Supplement to

A1C and Hypoglycemia Reduction 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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Insulin Dose Adjustment Algorithms

Investigators were given the following dose adjustment algorithms to use as a guide during the study.

Insulin Dose Adjustment Guidelines for Multiple Daily Insulin Injections (MDI) Basal-Bolus Therapy

Before making changes to insulin per gram of carbohydrate (I/C ratio), it is recommended that the amount of high blood glucose correction bolus (sliding scale) regular insulin (regular) or rapid-acting insulin analogue (RAI) coverage is evaluated for appropriateness.

Glucose pattern (2-3 days)	Suggested changes
BG pre-breakfast	**HIGH** • If bedtime BG is out of range, consider correcting that prior to changing the overnight basal insulin • If taking 1 daily dose of basal insulin, then consider increasing dose by ~10% • If taking 2 daily doses of basal insulin, then consider increasing EVENING dose by ~10% • Consider increasing bedtime snack I/C ratio, by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • Consider stopping bedtime snack • After increasing basal insulin or I/C ratio of bedtime snack, consider checking some blood sugars overnight to make sure they are not low

Glucose pattern (2-3 days)	Suggested changes
	LOW • If bedtime BG is out of range, consider correcting that prior to changing the overnight insulin. • If taking 1 daily dose of basal insulin, then consider decreasing dose by ~10 to 20% • If taking 2 daily doses of basal insulin, then consider decreasing EVENING dose by ~10 to 20% • Consider decreasing bedtime snack I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • Consider adding protein or fat to bedtime snack
BG post-breakfast	**HIGH** • Consider increasing Breakfast I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10)
	LOW • Consider Decreasing Breakfast I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20)
BG pre-lunch	**HIGH** • Consider increasing morning snack I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • Consider stopping morning snack

SUPPLEMENTARY DATA

Glucose pattern (2-3 days)	Suggested changes
	LOW • Consider decreasing morning snack ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • Consider adding morning snack if no current morning snack
BG post-lunch	**HIGH** • Consider increasing lunch I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10)
	LOW • Consider decreasing the Lunch I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20)

Glucose pattern (2-3 days)	Suggested changes
BG pre-dinner	**HIGH** • Consider eliminating afternoon snack or increase snack I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • If BG post lunch in range, and taking 1 daily dose of basal insulin, then consider increasing dose by ~10% • If BG post lunch in range, and taking 2 daily doses of basal insulin, then consider increasing MORNING dose by ~10% • After increasing basal insulin, consider checking some blood sugars overnight to make sure they are not low
	LOW • Consider decreasing the afternoon snack I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • If BG post lunch in range, and taking 1 daily dose of basal insulin, then consider decreasing dose by ~10 to20% • If BG post lunch in range, and taking 2 daily doses of basal insulin, then consider decreasing MORNING dose by ~10 to 20%
BG post-dinner or Bedtime	**HIGH** • Consider increasing dinner I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • After increasing dinner I/C ratio, consider checking some blood sugars overnight to make sure they are not low

Glucose pattern (2-3 days)	Suggested changes
	LOW • Consider decreasing dinner I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20)

Insulin Dose Adjustment Guidelines for Pump Therapy

Before making changes to insulin per gram of carbohydrate (I/C ratio), it is recommended that the amount of high blood glucose correction bolus (sliding scale) regular insulin (regular) or rapid-acting insulin analogue (RAI) coverage is evaluated for appropriateness.

Glucose pattern (2-3 days)	Suggested changes
BG pre-breakfast	**HIGH** • If bedtime BG is out of range, consider correcting that prior to changing the overnight basal insulin. • Consider increasing the basal rate by ~10% from midnight to 1 hour prior to pre-breakfast BG check • Consider increasing bedtime snack I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • Consider stopping bedtime snack • After increasing overnight basal insulin or I/C ratio of bedtime snack, consider checking some blood sugars overnight to make sure they are not low

Glucose pattern (2-3 days)	Suggested changes
	LOW • If bedtime BG is out of range, consider correcting that prior to changing the overnight basal insulin. • Consider decreasing the basal insulin rate by ~10 to 20% starting ~3-4 hours before morning BG is checked • Consider decreasing bedtime snack I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • Consider adding protein or fat to bedtime snack
BG post-breakfast	**HIGH** • Consider increasing breakfast I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10)
	LOW • Consider decreasing breakfast I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20)
BG pre-lunch	**HIGH** • Consider increasing morning snack I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • Consider stopping morning snack Consider increasing the basal rate by ~ 10% for the period after breakfast to before lunch

Glucose pattern (2-3 days)	Suggested changes
	LOW • Consider decreasing morning snack ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • Consider adding morning snack if no current morning snack Consider decreasing the basal rate by ~10 to 20% for the period after breakfast to before lunch
BG post-lunch	**HIGH** • Consider increasing lunch I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10)
	LOW • Consider decreasing the Lunch I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20)

Glucose pattern (2-3 days)	Suggested changes
BG pre-dinner	**HIGH** • Consider eliminating afternoon snack or increasing snack I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) Consider increasing the basal rate by ~ 10% for the period after lunch to before dinner
	LOW • Consider decreasing the afternoon snack I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) Consider decreasing the basal rate by ~10 to 20% for the period after lunch to before dinner
BG post-dinner or Bedtime	**HIGH** • Consider increasing dinner I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • If BG post-dinner not high, but BG at bedtime is high, then consider increasing the basal rate by ~10% between dinner and Bedtime After increasing dinner I/C ratio or basal insulin, consider checking some blood sugars overnight to make sure they are not low

Glucose pattern (2-3 days)	Suggested changes
	LOW • Consider decreasing dinner I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) If BG post-dinner not low, but BG at bedtime is low, then consider decreasing the basal rate by ~10 to 20% between dinner and Bedtime

Inclusion and Exclusion Criteria

Inclusion Criteria

To participate in the trial, patients had to meet all of the following criteria:

- Men or nonpregnant women age ≥18 to ≤ 75 years of age with a diagnosis of type 1 diabetes (T1D) made at least 1 year prior to informed consent
- Treatment with insulin or insulin analog(s) delivered via continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI) with no change in insulin delivery (CSII to MDI or vice-versa) within 3 months of screening
- A1C 7.0% to 11.0%, inclusive, at screening
- Willing and able to perform SMBG and complete the study diary as required per protocol
- For women of childbearing potential, use of an adequate method of contraception to avoid pregnancy for the duration of the study through 30 days after the last dose of study drug

Exclusion Criteria

- Patients meeting any of the following criteria were excluded from the study:
- Use of antidiabetic agent other than insulin at the time of screening (any medication other than insulin or insulin analog used for treatment of T1D must be washed out for at least 8 weeks prior to the screening visit)
- Any prior exposure to sotagliflozin
- Use of any sodium glucose cotransporter (SGLT) inhibitors within 8 weeks prior to screening

- Chronic systemic corticosteroid use, defined as any dose of systemic corticosteroid taken for more than 4 consecutive weeks within the 6 months prior to the screening visit. Topical, inhaled, ocular, or nasal sprays containing corticosteroids were allowed.
- Type 2 diabetes, or severely uncontrolled diabetes as determined by the Investigator
- History of severe hypoglycemic event within 1 month prior to the screening visit
- History of DKA within 1 month prior to screening visit, or more than 2 episodes within 6 months prior to the screening visit
- History of nonketotic hyperosmolar state within 6 months prior to the screening visit
- Estimated glomerular filtration rate <45 mL/min/1.73 m^2 at screening, as determined by the 4 variable Modification of Diet in Renal Disease (MDRD) equation
- Fasting triglycerides >600 mg/dL (>6.77 mmol/L)
- Abnormal liver function at screening defined as any of the following: aspartate aminotransferase (AST) >2X upper limit of the normal reference range (ULN), ALT >2X ULN, serum total bilirubin (TB) >1.5X ULN
- Beta-hydroxy butyrate (BHB) >0.6 mmol/L at screening
- Pregnant or breastfeeding or intend to be during the course of the study
- Current infectious liver disease (hepatitis A, B, or C), including antihepatitis A virus (immunoglobulin M), hepatitis B surface antigen, or antihepatitis C virus
- Difficulty swallowing such that the patient cannot take the study drug
- History of pancreatitis within 12 months of screening, or any prior history of recurrent pancreatitis
- Initiation of chronic dialysis within 30 days prior to the screening visit or expected to occur within 180 days after the screening visit

- Renal disease that required treatment with immunosuppressive therapy, or a history of dialysis or renal transplant
- History of hereditary glucose-galactose malabsorption or primary renal glucosuria
- New York Heart Association Class III or IV heart failure within 3 months prior to screening visit
- Hypertensive urgency or emergency within 30 days prior to randomization
- Patients with unstable/symptomatic or life-threatening arrhythmia or heart block
- Hospitalization due to unstable angina, myocardial infarction, or coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty within 3 months of screening
- Transient ischemic attack (TIA) or significant cerebrovascular disease
- History of hemoglobinopathies (sickle cell anemia, thalassemia major, sideroblastic anemia) or other disorder that may interfere with A1C determination
- Donation or loss of >400 mL of blood or blood product(s) within 8 weeks prior to screening
- Known severe immunocompromised status, including, but not limited to, patients who have undergone organ transplantation (Patients with human immunodeficiency virus (HIV) were permitted if the Investigator considered them otherwise suitable candidates)
- Malignancy or active treatment for malignancy (ie, radiation or chemotherapy, including monoclonal antibodies) within 5 years prior to the screening visit
- Current eating disorder or increase or decrease of weight within the 12 weeks prior to screening by more than 10%

- Known allergies, hypersensitivity, or intolerance to sotagliflozin or any inactive component of sotagliflozin or placebo (ie, microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicon dioxide, and magnesium stearate [nonbovine]), unless the reaction is deemed irrelevant to the study by the Investigator
- Administration of any other investigational drug or participation in an interventional clinical research study within 30 days or 5 half-lives (whichever is longer) of planned screening visit
- History of alcohol or illicit drug abuse within 12 months prior to the screening visit
- Patient is a study coordinator, employee of an Investigator or Investigator's site, or immediate family member of any of the aforementioned
- Any condition that, in the opinion of the Investigator, may render the patient unable to complete the study
- The presence of a clinically significant medical history, physical examination, or laboratory finding that, in the opinion of the Investigator or the Sponsor, may interfere with any aspect of study conduct or interpretation of results

DKA and SH Procedures

Definition of Hypoglycemia

Documented hypoglycemia (SMBG ≤3.9 mmol/L [≤70 mg/dL] regardless of symptoms) was not considered an adverse event (AE) unless it was characterized as a serious AE.

Severe hypoglycemia was defined as an event consistent with hypoglycemia (regardless of whether biochemical documentation of a low glucose value was obtained) when the answer was yes to any of the following three questions:

- Did the patient have an episode of suspected hypoglycemia treated with any form of carbohydrate or with glucagon that required the assistance of others to treat?
- Did the patient lose consciousness during the episode?
- Did the patient have a seizure during the episode?

The phrase “patient requires the assistance of others to treat” meant that the neurologic impairment was severe enough to prevent self-treatment in the opinion of those providing assistance to treat. Assisting a patient out of kindness, when assistance is not required, was not considered as “requiring the assistance of others to treat.”

The following terms were used to identify possible severe hypoglycemia events:

Coma	Hypoglycemic seizure
Convulsions	Hypoglycemic unconsciousness
Hypoglycemic coma	Loss of consciousness
Hypoglycemic encephalopathy	Shock hypoglycemia

Note: only those hypoglycemic cases which met criteria for severe hypoglycemia as defined in the protocol or those reported as a serious AE were submitted to the clinical endpoint committee for adjudication.

Definition of Diabetic Ketoacidosis

DKA was diagnosed based on evidence of anion-gap metabolic acidosis related to excessive ketone production without a satisfactory alternative cause for anion-gap acidosis, as outlined in Kitabchi et al 2009, which was also provided to all investigators.[1] However, final diagnosis of metabolic acidosis, including diabetic ketoacidosis, was made by the adjudication committee. All possible DKA events were adjudicated and were classified as “Yes, with certainty”; “Yes, probably”; “No, unlikely”; “No, with certainty”; “Unclassifiable”; or “Insufficient data,” and events meeting either “Yes” criterion (with certainty or probably) were assessed as positively adjudicated.

