Received: 22 January 2019 | Revised: 20 June 2019 | Accepted: 26 June 2019

DOI: 10.1111/dom.13825

ORIGINAL ARTICLE

WILEY

Dose-dependent glycometabolic effects of sotagliflozin on type 1 diabetes over 12 weeks: The inTandem4 trial

Claire Baker MD[1] | Suman Wason MD[2] | Phillip Banks MS[2] | Sangeeta Sawhney MD[2] | Anna Chang MD[3] | Thomas Danne MD[4] | Diane Gesty-Palmer MD[2] | Jake A. Kushner MD[5] | Darren K. McGuire MD[6] | Frank Mikell MD[7] | Mark O'Neill MS[2] | Anne L. Peters MD[8] | Paul Strumph MD[2]

[1]Diabetes and Endocrine Associates, Omaha, Nebraska

[2]Lexicon Pharmaceuticals, Inc., The Woodlands, Texas

[3]John Muir Physician Network, Concord, California

[4]Department of Diabetes, Endocrinology, and Clinical Research, Children's and Youth Hospital Auf der Bult, Hannover Medical School, Hannover, Germany

[5]McNair Interests & McNair Medical Institute, Houston, Texas

[6]Department of Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, Texas

[7]Chief Physician Executive, Hospital Sisters Health System, Springfield, Illinois

[8]Department of Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, California

Correspondence
Claire Baker, MD, Diabetes and Endocrine Associates, P.C., 7831 Chicago Court, Omaha, NE 68114.
Email: doc.baker@deomaha.com

Present address
Diane Gesty-Palmer, BioCryst Pharmaceuticals, Durham, North Carolina.
Paul Strumph, Metavant Sciences, Inc., Durham, North Carolina.

Funding information
This study was supported and conducted by Lexicon Pharmaceuticals, Inc., and Sanofi entered a license agreement effective November 2015 and are collaborating on the development and commercialization of sotagliflozin

Peer Review
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.13825.

Abstract

Aims: To assess the dose-related effects of sotagliflozin, a novel dual inhibitor of sodium-glucose co-transporters-1 and -2, in type 1 diabetes (T1D).

Materials and methods: In this 12-week, multicentre, randomized, double-blind, placebo-controlled dose-ranging trial, adults with T1D were randomized to once-daily placebo (n = 36) or sotagliflozin 75 mg (n = 35), 200 mg (n = 35) or 400 mg (n = 35). Insulin was maintained at baseline doses. The primary endpoint was least squares mean (LSM) change in glycated haemoglobin (HbA1c) from baseline. Other endpoints included proportion of participants with ≥0.5% HbA1c reduction and assessments of 2-hour postprandial glucose (PPG), weight, and urinary glucose excretion (UGE).

Results: From a mean baseline of 8.0% ± 0.8% (full study population), placebo-adjusted LSM HbA1c decreased by 0.3% (P = .07), 0.5% (P < .001) and 0.4% (P = .006) with sotagliflozin 75 mg, 200 mg and 400 mg, respectively, at week 12. In the placebo and sotagliflozin 75 mg, 200 mg and 400 mg groups, 33.3%, 37.1%, 80.0% and 65.7% of participants achieved an HbA1c reduction ≥0.5%. Placebo-adjusted PPG decreased by 22.2 mg/dL (P = .28), 28.7 mg/dL (P = .16) and 50.2 mg/dL (P = .013), UGE increased by 41.8 g/d (P = .006), 57.7 g/d (P < .001) and 70.5 g/d (P < .001), and weight decreased by 1.3 kg (P = .038), 2.4 kg (P < .001) and 2.6 kg (P < .001) with sotagliflozin 75 mg, 200 mg and 400 mg, respectively. One case of severe hypoglycaemia occurred in each sotagliflozin group and one case of diabetic ketoacidosis (DKA) occurred with sotagliflozin 400 mg.

Conclusions: Combined with stable insulin doses, sotagliflozin 200 mg and 400 mg improved glycaemic control and weight in adults with T1D. Sotagliflozin 400 mg reduced PPG levels. UGE increased with all sotagliflozin doses. Rates of severe hypoglycaemia and DKA were low (NCT02459899).

KEYWORDS
glycaemic control, insulin therapy, phase 2 study, randomized trial, SGLT2 inhibitor, type 1 diabetes

1 | INTRODUCTION

In type 1 diabetes (T1D), hypoglycaemia, wide glucose fluctuations, and weight gain frequently increase long-term health risks.[1-5] The challenge of reducing glycaemia without incurring these side effects has prompted numerous investigations into insulin adjunctive medical therapies, which have had little success.[6-10] Although pramlintide is approved as an insulin adjunct and may reduce weight as well as glycated haemoglobin (HbA1c), it requires multiple daily injections (MDI) and may increase the risk of severe hypoglycaemia.[1,10,11] Oral sodium-glucose co-transporter (SGLT) inhibitors, when combined with insulin for the treatment of T1D, represent a possible approach to improving glycaemic control without increasing weight or hypoglycaemic events.[12-17]

Sotagliflozin (LX4211) is a novel dual inhibitor of SGLT1 and SGLT2. Similar to selective SGLT2 inhibitors marketed for the treatment of T2D, sotagliflozin decreases renal glucose reabsorption through SGLT2 inhibition, which has been shown to improve glycaemic control via reduction in HbA1c, as well as reducing body weight and systolic blood pressure (SBP). In addition, local SGLT1 inhibition reduces the glucose absorption rate in the proximal gastrointestinal tract, causing a blunting and delay of post-meal glucose increases, which leads to reduced postprandial glucose excursions that are difficult to control, especially in patients with T1D.[18-20]

This phase 2 dose-ranging study (NCT02459899) evaluated the effects of three doses of sotagliflozin combined with stable doses of insulin delivered as MDI or continuous subcutaneous insulin infusion (CSII) in adults with T1D. The primary outcome was change in HbA1c over 12 weeks.

2 | MATERIALS AND METHODS

2.1 | Design overview

This phase 2b, multicentre, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study was conducted at 17 sites in the United States and evaluated the efficacy of 12 weeks of oral sotagliflozin 75, 200 or 400 mg once daily in combination with insulin in adults with inadequately controlled T1D. Randomization was stratified by insulin delivery method (MDI or CSII). To qualify for randomization, patients had to demonstrate ≥80% adherence to taking the expected amount of placebo tablets during a 2-week placebo run-in period.

Institutional review boards approved the protocol and consent forms. All participants provided written informed consent. An independent clinical endpoint committee, blinded to trial treatment, adjudicated the following: severe hypoglycaemia; metabolic acidosis, including diabetic ketoacidosis (DKA); major adverse cardiovascular events; drug-induced liver injury; and deaths. An independent data monitoring committee reviewed trial conduct and patient safety. An independent statistician performed the statistical analysis.

