HbA_{1c} and Hypoglycemia Reductions at 24 and 52 Weeks With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: The European inTandem2 Study

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OBJECTIVE

The objective of this study was to evaluate the efficacy and safety of the dual sodium–glucose cotransporter 1 and 2 inhibitor sotagliflozin compared with placebo when combined with optimized insulin in adults with type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

In a double-blind, 52-week, international phase 3 trial, adults with T1D were randomized to placebo (n = 258) or once-daily oral sotagliflozin 200 mg (n = 261) or 400 mg (n = 263) after 6 weeks of insulin optimization. The primary outcome was change in HbA_{1c} from baseline to 24 weeks. The first secondary end point was a composite of the proportion of patients with HbA_{1c} <7.0%, no episode of severe hypoglycemia, and no episode of diabetic ketoacidosis (DKA) at week 24. Fasting glucose, weight, insulin dose, and safety end points were assessed through 52 weeks.

RESULTS

At 24 weeks, placebo-adjusted changes in HbA_{1c} from baseline (7.8%) were −0.37% and −0.35% with sotagliflozin 200 and 400 mg, respectively (P < 0.001), and differences were maintained at 52 weeks. At 52 weeks, greater proportions of sotagliflozin-treated patients (200 mg: 25.67%; 400 mg: 26.62%) than placebo-treated patients (14.34%; $P \leq 0.001$) met the composite end point, and sotagliflozin 400 mg reduced fasting plasma glucose (−0.87 mmol/L; P = 0.008), weight (−2.92 kg; P < 0.001), and total daily insulin dose (−8.2%; P = 0.001). In a 24-week continuous glucose monitoring (CGM) substudy, postprandial glucose decreased ($P \leq 0.009$) and CGM demonstrated up to 3 h more time in the target range of 3.9–10.0 mmol/L with sotagliflozin. Treatment satisfaction increased and diabetes distress decreased with sotagliflozin (P < 0.05 vs. placebo). The frequency of documented hypoglycemia was lower with sotagliflozin, and severe hypoglycemia occurred by week 52 in 13 patients (5.0%), 13 patients (5.0%), and 6 patients (2.3%) treated with placebo and sotagliflozin 200 and 400 mg, respectively. DKA occurred in 0 of 258 patients, 6 of 261 patients (2.3%), and 9 of 263 patients (3.4%) in these respective groups.

CONCLUSIONS

In a 1-year study, sotagliflozin was associated with statistically significant HbA_{1c} reductions. More episodes of DKA and fewer episodes of documented and severe hypoglycemia were observed in patients using sotagliflozin relative to those receiving placebo (ClinicalTrials.gov, NCT02421510).

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Most adults with type 1 diabetes (T1D) have HbA_{1c} ≥7.0% and are overweight or obese, putting them at risk for diabetes complications (1–3). Approximately 85% report hypoglycemia, at a rate of ~75 events/patient-year (4,5). The incidence of diabetic ketoacidosis (DKA) has reached 263 events/1,000 person-years (6). DKA incidence tends to decline during adulthood, but the incidence of severe hypoglycemia increases, especially in patients >65 years old (1,6,7).

Adjuncts to insulin could potentially address these unmet needs, but most, such as pramlintide, incretin therapies, and metformin, have shown few, if any, benefits (1,8–13). Recent 6-month studies of sodium–glucose cotransporter (SGLT) inhibitors in T1D suggest they may be safe and effective in combination with insulin (14,15). Sotagliflozin (LX4211) is a novel dual inhibitor of SGLT1 and SGLT2. Local SGLT1 inhibition in the proximal intestine reduces glucose reabsorption, thereby blunting and delaying postprandial hyperglycemia, whereas systemic SGLT2 inhibition decreases renal glucose reabsorption (16–19). In the global inTandem3 study, which involved 1,402 patients with T1D, sotagliflozin significantly reduced HbA_{1c}, weight, and systolic blood pressure (SBP) without increasing severe hypoglycemia, but it was associated with an increased incidence of DKA (14). Similar results were found in a 24-week study of the selective SGLT2 inhibitor dapagliflozin in T1D (15).

Because HbA_{1c} outcomes and acute diabetes complications may differ substantially among regions (2–4), we recruited adults with T1D from 96 European and Israeli sites to study the efficacy and safety of sotagliflozin versus placebo in combination with insulin for 52 weeks. Insulin optimization was started 6 weeks before initiating combination therapy in order to identify incremental effects of sotagliflozin that could not be achieved by merely increasing insulin doses.

RESEARCH DESIGN AND METHODS

Design Overview

This phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of once-daily oral sotagliflozin 200 or 400 mg in combination with insulin in adults with T1D who had inadequate glycemic control (clinical trial reg. no NCT02421510, clinicaltrials.gov). Double-blind treatment continued for 52 weeks, and the primary end point was assessed at week 24 (Fig. 1). Randomization was stratified according to HbA_{1c} level at screening and use of multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII). A subgroup of patients underwent blinded continuous glucose monitoring (CGM) with a Dexcom G4 monitor (Dexcom Inc., San Diego, CA) during specified 1-week intervals throughout the first 24 weeks.

Insulin therapy optimization began 6 weeks before randomization and continued throughout the trial (Fig. 1). 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 postprandial glucose (PPG) at <10 mmol/L (<180 mg/dL) (Supplementary Data, Insulin Dose Algorithms). An independent insulin dose monitoring committee (IDMC), comprising diabetologists and certified diabetes educators, blindly reviewed insulin titration decisions starting 6 weeks before baseline through week 24 to determine whether insulin adjustment was consistent with self-monitored blood glucose (SMBG) patterns.

The institutional review board at each study center or the local ethics committee approved the protocol, consent form, and associated documents. All patients provided written informed consent. An independent clinical end point committee, blinded to trial treatment, adjudicated episodes of severe hypoglycemia, episodes of DKA, major adverse cardiovascular events, drug-induced liver injuries, and deaths. An independent data monitoring committee reviewed safety. An independent statistician performed statistical analyses.

Study Population

The study included men and nonpregnant women aged 18 years or older who had T1D treated with insulin delivered through MDI or CSII and who had HbA_{1c} between 7.0 and 11.0% at screening. Patients with β-hydroxybutyrate (BHB) >0.6 mmol/L at screening were excluded (see the Supplementary Data for all inclusion and exclusion criteria).

