvements in glycemic variability shown in this study may be related to significant improvements in patient-reported outcomes reported in the pivotal studies of sotagliflozin (12,13).

Improvements in TIR have been reported with other SGLT2 inhibitors (14,31). These studies were performed in patients with higher baseline mean HbA_{1c} and glucose values than in the current study; therefore, improvements in TIR may have been amplified. In a small CGM substudy involving 89 patients with type 1 diabetes, 18 months of canagliflozin treatment increased the time spent with glucose values between 3.9 and

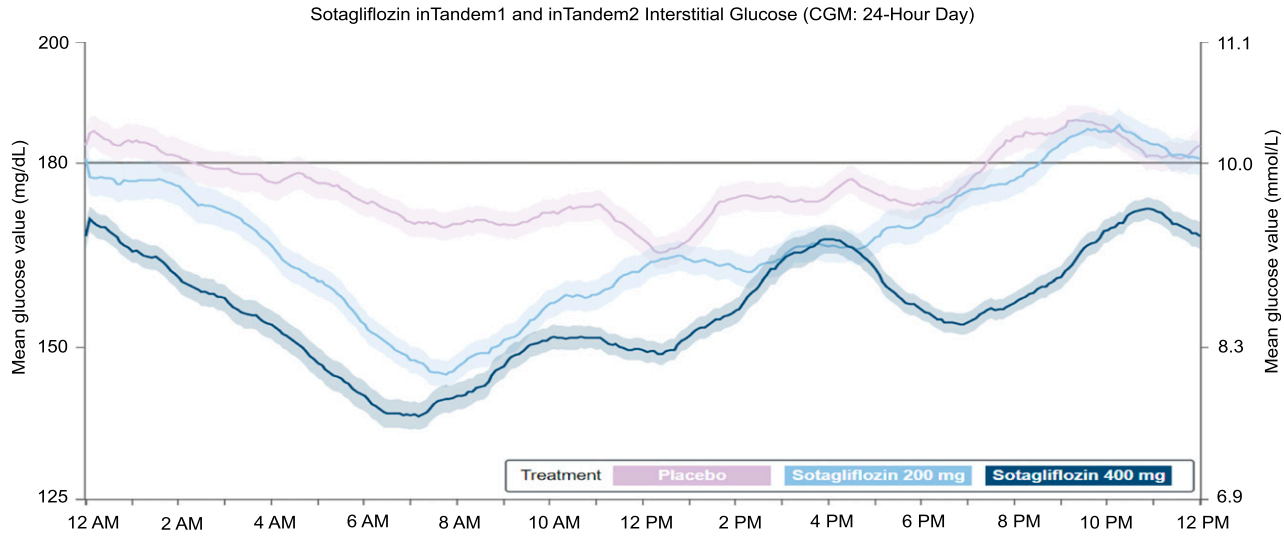

Figure 2—Average day represented by a 24-h CGM tracing consisting of interstitial glucose readings collected every 5 min from the week prior to the week 24 visit. The figure shows data collected from midnight (0000 h). The actual start time for 24-h readings may vary for each patient. Solid lines represent mean values from each treatment group (light purple = placebo [*n* = 93]; light blue = sotagliflozin 200 mg [*n* = 89]; dark blue = sotagliflozin 400 mg [*n* = 96]); shaded areas represent ± 1 SEM. Top of the target CGM range = 10.0 mmol/L (180 mg/dL). The decline in mean glucose value from 12:00 to 6:00 A.M. in patients treated with sotagliflozin was not associated with a significant increase in nocturnal hypoglycemia. Ambulatory glucose profiles (AGPs) for CGM data collected from each treatment group in the week prior to week 24 appear in the Supplementary Data. Patient and aggregate visualizations of CGM data, as well as AGPs, were generated by Cenduit, LLC (Durham, NC) and any reproductions must acknowledge Cenduit.

10.0 mmol/L (70 and 180 mg/dL), decreased the time spent above and below this range, and modestly improved glycemic variability indices (31). After 24 weeks in the DEPICT-1 Trial, dapagliflozin significantly reduced CGM mean glucose and MAGE and increased the percentage of time spent within the target range of 3.9–10.0 mmol/L (14). The effect of canagliflozin and dapagliflozin on PPG in the type 1 diabetes population has not been reported, although this was a prespecified end point of the studies (14,31).