2.2 | Study population

The study included men and non-pregnant women aged ≥18 years with T1D whose HbA1c level was 7.0% to 10.0% at screening. Either MDI or CSII could be used for insulin delivery, although the method of administration could not have changed within 3 months prior to study start and the basal insulin dose could not have changed by more than ±20% within 2 weeks of study start. Patients with serum beta-hydroxy-butyrate (BHB) levels >0.6 mmol/L or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at screening were excluded. All inclusion and exclusion criteria are listed in the Supporting Information (Appendix S1).

2.3 | Interventions and procedures

Participants were randomly assigned 1:1:1:1 to placebo or sotagliflozin 75, 200 or 400 mg administered once daily before the first meal of the day, with randomization stratified by mode of insulin administration.

On the morning of day 1, prior to administration of study medication, all participants consumed a standardized mixed meal for breakfast and had blood samples drawn 2 hours later to evaluate postprandial glucose (PPG) levels at baseline, and the same 2-hour standardized mixed meal procedure was administered during the last visit at week 12 after administration of study drug (see Supporting Information, Appendix S2, for details). The study medication was given prior to lunch on day 1 (after the 2-hour PPG test), and bolus insulin was reduced by 30% for this meal on day 1 only.[21]

To minimize the effect of insulin dose changes on glycaemic efficacy in this dose-ranging study, during the 12-week double-blind period, total insulin dose could not exceed the total dose at baseline. Investigators could downtitrate basal or bolus insulin at any time to treat or prevent hypoglycaemia. After downtitration, insulin could be

uptitrated as clinically indicated as long as the total insulin dose did not exceed the baseline level. For prandial insulin given after the lunchtime meal on day 1, investigators could increase the mealtime bolus insulin as needed to control high blood glucose levels in the postprandial period, but the adjusted dose could not exceed the participant's baseline mealtime carbohydrate bolus insulin.

All patients received urine ketone strips and blood BHB meters and strips, as well as instructions on detecting and treating ketosis, urogenital hygiene, and proper hydration. Study centres received recommendations for ketosis and DKA diagnosis and management, as detailed in the phase 3 sotagliflozin trial reports (inTandem1, 2 and 3).[12-14]

2.4 | Endpoints

The primary endpoint was the change in least squares mean (LSM) HbA1c from baseline to week 12. The secondary endpoints were the change from baseline to week 12 in LSM for 2-hour PPG following a standardized mixed-meal tolerance test, body weight measured as absolute and percent change, daily urinary glucose excretion (UGE), and fasting plasma glucose (FPG). HbA1c, weight, UGE and FPG were also assessed at each visit. Other endpoints included assessment of total, basal and bolus insulin doses as a daily average over the week prior to each visit by insulin delivery method (CSII or MDI); the proportion of participants achieving HbA1c reductions ≥0.5%; and the change from baseline in SBP and diastolic blood pressure (DBP).

Safety endpoints included hypoglycaemic events documented by self-monitored blood glucose (SMBG) ≤70 mg/dL, measures of kidney function, clinically significant laboratory results, adverse events (AEs), severe AEs, events of special interest (ie, documented hypoglycaemia [SMBG ≤70 mg/dL], severe hypoglycaemia, acidosis-related events, DKA, genital mycotic infection, urinary tract infection, diarrhoea, bone fracture, and malignancy), and deaths.

2.5 | Statistical methods

Efficacy analyses were based on the modified intention-to-treat (mITT) population, which was defined as all randomized participants who took at least one dose of study drug. The 2-hour PPG levels were evaluated in the mITT and per-protocol (PP) population, which was defined as all patients in the mITT population who took the study drug appropriately at the designated time on day 1 and at the final week 12 visit, whose mealtime bolus insulin dose was approximately the same, based on the carbohydrate content of the standard meal on day 1 and at the week 12 visit, and who consumed ≥50% and same amount of the standardized mixed meal on the testing days.

A mixed-effects model for repeated measures (MMRM) was used for analysis of the primary efficacy endpoint based on the restricted maximum likelihood method for estimation. The analysis model included: fixed, categorical effects of treatment; insulin delivery method (CSII, MDI); time (study week); baseline HbA1c-by-time interaction; and a treatment-by-time interaction. The adjusted mean change in HbA1c from baseline to week 12 for each treatment group was estimated in the framework of this model, as well as the between-group differences (comparing each sotagliflozin group to placebo), and the 95% confidence intervals (CIs) for the adjusted means. Analysis visit windows were applied to all observations, including data collected after the discontinuation of study drug, to determine the values to be used in the MMRM. The primary treatment comparison was based on a linear trend test statistic defined by the use of orthogonal contrast coefficients. Additional analyses were made by testing each sotagliflozin treatment group versus placebo. Analyses of the secondary and other efficacy endpoints were based on the mITT population, except for PPG, which is based on the PP population because 2-hour blood glucose is highly dependent on meal consumed, insulin dose, and whether study drug was taken as directed in the protocol.

For continuous endpoints, MMRM, as specified for the primary efficacy analysis, or analysis of covariance (ANCOVA) models were used, with the corresponding baseline value (interaction with time, if MMRM) in the model. The choice in statistical models depended on whether the measurement process was over multiple time points (MMRM) or at a single time point (ANCOVA). For binary endpoints, a Cochran–Mantel–Haenszel test, stratified by the insulin delivery method was used. Missing observations at week 12 were imputed as non-response. In addition, 95% CIs for the difference between two proportions contrasting each sotagliflozin group versus placebo were calculated based on the asymptotics of the Wald test statistic.

The summary of the inferential statistics was to include the linear trend *P* value, LSM, standard error (SE) of the estimates, *P* values, and two-sided CIs. These statistics were to be provided for the within-treatment group changes from baseline and for the comparison of each sotagliflozin group versus placebo for the change from baseline scores.

Safety events were analysed using descriptive statistics by treatment group.

3 | RESULTS

Between July 2015 and August 2016, 141 people with T1D were randomly assigned to placebo (n = 36), sotagliflozin 75 mg (n = 35), sotagliflozin 200 mg (n = 35), and sotagliflozin 400 mg (n = 35), and 130 completed 12 weeks of treatment (Figure 1). Seventy-three participants (52%) received insulin by CSII; 68 participants (48%) used MDI. Baseline demographics were comparable between treatment groups (Table 1).

