Supplement to

Sotagliflozin in Combination with Optimized Insulin Therapy in Adults with Type 1 Diabetes: The North American inTandem1 Study

John B. Buse[1], Satish K. Garg[2], Julio Rosenstock[3], Timothy S. Bailey[4], Phillip Banks[5], Bruce W. Bode[6], Thomas Danne[7], Jake A. Kushner[8], Wendy S. Lane[9], Pablo Lapuerta[5], Darren K. McGuire[10], Anne L. Peters[11], John Reed[12], Sangeeta Sawhney[5], and Paul Strumph[5]

Principal Investigators List

Andrew Ahmann, Oregon Health & Science University, Portland, OR, USA; Buki Ajala, LMC Diabetes and Endocrinology, Calgary, Alberta, Canada; Laura Akright, Northeast Endocrinology Associates, PA, Schertz, TX, USA; Amer Al-Karadsheh, The Endocrine Center Research Consultants, Houston, TX, USA; Hani Alasaad, LMC Diabetes and Endocrinology, Barrie, Ontario, Canada; Stephen Aronoff, Research Institute of Dallas, , Dallas, TX, USA; Ronnie Aronson, LMC Diabetes and Endocrinology, Toronto, Ontario, Canada; Timothy Bailey, AMCR Institute, Inc., Escondido, CA, USA; Arti Bhan, Henry Ford Hospital, Detroit, MI, USA; Bruce Bode, Atlanta Diabetes Associates, Atlanta, GA, USA; John Buse, UNC Health Care System, Chapel Hill, NC, USA; Tira Chaica Brom, Texas Diabetes and Endocrinology, Austin, TX, USA; Mark Christiansen, Diablo Clinical Research, Walnut Creek, CA, USA; Elena Christofides, Endocrinology Associates, Inc, Columbus, OH, USA; Jay Cohen, The Endocrine Clinic, PC, Memphis, TN, USA; Thomas Elliott, Vancouver General Hospital, Vancouver, BC, Canada; Norman Fishman, Diabetes Endocrinology Specialists, Inc., Chesterfield, MO, USA; David Fitz-Patrick, East-West Medical Research Institute, Honolulu, HI, USA; Juan Pablo, Frias, National Research Institute, Los Angeles, CA, USA; Satish Garg, Barbara Davis Center, University of Colorado Denver, Aurora, CO; USA; W. Timothy Garvey, University of Alabama at Birmingham, Birmingham, AL, USA; Linda Gaudiani, Marin Endocrine Care and Research, Inc., Greenbrae, CA, USA; Gregg Gerety, AMC Division of Community Endocrinology, Albany, NY, USA; Ronald Goldenberg, LMC Diabetes and Endocrinology, Thornhill, Ontario, Canada; Carl Griffin, Lynn Health Science Institute (LHSI), Oklahoma City, OK, USA; Yehuda Handelsman, Metabolic Institute of America, Tarzana, CA, USA; Priscilla Hollander, Baylor Endocrine Center, Dallas, TX, USA; Barry Horowitz, Metabolic Research Institute, Inc., West

Palm Beach, FL, USA; Irene Hramiak, St. Joseph's Health Care, London, Ontario, Canada; David Huffman, University Diabetes & Endocrine Consultants, Chattanooga, TN, USA; Michael Jardula, Desert Oasis Healthcare Medical Group, Palm Springs, CA, USA; Erin Keely, Ottawa Hospital, Riverside Campus, Ottawa, Ontario, Canada; Leslie Klaff, Rainier Clinical Research Center, Renton, WA, USA; David Klonoff, Mills-Peninsula Health Services, San Mateo, CA, USA; Wendy Lane, Mountain Diabetes and Endocrine Center, Asheville, NC, USA; James Larocque, Virginia Endocrinology Research, Chesapeake, VA, USA; Philip Levin, Model Clinical Research, , Baltimore, MD, USA; Carol Levy, Icahn School of Medicine at Mount Sinai, New York, NY, USA; William Litchfield, Desert Endocrinology, Henderson, NV, USA; Kathryn Lucas, Diabetes & Endocrinology Consultants, Morehead City, NC, USA; Ivy-Joan Madu, Diabetes Associates Medical Group, Orange, CA, USA; Hiralal Maheshwari, Midwest Endocrinology, Crystal Lake, IL, USA; Ronald Mayfield, Mountainview Clinical Research, Greer, SC, USA; Janet McGill, Washington University School of Medicine in St. Louis, St. Louis, MO, USA; Wendell Miers, Kentucky Diabetes Endocrinology Center, Lexington, KY, USA; Frank Mikell, Springfield Diabetes and Endocrine Center, Springfield, IL, USA; Samer Nakhle, Palm Medical Group, Las Vegas, NV, USA; Ola Odugbesan, Physicians Research Associates, LLC, Lawrenceville, GA, USA; Rakesh Patel, Endocrine and Psychiatry Center, Houston, TX, USA; Athena Philis-Tsimikas, Scripp Whittier Diabetes Institute, La Jolla, CA, USA; Antonio Pinero-Pilona, Suncoast Clinical Research, New Port Richey, FL, USA; David Podlecki, IMMUNOe International Research Centers, Longmont, CO, USA; Zubin Punthakee, McMaster University, Hamilton, Ontario, Canada; Remi Rabasa-Lhoret, Institut de Recherches Cliniques de Montréal (IRCM), Montreal, Quebec, Canada; Thomas Ransom, Nova Scotia Health Authority, Halifax, Nova Scotia, Canada; John Reed, Endocrine Research Solutions, Inc.,