Interventions

After the 6-week insulin optimization phase, patients were randomly assigned

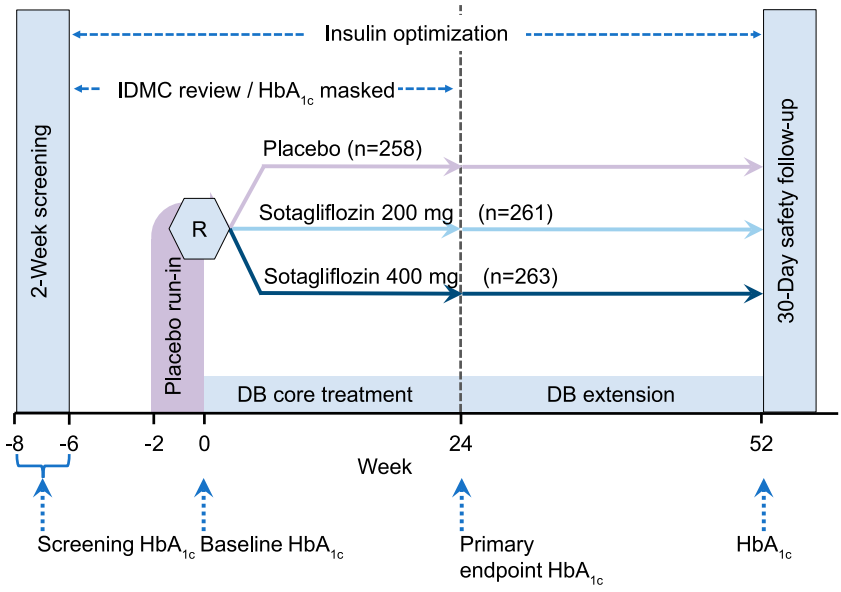

Figure 1—Study design. After a 2-week screening period, insulin therapy was optimized for 6 weeks before randomization (R), and optimized insulin continued until the study concluded at week 52. After a 2-week placebo run-in, patients were randomly assigned to double-blind (DB) treatment with sotagliflozin 400 or 200 mg, or placebo, for 52 weeks. An IDMC reviewed insulin titration decisions from week −6 to week 24 (primary end point); HbA_{1c} values were masked to study staff during this period. Between weeks 24 and 52, insulin optimization continued without input from the IDMC, and HbA_{1c} values were unmasked. Safety was monitored for 30 days after the last dose of study medication.

at a 1:1:1 ratio to oral sotagliflozin 200 mg, oral sotagliflozin 400 mg, or placebo, all of which were administered once daily for 52 weeks. All study medications were given as two tablets before the first meal of the day. Sotagliflozin 200 mg was given as one sotagliflozin 200-mg tablet and one placebo tablet; the 400-mg dose was given as two sotagliflozin 200-mg tablets.

Bolus insulin was reduced by 30% for the first meal after the first dose of study medication on day 1 only (20). Thereafter and throughout the 52-week study, investigators adjusted insulin doses according to SMBG results, and the IDMC evaluated the doses until week 24. In addition to premeal testing to determine bolus insulin doses, patients were asked to test blood glucose before breakfast, before and 2 h after lunch, and before dinner and bedtime (five-point profile) at least three times a week before a clinic visit. An eight-point profile (2 h after breakfast and dinner and at 2 or 3 A.M., in addition to the five-point profile) was recommended once during the week before a clinic visit. HbA_{1c} and laboratory fasting plasma glucose (FPG) results were masked to study staff from the start of the 6-week lead-in through week 24 (after week 12, HbA_{1c} values >11% were unmasked to allow appropriate intervention). After week 24, HbA_{1c} and laboratory FPG values were unmasked to investigators. From baseline to week 12, antihypertensive treatment was not adjusted unless required for patient safety.

All study participants received urine ketone strips, point-of-care blood BHB meters and strips, and information on urogenital hygiene, proper hydration, and detecting and treating ketosis. Study centers received recommendations for ketosis and DKA diagnosis and management (see Supplementary Data).

End Points

The primary end point was the placebo-adjusted change in HbA_{1c} from baseline to week 24. The first secondary end point was a composite of the proportion of patients with HbA_{1c} <7.0% (<53 mmol/mol), no episode of severe hypoglycemia, and no episode of DKA at week 24. Additional key secondary end points were the changes from baseline to week 24 in body weight, daily bolus insulin dose, FPG, and scores on the Diabetes Treatment Satisfaction Questionnaire status and the two-item Diabetes Distress Screening Scale. Other objectives included examining the change in SBP and diastolic blood pressure (DBP) in the entire study population, and the change in SBP in those with SBP ≥130 mmHg at baseline, from baseline to week 12 (per protocol, antihypertensive therapies could be adjusted thereafter). HbA_{1c}, FPG, daily insulin dose, frequency of SMBG-documented hypoglycemic events (glucose ≤3.9 and ≤3.0 mmol/L [≤70 and ≤55 mg/dL]), and kidney function were assessed at each study visit through 52 weeks, and composite end points evaluating the proportions of patients meeting HbA_{1c} targets without severe hypoglycemia, DKA, or weight gain were calculated at weeks 24 and 52. The CGM substudy did not meet enrollment targets (n = 70 patients per arm). Therefore, before investigators and staff were unblinded to data, the inTandem1 (conducted in the U.S. and Canada with an identical study design) and inTandem2 protocols were modified to include a prespecified pooled analysis of CGM data, the primary end point of which was the percentage of readings in the target range of 3.9–10.0 mmol/L (70–180 mg/dL).

Safety and tolerability were evaluated throughout the study. DKA diagnosis was based on evidence of metabolic acidosis and other criteria, as reviewed and adjudicated centrally by a blinded events committee (see Supplementary Data).