Diabetic Ketoacidosis Events. The following ketosis-related adverse event terms were used to identify possible metabolic acidosis or diabetic ketoacidosis events:

Trigger terms typically associated with elevated BHB	**Trigger terms that may not be associated with elevated BHB**
Acetonemia	Acidosis
Blood ketone body	Acidosis hyperchloremic
Blood ketone body increased	Diabetic coma
Blood ketone body present	Diabetic hyperglycemic coma
Diabetic ketoacidosis	Diabetic metabolic decompensation
Diabetic ketoacidotic hyperglycemic coma	Hyperglycemic coma
Ketoacidosis	Hyperglycemic seizure
Ketosis	Hyperglycemic unconsciousness
Urine ketone body	Lactic acidosis
Urine ketone body present	Metabolic acidosis
	Renal tubular acidosis
	Uremic acidosis

Patient and Provider Instructions to Mitigate Diabetic Ketoacidosis and Other Adverse Events

Wallet Card

Study LX4211.1-310-DM
EudraCT number 2014-005153-39

Lexicon Pharmaceuticals, Inc.
PO Box: 132167
The Woodlands, Texas 77393-2167

Study Title:
A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of LX4211 as Adjunct Therapy in Adult Patients with Type 1 Diabetes Mellitus Who Have Inadequate Glycemic Control with Insulin Therapy

If you have any concerns regarding the study or if major changes in your health condition occur, contact your study doctor.

If you see another health care professional or are admitted to a hospital between study visits, you must tell them that you are taking part in this study, and that they can contact your study doctor for information.

You should also inform your study doctor as soon as possible if you see another health care professional or are admitted to a hospital between study visits.

After starting the study medication, you are requested to visit our clinic and after completing study treatment , you will be asked to return to the clinic once more for follow up, approximately 1 week after your final dose of study medication.

24 HOUR EMERGENCY NUMBER
(the following numbers should only be used by medical staff in case of emergency only. The numbers are not to be used by patients or family members):

[redacted]

Patient contact Card, Core English Version 3.0 dated 30NOV2015

Study LX4211.1-310-DM
EudraCT number 2014-005153-39

Please carry this card with you for the duration of the trial

Mr/Ms _____is currently participating in a blinded clinical study and has received study medication containing either the investigational study drug LX4211, or placebo beginning on _____.
(date of first dose)

This phase III study is investigating the new drug LX4211 in patients with Type 1 diabetes mellitus.

Note: DKA is always preceded by ketosis. It is possible that in patients taking SGLT inhibitors, ketosis or DKA may present with non-specific / vague symptoms, and normal or low blood glucose levels, rather than high blood glucose which is traditionally associated with DKA. To correct ketosis / acidosis, it is vital to ensure that rapid acting insulin is administered frequently regardless of blood sugar levels (even if blood sugar is not elevated). Glucose containing foods or liquids should be given when this extra insulin is administered.

Subject Identification Number #

_____

First study drug bottle number assigned at randomization

_____

If any problems occur please contact:

_____
(Clinic, Department)

Dr. _____

Address _____

Phone _____

Patient contact Card, Core English Version 3.0 dated 30NOV2015

Recommendations Letter

Lexicon pharmaceuticals

To: LX4211.1- 310 Investigators and Study Coordinators

From: [redacted]

Re: Protocol LX4211.1-310-T1DM

A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of LX4211 as Adjunct Therapy in Adult Patients with Type 1 Diabetes Mellitus Who Have Inadequate Glycemic Control with Insulin Therapy

Date: 01 October 2015

Dear Investigators and Study Coordinators,

This correspondence is being shared with you as an expert recommendation to mitigate DKA risk in T1D patients taking SGLT2 inhibitors (presentations at EASD and ADA).

*Note: *These recommendations also apply for patients enrolled in all sotagliflozin (LX4211) trials*

- Never forget that DKA CAN occur with low, normal or high blood sugars in T1D patients taking SGLT inhibitors
- Any T1D patient using an SGLT inhibitor MUST be adherent to ketone testing
  - Urine Ketones can be used as screen
  - Blood Ketones (BHB) should be used to
    - Establish degree of ketosis – is it above 0.6 mmol/L?
    - Inform decision-maker: is ketosis improving or worsening?
- Test ketones for general malaise, abdominal pain, not eating, more physically active, or drinking ETOH, REAGARDLESS of BG level
- If ketones positive (blood ketones ≥ 0.6 mmol/L or urine ketones moderate or higher)
  - Hold the SGLT inhibitor
  - Do not hold insulin, consider increasing basal insulin
  - Consume 15-30 grams of carbs each hour (glucose containing sports drink/oral rehydration fluid)
  - Give bolus insulin (by pen/syringe) for the carbs EVEN if BG normal
  - Make sure patient has antiemetic

Instructions provided for DKA Recognition and Management in the sotagliflozin protocols:

Instructions for the patient and site staff:
It is possible that GI or other AEs occurring with LX4211 may mask presenting symptoms of DKA (Appendix H). Therefore, it is important that patients with GI complaints or intercurrent illness be instructed by the site to measure their blood or urine ketone or blood BHB levels.

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These symptoms include but are not limited to: inability to maintain oral intake, generalized weakness, excessive thirst, abdominal pain, nausea, vomiting, rapid weight loss, fever, frequent urination, fruity-scented breath, confusion, acute illness and or consistently elevated blood glucose.
If a patient is scheduled for a procedure or surgery that requires withholding oral intake (NPO), it is recommended that study drug is held from the day prior to procedure or surgery and resumed the day after procedure or surgery is complete and patient is tolerating adequate oral intake.

At every clinic visit blood BHB (central laboratory and point-of-care) testing will be conducted. At visits where UA is performed, the evaluation will include urine ketone determination by dipstick. If the urine ketones are positive or blood BHB level is >0.6 mmol/L, the patients will be asked to contact the investigative site immediately. In this situation, the patient should take additional rapid acting insulin by syringe (not insulin pump) according to the correction dose algorithm provided by the Investigator. Typically the additional rapid acting insulin dose is given every 2 hours until normalization of glucose and urine ketone (or glucose and blood BHB level). The site will evaluate if an assessment for metabolic acidosis is appropriate. If laboratory testing confirms presence of metabolic acidosis, then the "Possible DKA" eCRF will be completed.

If nausea and vomiting are present and the patient is unable to keep liquids down, the patient should be evaluated in an Emergency Room.

Ketone testing in sotagliflozin protocols:

- BHB POC and central lab is tested at every clinic visit
- Ketostix (or similar) for home use are provided to all patients at the Screening visit
- BHB meter and testing strips for home use are provided to all patients at the Run-in visit (Week -2)
- Whenever a patient has symptoms suspicious for DKA (as noted in paragraph 1 above), they must use Ketostix (or similar) to check for urine ketones as a screen. If urine ketones are positive, then use BHB meter to determine if BHB > 0.6 mmol/L. If BHB > 0.6 mmol/L, patients must call the site for further instructions.

Aligned with testing of BHB in all sotagliflozin T1D studies, any BHB result > 0.6 mmol/L is being closely monitored. If a patient randomized in a sotagliflozin study at your site meets the threshold of BHB > 0.6 mmol/L, you will receive a query from the Covance Medical Monitor asking for confirmation of patient's clinical status, based on which further testing may be necessary (including repeating central and POC BHB test to follow resolution of ketosis). Please respond to these queries within 2 business days. If you have any question related to BHB testing or interpretation, please do not hesitate to contact the Covance Medical Monitor.

Sincerely,

[redacted]

Lexicon Pharmaceuticals, Inc.

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Protocol Instructions for the Patient and Site Staff

At every clinic visit blood BHB (central laboratory and point-of-care) testing will be conducted. At visits where UA is performed, the evaluation will include urine ketone determination by dipstick.

It is possible that GI or other AEs occurring with LX4211 may mask presenting symptoms of diabetic ketoacidosis. These symptoms include but are not limited to: inability to maintain oral intake, generalized weakness, excessive thirst, abdominal pain, nausea, vomiting, rapid weight loss, fever, frequent urination, fruity-scented breath, confusion, acute illness and/or consistently elevated blood glucose. Therefore, it is important that patients with GI complaints or intercurrent illness be instructed by the site to measure their blood or urine ketone or blood BHB levels. (Note: In some patients alcohol may be a possible trigger for ketosis).

If ketosis is present (moderate or higher for urine ketones or blood BHB level is >0.6 mmol/L), then the patient will be asked to contact the Investigative site immediately. In this situation, the investigator should consider instructing the patient to take rapid acting insulin by syringe (not insulin pump) as well as eat carbohydrates in order to reverse the ketosis. After rechecking the ketones, the investigator should consider instructing the patient to take additional doses of rapid acting insulin every 2 hours until elevated ketones are normalized. Because the amount of insulin needed to lower ketones will also lower blood glucose, it is necessary for the patient to increase carbohydrate intake. Typically this would be 15-30 grams of carbohydrate each hour provided by a glucose containing sports drink or oral rehydration fluid. The site will evaluate if an assessment for metabolic acidosis is appropriate. If laboratory testing confirms presence of metabolic

acidosis, then the “Possible diabetic ketoacidosis” eCRF will be completed. If nausea and vomiting are present and the patient is unable to keep liquids down the patient should be evaluated in an Emergency Room.

If a patient is scheduled for a procedure or surgery that requires withholding oral intake (NPO), it is recommended that study drug is held from the day prior to procedure or surgery and resumed the day after procedure or surgery is complete and patient is tolerating adequate oral intake.

An independent adjudication committee composed of experts in T1D will adjudicate cases of diabetic ketoacidosis (including all cases of metabolic acidosis) in a blinded fashion.

Patient Communication Card Text

The following list may help you to recognize Diabetic Ketoacidosis (DKA).

- Inability to maintain oral intake
- Generalized weakness
- Abdominal (belly) pain
- Increased weight loss
- Fever
- Frequent urination, including at night
- Fruity-scented breath
- Confusion
- Acute illness

- Consistently elevated blood glucose
- Feeling very thirsty or drinking a lot
- Nausea or vomiting
- Having trouble thinking clearly or feeling tired

It is possible to have DKA even if your blood glucose is not elevated. Regardless of your blood glucose level, if you have any of these symptoms on the list, then measure your blood or urine ketone or blood BHB level. If the urine ketones are high (your study doctor may instruct you that this is a level of “moderate” or more than “moderate”) or blood BHB level is above 0.6 mmol/L, then contact your study site immediately for assistance with managing your diabetes.”

In some patients alcohol use may lead to production of ketones by your body.

If you are scheduled for a procedure or surgery that requires you to not take any food or liquids, please contact your study doctor for instructions on continuing study drug. In such cases your study doctor may advise you NOT to take your study drug from the day prior to the procedure or surgery until after the procedure or surgery is complete, and you are taking food and liquids as you normally do.

Statistical Approaches

Efficacy Analyses

The primary dataset used to conduct the efficacy analyses was modified intent-to-treat (mITT) population, which included all randomized patients who had taken at least 1 dose of study drug.

The 24-week core treatment period data was used to satisfy analysis requirements for the primary and secondary efficacy endpoints. Use of the long-term extension period data was to be used in a supplemental manner for efficacy comparisons and to provide long term data on safety. The primary analysis of the primary efficacy endpoint used mixed-effects model for repeated measures (MMRM) statistics based on the restricted maximum likelihood (REML) method for estimation. The analysis model included fixed, categorical effects of treatment, insulin delivery (MDI, CSII), week -2 A1C (≤8.5%, >8.5%), time (study week), baseline A1C-by-time interaction, and a treatment-by-time interaction. An unstructured (co)variance structure was used to model the within-patient errors. Other structures may have been explored by use of Akaike's information criteria if the unstructured (co)variance structure did not result in model convergence. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. The adjusted mean change in A1C from baseline to week 24 for each treatment group were estimated in the framework of this model (ie, least squares mean), as well as the between-group differences (comparing LX4211 to placebo) and the 95% confidence intervals for the adjusted mean. All post-baseline observations collected at scheduled visits were used in the MMRM, including data collected after the discontinuation of study drug.

SUPPLEMENTARY DATA

A key assumption for drawing valid conclusions using the MMRM analysis was that the reason for missing data was expected to be a function of the missing at random (MAR) mechanism. This appeared to be a reasonable assumption for this particular dataset. Since one cannot be fully certain that other mechanisms can underlie the reason for missing data (eg, missing not at random; MNAR), it was important to perform sensitivity analyses of the MMRM results. Under an assumption of MNAR, several statistical models were proposed to analyze the data: 2 of the more commonly employed methods being the Pattern Mixture Model (PMM) and the selection model. Of these candidate models, the PMM method with control-based pattern imputation was used in the sensitivity analysis for this study. Methods were adopted to estimate for both non-monotone and monotone missing data patterns. Imputations for the non-monotone missing data pattern were the initial step, used an imputation algorithm based on Monte Carlo Markov Chain methodology, and assumed a MAR mechanism for the missing data. Multiple imputations were performed to assign the response variable at consecutive study weeks in a sequential manner for the monotone missing data pattern. For this chain-based method, control-based imputation was applied so that there was no direct use of observed data from the LX4211 treatment groups in estimating the imputation model. The method was derived such that it built its imputation only on the placebo group data. The resulting imputed datasets were analyzed by an analysis of covariance (ANCOVA) model fitted for the fixed, categorical effects of treatment, insulin delivery method (MDI, CSII), Week -2 A1C (≤8.5%, >8.5%), and the continuous, fixed covariate of baseline A1C. Summary statistics from applying the ANCOVA model across the multiple imputed datasets were combined to yield an overall estimate of the treatment group differences. The PMM analysis was applied to primary and secondary efficacy endpoints.