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Roswell, GA, USA; Michael Reeves, Private Practice, Chattanooga, TN, USA; Marc Rendell, Creighton University Medical Center, Omaha, NE, USA; Thomas Repas, Regional Health Clinical Research, Rapid City, SD, USA; Paul Rosenblit, Diabetes Lipid Management and Research Center, Huntington Beach, CA, USA; Julio Rosenstock, Dallas Diabetes and Endocrine Center, Dallas, TX, USA; Katarzyna Sadurska, Eastern Maine Medical Center, Bangor, ME, USA; Senan Sultan, East Coast Institute for Research, Fleming Island, FL, USA; David Sutton, Northeast Florida Endocrine & Diabetes Associates, Jacksonville, FL, USA; James Thrasher, Medical Investigations, Inc., Little Rock, AR, USA; Elena Toschi, Joslin Diabetes Center, Boston, MA, USA; Subbulaxmi Trikudanathan, University of Washington Medical Center, Seattle, WA, USA; Shyjauddin Valika, Associates in Endocrinology, Elgin, IL, USA; Joanna Van, Diabetes Research Center, Tustin, CA, USA; Arnold Vera, Peninsula Research Inc., Ormond Beach , FL, USA; Khurram Wadud, East Coast Institute for Research, Jacksonville, FL, USA; Michelle Welch, Diabetes and Metabolism Specialists, San Antonio, TX, USA; Vincent Woo, Diabetes Research Group, Winnipeg, Manitoba, Canada; Alan Wynne, Cotton-O'Neil Clinical Research Center, Topeka, KS, USA; Zeina Yared, LMC Diabetes and Endocrinology, Ville Saint-Laurent, Quebec, Canada

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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 LX4211.1-309-DM

Lexicon pharmaceuticals

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.

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):

███████ ███████████

Study LX4211.1-309-DM

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 _____. Site Number- ___ ___ ___ ___
(date of first dose)

This phase III study is investigating the new drug LX4211 in patients with Type 1 diabetes mellitus. LX4211 is a dual SGLT-1/SGLT-2 inhibitor.

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 (Complete all blanks below for patient number)

309-___ ___ ___ ___ -___ ___ ___

Date Of Birth- ___ / ___ / ___ ___
          Day   Month   Year

If any problems occur please contact:

_____
(Clinic, Department)

Dr. _____

Address _____

Phone _____

Covance Telephone Number : ██████████
Sponsor Telephone Number : ██████████
Core English Version 3.0 dated 30NOV2015

Recommendations Letter

Lexicon
pharmaceuticals

To:	LX4211.1- 309 Investigators and Study Coordinators
From:	▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮
Re:	Protocol LX4211.1-309-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.

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
- BHB meter, testing strips, and Ketostix for home use are provided to all patients at the Screening visit
- Whenever a patient has symptoms suspicious for DKA (as noted in paragraph 1 above), they must use ketostix 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,

Lexicon Pharmaceuticals, Inc.

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 sotagliflozin 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

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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 sample size was based on satisfying design assumptions for the primary efficacy endpoint.

Assuming a true treatment difference of -0.4% and a common standard deviation of 1.0%, 157

patients per treatment group provided 90% power to determine if either sotagliflozin 200 mg or

sotagliflozin 400 mg differed from placebo in the mean A1C change from Baseline to Week 24

at an overall 0.05 α-level (2-sided). This calculation was based on a 2.5% significance level

(α=0.025) assigned to each LX4211 comparison to placebo. This α-level corresponded to the per

comparison error rate used in applying a Bonferroni test to the primary endpoint and provided

strong control of the local family-wise error rate (FWER) at 0.05. The Bonferroni procedure was

part of a tree gatekeeping method used to maintain strong control of the study-wise type I error

rate in testing hypotheses among the primary and secondary efficacy endpoints. The sample size

estimate was further adjusted to account for dropouts in a manner that reflected the primary

analysis was conducted in the modified Intent-to-treat (mITT) patients. It was assumed that the

dropped sotagliflozin patients would respond as the placebo patients and that there was no drop-

in patients in the placebo group. These assumptions netted an adjusted effect size for detection of

-0.4% x (1-0.20) = -0.320%, where the dropout rate over 24 weeks was assumed uniformly to be

20%. Based on this adjusted effect size, 244 patients were required per treatment group, for a

total of 732 patients across the 3 treatment groups. These estimates were rounded upward for a

requirement of 250 patients per treatment group or 750 total patients.