3.1 | Glucose control

From a mean baseline HbA1c of 8.0% to 8.1% across the four randomized groups, LSM ± SE HbA1c decreased by 0.4% ± 0.1, 0.6% ± 0.1, 0.8% ± 0.1, and 0.7% ± 0.1 in the placebo and sotagliflozin 75, 200 and 400 mg groups, respectively, at week 12 (Figure 2A). The LSM differences from placebo were −0.3% (95% CI −0.5 to 0.02; *P* = .07) for sotagliflozin 75 mg, −0.5% (95% CI −0.8 to −0.2; *P* < .001) for sotagliflozin 200 mg, and −0.4% (95% CI −0.7 to −0.1; *P* = .006) for sotagliflozin 400 mg. In the placebo and sotagliflozin 75, 200 and 400 mg groups, 33.3%, 37.1%, 80.0% and 65.7% of participants, respectively, achieved HbA1c reductions ≥0.5%, with significant

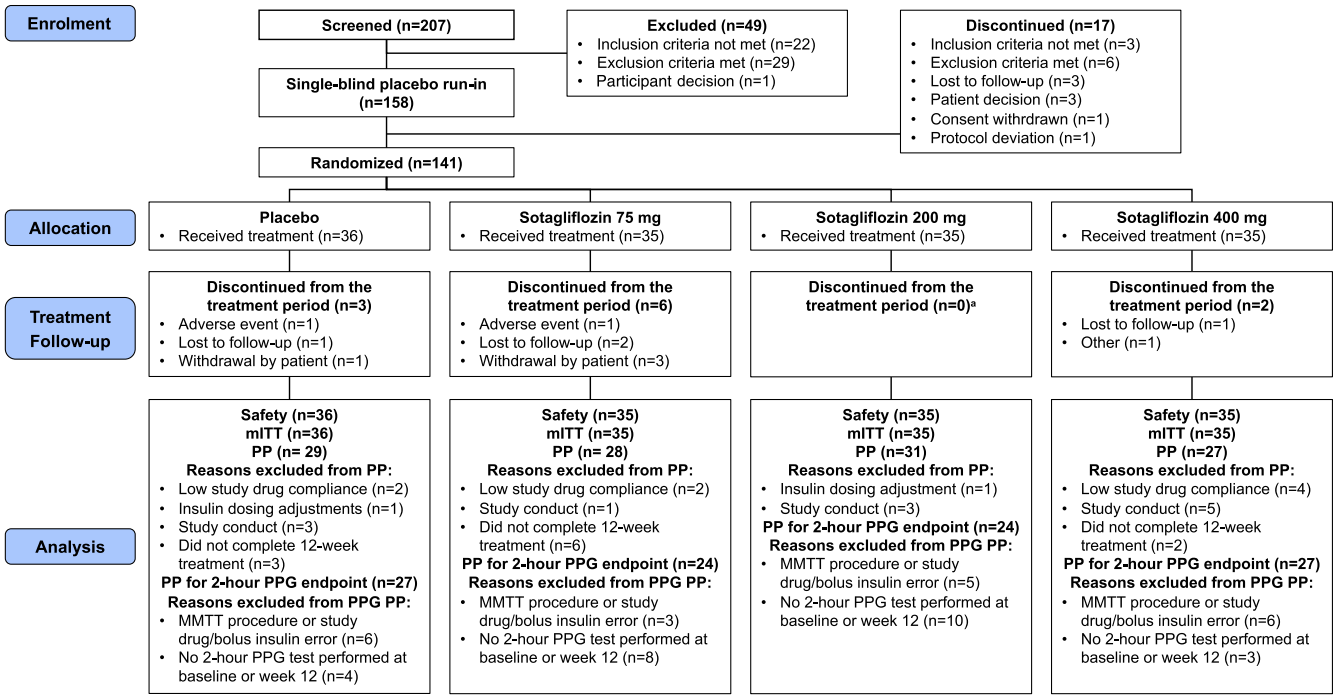

FIGURE 1 Participant disposition. [a]One participant from the sotagliflozin 200 mg group stopped study treatment on day 65 owing to pregnancy, which was not reported as an adverse event. The treatment discontinuation was not recorded in the clinical database and the participant completed the study and was included in the per protocol (PP) population. mITT, modified intent to treat population; MMTT, mixed meal tolerance test; PPG, postprandial glucose

treatment differences in the groups receiving sotagliflozin 200 mg (46.7% [95% CI 26.4 to 67.0]; $P < .001$) and 400 mg (32.4% [95% CI 10.4 to 54.4]; $P = .007$).

Relative to placebo in the PP population (placebo, n = 29; sotagliflozin 75 mg, n = 28; 200 mg, n = 31; 400 mg, n = 27), no significant differences in 2-hour PPG were observed for sotagliflozin 75 mg (−22.2 mg/dL [95% CI −62.7 to 18.2]; $P = .28$) or 200 mg (−28.7 mg/dL [95% CI −69.2 to 11.9]; $P = .16$), but PPG was reduced by 50.2 mg/dL (95% CI −89.7 to −10.8; $P = .013$) with 400 mg (Figure 2B). Results were similar in the mITT population, wherein sotagliflozin 400 mg reduced PPG by 49.5 ± 17.67 (95% CI −84.5 to −14.4; $P = .006$) relative to placebo, but significant differences from placebo were not observed with sotagliflozin 75 or 200 mg.

No significant differences from placebo in FPG at week 12 were observed, with changes of −8.6 mg/dL (95% CI −34.6 to 17.4; $P = .51$), −8.9 mg/dL (95% CI −33.8 to 15.9; $P = .48$), and −21.4 mg/dL (95% CI −46.7 to 3.9; $P = .10$) for the sotagliflozin 75, 200 and 400 mg groups, respectively.

3.2 | Non-glycaemic endpoints

Relative to placebo, LSM UGE increased in a dose-dependent manner by 41.8 g/d (95% CI 12.0 to 71.5; $P = .006$), 57.7 g/d (95% CI 28.3 to 87.2; $P < .001$), and 70.5 g/d (95% CI 41.3 to 99.6; $P < .001$) with sotagliflozin 75, 200 and 400 mg, respectively, from baseline to week 12 (Figure 2C).

Over 12 weeks, LSM body weight decreased by 1.2% (1.3 kg [95% CI −2.5 to −0.08]; $P = .038$), 2.7% (2.4 kg [95% CI −3.6 to −1.2]; $P < .001$), and 2.9% (2.6 kg [95% CI − 3.8 to −1.4]; $P < .001$) in the sotagliflozin 75, 200 and 400 mg groups relative to placebo (Figure 2D).

By week 12, LSM SBP decreased by −6.1 mmHg (95% CI −11.0 to −1.3; $P = .014$) relative to placebo in the sotagliflozin 400 mg group. Placebo-adjusted differences in SBP were not significant from the other sotagliflozin doses, and there were no significant treatment differences in DBP. Only 31 participants had SBP ≥130 mmHg at baseline, with baseline means of 144.8 ± 12.37, 141.0 ± 5.96, 135.3 ± 4.80 and 141.3 ± 8.06 mmHg in the placebo (n = 6) and sotagliflozin 75 mg (n = 5), 200 mg (n = 8) and 400 mg (n = 12) groups, respectively. In this small subgroup, sotagliflozin 400 mg reduced LSM SBP by 14.3 mmHg (95% CI −25.3 to −3.3; $P = 0.013$) relative to placebo. Placebo-adjusted decreases in the sotagliflozin 75 and 200 mg groups of 8.4 and 6.8 mmHg, respectively, were not statistically significant.

Mean absolute changes between baseline and week 12 in eGFR were 1.8 ± 11.0 mL/min/1.73 m^2, −2.2 ± 10.7 mL/min/1.73 m^2, −0.8 ± 7.8 mL/min/1.73 m^2 and 0.02 ± 9.6 mL/min/1.73 m^2 in the placebo and sotagliflozin 75, 200 and 400 mg groups, respectively.