Continuous secondary and other endpoints were summarized using standard descriptive statistics, and in many instances, the treatment effects were evaluated using MMRM statistics as specified for the primary efficacy analysis with the replacement of the baseline A1C- by-time interaction specific to the dependent variable under test. An ANCOVA analysis was applied where only 1 post-baseline scheduled visit occurred. All post-baseline data at scheduled visits were used in these analyses, including observations occurring after discontinuation of study drug.

For binary endpoints, the frequency and percent of outcome were presented by treatment group. The primary analysis of these endpoints used a Cochran-Mantel-Haenszel (CMH) test stratified by the different levels of the randomization stratification factors of insulin delivery method (MDI, CSII) and week -2 A1C (≤8.5%, >8.5%). The treatment group comparisons were performed separately at week 24 only, with descriptive statistics provided for each clinic visit. Missing observations at week 24 were imputed as nonresponse.

Multiplicity in statistical testing of the efficacy variables at week 24 occurred from 2 main sources: (a) testing of the primary endpoint and multiple secondary endpoints, and (b) testing of two sotagliflozin dose groups against placebo for each endpoint. These considerations yielded 14 hypotheses to be tested that were grouped into seven families. Each family corresponded to the specific endpoint under test. Family F1 consisted of the sotagliflozin 200 mg versus placebo and sotagliflozin 400 mg versus placebo comparisons for the primary endpoint. Family F2 included the same treatment group comparisons for the first listed secondary endpoint; F3 included the same comparisons for the second listed secondary endpoint, and so on. The seven families were to be tested sequentially with the restriction that the test of each treatment group

comparison required all prior tests of that particular comparison to meet statistical significance criteria. The primary endpoint hypotheses were to be tested by a Bonferroni procedure with $\alpha = 0.05$ (2-sided) and use of equal weights so that the per comparison error rate = 0.025 (2-sided). The raw *P* value for each treatment contrast was to be compared with $\alpha = 0.025$ and if the raw *P* value was less than or equal to 0.025, the comparison was to be declared statistically significant and testing for that contrast could proceed to the next listed endpoint. Consistent with testing the primary endpoint, the family-wise error rate (FWER) within each secondary endpoint family was 0.05 (2-sided), and with hypothesis weights of 0.5 assigned to each contrast within each testable family, the per comparison α-level = 0.025 (2-sided). Assessment of the testable hypotheses for the secondary endpoints was to be made in the same manner that was applied to the primary endpoint. Formal testing of a particular treatment comparison was to stop at that endpoint for which a raw *P* value exceeded 0.025. Progression in testing across the hypothesis families was to be carried out, in essence, using a tree gatekeeping test procedure so that the study-wise error rate across all primary and secondary hypotheses tested was to be strongly controlled at $\alpha = 0.05$. This procedure was not applied to the week 52 comparisons.

Subgroup Analyses

Subgroup analyses of the primary efficacy variable were to be performed for different categories of Baseline characteristics and the randomization stratification factors. Analysis of treatment effects for each subgroup was to use a MMRM model that included fixed, categorical effects of treatment, insulin delivery (MDI, CSII; excluded if it was a subgroup variable), week -2 A1C (≤8.5%, >8.5%; excluded if it was a subgroup variable), time (study week), baseline A1C-by-time interaction, and a treatment-by-time interaction.

In addition, change from baseline in SBP (mm Hg) at week 12 was to be summarized and analyzed using MMRM model fitted for the fixed, categorical effects of treatment, insulin delivery (MDI, CSII), Week -2 A1C (≤8.5%, >8.5%), time (study week), baseline SBP-by-time interaction, and a treatment-by-time interaction for the following subgroups:

- Baseline SBP <130 mm Hg
- Baseline SBP ≥130 mm Hg

All subgroup analyses were to be exploratory.

Safety Analyses

Safety analysis primarily involved examination of descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Summaries were prepared by treatment group and, as needed, by clinic visit. These summaries were based on the safety population and other subpopulations as needed. All safety data (adverse events [AEs], events of special interest, laboratory test results, vital signs, electrocardiogram (ECG) results, and physical examinations) were provided in listings.

Vital signs, physical examination findings, laboratory results, and ECGs were summarized descriptively at each study visit. Actual and change from baseline data were calculated and summarized. In addition, shift table analyses were presented for the laboratory data.

Because of the importance of hypoglycemia in this patient population, various measures of this variable were analyzed. Change from baseline in hypoglycemic events calculated as a daily average over the week prior to the visit was to be analyzed as a continuous variable as described

previously. Since events data also served as a measure of safety, additional analyses were conducted. The first analysis of hypoglycemic events was conducted using CMH tests stratified by the randomization factors at each study visit. These tests provided inferential and descriptive summaries of the relative risk estimate for each of the four hypoglycemic event definitions: ≤3.8 mmol/L (≤70 mg/dL) by SMBG, ≤3.9 mmol/L (<70 mg/dL) by CGM, ≤3.0 mmol/L (≤55 mg/dL) by SMBG, and ≤3.0 mmol/L (<55 mg/dL) by CGM. The patient incidence of these hypoglycemic events was counted over the week prior to the scheduled study visit used in the analysis. The second analysis of these data examined the relative risk for each of the hypoglycemic event definitions over the entire core treatment period by use of a generalized linear model (GLM). The GLM included fixed, categorical effects of treatment, randomization strata of insulin delivery method (MDI, CSII), randomization strata of Week -2 A1C (≤8.5%, >8.5%), and an offset term for the log of the treatment duration during the core treatment period (first 24 weeks). The event rates were modeled as a negative binomial process. Similarly, event rates during the overall treatment period were to be modeled using the GLM model, with log of the total treatment duration as the offset term.

Adverse Events

All AEs were coded and listed by body system and preferred term based on Medical Dictionary for Regulatory Activities (MedDRA). Summaries using descriptive statistics were provided for treatment-emergent AEs, drug-related AEs, and AEs by intensity. Treatment-emergent AEs (TEAEs) were those events not present at baseline, but occurring after the start of study treatment, or if existing at baseline, increasing in intensity after the initiation of study drug. When multiple occurrences of the same event were reported for the same patient, summaries

made by intensity selected the event with the highest intensity. In a similar manner, summaries prepared by drug relationship selected the event with the greatest degree of relationship when a patient reports multiple occurrences of the same event. Summaries of TEAEs were presented for the 24-week core treatment period, the 28-week long term extension period, and the overall treatment period by treatment group for the safety population. TEAE displays were to include the overall incidence (by system organ class and preferred term), events by maximum intensity, events by relationship to study drug, events leading to discontinuation of study drug, events of special interest, and serious adverse events.

On-study deaths were reported for deaths occurring during the active phase of the treatment period and 30 days after stopping study drug. Also, deaths occurring outside the 30-day window, but secondary to an AE reported within the 30-day post-treatment period, were reported. Listings were provided for deaths, SAEs, and discontinuations due to AEs.

Volume Depletion Events

The following terms were used to identify possible volume depletion events.

Acute prerenal failure
Blood pressure abnormal
Blood pressure ambulatory abnormal
Blood pressure ambulatory decreased
Blood pressure decreased
Blood pressure diastolic abnormal
Blood pressure diastolic decreased
Blood pressure fluctuation
Blood pressure immeasurable
Blood pressure inadequately controlled
Blood pressure orthostasis abnormal
Blood pressure orthostatic decreased
Blood pressure systolic abnormal
Blood pressure systolic decreased
Blood pressure systolic inspiratory decreased
Brachial pulse abnormal
Brachial pulse decreased
Brachial pulse increase
BUN/creatinine ratio increased
Capillary nail refill test abnormal
Cardiac index abnormal
Cardiac index decreased
Cardiac output decreased
Cardiogenic shock
Cardiovascular insufficient
Carotid pulse abnormal
Carotid pulse decreased
Central venous pressure abnormal
Central venous pressure decreased
Circulatory collapse
Decreased ventricular preload
Dehydration
Diastolic hypotension
Distributive shock
Femoral pulse abnormal
Femoral pulse decreased
Hemodynamic test abnormal
Heart rate abnormal
Heart rate decreased
Heart rate increased
Heart rate irregular

Hypoperfusion
Hypotension
Hypovolemia
Hypovolemic shock
Labile blood pressure
Left ventricular end-diastolic pressure decreased
Maximum heart rate decreased
Mean arterial pressure decreased
Orthostatic heart rate response increased
Orthostatic hypotension
Orthostatic intolerance
Pedal pulse abnormal
Pedal pulse decreased
Peripheral circulatory failure
Peripheral coldness
Peripheral pulse decreased
Popliteal pulse abnormal
Popliteal pulse decreased
Prerenal failure
Presyncope
Pulse abnormal
Pulse absent
Pulse pressure abnormal
Pulse pressure decreased
Pulse volume decreased
Pulse waveform abnormal
Radial pulse abnormal
Radial pulse decreased
Renal ischemia
Schelling test
Shock
Stress polycythemia
Syncope
Thirst
Tilt table test positive
Urine albumin/creatinine ratio increased
Urine flow decreased
Urine output decreased
Urine protein/creatinine ratio increased
Vascular test abnormal
Venous pressure abnormal
Venous pressure decreased
Venous pressure jugular abnormal
Venous pressure jugular decreased
Volume blood decreased

Renal Events

The following terms were used to identify possible renal events.

Acute prerenal failure
Anuria
Azotemia
Blood creatine abnormal
Blood creatine decreased
Blood creatine increased
Blood creatinine abnormal
Blood creatinine decreased
Blood creatinine increased
Blood urea abnormal
Blood urea increased
Blood urea nitrogen/creatinine ratio increased
Coma uremic
Computerized tomogram kidney abnormal
Creatine urine abnormal
Creatine urine decreased
Creatine urine increased
Creatinine renal clearance abnormal
Creatinine renal clearance decreased
Creatinine urine abnormal
Creatinine urine decreased
Creatinine urine increased
Cystatin C abnormal
Cystatin C increased
Diabetic end stage renal disease
Glomerular filtration rate abnormal
Glomerular filtration rate decreased
Glomerular filtration rate increased
Hypercreatinemia
Hyperparathyroidism secondary
Inulin renal clearance abnormal
Inulin renal clearance decreased
Kidney fibrosis
Nephrogenic anemia
Nitrogen balance negative
Edema due to renal disease
Oliguria
Pericarditis uremic
Phenolsulfonphthalein test abnormal
Postoperative renal failure
Prerenal failure