Statistical Methods

Efficacy analyses were based on the modified intent-to-treat population, which included all randomized patients who had taken at least one dose of the study drug. Primary efficacy end point data were analyzed using mixed-effects model for repeated measures (MMRM) statistics based on the restricted maximum likelihood method for estimation. The analysis model included fixed categorical effects of treatment, randomization strata based on use of MDI or CSII, HbA_{1c} ≤8.5% or >8.5% at week −2, and other covariates. MMRM or ANCOVA was used for continuous secondary and other efficacy end points, with the corresponding end point and baseline value (including first-order interactions in the MMRM) in the model. A Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors, was used for binary end points. The treatment groups were compared at week 24, and descriptive statistics were provided for each clinic visit through week 52. Missing observations at week 24 were imputed as nonresponse. See the Supplementary Data for additional details.

RESULTS

Between May 2015 and June 2017, at 96 sites in 17 European countries and Israel, 800 patients entered the placebo run-in, and 782 were randomly assigned to treatment with placebo (n = 258), sotagliflozin 200 mg (n = 261), or sotagliflozin 400 mg (n = 263); 236, 239, and 240 patients, respectively, completed 24 weeks of treatment (Supplementary Fig. 1). During the 28-week extension period, 13 patients in each sotagliflozin group and 11 in the placebo group discontinued participation. Baseline characteristics were similar between groups (Supplementary Table 1). In the total cohort, 581 patients (74.3%) used MDI and 201 patients (25.7%) received CSII (Supplementary Table 1).

Glycemic Control and Insulin Dosing

Mean HbA_{1c} at screening was 8.42% (68.6 mmol/mol), 8.35% (67.8 mmol/mol), and 8.38% (68.1 mmol/mol) in the placebo and sotagliflozin 200- and 400-mg groups, respectively. During 6 weeks of insulin optimization before randomization, HbA_{1c} decreased to baseline levels of 7.79% (61.6 mmol/mol), 7.74% (61.1 mmol/mol), and 7.71% (60.8 mmol/mol), respectively. At baseline, 44 patients (17.1%) in the placebo group, 50 patients (19.2%) in the sotagliflozin 200-mg group, and 46 patients (17.5%) in the sotagliflozin 400-mg group had HbA_{1c} <7.0%.

After 24 weeks, the difference from placebo for the primary end point of HbA_{1c}, as measured by the least squares mean (LSM) difference, was −0.37% (95% CI −0.48 to −0.25) and −0.35% (−0.47 to −0.24) with sotagliflozin 200 and 400 mg (both P < 0.001 vs. placebo). LSM differences between sotagliflozin and placebo were maintained at 52 weeks: sotagliflozin 200 mg −0.21% (−0.35 to −0.07; P = 0.003); sotagliflozin 400 mg −0.32% (−0.46 to −0.18; P < 0.001) (Fig. 2*A* and Supplementary Table 2). Across the entire study population,

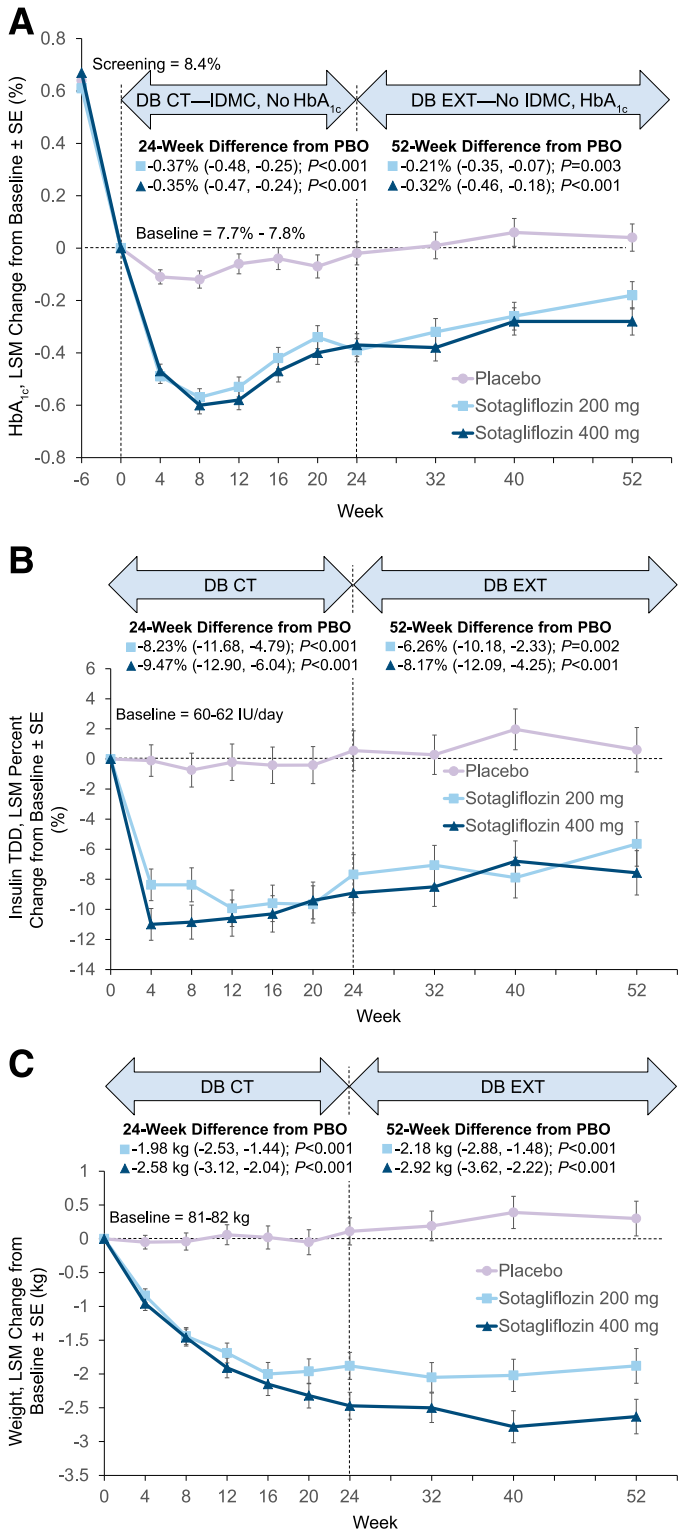

Figure 2—Primary and other selected end points. Error bars represent the SE. *A*: LSM change from baseline in HbA_{1c} over 52 weeks. Data between week −6 to week 0 depict arithmetic mean differences between screening and baseline HbA_{1c} values to illustrate the effect of insulin optimization. During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

15.1% of the placebo group, 33.3% of the sotagliflozin 200-mg group, and 33.8% of the sotagliflozin 400-mg group achieved HbA_{1c} <7.0% at 24 weeks; at 52 weeks the proportions were 15.5%, 27.2%, 27.8%, respectively. Among the subgroup of patients with HbA_{1c} ≥7.0% at baseline, HbA_{1c} <7.0% was achieved after 24 weeks by 13 of 214 (6.1%), 52 of 211 (24.6%; $P < 0.001$ vs. placebo), and 57 of 217 (26.3%; $P < 0.001$) patients receiving placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively. After 52 weeks, 8.8%, 20.2%, and 21.6% of patients with HbA_{1c} ≥7.0% at baseline in the placebo, sotagliflozin 200-mg, and sotagliflozin 400-mg groups had HbA_{1c} <7.0%.