3.3 | Insulin dose

Among participants using CSII and receiving sotagliflozin 400 mg, LSM total daily insulin doses decreased by 8.9 IU/d (95% CI −14.7 to −3.0; $P = .004$) relative to placebo (Figure S1A). Differences

TABLE 1 Baseline demographics

Characteristic	Placebo (n = 36)	Sotagliflozin 75 mg (n = 35)	Sotagliflozin 200 mg (n = 35)	Sotagliflozin 400 mg (n = 35)	Total (N = 141)
Age, years	48.1 ± 11.3	42.4 ± 12.0	47.0 ± 14.0	44.8 ± 15.4	45.6 ± 13.3
Female, n (%)	21 (58.3)	22 (62.9)	15 (42.9)	15 (42.9)	73 (51.8)
Race, n (%)					
White	34 (94.4)	31 (88.6)	31 (88.6)	35 (100.0)	131 (92.9)
Black	0	4 (11.4)	3 (8.6)	0	7 (5.0)
Asian	1 (2.8)	0	1 (2.9)	0	2 (1.4)
Other	1 (2.8)	0	0	0	1 (0.7)
Hispanic ethnicity, n (%)	4 (11.1)	6 (17.1)	6 (17.1)	6 (17.1)	22 (15.6)
Body weight, kg	91.9 ± 19.7	80.0 ± 14.4	82.9 ± 17.1	87.0 ± 20.9	85.5 ± 18.6
BMI, kg/m^2	31.8 ± 5.8	27.4 ± 5.0	28.0 ± 4.7	29.4 ± 5.8	29.2 ± 5.6
BMI ≥30 kg/m^2, n (%)	21 (58.3)	10 (28.6)	9 (25.7)	12 (34.3)	52 (36.9)
SBP, mm Hg	119.6 ± 15.29	114.3 ± 14.98	120.7 ± 12.07	123.7 ± 15.59	119.6 + 14.80
SBP ≥130 mmHg, n (%)	6 (16.7)	5 (14.3)	8 (22.9)	12 (34.3)	31 (22.0)
T1D duration, years	26.9 ± 13.5	22.2 ± 13.0	23.4 ± 13.2	24.0 ± 15.0	24.1 ± 13.7
Insulin delivery method, n (%)					
CSII	19 (52.8)	18 (51.4)	18 (51.4)	18 (51.4)	73 (51.8)
MDI	17 (47.2)	17 (48.6)	17 (48.6)	17 (48.6)	68 (48.2)
Total daily insulin, IU/kg	0.68 ± 0.31	0.65 ± 0.23	0.70 ± 0.30	0.77 ± 0.41	0.70 ± 0.32
Ratio of bolus to total insulin	0.45 ± 0.13	0.39 ± 0.15	0.44 ± 0.13	0.44 ± 0.14	0.43 ± 0.14
HbA1c, %	7.95 ± 0.85	8.00 ± 0.84	8.07 ± 0.93	8.05 ± 0.74	8.02 ± 0.83
HbA1c, mmol/mol	63.4 ± 9.4	64.0 ± 9.2	64.7 ± 10.2	64.5 ± 8.0	64.1 ± 9.1
2-h PPG, mg/dL	215.1 ± 80.1	199.3 ± 80.8	211.8 ± 75.8	208.0 ± 95.2	208.5 ± 82.9
FPG, mg/dL	150.1 ± 80.3	158.3 ± 90.2	142.0 ± 59.2	179.5 ± 94.4	157.4 ± 82.4
UGE, g/day	6.87 ± 13.4	15.83 ± 23.3	6.61 ± 11.9	10.00 ± 25.7	9.99 ± 19.9
BHB	0.22 ± 0.18	0.15 ± 0.09	0.21 ± 0.24	0.21 ± 0.25	0.20 ± 0.20
eGFR, mL/min/1.73 m^2	87.4 ± 18.1	90.6 ± 15.7	91.1 ± 18.4	88.7 ± 19.1	89.4 ± 17.7
Documented hypoglycaemia (SMBG < 70 mg/dL), events/patient/day	0.19 ± 0.20	0.29 ± 0.40	0.31 ± 0.28	0.28 ± 0.36	0.27 ± 0.32

Abbreviations: BHB, beta-hydroxybutyrate; BMI, body mass index; CSII, continuous subcutaneous insulin infusion; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; MDI, multiple daily insulin injections; PPG, postprandial glucose; SBP, systolic blood pressure; SMBG, self-monitored blood glucose; T1D, type 1 diabetes; UGE, urinary glucose excretion.
Data are mean ± SD unless otherwise indicated.

between placebo and the other sotagliflozin doses were not significant. LSM bolus insulin doses also decreased significantly versus placebo in the sotagliflozin 400 mg group (−8.1 IU/d [95% CI −13.1 to −3.2]; P = .002), but not in the other sotagliflozin dose groups (Figure S1A). Changes in basal insulin doses were not significantly different between treatment groups. Among MDI users, insulin doses did not differ significantly between treatment groups (Figure S1B).

3.4 | Hypoglycaemia

Documented hypoglycaemia (≤70 mg/dL) was reported by 35 (97.2%), 33 (94.3%), 32 (91.4%) and 34 participants (97.1%) in the placebo and sotagliflozin 75, 200 and 400 mg groups, respectively (Table 2). The mean number of hypoglycaemic events per patient per day increased from baseline to week 12 by 0.03 ± 0.32 in the placebo group and decreased by 0.03 ± 0.29, 0.06 ± 0.33 and 0.06 ± 0.38 in the sotagliflozin 75, 200 and 400 mg groups, respectively. Positively adjudicated severe hypoglycaemia occurred in one participant from each sotagliflozin group; the event in the sotagliflozin 75 mg group led to study discontinuation (Table 2).

3.5 | BHB, ketosis-related adverse events and DKA

From a mean fasting BHB of ~0.2 mmol/L at baseline, mean fasting BHB had decreased by 0.04 ± 0.19 mmol/L in the placebo group and increased by 0.11 ± 0.22 mmol/L, 0.07 ± 0.30 mmol/L, and