Renal cortical necrosis

Renal disorder

Renal failure

Renal failure acute

Renal failure chronic

Renal function test abnormal

Renal impairment

Renal injury

Renal necrosis

Renal papillary necrosis

Renal scan abnormal

Renal tubular acidosis

Renal tubular atrophy

Renal tubular disorder

Renal tubular necrosis

Ultrasound kidney abnormal

Uremia odor

Uremic acidosis

Uremic encephalopathy

Uremic gastropathy

Uremic neuropathy

Uremic pruritus

Urea renal clearance

Urea renal clearance decreased

Urea renal clearance increased

Uridosis

Urine albumin/creatinine ratio abnormal

Urine albumin/creatinine ratio decreased

Urine albumin/creatinine ratio increased

Urine output

Urine output decreased

Urine output increased

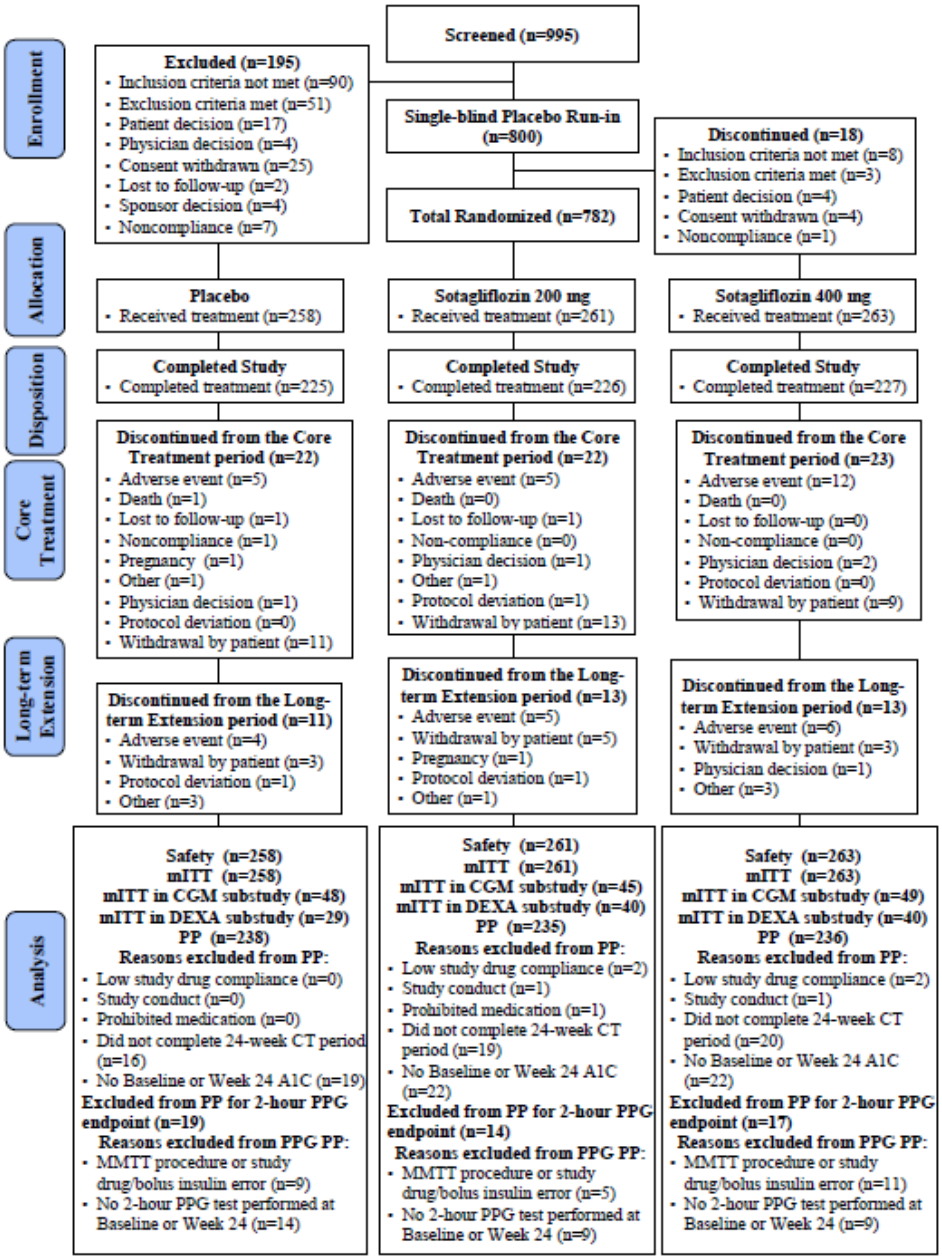
Urine protein/creatinine ration abnormal

Urine protein/creatinine ratio decreased

Urine protein/creatinine ratio increased

SUPPLEMENTARY DATA

Figure 1. Patient disposition



SUPPLEMENTARY DATA

Table 1. Baseline characteristics

Characteristic	Placebo (n=258)	Sotagliflozin 200 mg (n=261)	Sotagliflozin 400 mg (n=263)	Total (N=782)
Age (years)	39.7 (13.42)	42.3 (13.59)	41.7 (13.23)	41.2 (13.44)
Female sex, n (%)	124 (48.1)	122 (46.7)	130 (49.4)	376 (48.1)
Race or ethnic group, n (%)*				
White	250 (96.9)	252 (96.6)	250 (95.1)	752 (96.2)
Black	1 (0.4)	0	0	1 (0.1)
Asian	0	3 (1.1)	3 (1.1)	6 (0.8)
Other	7 (2.7)	6 (2.3)	10 (3.8)	23 (2.9)
Hispanic/Latino ethnicity	4 (1.6)	7 (2.7)	7 (2.7)	18 (2.3)
Diabetes duration (years)	18.1 (10.72)	18.2 (10.82)	18.9 (11.18)	18.4 (10.90)
A1C (%)	7.79 (0.881)	7.74 (0.806)	7.71 (0.819)	7.75 (0.835)
A1C (mmol/mol)	61.6 (9.63)	61.1 (8.77)	60.8 (8.95)	61.2 (9.12)
A1C <7.0% at baseline, n (%)	44 (17.1)	50 (19.2)	46 (17.5)	140 (17.9)
Fasting plasma glucose (mmol/L) (mg/dL ± SD)	8.91 (3.63) (160.5 ± 65.36)	9.09 (4.13) (163.7 ± 74.48)	9.19 (3.94) (165.5 ± 71.06)	9.06 (3.90) (163.2 ± 70.36)
Weight (kg)	81.08 (16.857)	81.93 (17.386)	81.97 (17.963)	81.66 (17.394)
Body mass index (kg/m^2)	27.50 (5.170)	27.97 (5.275)	27.85 (4.921)	27.77 (5.121)
Body mass index ≥30 kg/m^2, n (%)	72 (27.9)	84 (32.2)	78 (29.7)	234 (29.9)

Characteristic	Placebo (n=258)	Sotagliflozin 200 mg (n=261)	Sotagliflozin 400 mg (n=263)	Total (N=782)
Blood pressure (mm Hg)	123.1/76.3 (15.53/8.48)	123.0/77.4 (15.08/9.83)	123.1/76.2 (13.69/8.37)	123.1/76.6 (14.76/8.92)
Systolic blood pressure ≥130 mm Hg, n (%)	85 (32.9)	86 (33.0)	80 (30.4)	251 (32.1)
Total daily insulin dose (IU/kg)	0.75 (0.295)	0.73 (0.277)	0.74 (0.267)	0.74 (0.280)
Insulin dose (IU/day)				
Total	61.85 (30.862)	60.30 (28.963)	61.38 (28.653)	61.17 (29.472)
Basal	29.76 (14.424)	29.18 (15.808)	29.50 (14.324)	29.48 (14.851)
Bolus and corrections	32.08 (21.460)	31.12 (17.555)	31.89 (19.163)	31.70 (19.431)
Insulin therapy, n (%)				
MDI	192 (74.4)	193 (73.9)	196 (74.5)	581 (74.3)
CSII	66 (25.6)	68 (26.1)	67 (25.5)	201 (25.7)

Data are mean (SD) unless otherwise indicated.

*Determined according to patient self-report.

SUPPLEMENTARY DATA

Table 2. Primary, secondary, and other prespecified endpoints.

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
A1C (%)*						
No. patients	239	239	241	229	227	230
Baseline, mean ± SD	7.79 ± 0.881	7.74 ± 0.806	7.71 ± 0.819	7.79 ± 0.881	7.74 ± 0.806	7.71 ± 0.819
Difference from baseline, LSM ± SE	-0.02 ± 0.044	-0.39 ± 0.044	-0.37 ± 0.043	0.04 ± 0.052	-0.18 ± 0.052	-0.28 ± 0.052
95% CI	-0.11 to 0.07	-0.47 to -0.30	-0.46 to -0.29	-0.07 to 0.14	-0.28 to -0.07	-0.38 to -0.18
P value	0.63	<0.001	<0.001	0.50	<0.001	<0.001
Difference from placebo, LSM ± SE		-0.37 ± 0.058	-0.35 ± 0.058		-0.21 ± 0.071	-0.32 ± 0.071
95% CI		-0.48 to -0.25	-0.47 to -0.24		-0.35 to -0.07	-0.46 to -0.18
P value		<0.001	<0.001		0.003	<0.001
A1C (mmol/mol)						
No. patients	239	239	241	229	227	230
Baseline, mean ± SD	61.6 ± 9.63	61.1 ±8.77	60.8 ± 8.95	61.6 ± 9.63	61.1 ±8.77	60.8 ± 8.95
Difference from baseline, LSM ± SE	-0.2 ± 0.48	-4.2 ± 0.48	-4.1 ± 0.47	0.3 ± 0.57	-2.0 ± 0.57	-3.1 ± 0.57
95% CI	-1.2 to 0.7	-5.2 to -3.3	-5.1 to -3.2	-0.8 to 1.5	-3.1 to -0.9	-4.2 to -2.0

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
P value	0.62	<0.001	<0.001	0.54	<0.001	<0.001
Difference from placebo, LSM ± SE		-4.0 ± 0.64	-3.9 ± 0.64		-2.4 ± 0.78	-3.4 ± 0.77
95% CI		-5.2 to -2.7	-5.1 to -2.6		-3.9 to -0.8	-4.9 to -1.9
P value		<0.001	<0.001		0.003	<0.001
FPG (mmol/L)†						
No. patients	239	237	239	228	228	232
Baseline, mean ± SD	8.91 ± 3.628	9.09 ± 4.134	9.19 ± 3.942	8.91 ± 3.628	9.09 ± 4.134	9.19 ± 3.942
Difference from baseline, LSM ± SE	0.49 ± 0.219	-0.71 ± 0.220	-0.93 ± 0.220	0.13 ± 0.241	-0.15 ± 0.241	-0.75 ± 0.240
95% CI	0.06 to 0.92	-1.14 to -0.28	-1.36 to -0.50	-0.35 to 0.60	-0.62 to 0.33	-1.22 to -0.28
P value	0.026	0.001	<0.001	0.60	0.54	0.002
Difference from placebo, LSM ± SE		-1.20 ± 0.299	-1.42 ± 0.298		-0.27 ± 0.331	-0.87 ± 0.330
95% CI		-1.79 to -0.61	-2.01 to -0.84		-0.92 to 0.38	-1.52 to -0.23
P value		<0.001	<0.001		0.41	0.008
Body weight (kg)†						
No. patients	240	240	241	230	228	233
Baseline, mean ± SD	81.08 ±	81.93 ±	81.97 ±	81.08 ±	81.93 ±	81.97 ±

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
	16.857	17.386	17.963	16.857	17.386	17.963
Difference from baseline, LSM ± SE	0.11 ± 0.201	-1.88 ± 0.200	-2.47 ± 0.199	0.30 ± 0.257	-1.88 ± 0.257	-2.63 ± 0.255
95% CI	-0.29 to 0.50	-2.27 to -1.49	-2.86 to -2.08	-0.21 to 0.80	-2.39 to -1.38	-3.13 to -2.13
P value	0.60	<0.001	<0.001	0.25	<0.001	<0.001
Difference from placebo, LSM ± SE		-1.98 ± 0.276	-2.58 ± 0.276		-2.18 ± 0.357	-2.92 ± 0.356
95% CI		-2.53 to -1.44	-3.12 to -2.04		-2.88 to -1.48	-3.62 to -2.22
P value		<0.001	<0.001		<0.001	<0.001
Percent difference from baseline, LSM ± SE	0.10 ± 0.245	-2.38 ± 0.245	-2.99 ± 0.244	0.43 ± 0.312	-2.35 ± 0.312	-3.08 ± 0.310
95% CI	-0.38 to 0.58	-2.86 to -1.90	-3.46 to -2.51	-0.19 to 1.04	-2.96 to -1.74	-3.68 to -2.47
P value	0.69	<0.001	<0.001	0.17	<0.001	<0.001
Percent difference from placebo, LSM ± SE		-2.48 ± 0.337	-3.08 ± 0.336		-2.78 ± 0.434	-3.50 ± 0.432
95% CI		-3.14 to -1.82	-3.74 to -2.42		-3.63 to -1.93	-4.35 to -2.65
P value		<0.001	<0.001		<0.001	<0.001
Bolus insulin dose (IU)†						
No. patients	238	237	239	227	228	227

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
Baseline, mean ± SD	32.08 ± 21.460	31.12 ± 17.555	31.89 ± 19.163	32.08 ± 21.460	31.12 ± 17.555	31.89 ± 19.163
Difference from baseline, LSM ± SE	-1.19 ± 0.635	-4.38 ± 0.636	-4.78 ± 0.634	-2.71 ± 0.687	-3.79 ± 0.687	-3.80 ± 0.687
95% CI	-2.44 to 0.06	-5.63 to -3.14	-6.03 to -3.54	-4.06 to -1.36	-5.14 to -2.45	-5.15 to -2.45
P value	0.06	<0.001	<0.001	<0.001	<0.001	<0.001
Difference from placebo, LSM ± SE		-3.20 ± 0.847	-3.59 ± 0.845		-1.08 ± 0.927	-1.09 ± 0.927
95% CI		-4.86 to -1.53	-5.25 to -1.93		-2.90 to 0.74	-2.91 to 0.73
P value		<0.001	<0.001		0.24	0.24
Percent difference from baseline, LSM ± SE	5.90 ± 2.870	-7.04 ± 2.872	-10.47 ± 2.857	4.21 ± 3.246	-3.48 ± 3.239	-7.94 ± 3.232
95% CI	0.27 to 11.53	-12.68 to -1.40	-16.07 to -4.86	-2.16 to 10.58	-9.84 to 2.87	-14.28 to -1.59
P value	0.040	0.014	<0.001	0.19	0.28	0.014
Percent difference from placebo, LSM ± SE		-12.94 ± 3.851	-16.37 ± 3.840		-7.70 ± 4.405	-12.15 ± 4.400
95% CI		-20.50 to -5.38	-23.90 to -8.83		-16.35 to 0.95	-20.79 to -3.51