FPG decreased significantly in both sotagliflozin groups, with placebo-adjusted differences of −1.20 mmol/L (−21.6 mg/dL [95% CI −1.79 to −0.61 mmol/L]; $P < 0.001$) and −1.42 mmol/L (−25.7 mg/dL [−2.01 to −0.84 mmol/L]; $P < 0.001$) for sotagliflozin 200 and 400 mg, respectively, at 24 weeks. At 52 weeks, FPG was reduced by 0.27 mmol/L (4.9 mg/dL [−0.92 to 0.38 mmol/L]; $P = 0.41$) and 0.87 mmol/L (15.8 mg/dL [−1.52 to −0.23 mmol/L]; $P = 0.008$) relative to placebo (Supplementary Table 2).

The inTandem2 CGM subgroup included 48, 45, and 49 patients randomized to placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively. Glycemic variability, measured on the basis of the mean amplitude of glycemic excursions and CGM SD, improved with both sotagliflozin doses (Fig. 3 and Supplementary Table 3). Relative to placebo, patients treated with sotagliflozin 200 and 400 mg spent, respectively, 8.4% ($P = 0.044$) and 13.4% ($P < 0.001$) more time with glucose values in the target range 3.9–10.0 mmol/L (70–180 mg/dL) and had lower PPG: −2.80 mmol/L ($P = 0.009$) and −4.20 mmol/L ($P < 0.001$) (Supplementary Table 3).

Insulin optimization continued in all three treatment groups. Sotagliflozin was associated with reductions in total daily insulin dose that stabilized by week 4 (Fig. 2*B* and Supplementary Table 2). At 24 weeks, the LSM percentage differences from placebo in daily bolus insulin were −12.94% (95% CI −20.50 to −5.38; $P < 0.001$) with sotagliflozin 200 mg and −16.37% (−23.90 to −8.83; $P < 0.001$) with sotagliflozin 400 mg.

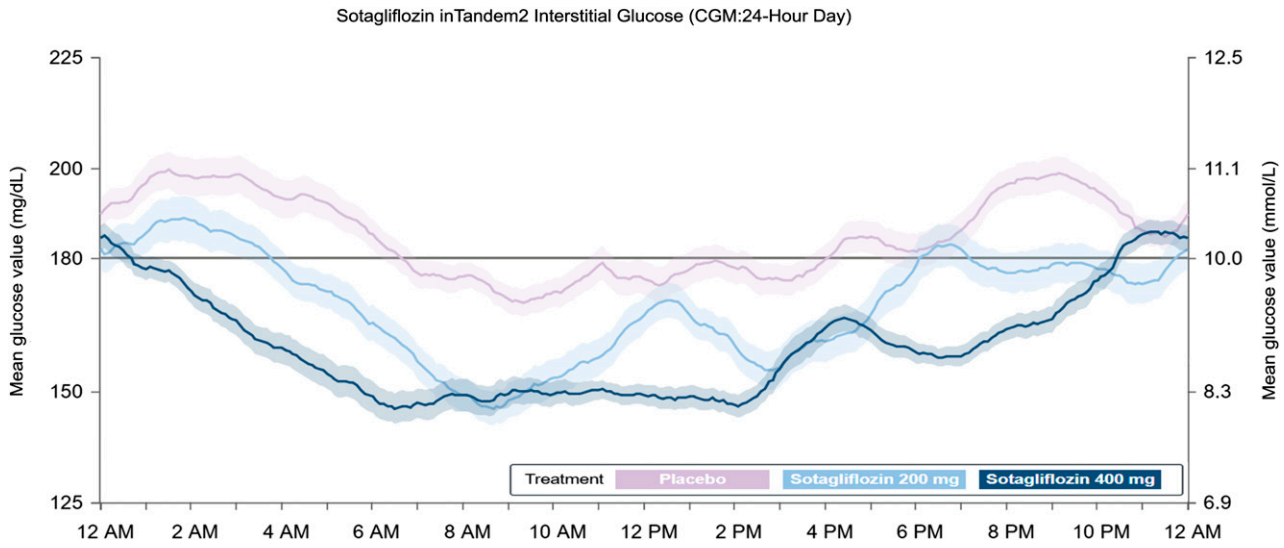

Figure 3—A 24-h CGM tracing consisting of interstitial glucose readings collected every 5 min. Solid lines represent mean values from each treatment group (light purple, placebo [*n* = 48]; light blue, sotagliflozin 200 mg [*n* = 45]; dark blue, sotagliflozin 400 mg [*n* = 49]). Shaded areas represent ±1 SEM. The figure shows data collected starting at midnight. The actual start time for 24-h readings may vary for each subject. The top of the target CGM range was 10.0 mmol/L (180 mg/dL). Subject and aggregate visualizations of CGM data were generated by Cenduit, LLC (Durham, NC), and any reproductions must acknowledge Cenduit.

Daily basal insulin dose decreased by 5.82% (P = 0.007) and 4.67% (P = 0.03) with sotagliflozin 200 and 400 mg, respectively, relative to placebo). P values were <0.05 for placebo-adjusted percentage changes in total, bolus, and basal insulin at 52 weeks, except for daily bolus insulin in the sotagliflozin 200-mg group (Supplementary Table 2 and Supplementary Fig. 2*A*).