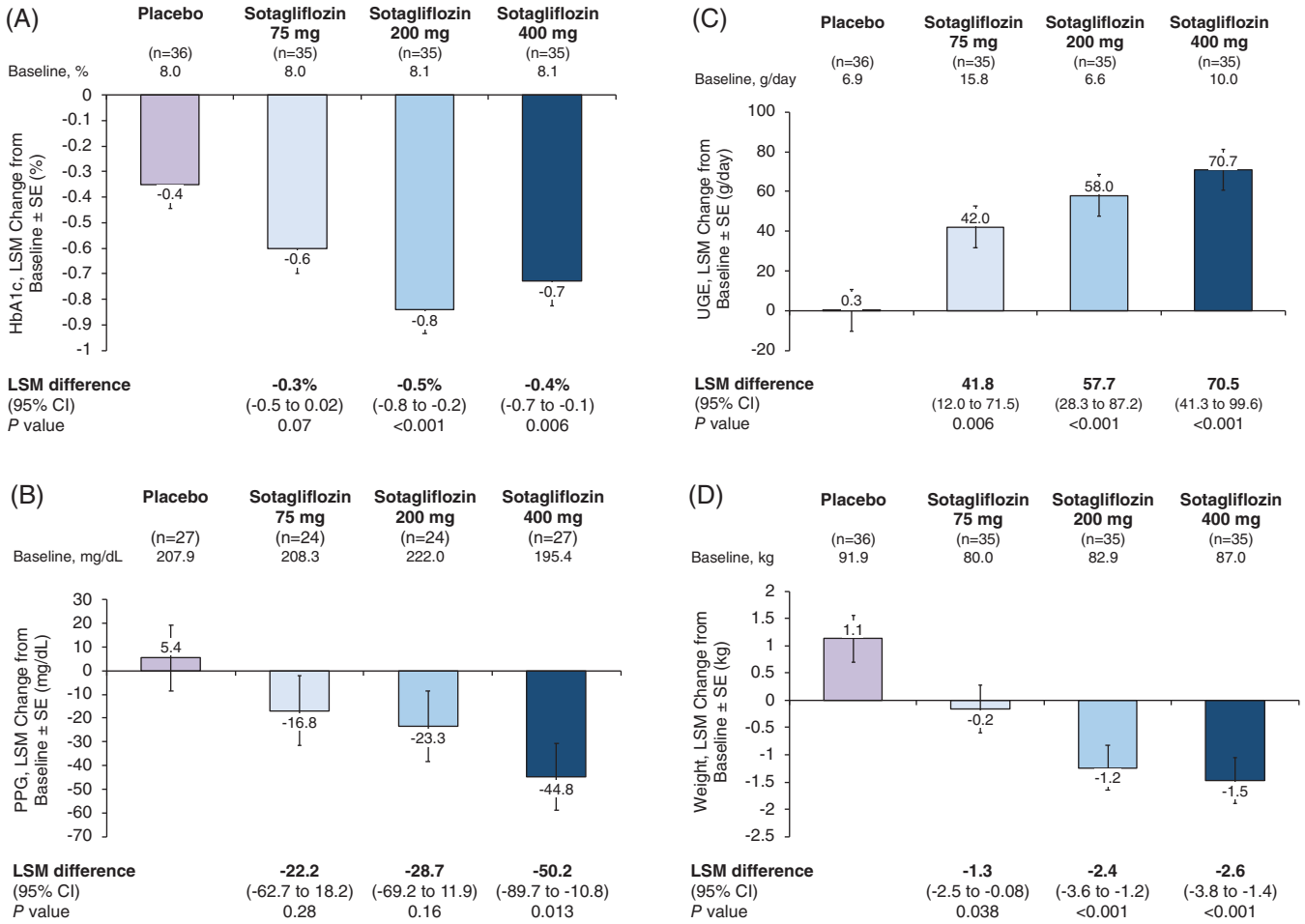

FIGURE 2 Change from baseline to week 12 for the primary endpoint and other selected endpoints. A, Glycated haemoglobin (HbA1c), modified intent to treat (mITT) population. B, 2-hour postprandial glucose (PPG), per-protocol population. C, Urinary glucose excretion (UGE), mITT population. D, Weight, mITT population. LSM, least squares means

0.08 ± 0.32 mmol/L with sotagliflozin 75, 200 and 400 mg, respectively, at week 12 (Figure 3).

Two serious ketosis-related AEs were reported. One in the sotagliflozin 200 mg group was negatively adjudicated as DKA and deemed not related to study drug (a kinked CSII catheter was identified as the probable cause). One positively adjudicated DKA event occurred in a participant with a remote history of DKA (>10 years prior) who was taking sotagliflozin 400 mg. The participant was using an insulin pump, although no evidence of pump malfunction was provided. Blood glucose was 300 mg/dL, peak BHB was 1.8 mmol/L, serum bicarbonate was 12 mEq/L, and anion gap was 21 mEq/L. The event resolved after 2 days. The study drug was permanently discontinued.

3.6 | Other safety data

Table 2 lists key safety data. Overall, AEs occurred in 18 (50.0%), 17 (48.6%), 10 (28.6%), and 12 participants (34.3%) receiving placebo or sotagliflozin 75, 200 and 400 mg, respectively. There were no deaths, major adverse cardiovascular events, or drug-induced liver injuries. One participant in the sotagliflozin 200 mg group became pregnant during the trial, and study drug was discontinued. One serious AE occurred in each treatment group, including: one placebo-treated participant with neurosensory deafness that led to study discontinuation; a traumatic fracture of the fibula and tibia secondary to a fall in a participant taking sotagliflozin 75 mg; and the ketosis and DKA cases described above, which occurred in the sotagliflozin 200 and 400 mg groups, respectively.

After hypoglycaemia, the most common event of special interest occurring in sotagliflozin-treated participants was genital mycotic infection, which occurred in one participant from each sotagliflozin group and no participant taking placebo. No other events of special interest, including diarrhoea, urinary tract infections and bone fractures, were more frequent among sotagliflozin- than placebo-treated participants (Table 2). One participant was diagnosed with bladder transitional cell carcinoma during the 30-day follow-up period.

4 | DISCUSSION

In this phase 2 dose-ranging study of sotagliflozin 75, 200 and 400 mg versus placebo combined with stable insulin therapy in adults with T1D, sotagliflozin 200 and 400 mg significantly reduced HbA1c

TABLE 2 Adverse events and events of special interest

Event, n (%)	Placebo (n = 36)	Sotagliflozin 75 mg (n = 35)	Sotagliflozin 200 mg (n = 35)	Sotagliflozin 400 mg (n = 35)
Any AE	18 (50.0)	17 (48.6)	10 (28.6)	12 (34.3)
Serious AE	1 (2.8)	1 (2.9)	1 (2.9)	1 (2.9)
Severe AE	0	1 (2.9)	0	0
Deaths	0	0	0	0
Events of special interest				
Any	35 (97.2)	34 (97.1)	32 (91.4)	34 (97.1)
Hypoglycaemia				
Documented (SMBG ≤ 70 mg/dL)	35 (97.2)	33 (94.3)	32 (91.4)	34 (97.1)
Positively adjudicated severe hypoglycaemia	0	1 (2.9)	1 (2.9)	1 (2.9)
Acidosis-related event	0	0	1 (2.9)	1 (2.9)
Positively adjudicated DKA	0	0	0	1 (2.9)
Genital mycotic infection	0	1 (2.9)	1 (2.9)	1 (2.9)
Urinary tract infection	2 (5.6)	0	0	1 (2.9)
Diarrhoea	3 (8.3)	0	1 (2.9)	1 (2.9)
Bone fracture	1 (2.8)	2 (5.7)	0	0
Malignancy	0	0	0	1 (2.9)

Abbreviations: AE, adverse event; DKA, diabetic ketoacidosis; SMBG, self-monitored blood glucose.