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
P value		<0.001	<0.001		0.08	0.006
Total daily insulin dose (IU)						
No. patients	238	237	239	226	228	227
Baseline, mean ± SD	61.85 ± 30.862	60.30 ± 28.963	61.38 ± 28.653	61.85 ± 30.862	60.30 ± 28.963	61.38 ± 28.653
Difference from baseline, LSM ± SE	-0.92 ± 0.778	-5.72 ± 0.780	-5.87 ± 0.776	-1.98 ± 0.847	-4.79 ± 0.845	-5.35 ± 0.844
95% CI	-2.44 to 0.61	-7.25 to -4.19	-7.40 to -4.35	-3.64 to -0.32	-6.45 to -3.13	-7.00 to -3.69
P value	0.24	<0.001	<0.001	0.020	<0.001	<0.001
Difference from placebo, LSM ± SE		-4.80 ± 1.043	-4.96 ± 1.039		-2.81 ± 1.144	-3.37 ± 1.143
95% CI		-6.85 to -2.76	-7.00 to -2.92		-5.06 to -0.57	-5.61 to -1.13
P value		<0.001	<0.001		0.014	0.003
Percent difference from baseline, LSM ± SE	0.55 ± 1.317	-7.68 ± 1.319	-8.92 ± 1.312	0.61 ± 1.480	-5.65 ± 1.476	-7.57 ± 1.473
95% CI	-2.03 to 3.14	-10.27 to -5.09	-11.49 to -6.34	-2.30 to 3.51	-8.55 to -2.75	-10.46 to -4.68
P value	0.67	<0.001	<0.001	0.68	<0.001	<0.001

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
Percent difference from placebo, LSM ± SE		-8.23 ± 1.755	-9.47 ± 1.749		-6.26 ± 2.000	-8.17 ± 1.997
95% CI		-11.68 to -4.79	-12.90 to -6.04		-10.18 to -2.33	-12.09 to -4.25
P value		<0.001	<0.001		0.002	<0.001
Basal insulin dose (IU)						
No. patients	238	239	241	226	229	229
Baseline, mean ± SD	29.76 ± 14.424	29.18 ± 15.808	29.50 ± 14.324	29.76 ± 14.424	29.18 ± 15.808	29.50 ± 14.324
Difference from baseline, LSM ± SE	0.24 ± 0.393	-1.34 ± 0.393	-1.14 ± 0.390	0.62 ± 0.442	-1.08 ± 0.442	-1.58 ± 0.439
95% CI	-0.53 to 1.01	-2.11 to -0.57	-1.91 to -0.38	-0.25 to 1.49	-1.95 to -0.22	-2.44 to -0.72
P value	0.54	<0.001	0.004	0.16	0.014	<0.001
Difference from placebo, LSM ± SE		-1.59 ± 0.531	-1.38 ± 0.529		-1.70 ± 0.603	-2.20 ± 0.601
95% CI		-2.63 to -0.54	-2.42 to -0.34		-2.89 to -0.52	-3.38 to -1.02
P value		0.003	0.009		0.005	<0.001
Percent difference from baseline, LSM ± SE	1.66 ± 1.576	-4.16 ± 1.573	-3.01 ± 1.563	3.22 ± 1.757	-3.51 ± 1.754	-3.46 ± 1.743

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
95% CI	-1.43 to 4.75	-7.24 to -1.07	-6.08 to 0.05	-0.23 to 6.67	-6.95 to -0.06	-6.88 to -0.04
P value	0.29	0.008	0.054	0.07	0.046	0.047
Percent difference from placebo, LSM ± SE		-5.82 ± 2.152	-4.67 ± 2.144		-6.73 ± 2.416	-6.68 ± 2.407
95% CI		-10.04 to -1.59	-8.88 to -0.47		-11.47 to -1.99	-11.41 to -1.96
P value		0.007	0.030		0.005	0.006
SBP, mITT population (mm Hg)						
No. patients	240	241	247	230	228	233
Baseline, mean ± SD	123.1 ± 15.53	123.0 ± 15.08	123.1 ± 13.69	123.1 ± 15.53	123.0 ± 15.08	123.1 ± 13.69
Difference from baseline (week 12, week 52), LSM ± SE	-2.4 ± 0.68	-2.8 ± 0.67	-5.2 ± 0.67	0.6 ± 0.71	-2.3 ± 0.71	-2.2 ± 0.70
95% CI	-3.7 to -1.1	-4.1 to -1.5	-6.5 to -3.9	-0.7 to 2.0	-3.7 to -0.9	-3.5 to -0.8
P value	<0.001	<0.001	<0.001	0.36	0.001	0.002
Difference from placebo, LSM ± SE		-0.4 ± 0.89	-2.8 ± 0.89		-3.0 ± 0.94	-2.8 ± 0.94
95% CI		-2.2 to 1.3	-4.6 to -1.1		-4.8 to -1.1	-4.7 to -1.0
P value		0.64	0.001		0.002	0.003

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
DBP, mITT population (mm Hg)						
No. patients	240	241	247	230	228	233
Baseline, mean ± SD	76.3 ± 8.48	77.4 ± 9.83	76.2 ± 8.37	76.3 ± 8.48	77.4 ± 9.83	76.2 ± 8.37
Difference from baseline (week 12, week 52), LSM ± SE	-0.4 ± 0.44	-0.9 ± 0.44	-1.0 ± 0.44	-0.3 ± 0.47	-1.6 ± 0.47	-0.9 ± 0.47
95% CI	-1.2 to 0.5	-1.8 to -0.1	-1.9 to -0.2	-1.2 to 0.6	-2.5 to -0.7	-1.8 to 0.0
P value	0.42	0.034	0.021	0.51	<0.001	0.053
Difference from placebo, LSM ± SE		-0.6 ± 0.59	-0.7 ± 0.58		-1.3 ± 0.63	-0.6 ± 0.63
95% CI		-1.7 to 0.6	-1.8 to 0.5		-2.5 to -0.1	-1.8 to 0.6
P value		0.32	0.26		0.040	0.34
SBP, patients with baseline SBP ≥130 mm Hg (mm Hg)						
No. patients	81	84	74	76	76	70
Baseline, mean ± SD	140.0 ± 9.63	139.6 ± 8.80	138.9 ± 8.45	140.0 ± 9.63	139.6 ± 8.80	138.9 ± 8.45
Difference from baseline (week 12, week 52), LSM ± SE	-6.6 ± 1.44	-8.6 ± 1.42	-10.7 ± 1.47	-5.6 ± 1.41	-9.5 ± 1.41	-7.9 ± 1.45

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
95% CI	-9.4 to -3.7	-11.4 to -5.8	-13.6 to -7.8	-8.4 to -2.8	-12.3 to -6.7	-10.7 to -5.0
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Difference from placebo, LSM ± SE		-2.0 ± 1.80	-4.1 ± 1.85		-3.9 ± 1.79	-2.3 ± 1.83
95% CI		-5.5 to 1.6	-7.8 to -0.5		-7.4 to -0.4	-5.9 to 1.4
P value		0.27	0.027		0.030	0.22
Urine ACR (mg/mmol)						
No. patients	238	235	240	228	225	235
Baseline, mean ± SD	5.6179 ± 38.69545	4.0457 ± 16.29162	6.6171 ± 28.47268	5.6179 ± 38.69545	4.0457 ± 16.29162	6.6171 ± 28.47268
Difference from baseline, LSM ± SE	3.3203 ± 1.79553	-0.1805 ± 1.80512	-2.6997 ± 1.78634	1.0631 ± 1.01737	-0.6950 ± 1.02091	-1.2288 ± 1.00748
95% CI	-0.2045 to 6.8450	-3.7241 to 3.3630	-6.2064 to 0.8070	-0.9338 to 3.0600	-2.6988 to 1.3088	-3.2063 to 0.7487
P value	0.06	0.92	0.13	0.30	0.50	0.22
Difference from placebo, LSM ± SE		-3.5008 ± 2.49799	-6.0199 ± 2.48438		-1.7581 ± 1.36058	-2.2919 ± 1.35115
95% CI		-8.4050 to 1.4034	-10.8974 to -1.1424		-4.4291 to 0.9129	-4.9443 to 0.3606

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
P value		0.16	0.016		0.20	0.09
eGFR (mL/min/1.73 m^2)						
No. patients	237	236	238	226	226	228
Baseline, mean ± SD	92.89 ± 18.245	91.56 ± 18.778	91.66 ± 17.405	92.89 ± 18.245	91.56 ± 18.778	91.66 ± 17.405
Difference from baseline, LSM ± SD	-1.70 ± 0.735	-1.66 ± 0.735	-1.39 ± 0.732	0.34 ± 0.794	-1.86 ± 0.792	-0.33 ± 0.790
95% CI	-3.15 to -0.26	-3.10 to -0.22	-2.83 to 0.05	-1.22 to 1.89	-3.41 to -0.30	-1.88 to 1.22
P value	0.021	0.024	0.058	0.67	0.019	0.68
Difference from placebo, LSM ± SD		0.04 ± 0.977	0.31 ± 0.975		-2.19 ± 1.067	-0.66 ± 1.063
95% CI		-1.87 to 1.96	-1.60 to 2.23		-4.29 to -0.10	-2.75 to 1.42
P value		0.96	0.75		0.040	0.53
Documented blood glucose ≤3.9 mmol/L (≤70 mg/dL) (events/patient/day)						
No. patients	239	239	241	230	230	237
Baseline, mean ± SD	0.347 ± 0.3340	0.332 ± 0.3444	0.335 ± 0.3369	0.347 ± 0.3340	0.332 ± 0.3444	0.335 ± 0.3369

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
Difference from baseline, LSM ± SD	-0.071 ± 0.0185	-0.138 ± 0.0185	-0.150 ± 0.0185	-0.093 ± 0.0198	-0.168 ± 0.0198	-0.160 ± 0.0196
95% CI	-0.108 to -0.035	-0.174 to -0.101	-0.186 to -0.113	-0.132 to -0.054	-0.206 to -0.129	-0.198 to -0.122
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Difference from placebo, LSM ± SD		-0.066 ± 0.0248	-0.078 ± 0.0248		-0.075 ± 0.0269	-0.067 ± 0.0268
95% CI		-0.115 to -0.017	-0.127 to -0.029		-0.128 to -0.022	-0.120 to -0.015
P value		0.008	0.002		0.006	0.012
Documented blood glucose ≤3.9 mmol/L (≤70 mg/dL) (event rate)						
No. patients	258	261	263	258	261	263
Patients with events, n (%)	249 (96.5)	252 (96.6)	257 (97.7)	252 (97.7)	255 (97.7)	260 (98.9)
Events per person-year	103.0	90.7	88.2	95.1	78.5	77.5
Event rate	86.84	76.55	78.56	79.90	67.14	70.27
95% CI	77.07 to	67.87 to	69.80 to	70.85 to	59.47 to	62.41 to

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
	97.85	86.35	88.42	90.11	75.80	79.13
Relative rate		0.88	0.90		0.84	0.88
95% CI		0.76 to 1.02	0.78 to 1.05		0.72 to 0.98	0.76 to 1.02
P value vs placebo		0.10	0.19		0.024	0.10
Documented blood glucose ≤3.0 mmol/L (≤55 mg/dL) (events/patient/day)						
No. patients	239	239	241	230	230	237
Baseline, mean ± SD	0.073 ± 0.1335	0.071 ± 0.1365	0.084 ± 0.1355	0.073 ± 0.1335	0.071 ± 0.1365	0.084 ± 0.1355
Difference from baseline, LSM ± SD	-0.015 ± 0.0071	-0.043 ± 0.0071	-0.046 ± 0.0071	-0.016 ± 0.0079	-0.042 ± 0.0079	-0.046 ± 0.0078
95% CI	-0.029 to -0.001	-0.057 to -0.029	-0.060 to -0.032	-0.032 to -0.001	-0.058 to -0.027	-0.061 to -0.031
P value	0.031	<0.001	<0.001	0.041	<0.001	<0.001
Difference from placebo, LSM ± SD		-0.028 ± 0.0096	-0.031 ± 0.0096		-0.026 ± 0.0109	-0.030 ± 0.0108
95% CI		-0.047 to -0.009	-0.049 to -0.012		-0.048 to -0.005	-0.051 to -0.009

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
P value		0.004	0.001		0.017	0.006
Documented blood glucose ≤3.0 mmol/L (≤55 mg/dL) (event rate)						
No. patients	258	261	263	258	261	263
Patients with events, n (%)	215 (83.3)	213 (81.6)	226 (85.9)	230 (89.1)	231 (88.5)	238 (90.5)
Events per person-year	20.9	17.2	16.0	19.8	14.8	14.1
Event rate	17.37	14.10	14.17	16.66	12.60	12.90
95% CI	14.75 to 20.46	11.91 to 16.69	12.00 to 16.73	14.24 to 19.48	10.73 to 14.79	11.02 to 15.11
Relative rate		0.81	0.82		0.76	0.77
95% CI		0.66 to 1.00	0.66 to 1.00		0.62 to 0.92	0.63 to 0.95
P value vs placebo		0.050	0.055		0.006	0.012
DTSQs score[†‡]						
No. patients	252	255	262	—	—	—
Baseline, mean ± SD	28.2 ± 5.14	28.3 ± 5.13	28.4 ± 4.97	—	—	—
Difference from baseline, LSM ± SE	-0.1 ± 0.28	1.9 ± 0.28	1.6 ± 0.28	—	—	—

SUPPLEMENTARY DATA

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
95% CI	-0.6 to 0.5	1.4 to 2.5	1.1 to 2.2	—	—	—
P value	0.84	<0.001	<0.001	—	—	—
Difference from placebo, LSM ± SE		2.0 ± 0.37	1.7 ± 0.36	—	—	—
95% CI		1.3 to 2.7	1.0 to 2.4	—	—	—
P value		<0.001	<0.001	—	—	—
DDS2 score[†]						
No. patients	232	232	243	225	219	234
Baseline, mean ± SD	5.3 ± 2.11	5.6 ± 2.03	5.5 ± 2.19	5.3 ± 2.11	5.6 ± 2.03	5.5 ± 2.19
Difference from baseline, LSM ± SE	0.0 ± 0.12	-0.3 ± 0.12	-0.4 ± 0.11	-0.2 ± 0.12	-0.4 ± 0.12	-0.5 ± 0.12
95% CI	-0.2 to 0.3	-0.5 to -0.1	-0.6 to -0.2	-0.4 to 0.0	-0.6 to -0.1	-0.7 to -0.3
P value	0.78	0.008	<0.001	0.12	0.002	<0.001
Difference from placebo, LSM ± SE		-0.3 ± 0.15	-0.4 ± 0.15		-0.2 ± 0.16	-0.3 ± 0.16
95% CI		-0.6 to -0.0	-0.7 to -0.2		-0.5 to 0.1	-0.6 to -0.0
P value		0.025	0.003		0.23	0.046

*Primary endpoint.