Nonglycemic End Points

Body weight decreased significantly with sotagliflozin treatment throughout the study (Fig. 2*C*). Sotagliflozin 200 mg was associated with placebo-adjusted LSM weight reductions of 1.98 kg (2.48% [95% CI −2.53 to −1.44 kg]) and 2.18 kg (2.78% [−2.88 to −1.48 kg]) at 24 and 52 weeks, respectively (both $P < 0.001$). Mean weight loss in the sotagliflozin 400-mg group was −2.58 kg (−3.08% [−3.12 to −2.04 kg]) at 24 weeks and −2.92 kg (−3.50% [−3.62 to −2.22 kg]) at 52 weeks relative to the placebo group (both $P < 0.001$).

After 12 weeks, patients receiving sotagliflozin 400 mg experienced SBP reductions, with an LSM difference from placebo of −2.8 mmHg (95% CI −4.6 to −1.1 mmHg; P = 0.001). The placebo-adjusted difference in DBP was not significant with sotagliflozin 400 mg, and sotagliflozin 200 mg was not associated with significant changes in either SBP or DBP (Supplementary Table 2). Among patients with SBP ≥130 mmHg at baseline, sotagliflozin 400 mg reduced SBP by 4.1 mmHg (−7.8 to −0.5 mmHg; P = 0.027) relative to placebo at 12 weeks.

Over 52 weeks, total cholesterol increased by 0.07 mmol/L with placebo and 0.3 mmol/L in the sotagliflozin groups, and LDL cholesterol increased by 0.05 with placebo, 0.14 with sotagliflozin 200 mg, and 0.13 mmol/L with sotagliflozin 400 mg. Other lipid changes were small and not considered clinically meaningful.

In the sotagliflozin arms, an initial decrease in estimated glomerular filtration rate of >3 mL/min/1.73 m^2 in the sotagliflozin groups at week 4 resolved by week 24 (placebo −1.70 mL/min/1.73 m^2; sotagliflozin 200 mg −1.66 mL/min/1.73 m^2; sotagliflozin 400 mg −1.39 mL/min/1.73 m^2) (Supplementary Fig. 3 and Supplementary Table 2).

Composite End Points

At 24 weeks, 15.12%, 31.42%, and 32.32% of patients receiving placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively, achieved HbA_{1c} <7.0% without experiencing severe hypoglycemia or DKA (Supplementary Fig. 4). Treatment differences at week 24 were 16.30% (95% CI 8.79–23.82; $P < 0.001$) for sotagliflozin 200 mg and 17.20% (9.67–24.73; $P < 0.001$) for sotagliflozin 400 mg versus placebo; differences at week 52 were 11.33% (4.13–18.52; P = 0.001) and 12.27% (5.05–19.50; $P < 0.001$) for the sotagliflozin 200- and 400-mg doses, respectively, versus placebo (Supplementary Fig. 4). The proportions of sotagliflozin-treated patients who achieved HbA_{1c} <7.0% but also experienced severe hypoglycemia (<2%) or DKA (<1%) were not statistically different from those receiving placebo (≤1%) throughout the study (Supplementary Fig. 4). At 24 and 52 weeks, 44.87% and 37.26% of patients receiving sotagliflozin 400 mg achieved an HbA_{1c} reduction ≥0.5% without severe hypoglycemia or DKA, compared with 17.44% and 19.38% receiving placebo, respectively (Supplementary Fig. 4).

When HbA_{1c} and weight effects at 24 weeks were evaluated together, 25.67% of patients treated with sotagliflozin 200 mg and 29.66% of those treated with sotagliflozin 400 mg achieved HbA_{1c} <7.0% while not gaining weight, versus 6.98% of patients receiving placebo (Supplementary Fig. 5); at 52 weeks, the respective proportions were 19.92%, 22.81%, and 8.53% (Supplementary Table 4). More patients who achieved HbA_{1c} <7.0% lost >5% of body weight at 24 weeks while taking sotagliflozin 200 mg (difference from placebo, 6.12% [95% CI 2.32–9.91%]; $P < 0.001$) or sotagliflozin 400 mg

(8.34% [4.18–12.51%]; $P < 0.001$) (Supplementary Table 4). Similar patterns were observed at 52 weeks, and for patients with an HbA_{1c} reduction ≥0.5% at 24 and 52 weeks (Supplementary Fig. 6 and Supplementary Table 4).

A composite of HbA_{1c} <7.0%, no weight gain, no severe hypoglycemia, and no DKA was achieved at 24 weeks by 24.14% of patients treated with sotagliflozin 200 mg and 28.14% of those treated with sotagliflozin 400 mg compared with 6.98% of those in the placebo group (Supplementary Fig. 5); the respective proportions were 18.39%, 21.67%, and 7.75% at 52 weeks (Supplementary Table 4).

Patient-Reported Outcomes

Diabetes Treatment Satisfaction Questionnaire status scores increased significantly from baseline to week 24 in both sotagliflozin groups but did not change significantly in the placebo group, resulting in differences of 2.0 (95% CI 1.3–2.7; $P < 0.001$) in the sotagliflozin 200-mg group and 1.7 (1.0–2.4; $P < 0.001$) in the sotagliflozin 400-mg group (Supplementary Fig. 7 and Supplementary Table 2). At week 24, distress among sotagliflozin-treated patients, as measured by the two-item Diabetes Distress Screening Scale, decreased by 0.3 (−0.6 to 0.0; $P = 0.025$) and 0.4 (−0.7 to −0.2; $P = 0.003$) with the 200- and 400-mg doses relative to placebo. Distress values among patients in the placebo group did not change from baseline. At week 52, LSM differences from placebo were −0.2 (−0.5 to 0.1; $P = 0.23$) for sotagliflozin 200 mg and −0.3 (−0.6 to 0.0; $P = 0.046$) for sotagliflozin 400 mg.