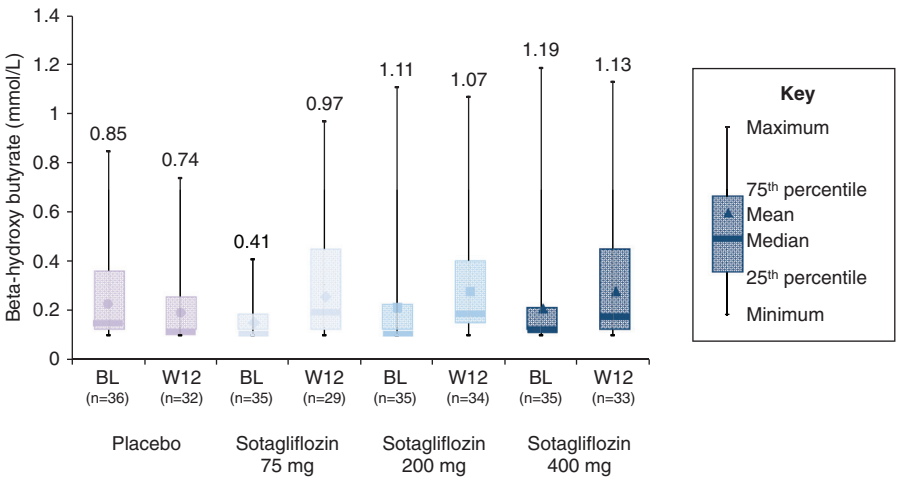

FIGURE 3 Boxplot of beta-hydroxy butyrate (mmol/L) at baseline (BL) and week (W) 12. Mean values are represented by circles (placebo), diamonds (sotagliflozin 75 mg), squares (sotagliflozin 200 mg), or triangles (sotagliflozin 400 mg). Bottom and top of box are first and third quartiles, respectively. Band inside the box represents median values. Bottom and top whiskers are the minimum and maximum, respectively. All medians were <0.2 mmol/L at the end of double-blind treatment, and the means reflected an increase of ~0.1 mmol/L from baseline

and weight compared with placebo. Adjunct therapy with sotagliflozin is meant to address the frequent limitations of insulin therapy in T1D, such as hypoglycaemia, weight gain or frequent glucose fluctuations. This must be balanced against potential dose-dependent side effects associated with this mechanism of action, such as urogenital mycotic infections, diarrhoea, or DKA, making treatment with the lowest efficacious dose desirable. The present study provides evidence that sotagliflozin 75 mg is not sufficiently efficacious for adjunct therapy. In contrast, sotagliflozin 400 mg significantly reduced 2-hour PPG, a finding consistent with SGLT1 inhibition, and was associated with modest reductions in bolus and total daily insulin doses among CSII users. SBP in the total population and the subgroup with SBP

≥130 mmHg at baseline was also significantly decreased with sotagliflozin 400 mg relative to placebo. UGE, consistent with SGLT2 inhibition, increased significantly in a dose-dependent manner with all three sotagliflozin doses relative to placebo. Sotagliflozin was well tolerated, with the frequency of AEs not different from placebo and a low incidence of positively adjudicated severe hypoglycaemia and DKA. Together, these findings suggest that sotagliflozin 200 and 400 mg may elicit similar HbA1c reductions, but the higher dose may provide additional efficacy beyond HbA1c, including reductions in weight, SBP and PPG.

The results of this dose-ranging study were confirmed in three larger, previously published, phase 3 trials, in which sotagliflozin significantly reduced HbA1c, weight and SBP with lower bolus and total insulin doses.[12-14] A pooled analysis of data from the inTandem1 and inTandem2 studies confirmed the PPG reductions seen in the present study.[22] In contrast to the phase 3 studies, insulin doses were maintained at or below baseline levels to isolate the effect of sotagliflozin on HbA1c and other glycaemic endpoints in this study. Downtitration of insulin was allowed to treat or avoid hypoglycaemia, and insulin could be subsequently uptitrated to no more than the total daily dose at baseline; therefore, the significant, placebo-adjusted decreases of 0.4% to 0.5% in HbA1c observed in the present study reflect the effect of sotagliflozin alone. In the inTandem1 and inTandem2 phase 3 trials, maximum tolerated standard of care insulin dosing (optimized insulin) was implemented prior to baseline and continued throughout the 1-year treatment period.[13,14] In the 24-week inTandem3 trial, insulin doses were not optimized prior to baseline, and investigators could adjust insulin doses according to standard of care during the treatment period.[12] Despite these different insulin therapy strategies, the placebo-adjusted primary endpoint HbA1c reductions in all four trials ranged between 0.4% and 0.5% with either dose of sotagliflozin.

Approximately half of individuals with T1D are overweight or obese, and approximately two in five have hypertension.[23,24] The reductions in both weight and SBP seen in the present study and the phase 3 trials are of benefit to many patients with these comorbid conditions.

In phase 2 insulin adjunct studies in T1D, selective SGLT2 inhibitors have demonstrated modest improvements in glucose control and weight but not PPG or SBP. After 18 weeks, canagliflozin 100 mg and 300 mg reduced HbA1c by 0.3% each and weight by 2.6 kg and 4.2 kg, respectively, with total daily insulin dose reductions of 8.9% and 12.9% (driven mainly by basal insulin reductions). Changes in PPG, UGE and SBP were not reported.[16] After 4 weeks of treatment, HbA1c and weight decreased by 0.4% and 1.6 kg, respectively, with empagliflozin 10 mg and by 0.5% and 1.7 kg with empagliflozin 25 mg relative to placebo. PPG was not reported, and treatment differences in SBP were not significant.[25] In a 2-week pilot study with dapagliflozin, no differences were observed in glycaemic endpoints, although there was a trend favouring higher doses of dapagliflozin.[26]

In the separate phase 2 studies, placebo-adjusted increases in UGE were 109 g/d after 7 days of dapagliflozin 10 mg,[26] 109 g/d after 4 weeks of empagliflozin 25 mg[25] and 70 g/d after 12 weeks of sotagliflozin 400 mg. Sotagliflozin's dual action of inhibiting SGLT1 and SGLT2 can be hypothesized to contribute to the lower observed UGE.

The robust reduction in PPG observed with sotagliflozin 400 mg was achieved with only a modest increase in UGE compared with baseline. These results are consistent with reduction of gastrointestinal glucose absorption rate via local SGLT1 inhibition, causing a blunting and delay of PPG increases and resulting in lower UGE than reported with selective SGLT2 inhibitors.[25,26] Similar results were observed in a phase 2 study of sotagliflozin in patients with type 2 diabetes treated with metformin. In this population, glycaemic control improved without corresponding increases in UGE, suggesting a clinically meaningful inhibitory effect on SGLT1 in the gastrointestinal tract.[27] Additionally, in a crossover study involving healthy volunteers, sotagliflozin delayed the rate of appearance of oral glucose, resulting in lower postprandial levels of glucose and insulin. The mechanism was likely a prolonged local inhibition of intestinal SGLT1 that persisted, despite feeding, during at least the first 5 hours after oral sotagliflozin dosing. The sotagliflozin-mediated decrease in glucose-dependent insulinotropic polypeptide levels and increases in glucagon-like peptide 1 and peptide YY levels after oral glucose challenge are consistent with local inhibition of intestinal SGLT1.[28] A lower degree of UGE could potentially lead to a lower risk of volume-related AEs compared to selective SGLT2 inhibitors; however, the incidence of gastrointestinal adverse events may be increased with SGLT1 inhibition. In phase 3 trials with sotagliflozin, mild to moderate and mostly transient diarrhoea was more common among sotagliflozin-treated patients.[12-14] The blunting and delay of PPG increases accompanied by modest UGE is the clinical signature of dual SGLT1 and SGLT2 inhibition, which may also contribute to a lower risk of hypoglycaemia.