†Secondary endpoint.

‡Assessed only at week 24.

Abbreviations: ACR, albumin-creatinine ratio; Ca/Cr, calcium-creatinine ratio; DBP, diastolic blood pressure; DTSQs, Diabetes Treatment Satisfaction Questionnaire status; DDS2, 2-item Diabetes Distress Screening Scale; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GCR, glucose-creatinine ratio; SBP, systolic blood pressure.

SUPPLEMENTARY DATA

Table 3. Changes in CGM values and 2-h PPG at week 24 in the CGM substudy.*

	Placebo (n=48)	**Sotagliflozin 200 mg (n=45)**	**Sotagliflozin 400 mg (n=49)**
Mean daily glucose, mmol/L ± SD (mg/dL ± SD)			
No. patients	25	26	35
Mean baseline	10.06 ± 1.80 (181.24 ± 32.49)	9.99 ± 1.84 (180.05 ± 33.18)	10.18 ± 2.01 (183.41 ± 36.23)
Difference from baseline, LSM ± SE	0.11 ± 0.33 (1.92 ± 6.03)	-0.56 ± 0.33 (-10.00 ± 5.98)	-1.07 ± 0.29 (-19.28 ± 5.19)
95% CI	-0.56 to 0.77 (-10.05 to 13.88)	-1.21 to 0.10 (-21.85 to 1.86)	-1.64 to -0.50 (-29.59 to -8.97)
P value	0.75	0.10	<0.001
Difference from placebo		-0.66 ± 0.44 (-11.91 ± 7.96)	-1.18 ± 0.41 (-21.20 ± 7.46)
95% CI		-1.54 to 0.22 (-27.73 to 3.92)	-2.00 to -0.35 (-36.03 to -6.37)
P value		0.14	0.006
MAGE, mmol/L ± SD (mg/dL ± SD)			
No. patients	25	26	35
Mean baseline	9.53 ± 2.06 (171.71 ± 37.18)	9.03 ± 1.97 (162.65 ± 35.41)	8.81 ± 2.16 (158.67 ± 38.87)
Difference from baseline, LSM ± SE	-0.04 ± 0.35 (-0.73 ± 6.28)	-1.37 ± 0.34 (-24.73 ± 6.16)	-1.36 ± 0.29 (-24.47 ± 5.31)
95% CI	-0.73 to 0.65 (-13.19 to 11.73)	-2.05 to -0.69 (-36.96 to -12.51)	-1.94 to -0.77 (-35.02 to -13.92)
P value	0.91	<0.001	<0.001

	Placebo (n=48)	**Sotagliflozin 200 mg (n=45)**	**Sotagliflozin 400 mg (n=49)**
Difference from placebo		-1.33 ± 0.46 (-24.00 ± 8.24)	-1.32 ± 0.43 (-23.73 ± 7.80)
(95% CI)		-2.24 to -0.42 (-40.37 to -7.62)	-2.18 to -0.46 (-39.24 to -8.22)
P value		0.005	0.003
Daily percent time in target CGM range 70 to 180 mg/dL (3.9 to 10.0 mmol/L)			
No. patients	25	26	35
Mean baseline	50.03 ± 14.62	50.16 ± 15.56	48.19 ± 15.32
Difference from baseline, LSM ± SE	-0.66 ± 3.08	7.75 ± 3.05	12.69 ± 2.64
95% CI	-6.77 to 5.44	1.71 to 13.79	7.46 to 17.93
Hours per day corresponding to percent time per day ± SE[†]	0.16 ± 0.74	1.86 ± 0.73	3.05 ± 0.63
P value	0.83	0.013	<0.001
Difference from placebo		8.41 ± 4.11	13.36 ± 3.85
95% CI		0.25 to 16.58	5.71 to 21.00
Hours per day corresponding to percent time per day ± SE[†]		2.02 ± 0.99	3.21 ± 0.92
P value		0.044	<0.001
Standard deviation, mmol/L ± SD (mg/dL ± SD)			
No. patients	25	26	35
Mean baseline	3.76 ± 0.89	3.71 ± 0.87	3.49 ± 0.88

	Placebo (n=48)	**Sotagliflozin 200 mg (n=45)**	**Sotagliflozin 400 mg (n=49)**
	(67.83 ± 16.10)	(66.82 ± 15.60)	(62.96 ± 15.82)
Difference from baseline, LSM ± SE	-0.06 ± 0.14 (-1.11 ± 2.51)	-0.61 ± 0.14 (-10.98 ± 2.47)	-0.48 ± 0.12 (-8.60 ± 2.12)
95% CI	-0.34 to 0.21 (-6.08 to 3.86)	-0.88 to -0.34 (-15.89 to -6.07)	-0.71 to -0.24 (-12.82 to -4.37)
P value	0.66	<0.001	<0.001
Difference from placebo		-0.55 ± 0.18 (-9.87 ± 3.28)	-0.42 ± 0.17 (-7.49 ± 3.11)
95% CI		-0.91 to -0.19 (-16.39 to -3.35)	-0.76 to -0.07 (-13.67 to -1.31)
P value		0.003	0.018
2-h PPG, mmol/L ± SD (mg/dL ± SD)[‡]			
No. patients (per-protocol population)	29	31	32
Mean baseline	12.59 ± 4.98 (226.6 ± 89.58)	12.58 ± 5.98 (226.5 ± 107.70)	11.62 ± 6.14 (209.3 ± 110.54)
Difference from baseline, LSM ± SE	0.57 ± 0.83 (10.2 ± 14.91)	-2.23 ± 0.83 (-40.1 ± 14.91)	-3.64 ± 0.79 (-65.5 ± 14.16)
95% CI	-1.08 to 2.21 (-19.4 to 39.8)	-3.88 to -0.58 (-69.7 to -10.5)	-5.20 to -2.07 (-93.7 to -37.4)
P value	0.50	0.008	<0.001
Difference from placebo		-2.80 ± 1.05 (-50.3 ± 18.97)	-4.20 ± 1.05 (-75.7 ± 18.88)
95% CI		-4.89 to -0.70 (-88.0 to -12.6)	-6.29 to -2.12 (-113.3 to -38.2)
P value		0.009	<0.001

Baseline data are mean ± SD.

CGM, continuous glucose monitoring; CI, confidence interval; SD, standard deviation; SE, standard error; LSM, least squares mean; MAGE, mean amplitude of glucose excursions; PPG, postprandial glucose.

*Conducted in a subgroup of patients who underwent blinded CGM with a Dexcom G4 monitor (Dexcom Inc., San Diego, CA) during specified 1-week intervals throughout the first 24 weeks.

†Assuming 100% daily CGM data available for analysis, 1.0% of daily CGM time = 0.24 hours.

‡In order to assess the change in PPG under standardized conditions, the per-protocol population was selected; 2-h PPG values were obtained after a standardized mixed meal.

SUPPLEMENTARY DATA

Figure 2. LSM percent (A) and absolute (B) change from baseline in insulin dose at 24 and 52 weeks. Baseline values are IU/day.

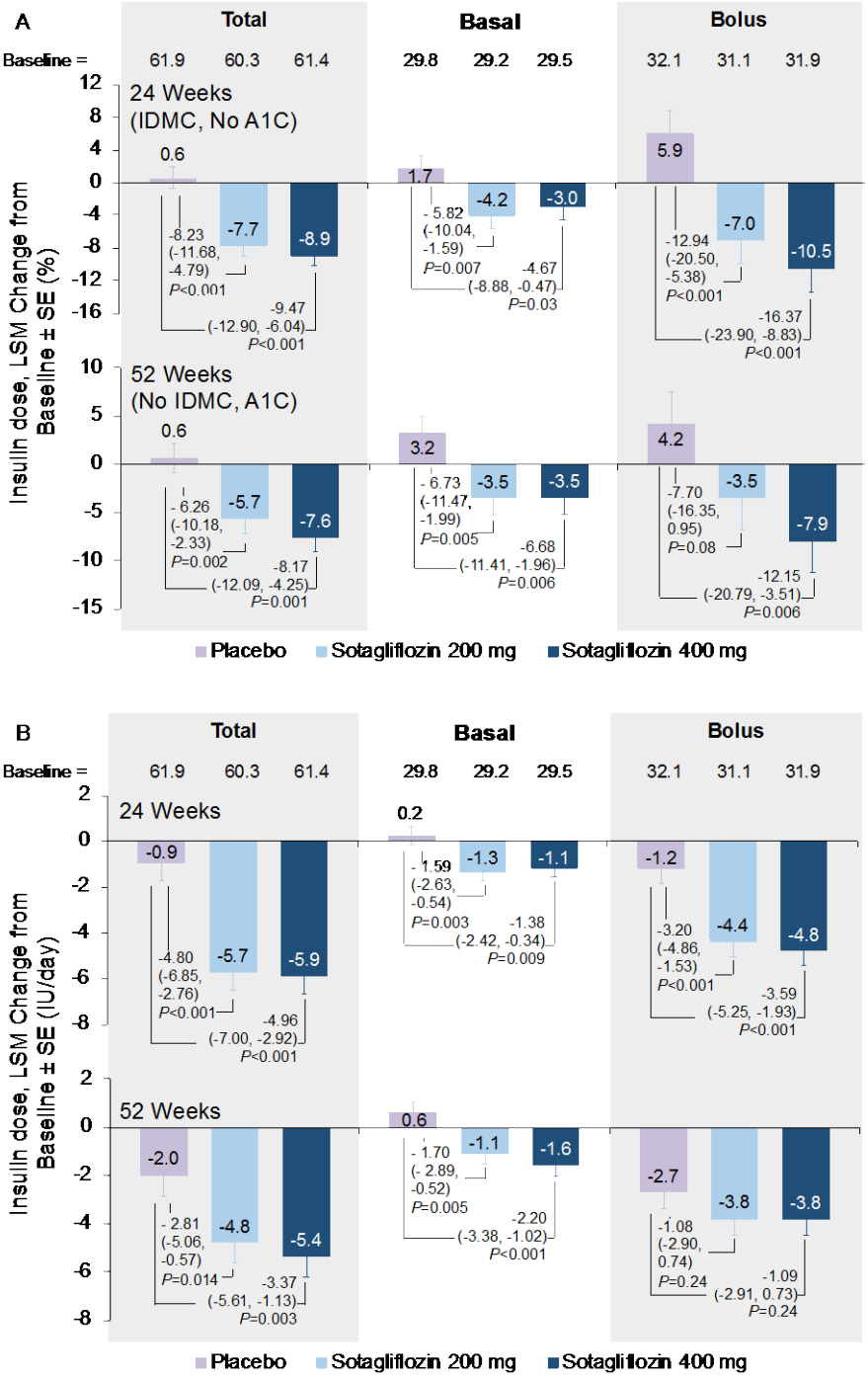


Figure 3. Least squares mean (LSM) change from baseline in estimated glomerular filtration rate (eGFR) over 52 weeks. Error bars represent standard error (SE).