Hypoglycemia

Documented hypoglycemia at thresholds of ≤3.0 mmol/L (≤55 mg/dL) and ≤3.9 mmol/L (≤70 mg/dL) decreased in both sotagliflozin groups relative to the placebo group (Supplementary Table 2). Between weeks 23 and 24, 16.7% and 15.4% of the sotagliflozin 200- and 400-mg groups, respectively, had SMBG ≤3.0 mmol/L, compared with 28.9% of the placebo group (relative risk vs. placebo: 0.579 [95% CI 0.410–0.817]; $P = 0.002$ for sotagliflozin 200 mg; 0.527 [0.369–0.753]; $P < 0.001$ for sotagliflozin 400 mg). LSM differences in events per patient per day were −0.028 (−0.047 to −0.009; $P = 0.004$) and −0.031 (−0.049 to −0.012; $P = 0.001$) at 24 weeks, and −0.026 (−0.048 to −0.005; $P = 0.017$) and −0.030 (−0.051 to −0.009; $P = 0.006$) at 52 weeks, with the sotagliflozin 200- and 400-mg doses, respectively, compared with placebo. Sotagliflozin treatment was also associated with a lower frequency of SMBG ≤3.9 mmol/L and with lower hypoglycemic event rates (Supplementary Table 2).

Over 52 weeks, 32 of 782 patients (4.1%) experienced one or more positively adjudicated severe hypoglycemia event (13 of 258 patients [5.0%] in the placebo group, 13 of 261 patients [5.0%] in the sotagliflozin 200-mg group, and 6 of 263 patients [2.3%] in the sotagliflozin 400-mg group) (Table 1), at rates of 0.07, 0.08, and 0.06 events/patient/year, respectively. No patients discontinued participation because of severe hypoglycemia.

DKA and Acidosis-Related Adverse Events

Over 52 weeks, 56 patients had serious or nonserious acidosis-related adverse events, and 15 of 782 patients (1.9%) had one or more positively adjudicated DKA event: none receiving placebo, 6 of 261 (2.3%) receiving sotagliflozin 200 mg (one of whom used CSII), and 9 of 263 (3.4%) receiving sotagliflozin 400 mg (five of whom used CSII) (Table 1 and Supplementary Table 5). During the first 24 weeks, two patients (0.8%) treated with sotagliflozin 200 mg and four patients (1.5%) treated with sotagliflozin 400 mg experienced one or more positively adjudicated DKA event. Over 52 weeks, four patients taking sotagliflozin 400 mg discontinued participation because of DKA (Table 1). Mean increases in BHB of ∼0.1 mmol/L were observed in the sotagliflozin groups (Supplementary Fig. 9).

Other Safety Outcomes

During 52 weeks of double-blind treatment, adverse events were reported by 61.2%, 68.2%, and 68.8% of patients treated with placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively; acidosis-related events accounted for the differences between treatment groups (Table 1 and Supplementary Table 5). Serious adverse events occurred in more sotagliflozin-treated than placebo-treated patients (sotagliflozin 200 mg: 26 [10.0%]; sotagliflozin 400 mg: 21 [8.0%]; placebo: 17 [6.6%]). Two deaths occurred in the placebo group: one due to cardiopulmonary failure and one as the result of a lung neoplasm. Major adverse cardiovascular events occurred in one patient receiving placebo, three patients receiving sotagliflozin 200 mg, and three patients receiving sotagliflozin 400 mg. Nine patients (3.5%) receiving placebo, 10 (3.8%) receiving sotagliflozin 200 mg, and 18 (6.8%) receiving sotagliflozin 400 discontinued participation because of an adverse event (including four who discontinued as a result of DKA).

Most adverse events were mild to moderate in severity. Diarrhea (consistent with SGLT1 inhibition) occurred in 12 patients (4.6%) taking sotagliflozin 200 mg and 19 patients (7.2%) taking sotagliflozin 400 mg, compared with 9 patients (3.5%) taking placebo (Table 1). The severity of symptoms was generally mild to moderate, and only two patients (0.8%) from each sotagliflozin group and one placebo-treated patient (0.4%) discontinued participation. Twenty-four patients (9.2%) receiving sotagliflozin 200 mg and 29 (11.0%) receiving sotagliflozin 400 mg reported a genital mycotic infection (consistent with SGLT2 inhibition), compared with six patients (2.3%) receiving placebo (Table 1). Two patients each from the sotagliflozin 400-mg and placebo groups and three patients from the sotagliflozin 200-mg group discontinued participation because of a genital mycotic infection. Urinary tract infections were reported by 13 patients (5.0%), 11 patients (4.2%), and 18 patients (6.8%) receiving placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg, respectively. Two patients (0.8%) from the sotagliflozin 200-mg group discontinued due to urinary tract infections. Bone fractures occurred in eight patients (3.1%) receiving placebo, six patients (2.3%) receiving sotagliflozin 200 mg, and five patients (1.9%) receiving sotagliflozin 400 mg. In the sotagliflozin 200-mg group, one patient had a toe amputated; this patient had a history of amputation of multiple toes.

CONCLUSIONS

Over 52 weeks of treatment, sotagliflozin 200 and 400 mg combined with an optimized insulin regimen significantly reduced HbA_{1c} compared with placebo and demonstrated clinically meaningful,