Relatively modest UGE may also be relevant to BHB changes by activation of a neural reflex connecting the kidney with pancreatic α cells or indirectly via activation of neuronal centres in the central nervous system that communicate with the α cells.[29] In the empagliflozin trial, no change in BHB was observed in the placebo group, whereas median (mean) values increased by ~0.2 (0.4), ~0.2 (0.2) and ~0.7 (0.4) mmol/L (maximal value of 2.2 mmol/L) with empagliflozin 2.5, 10 and 25 mg, respectively.[25,30] In the present trial, the median values were all below 0.2 mmol/L at the end of double-blind treatment, and the means reflected an increase of ~0.1 mmol/L from baseline. This mean increase of ~0.1 mmol/L is the smallest detectable increase in point-of-care blood BHB meters. The maximum values on sotagliflozin 200 mg and 400 mg were similar at baseline and the end of double-blind treatment, while the highest BHB value (1.2 mmol/L) was recorded at baseline. Similar changes in BHB were seen in the larger sotagliflozin studies.[12-14] If BHB changes with empagliflozin follow the same pattern established in the phase 2 data, the data may reflect differences in ketosis and DKA risk among SGLT inhibitors used as adjuncts to insulin therapy in T1D. In a noteworthy post hoc analysis of the dapagliflozin data, Henry et al[31] demonstrated correlations between higher UGE, greater total daily insulin dose reductions, and BHB elevations.

Risk of DKA is increased with SGLT2 inhibitor therapy in insulin-using patients.[32,33] Whether lower UGE and its relationship with BHB elevations affect the overall risk of DKA with SGLT2 inhibition remains to be determined. Although no head-to-head data are available, rates of DKA appear to be similar in phase 3 studies with

dapagliflozin and sotagliflozin.[12-15,17,34] In the present trial, the single case of positively adjudicated DKA occurred in a participant using CSII receiving sotagliflozin 400 mg. The participant's blood glucose and other laboratory findings met the criteria for classic (as opposed to euglycaemic) DKA, and the investigator report indicated possible insulin pump malfunction, although no supporting details were provided.

Although this phase 2 trial is limited by a small population size and short study duration, its findings are supported by the subsequent larger and longer phase 3 trials of sotagliflozin. Additional research on DKA risk factors and risk mitigation is needed to identify the characteristics of higher-risk patients and to prevent such occurrences. When SGLT inhibitors are administered, monitoring for ketosis, particularly during metabolically stressful situations, is recommended. SGLT inhibitors should be discontinued before scheduled surgical procedures, and patients and clinicians should remain in close consultation regarding other forms of behavioural and physiological stress.[35]

In conclusion, sotagliflozin 200 and 400 mg in combination with stable insulin doses improved glycaemic control and reduced weight in people with T1D who had an eGFR ≥60 mL/min/1.73 m^2 and normal BHB levels at screening. The 400-mg dose elicited efficacy beyond HbA1c, including greater weight loss and reductions in PPG and SBP, accompanied by a modest increase in UGE. The robust reduction in PPG accompanied by modest UGE is the clinical signature of dual SGLT1 and SGLT2 inhibition. Both doses were well tolerated, although more cases of DKA occurred with sotagliflozin than placebo.

ACKNOWLEDGMENTS

We thank the inTandem4 trial investigators, staff, and patients, for their participation and the following contributors for reviewing the manuscript: David Powell, MD, and Kristi Boehm, MS, ELS. Amanda Justice, BA, provided medical writing and editorial support, which was funded by Lexicon Pharmaceuticals, Inc. We thank Covance Inc. (Princeton, New Jersey) for providing the operational execution and medical monitoring of this study.

CONFLICT OF INTEREST

C.B. has received research support from Lexicon, Sanofi, Boehringer Ingelheim, Novo Nordisk, Mylan, Dexcom, Merck/Pfizer, AstraZeneca, Johnson & Johnson and Eli Lilly and Company. S.W., P.B., S.S. and M.O. are employees of Lexicon Pharmaceuticals, Inc. A.C. has no financial interests to disclose. T.D. has acted as consultant, advisory board member, steering committee member or speaker for Abbott, Medtronic, Roche, Lexicon, Menarini, Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Sanofi, Dexcom and Eli Lilly, and has received research grants from Abbott, AstraZeneca, Novo Nordisk, Medtronic and Sanofi. J.A.K. serves as medical director of McNair Interests, a private equity group with investments in T1D and other chronic illnesses and is also an advisor for Sanofi and Lexicon. D.K.M. has received consulting fees and fees for serving on a clinical trial executive committee from Applied Therapeutics, Boehringer Ingelheim, Sanofi US, Novo Nordisk and AstraZeneca, consulting fees from Lilly USA and Metavant Sciences, Ltd, advisory board fees and fees for serving on a clinical trial executive committee from Merck Sharp & Dohme, fees for serving on a data monitoring committee from Janssen Research and Development and GlaxoSmithKline, fees for chairing the steering committees for Lexicon Pharmaceuticals, Inc., and fees for serving on a clinical trial executive or steering committee from Eisai and Esperion. F.M. has no financial interests to disclose. A.L.P. has participated on advisory boards for Abbott Diabetes Care, Becton Dickinson, Bigfoot, Eli Lilly and Company, Livongo, MannKind, Medscape, Merck, Novo Nordisk, Omada Health, Sanofi, and Zafgen; is chair of the T1D steering committee at Lexicon; has participated in a speaker's bureau for NovoNordisk; and has received research funding from Astra Zeneca, Dexcom and MannKind. D.G.-P. and P.S. were employed by Lexicon at the time the study was conducted. D.G.-P. is now employed by BioCryst Pharmaceuticals, and P.S. is now employed by Metavant Sciences, Ltd.

AUTHOR CONTRIBUTIONS

C.B., S.W., S.S., T.D., D.G.-P., J.A.K., D.K.M., A.L.P. and P.S. conceived and conducted the study, including acquisition, analysis and interpretation of data. A.C. and F.M. conducted the study, including acquisition, analysis and interpretation of data. P.B. and P.S. were involved in approving the protocol and its amendments. S.W., P.B., D.G.-P. and P.S. reviewed the data quality prior to database lock. C.B., S.W., P.B., S.S., A.C., T.D., D.G.-P., J.A.K., D.K.M., F.M., M.O., A.L.P. and P.S. participated in the drafting and critical revision of the manuscript. P.B. contributed to the statistical design, analysis and interpretation of data, and oversaw the statistical analyses conducted by the independent statistician. All authors had full access to the data in the study and had final responsibility for the decision to publish.