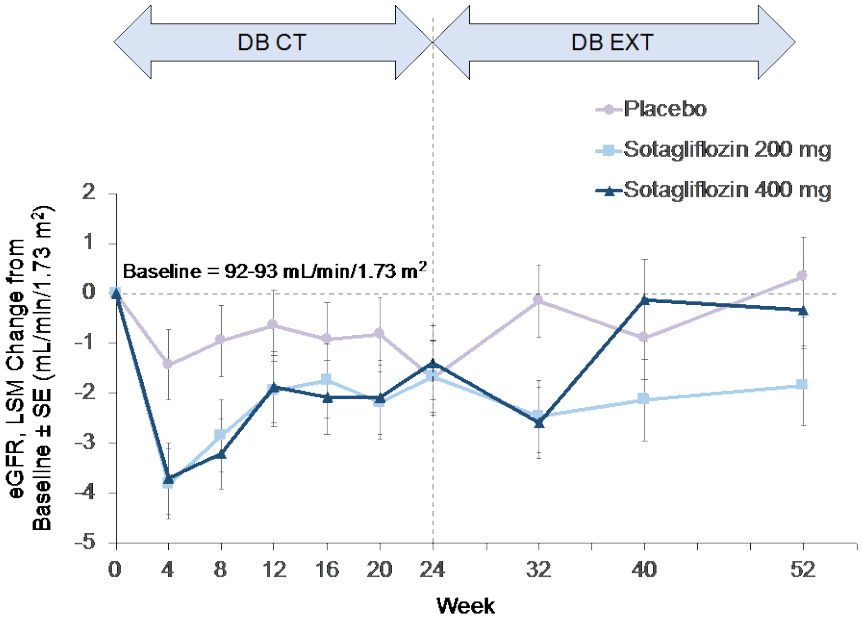
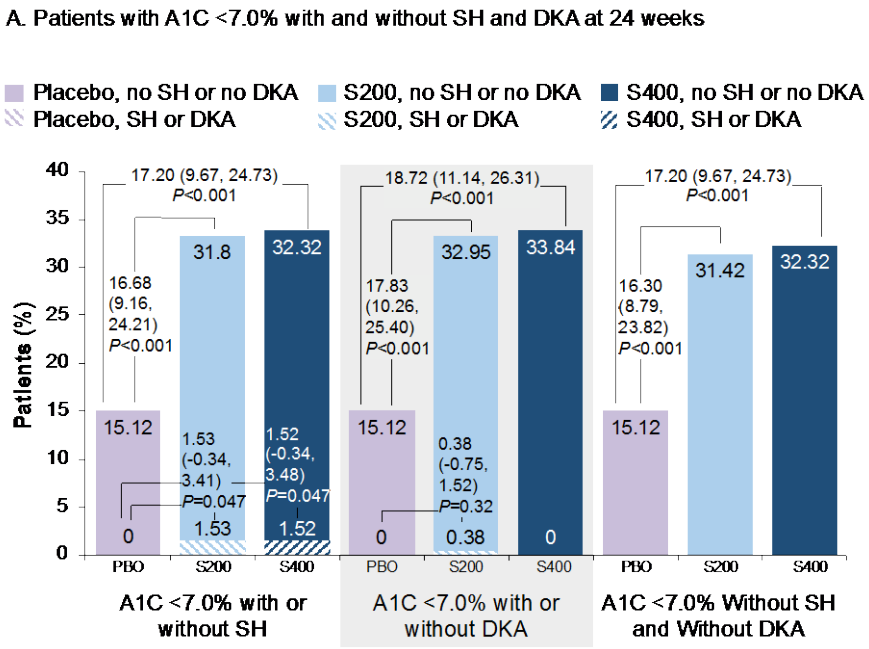
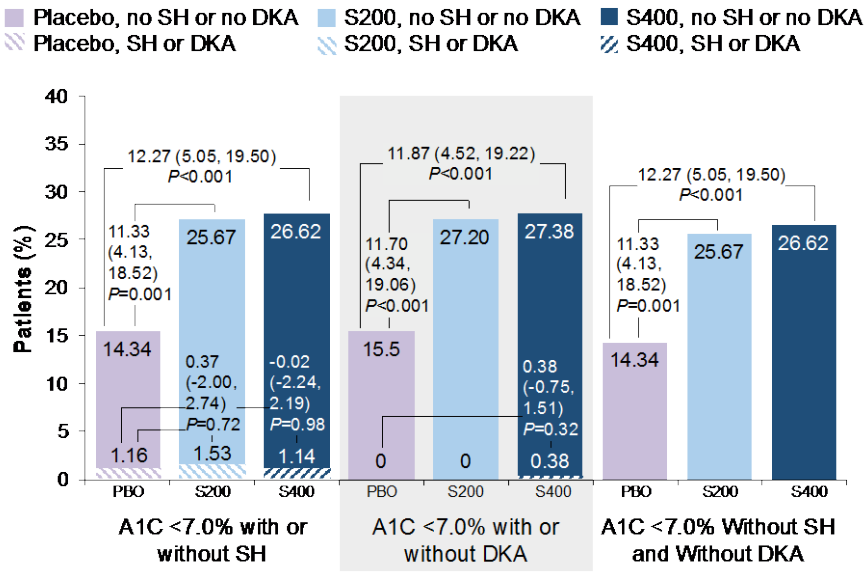


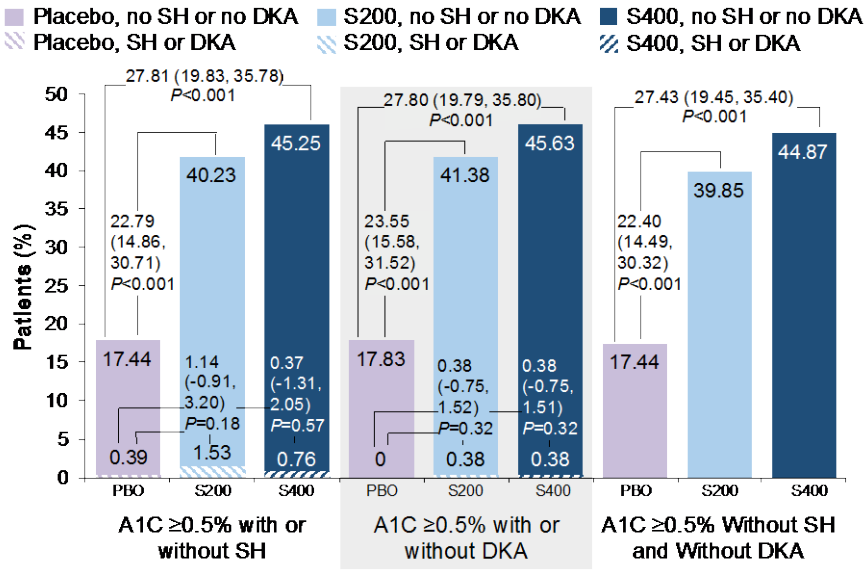
Figure 4. Proportions of patients with A1C <7.0%, severe hypoglycemia (SH), and/or diabetic ketoacidosis (DKA) at 24 weeks (*A*) and 52 weeks (*B*) and proportions of patients with a change in A1C ≥0.5%, SH, and/or DKA at 24 weeks (*C*) and 52 weeks (*D*). Solid bars, A1C <7.0% (*A, B*) or ≥0.5% (*C, D*) without SH, without DKA, or without both SH and DKA; hatched bars, A1C <7.0% (*A, B*) or ≥0.5% (*C, D*) with SH or with DKA. Least squares mean (LSM) differences between treatment groups are shown as percentages (95% confidence intervals). PBO, placebo. S400, sotagliflozin 400 mg; S200, sotagliflozin 200 mg.



B. Patients with A1C <7.0% with and without SH and DKA at 52 weeks



C. Patients with A1C reduction ≥0.5% with and without SH and DKA at 24 weeks



D. Patients with A1C reduction ≥0.5% with and without SH and DKA at 52 weeks

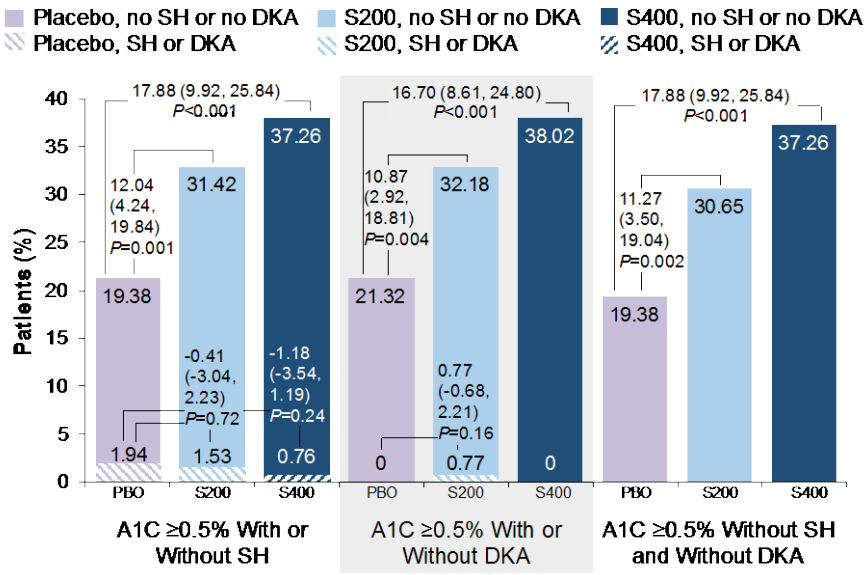


Figure 5. Overall summary of composite endpoints showing proportions of patients with A1C <7.0% who did not experience severe hypoglycemia (SH); diabetic ketoacidosis (DKA); weight gain; either weight gain or SH; weight gain, SH, or DKA; or documented hypoglycemia ≤3.0 mmol/L at 24 weeks. *P<0.05 vs placebo.

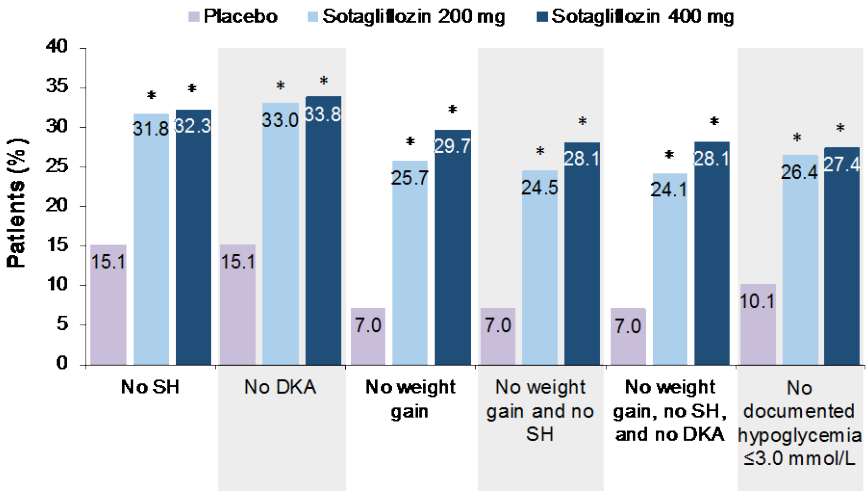


Figure 6. Proportions of patients meeting target A1C values who experienced weight gain; no weight gain; weight loss; no weight gain or severe hypoglycemia (SH); and no weight gain, severe hypoglycemia, or diabetic ketoacidosis (DKA). A) A1C <7.0% and weight effects at 24 weeks. B) A1C <7.0% and weight effects at 52 weeks. C) A1C reduction ≥0.5% and weight effects at 24 weeks. D) A1C reduction ≥0.5% and weight effects at 52 weeks. *P<0.001 vs placebo. See Table 3 for LSM differences between treatment groups. PBO, placebo. S200, sotagliflozin 200 mg. S400, sotagliflozin 400 mg.