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

	Placebo (*n* = 258)	Sotagliflozin 200 mg (*n* = 261)	Sotagliflozin 400 mg (*n* = 263)
Any adverse event	158 (61.2)	178 (68.2)	181 (68.8)
Serious adverse event	17 (6.6)	26 (10.0)	21 (8.0)
Severe adverse event	4 (1.6)	7 (2.7)	10 (3.8)
Death	2 (0.8)*	0	0
Positively adjudicated adverse events			
≥1 episode of severe hypoglycemia†	13 (5.0)	13 (5.0)	6 (2.3)
≥1 episode of severe nocturnal hypoglycemia†**	3 (1.2)	1 (0.4)	2 (0.8)
≥1 episode of DKA	0	6 (2.3)	9 (3.4)
≥1 episode of DKA among CSII users	0	1/68 (1.5)	5/67 (7.5)
≥1 episode of DKA among MDI users	0	5/193 (2.6)	4/196 (2.0)
MACE			
Myocardial infarction or hospitalization for unstable angina	0	1 (0.4)	2 (0.8)
Stroke	1 (0.4)	0	0
Hospitalization for heart failure	0	0	0
Coronary revascularization	0	2 (0.8)	1 (0.4)
Drug-induced liver injury	1 (0.4)	0	0
Acidosis-related adverse events‡			
Any	3 (1.2)	23 (8.8)	30 (11.4)
Serious	0	7 (2.7)	13 (4.9)
Events of special interest			
Any	254 (98.4)	255 (97.7)	261 (99.2)
Volume depletion§	1 (0.4)	6 (2.3)	2 (0.8)
Genital mycotic infection	6 (2.3)	24 (9.2)	29 (11.0)
Urinary tract infection	13 (5.0)	11 (4.2)	18 (6.8)
Diarrhea‖	9 (3.5)	12 (4.6)	19 (7.2)
Pancreatitis	0	0	1 (0.4)
Bone fracture	8 (3.1)	6 (2.3)	5 (1.9)
Venous thrombotic event	0	0	0
Renal event¶	3 (1.2)	1 (0.4)	3 (1.1)
Malignancy	2 (0.8)	1 (0.4)	1 (0.4)
Amputation	0	1 (0.4)	0
Any documented hypoglycemia (SMBG ≤3.9 mmol/L)#	252 (97.7)	255 (97.7)	260 (98.9)
Any nocturnal documented hypoglycemia**	196 (76.0)	189 (72.4)	201 (76.4)
Any SMBG value ≤3.0 mmol/L	230 (89.1)	231 (88.5)	238 (90.5)
Any adverse event leading to discontinuation	9 (3.5)	10 (3.8)	18 (6.8)
Any event of special interest leading to discontinuation††	6 (2.3)	7 (2.7)	12 (4.6)
DKA (positively adjudicated)	0	0	4 (1.5)
Diarrhea	1 (0.4)	2 (0.8)	2 (0.8)
Genital mycotic infection	2 (0.8)	3 (1.1)	2 (0.8)
Urinary tract infection	0	2 (0.8)	0
Potential drug-induced liver injury	0	0	1 (0.4)
Severe hypoglycemia (positively adjudicated)	0	0	0
Stroke	1 (0.4)	0	0
Neoplasm	2 (0.8)	0	1 (0.4)

Data are *n* (%) or *n*/*N* (%) and include patients who received at least one dose of a study drug and include events that occurred up to 30 days after the last dose of double-blind study treatment. *One death was due to cardiopulmonary failure and the other to a malignant lung neoplasm. †Severe hypoglycemia was defined as any hypoglycemic event that required assistance from another person or during which the patient lost consciousness or had a seizure. Hypoglycemic events include all those that occurred between administration of the first and last dose of study drug during the 52-week double-blind treatment period. ‡Acidosis-related adverse events, whether serious or nonserious, are adverse events that satisfy the trigger terms for metabolic acidosis, which are the following Medical Dictionary for Regulatory Activities preferred terms: acetonemia, acidosis, acidosis hyperchloremic, blood ketone body, blood ketone body increased, blood ketone body present, DKA, diabetic hyperglycemia coma, diabetic ketoacidotic hyperglycemic coma, diabetic metabolic decompensation, diabetic coma, hyperglycemic coma, hyperglycemic seizure, hyperglycemic unconsciousness, ketoacidosis, ketosis, lactic acidosis, metabolic acidosis, renal tubular acidosis, uremic acidosis, urine ketone body, and urine ketone body present. §Volume depletion events are listed in the Supplementary Data. ‖Diarrhea was mostly mild to moderate and transient. ¶Renal events are listed in the Supplementary Data. #Documented hypoglycemia was defined as blood glucose ≤70 mg/dL with or without symptoms of hypoglycemia. In the sotagliflozin development program, hypoglycemia is considered to be an event of special interest and requires a specialized case report form. Because analysis of hypoglycemia was based on data recorded on case report forms, investigators were asked to not submit hypoglycemic events on the adverse event case report form unless the episode met criteria for a serious adverse event. **Nocturnal hypoglycemia was defined as positively adjudicated severe hypoglycemia or investigator-reported documented hypoglycemia (blood glucose ≤70 mg/dL with or without symptoms of hypoglycemia) that occurred between midnight and 5:59 A.M., regardless of whether the patient was awake during the event. ††All events of special interest leading to discontinuation were reported by investigators, except for DKA and severe hypoglycemia, which were positively adjudicated.

improved outcomes beyond HbA_{1c} reduction, as recently recommended by Agiostratidou et al. (21). Sotagliflozin improved elements of efficacy beyond HbA_{1c}, such as CGM time in the target range of 3.9–10.0 mmol/L (70–180 mg/dL), glycemic variability, FPG, PPG, weight, SBP, and documented hypoglycemia events. These improvements were achieved with reductions in insulin dose. Because the changes beyond HbA_{1c} (notably body weight reduction and glycemic variability) were dose dependent, the sotagliflozin 400-mg dose may be appropriate for patients who would benefit from additional efficacy. Although the incidence of DKA with sotagliflozin was low and within the range reported among the general T1D population, there was an imbalance in DKA that favored placebo, as no DKA occurred in that group (1,6). At 24 and 52 weeks, clinically meaningful composite end points were achieved with sotagliflozin. At 1 year, ~1 in 5 sotagliflozin-treated patients achieved HbA_{1c} <7.0% without severe hypoglycemia, DKA, or weight gain, compared with 1 in 13 patients treated with placebo. These targets were achieved in a population whose insulin doses were optimized throughout the trial, and they are consistent with findings in the inTandem3 study, in which 24% and 7% of patients treated with sotagliflozin or placebo, respectively, on a background of nonoptimized insulin achieved the same goal. Patients receiving sotagliflozin also reported statistically significant and clinically meaningful increases in satisfaction with treatment and decreases in diabetes distress.

These results are consistent with the previously published results from inTandem3, in which sotagliflozin demonstrated an ability to significantly reduce HbA_{1c}, weight, and blood pressure, with a reduced rate of hypoglycemia occurrence and a low incidence of DKA when combined with insulin to treat T1D (14). The inTandem1 study, a 52-week trial conducted in the U.S. and Canada with a design identical to that of the current study, showed similar results (22).