ORCID

Claire Baker https://orcid.org/0000-0001-7526-2310

REFERENCES

1. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D exchange clinic registry. *Diabetes Care*. 2015;38(6):971-978.
2. McKnight JA, Wild SH, Lamb MJ, et al. Glycaemic control of type 1 diabetes in clinical practice early in the 21st century: an international comparison. *Diabet Med*. 2015;32(8):1036-1050.
3. Weiss R, Garg SK, Bode BW, et al. Hypoglycemia reduction and changes in hemoglobin A1c in the ASPIRE In-Home Study. *Diabetes Technol Ther*. 2015;17(8):542-547.
4. Lu CL, Shen HN, Hu SC, Wang JD, Li CY. A population-based study of all-cause mortality and cardiovascular disease in association with prior history of hypoglycemia among patients with type 1 diabetes. *Diabetes Care*. 2016;39(9):1571-1578.
5. Purnell JQ, Braffett BH, Zinman B, et al. Impact of excessive weight gain on cardiovascular outcomes in type 1 diabetes: results from the diabetes control and complications trial/epidemiology of diabetes interventions and complications (DCCT/EDIC) study. *Diabetes Care*. 2017;40(12):1756-1762.

6. Petrie JR, Chaturvedi N, Ford I, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017;5(8):597-609.
7. Garg SK, Moser EG, Bode BW, et al. Effect of sitagliptin on postprandial glucagon and GLP-1 levels in patients with type 1 diabetes: investigator-initiated, double-blind, randomized, placebo-controlled trial. *Endocr Pract*. 2013;19(1):19-28.
8. Ellis SL, Moser EG, Snell-Bergeon JK, Rodionova AS, Hazenfield RM, Garg SK. Effect of sitagliptin on glucose control in adult patients with type 1 diabetes: a pilot, double-blind, randomized, crossover trial. *Diabet Med*. 2011;28(10):1176-1181.
9. Mathieu C, Zinman B, Hemmingsson JU, et al. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. *Diabetes Care*. 2016;39(10):1702-1710.
10. Bode BW, Garg SK. The emerging role of adjunctive noninsulin antihyperglycemic therapy in the management of type 1 diabetes. *Endocr Pract*. 2016;22(2):220-230.
11. Lyons SK, Hermann JM, Miller KM, et al. Use of adjuvant pharmacotherapy in type 1 diabetes: international comparison of 49,996 individuals in the prospective diabetes follow-up and T1D exchange registries. *Diabetes Care*. 2017;40(10):e139-e140.
12. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med*. 2017;377:2337-2348.
13. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the north American inTandem1 study. *Diabetes Care*. 2018;41(9):1970-1980.
14. Danne T, Cariou B, Banks P, et al. HbA1c and hypoglycemia reduction at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the European inTandem2 study. *Diabetes Care*. 2018;41(9):1981-1990.
15. Dandona P, Mathieu C, Phillip M, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2017;5(11):864-876.
16. Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care*. 2015;38(12):2258-2265.
17. Mathieu C, Dandona P, Gillard P, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 Study): 24-week results from a randomized controlled trial. *Diabetes Care*. 2018;41(9):1938-1946.
18. Lapuerta P, Zambrowicz B, Strumph P, Sands A. Development of sotagliflozin, a dual sodium-dependent glucose transporter 1/2 inhibitor. *Diab Vasc Dis Res*. 2015;12(2):101-110.
19. Dobbins RL, Greenway FL, Chen L, et al. Selective sodium-dependent glucose transporter 1 inhibitors block glucose absorption and impair glucose-dependent insulinotropic peptide release. *Am J Physiol Gastrointest Liver Physiol*. 2015;308(11):G946-G954.
20. Zambrowicz B, Ogbaa I, Frazier K, et al. Effects of LX4211, a dual sodium-dependent glucose cotransporters 1 and 2 inhibitor, on postprandial glucose, insulin, glucagon-like peptide 1, and peptide tyrosine tyrosine in a dose-timing study in healthy subjects. *Clin Ther*. 2013;35(8):1162-1173.e1168.
21. Sands AT, Zambrowicz BP, Rosenstock J, et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. *Diabetes Care*. 2015;38(7):1181-1188.
22. Danne T, Cariou B, Buse JB, et al. 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. *Diabetes Care*. 2019;42(5):919-930.
23. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016-2018. *Diabetes Technol Ther*. 2019;21(2):66-72.
24. Maahs DM, Kinney GL, Wadwa P, et al. Hypertension prevalence, awareness, treatment, and control in an adult type 1 diabetes population and a comparable general population. *Diabetes Care*. 2005;28(2):301-306.
25. Pieber TR, Famulla S, Eilbracht J, et al. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). *Diabetes Obes Metab*. 2015;17(10):928-935.
26. Henry RR, Rosenstock J, Edelman S, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. *Diabetes Care*. 2015;38(3):412-419.
27. Rosenstock J, Cefalu WT, Lapuerta P, et al. Greater dose-ranging effects on A1C levels than on glucosuria with LX4211, a dual inhibitor of SGLT1 and SGLT2, in patients with type 2 diabetes on metformin monotherapy. *Diabetes Care*. 2015;38(3):431-438.
28. Powell DR, Zambrowicz B, Morrow L, et al. Sotagliflozin decreases postprandial glucose and insulin by delaying intestinal glucose absorption. Endo2019; March 23–26, 2019, 2019; New Orleans, LA.
29. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest*. 2014;124(2):509-514.
30. Pieber TR, Famula S, Eilbracht J, et al. Empagliflozin reduces HbA1c with lower insulin doses in patients with type 1 diabetes: a 4-week placebo-controlled trial (EASE-1). European Association for the Study of Diabetes Annual Meeting; 2015; Stockholm, Sweden.
31. Henry RR, Dandona P, Pettus J, Mudaliar S, Xu J, Hansen L. Dapagliflozin in patients with type 1 diabetes: a post hoc analysis of the effect of insulin dose adjustments on 24-hour continuously monitored mean glucose and fasting beta-hydroxybutyrate levels in a phase IIa pilot study. *Diabetes Obes Metab*. 2017;19(6):814-821.
32. Peters AL, Henry RR, Thakkar P, Tong C, Alba M. Diabetic ketoacidosis with canagliflozin, a sodium-glucose cotransporter 2 inhibitor, in patients with type 1 diabetes. *Diabetes Care*. 2016;39(4):532-538.
33. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care*. 2015;38(9):1687-1693.
34. Garg SK, Strumph P. Effects of sotagliflozin added to insulin in type 1 diabetes. *N Engl J Med*. 2018;378(10):967-968.
35. American Diabetes Association. 15. Diabetes care in the hospital: standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42(Suppl 1):S173-s181.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Baker C, Wason S, Banks P, et al. Dose-dependent glycometabolic effects of sotagliflozin on type 1 diabetes over 12 weeks: The inTandem4 trial. *Diabetes Obes Metab*. 2019;21:2440–2449. https://doi.org/10.1111/dom.13825