Across the inTandem program, sotagliflozin treatment was associated with significant decreases in bolus insulin doses of 7–12% at 24 weeks (11–13). Nevertheless, sotagliflozin significantly reduced PPG by up to 2.8 mmol/L (50 mg/dL). A comparison of canagliflozin and dapagliflozin suggested that SGLT1 inhibition in the proximal intestine may confer greater PPG lowering (32). This finding is consistent with preclinical and clinical evidence showing that SGLT1 inhibition delays and reduces postprandial hyperglycemia and also increases the release of glucagon-like peptide 1 and polypeptide tyrosine (18,19,33).

Measures to reduce postprandial hyperglycemia usually increase the risk for hypoglycemia (34,35). Sotagliflozin-associated PPG reductions occurred without an increase in hypoglycemia as defined by CGM hypoglycemic events per day, percentage of time per day, or CGM AUC below the threshold of 3.0 mmol/L (<55 mg/dL) or 3.9 mmol/L (<70 mg/dL). A decline in mean glucose value from 12:00 to 6:00 A.M. was observed in this substudy but was not associated with an increased risk of nocturnal hypoglycemia. A decrease in mean glucose level between 12:00 and 6:00 A.M., but no increase in nocturnal hypoglycemia at week 24, was also observed with dapagliflozin (36). In the full inTandem1 and inTandem2 study populations, the incidence of documented hypoglycemia (by SMBG) and severe hypoglycemia was numerically lower with sotagliflozin 400 mg than with 200 mg (12,13).

A key limitation of this study was the masking of CGM data from investigators and patients, which may have resulted in an underrepresentation of the efficacy of sotagliflozin in patients with type 1 diabetes who use CGM. Also, the study required only limited use of masked CGM at 1-week intervals. The substudy population also predominantly comprised non-Hispanic whites, and the applicability of these results to other ethnic and racial groups is unclear.

In summary, when used in combination with optimized insulin in patients with type 1 diabetes, sotagliflozin significantly improved multiple measures of glycemic control beyond HbA_{1c}. Compared with placebo, sotagliflozin-treated patients spent 1.3–2.8 h more time per day within the range of 3.9–10.0 mmol/L (70–180 mg/dL), with corresponding decreases in time spent at glucose levels of >10.0 mmol/L (>180 mg/dL). Decreases in PPG were accompanied by lower mean daily glucose and reductions in SD and the amplitude of glycemic excursions, while there was no increase in hypoglycemia. These data support the use of sotagliflozin in combination with insulin for the treatment of type 1 diabetes.

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Author Contributions. T.D., J.A.K., D.K.M., and A.L.P. conceived and conducted the study, including acquisition, analysis, and interpretation of the data; participated in the drafting and critical revision of the manuscript; had full access to the data in the study; and had final responsibility for the decision to publish. B.C., J.B.B., S.K.G., and J.R. conducted the study, including acquisition, analysis, and interpretation of data; participated in the drafting and critical revision of the manuscript; had full access to the data in the study; and had final responsibility for the decision to publish. P.B. participated in the drafting and critical revision of the manuscript; conceived the study, including analysis and interpretation of data; contributed to the statistical design, analysis, and interpretation of data; oversaw the statistical analyses conducted by the independent statistician; reviewed the data quality prior to database lock; was involved in approving the protocol and its amendments; had full access to the data in the study; and had final responsibility for the decision to publish. S.S. conceived and conducted the study, including acquisition, analysis, and interpretation of the data; participated in the drafting and critical revision of the manuscript; reviewed the data quality prior to database lock; and had full access to the data in the study and final responsibility for the decision to publish. P.S. participated in the drafting and critical revision of the manuscript; conceived and conducted the study, including acquisition, analysis, and interpretation of data; reviewed the data quality prior to database lock; was involved in approving the protocol and its amendments; had full access to the data in the study; and had final responsibility for the decision to publish. T.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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