In general, higher HbA_{1c} at baseline is associated with more robust HbA_{1c} reductions when using oral agents. In Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes (DEPICT-1), a 24-week study of dapagliflozin in T1D in which no patients with HbA_{1c} <7.0% were randomized, HbA_{1c} decreased from 8.5% at baseline to 8.0% at week 24; the percentage of patients achieving HbA_{1c} <7.0% was not reported (15). By contrast, at baseline in the current study, 18% of randomized patients had HbA_{1c} <7.0%, and mean HbA_{1c} was 7.8%. A 24-week decrease to HbA_{1c} of 7.4% with sotagliflozin 400 mg was maintained through 52 weeks. In this population, whose insulin therapy was optimized, ~25% of sotagliflozin-treated patients whose HbA_{1c} was ≥7.0% at baseline maintained a value <7.0% after 24 weeks (20% met this goal after 52 weeks), compared with ≤9% of the placebo group. Similar results were seen in the inTandem3 study, in which twice as many sotagliflozin- as placebo-treated patients achieved HbA_{1c} <7% with background insulin that was not optimized (14). In the general population with T1D, ≥70% of patients have HbA_{1c} ≥7.0% (1,2). A treatment that could help up to a quarter of these individuals achieve glucose levels that are closer to normal without experiencing hypoglycemia could be a major advance in therapy, taking into account that no other pharmacological options other than insulin regimen modifications are available to improve diabetes control in patients with T1D. Moreover, satisfactory measures for mitigating risk for DKA during SGLT inhibitor therapy are available.

CGM substudy data demonstrated PPG reductions and reductions in glycemic variability that endured throughout 24 h and showed a nearly 3-h/day increase in time in the target range of 3.9–10.0 mmol/L (70–180 mg/dL) with sotagliflozin 400 mg. The pattern of insulin dose reductions associated with these changes differed from those seen in DEPICT-1. With dapagliflozin 10 mg, total, basal, and bolus insulin doses decreased by 13%, 14%, and 18%, respectively, relative to placebo (15). With sotagliflozin 400 mg, total, basal, and bolus insulin decreased by 9%, 5%, and 16% after 24 weeks and by 8%, 7%, and 12% after 52 weeks, respectively. During the second half of this study, investigators had access to HbA_{1c} values and made insulin titration decisions without input from the IDMC, which may have affected outcomes. The more robust reductions in bolus insulin than in basal insulin doses in the current study compared with those in DEPICT-1 are consistent with the mechanism of SGLT1 inhibition, which delays and reduces glucose absorption in the proximal intestine and could help stabilize glucose levels by blunting PPG excursions. The modest reductions in basal insulin over 52 weeks are consistent with changes in bolus insulin, driving decreases in total daily insulin dose. These changes are hypothesized to contribute, at least in part, to lower observed rates of severe and documented hypoglycemia.

Insulin dose reduction is a risk factor for ketosis and could result in DKA (23,24). One hypothesis to be tested is whether modest versus large reductions in basal insulin dose could translate into lower risk for ketosis and, by extension, lower risk for DKA. Over the first 6 months, 1–2% of patients treated with sotagliflozin experienced a positively adjudicated DKA event. Similar rates with narrower adjudication criteria were reported for dapagliflozin (15,25). In this study, the majority of patients resumed therapy after temporary discontinuation of sotagliflozin because of a DKA event, which suggests that DKA risk is manageable. However, further work needs to be done to elucidate the risk factors for DKA. When SGLT inhibitors are administered, monitoring for ketosis is required, particularly during metabolically stressful situations. SGLT inhibitors should be temporarily discontinued before scheduled surgical procedures, and patients and clinicians should consult closely regarding other forms of behavioral and physiological stress (26).

Significant improvements in patient-reported outcomes were observed with sotagliflozin compared with placebo. These improvements may be related to lower HbA_{1c} and better glycemic control, because the measures of patient outcomes reflected distress at the inability to control glucose. Weight loss of 2–3 kg (3–4%) while taking sotagliflozin was also meaningful, as attempts to improve glycemic control with insulin alone usually result in weight gain (1–3,27,28).

An increase in the number of lower-limb amputations among patients receiving canagliflozin, as seen in the Canagliflozin Cardiovascular Assessment Study (CANVAS) (29), has prompted speculation that partial inhibition of SGLT1 may interfere with circulation and wound

healing. However, the rate of amputation among patients taking sotagliflozin in the inTandem program is lower than both that in CANVAS and the background rate reported for patients with T1D (30). No amputations occurred in inTandem3 (14); the current study and inTandem1 each had a single report of an amputation among sotagliflozin-treated patients.

This trial has some limitations. It was designed to demonstrate HbA_{1c} reduction in a setting of optimized insulin with more frequent SMBG assessments and insulin adjustments than are typical for clinical practice. Because of study design requirements, HbA_{1c} and FPG values were masked until the primary end point assessment at week 24. Composite end points are inherently limited, as they give equal weight to all components without regard to frequency or severity; among our composite end points, episodes of DKA, episodes of severe hypoglycemia, and weight gain were rare relative to achievement of HbA_{1c} $<7\%$ (see Supplementary Figs. 4 and 6). In addition, monitoring and patient education mitigated DKA incidence such that it was 0% in the placebo arm. This level of DKA mitigation may not be easily realized in real-world clinical practice.

In phase 3 data published to date, only recently developed automated insulin delivery devices have demonstrated the ability to reduce HbA_{1c} without increasing the risk for hypoglycemia; other therapeutic interventions with non-SGLT agents have not been successful (10–15,20,31–34). In this study, sotagliflozin significantly reduced HbA_{1c} while also decreasing documented and severe hypoglycemia events. DKA associated with sotagliflozin occurred at low rates. Sotagliflozin doubled the proportions of patients who achieved target HbA_{1c} levels without experiencing severe hypoglycemia, DKA, or weight gain. These findings support the use of sotagliflozin in combination with insulin in T1D.

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Author Contributions. T.D., J.A.K., P.L., D.K.M., A.L.P., S.S., and P.S. conceived and conducted the study and acquired, analyzed, and interpreted data. B.C., M.B., H.B., and E.F. conducted the study and acquired, analyzed, and interpreted data. P.B. contributed to the statistical design, analyzed and interpreted data, and oversaw the statistical analyses conducted by the independent statistician. P.B., P.L., and P.S. approved the protocol and its amendments. P.B., P.L., S.S., and P.S. reviewed the data quality before locking the database. P.L. provided safety oversight for monthly safety reviews. T.D., B.C., P.B., M.B., H.B., E.F., J.A.K., P.L., D.K.M., A.L.P., S.S., and P.S. drafted and critically revised the manuscript. T.D., B.C., P.B., M.B., H.B., E.F., J.A.K., P.L., D.K.M., A.L.P., S.S., and P.S. 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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