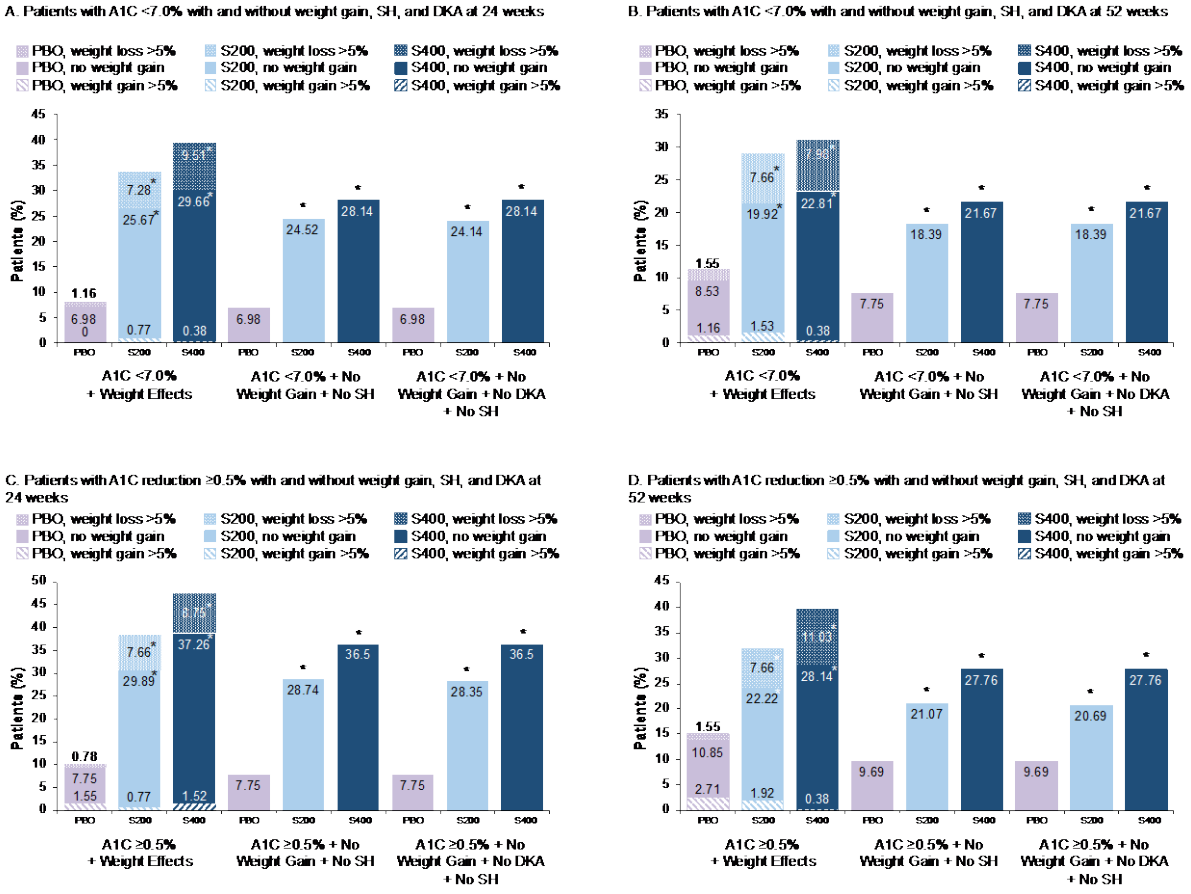


Table 4. Proportions of patients achieving weight-related composite outcomes.

Characteristic	**Placebo (n=258)**	**Sotagliflozin 200 mg (n=261)**	**Percent difference from placebo (95% CI) *P* value**	**Sotagliflozin 400 mg (n=263)**	**Percent difference from placebo (95% CI) *P* value**
Patients achieving A1C <7.0% at 24 weeks and:					
Weight gain >5%	0	2 (0.77)	0.77 (-0.68 to 2.21) 0.16	1 (0.38)	0.38 (-0.75 to 1.51) 0.32
No weight gain	18 (6.98)	67 (25.67)	18.69 (12.16 to 25.22) <0.001	78 (29.66)	22.68 (15.96 to 29.40) <0.001
Weight loss >5%	3 (1.16)	19 (7.28)	6.12 (2.32 to 9.91) <0.001	25 (9.51)	8.34 (4.18 to 12.51) <0.001
No severe hypoglycemia or weight gain	18 (6.98)	64 (24.52)	17.54 (11.08 to 24.00) <0.001	74 (28.14)	21.16 (14.52 to 27.80) <0.001

Characteristic	**Placebo (n=258)**	**Sotagliflozin 200 mg (n=261)**	**Percent difference from placebo (95% CI) *P* value**	**Sotagliflozin 400 mg (n=263)**	**Percent difference from placebo (95% CI) *P* value**
No severe hypoglycemia, DKA, or weight gain	18 (6.98)	63 (24.14)	17.16 (10.72 to 23.60) <0.001	74 (28.14)	21.16 (14.52 to 27.80) <0.001
Patients achieving A1C reduction ≥0.5% at 24 weeks and:					
Weight gain >5%	4 (1.55)	2 (0.77)	-0.78 (-3.01 to 1.44) 0.42	4 (1.52)	-0.03 (-2.53 to 2.47) 0.98
No weight gain	20 (7.75)	78 (29.89)	22.13 (15.31 to 28.96) <0.001	98 (37.26)	29.51 (22.43 to 36.59) <0.001
Weight loss >5%	2 (0.78)	20 (7.66)	6.89 (3.10 to 10.67) <0.001	23 (8.75)	7.97 (4.01 to 11.93) <0.001
No severe hypoglycemia or weight gain	20 (7.75)	75 (28.74)	20.98 (14.21 to 27.76) <0.001	96 (36.50)	28.75 (21.70 to 35.80) <0.001

Characteristic	**Placebo (n=258)**	**Sotagliflozin 200 mg (n=261)**	**Percent difference from placebo (95% CI) *P* value**	**Sotagliflozin 400 mg (n=263)**	**Percent difference from placebo (95% CI) *P* value**
No severe hypoglycemia, DKA, or weight gain	20 (7.75)	74 (28.35)	20.60 (13.85 to 27.35) <0.001	96 (36.50)	28.75 (21.70 to 35.80) <0.001
Patients achieving A1C <7.0% at 52 weeks and:					
Weight gain >5%	3 (1.16)	4 (1.53)	0.37 (-2.00 to 2.74) 0.71	1 (0.38)	-0.78 (-2.67 to 1.11) 0.31
No weight gain	22 (8.53)	52 (19.92)	11.40 (5.09 to 17.71) <0.001	60 (22.81)	14.29 (7.79 to 20.78) <0.001
Weight loss >5%	4 (1.55)	20 (7.66)	6.11 (2.17 to 10.06) <0.001	21 (7.98)	6.43 (2.44 to 10.42) <0.001
No severe hypoglycemia or weight gain	20 (7.75)	48 (18.39)	10.64 (4.53 to 16.75) <0.001	57 (21.67)	13.92 (7.58 to 20.26) <0.001

Characteristic	**Placebo (n=258)**	**Sotagliflozin 200 mg (n=261)**	**Percent difference from placebo (95% CI) *P* value**	**Sotagliflozin 400 mg (n=263)**	**Percent difference from placebo (95% CI) *P* value**
No severe hypoglycemia, DKA, or weight gain	20 (7.75)	48 (18.39)	10.64 (4.53 to 16.75) <0.001	57 (21.67)	13.92 (7.58 to 20.26) <0.001
Patients achieving A1C reduction ≥0.5% at 52 weeks and:					
Weight gain >5%	7 (2.71)	5 (1.92)	-0.80 (-3.77 to 2.18) 0.56	1 (0.38)	-2.33 (-4.83 to 0.17) 0.030
No weight gain	28 (10.85)	58 (22.22)	11.37 (4.67 to 18.07) <0.001	74 (28.14)	17.28 (10.27 to 24.30) <0.001
Weight loss >5%	4 (1.55)	20 (7.66)	6.11 (2.17 to 10.06) <0.001	29 (11.03)	9.48 (5.02 to 13.93) <0.001
No severe hypoglycemia or weight gain	25 (9.69)	55 (21.07)	11.38 (4.87 to 17.89) <0.001	73 (27.76)	18.07 (11.18 to 24.96) <0.001

Characteristic	**Placebo (n=258)**	**Sotagliflozin 200 mg (n=261)**	**Percent difference from placebo (95% CI) *P* value**	**Sotagliflozin 400 mg (n=263)**	**Percent difference from placebo (95% CI) *P* value**
No severe hypoglycemia, DKA, or weight gain	25 (9.69)	54 (20.69)	11.00 (4.52 to 17.48) <0.001	73 (27.76)	18.07 (11.18 to 24.96) <0.001

Data are n (%) unless otherwise indicated.

*The treatment effect for the primary endpoint is expressed as the sotagliflozin plus or minus placebo difference in binomial proportions (expressed as a percentage) and the accompanying 95% confidence interval (CI).

Figure 7. LS Mean change from baseline in Diabetes Treatment Satisfaction Questionnaire status (DTSQs) total score at week 24.

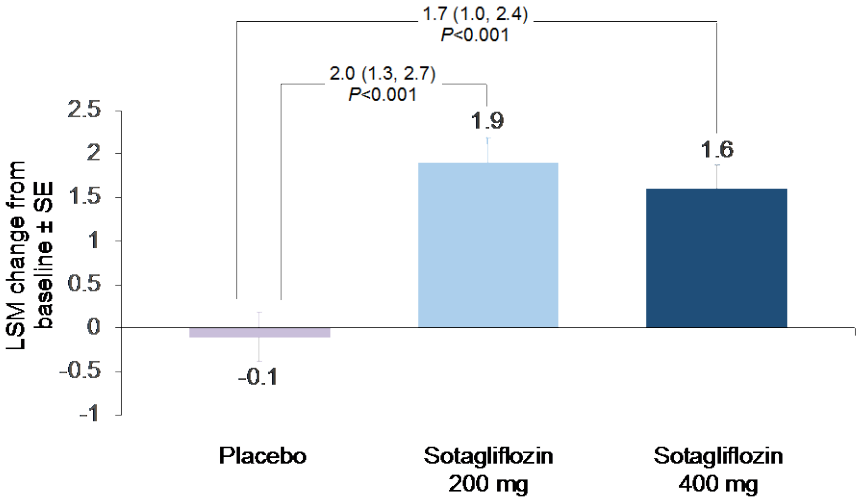


Figure 8. Mean change from baseline in Diabetes Distress Screening Scale (DDS2) total score by study visit.

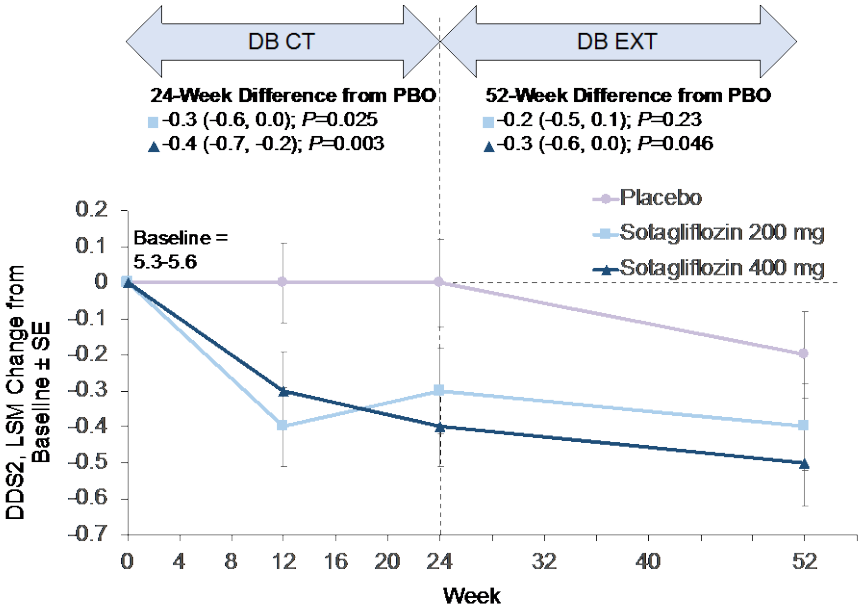


Table 5. Patients with acidosis-related events (baseline to 52 weeks).

Number of patients with ≥1 event (%)	**Placebo (n=258)**	**Sotagliflozin 200 mg (n=261)**	**Sotagliflozin 400 mg (n=263)**
Acidosis-related adverse events	3 (1.2)	23 (8.8)	30 (11.4)
Nonserious acidosis-related adverse events	3 (1.2)	16 (6.1)	20 (7.6)
Serious acidosis-related adverse events*	0	7 (2.7)	13 (4.9)
Positively adjudicated metabolic acidosis	0	8 (3.1)	10 (3.8)
Positively adjudicated metabolic acidosis that was also diabetic ketoacidosis†	0	6 (2.3)	9 (3.4)
Blood glucose at time of DKA >13.9 mmol/L (250 mg/dL)‡	0	3	6
Blood glucose at time of DKA 8.3 mmol (150 mg/dL) to 13.9 mmol/L (250 mg/dL)‡	0	3	3
Blood glucose at time of DKA <8.3 mmol/L (150 mg/dL)‡	0	0	0

*All serious acidosis-related adverse events required hospitalization.

[†]A systematic review of all positively adjudicated DKA dossiers was performed. For subjects with positively adjudicated DKA receiving sotagliflozin, the following features and outcomes were documented: Three patients (20%) were admitted to the ICU. Duration of hospitalization was as follows: 20% required 1 day, 33% required 2 to 3 days, and 47% required ≥ 4 days. Across the inTandem phase 3 program, ICU admission and duration of hospitalization reflected regional differences in health care delivery. A potential contributory factor was associated with 87% of the events, such as infection, concomitant illness, missed insulin dosing, or interruption of insulin pump infusion. With respect to lowest pH at the time of DKA diagnosis, 20% had pH <7.0, 60% had pH 7.0-7.24, and 20% had pH 7.25-7.30.

[‡]Blood glucose data at the time of presentation for evaluation of DKA and/or admission to the hospital was collected from review of DKA adjudication dossiers.

Figure 9. Boxplot of beta-hydroxy butyrate (mmol/L) at baseline and week 24. Mean values are represented by triangles (sotagliflozin 400 mg), squares (sotagliflozin 200 mg), or circles (placebo). 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. Median values at week 24 were 0.22 with sotagliflozin 400 mg, 0.18 with sotagliflozin 200 mg, and 0.15 with placebo.