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.

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 ($\leq$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 ($\leq$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

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

Figure 1. Patient disposition

Enrollment

Screened (n=1099)

Excluded (n=267)
- Inclusion criteria not met (n=149)
- Exclusion criteria met (n=67)
- Patient decision (n=39)
- Physician decision (n=2)
- Consent withdrawn (n=7)
- Lost to follow-up (n=7)
- Sponsor decision (n=1)
- Noncompliance (n=2)

Single-blind Placebo Run-in (n=832)

Discontinued (n=39)
- Inclusion criteria not met (n=6)
- Exclusion criteria met (n=10)
- Patient decision (n=14)
- Physician decision (n=2)
- Consent withdrawn (n=2)
- Lost to follow-up (n=1)
- Noncompliance (n=5)

Total Randomized (n=793)

Allocation

Placebo
- Received treatment (n=268)

Sotagliflozin 200 mg
- Received treatment (n=263)

Sotagliflozin 400 mg
- Received treatment (n=262)

Disposition

Completed Study
- Completed treatment (n=218)

Completed Study
- Completed treatment (n=228)

Completed Study
- Completed treatment (n=221)

Core Treatment

Discontinued from the Core Treatment period (n=33)
- Adverse event (n=8)
- Lost to follow-up (n=1)
- Noncompliance (n=1)
- Physician decision (n=1)
- Protocol deviation (n=3)
- Withdrawal by patient (n=18)
- Other (n=1)

Discontinued from the Core Treatment period (n=23)
- Adverse event (n=7)
- Lost to follow-up (n=1)
- Physician decision (n=1)
- Withdrawal by patient (n=14)

Discontinued from the Core Treatment period (n=26)
- Adverse event (n=11)
- Lost to follow-up (n=1)
- Non-compliance (n=1)
- Withdrawal by patient (n=13)

Long-term Extension

Discontinued from the Long-term Extension period (n=17)
- Adverse event (n=3)
- Lost to follow-up (n=2)
- Non-compliance (n=1)
- Withdrawal by patient (n=8)
- Other (n=3)

Discontinued from the Long-term Extension period (n=12)
- Adverse event (n=6)
- Lost to follow-up (n=1)
- Withdrawal by patient (n=5)

Discontinued from the Long-term Extension period (n=15)
- Adverse event (n=6)
- Pregnancy (n=1)
- Withdrawal by patient (n=7)
- Other (n=1)

Analysis

Safety (n=268)
mITT (n=268)
mITT in CGM substudy (n=45)
mITT in DEXA substudy (n=46)
PP (n=236)
Reasons excluded from PP:
- Low study drug compliance (n=2)
- Study conduct (n=2)
- Prohibited medication (n=1)
- Treatment allocation error (n=2)
- Did not complete 24-week CT period (n=25)
- No Baseline or Week 24 A1C (n=22)

PP for 2-hour PPG endpoint (n=28)
Reasons excluded from PPG PP:
- MMTT procedure or study drug/bolus insulin error (n=12)
- No 2-hour PPG test performed at Baseline or Week 24 (n=8)

Safety (n=263)
mITT (n=263)
mITT in CGM substudy (n=44)
mITT in DEXA substudy (n=44)
PP (n= 240)
Reasons excluded from PP:
- Low study drug compliance (n=2)
- Did not complete 24-week CT period (n=20)
- No Baseline or Week 24 A1C (n=18)

PP for 2-hour PPG endpoint (n=28)
Reasons excluded from PPG PP:
- MMTT procedure or study drug/bolus insulin error (n=6)
- No 2-hour PPG test performed at Baseline or Week 24 (n=12)

Safety (n=262)
mITT (n=262)
mITT in CGM substudy (n=47)
mITT in DEXA substudy (n=44)
PP (n= 236)
Reasons excluded from PP:
- Low study drug compliance (n=3)
- Did not complete 24-week CT period (n=19)
- No Baseline or Week 24 A1C (n=20)

PP for 2-hour PPG endpoint (n=30)
Reasons excluded from PPG PP:
- MMTT procedure or study drug/bolus insulin error (n=10)
- No 2-hour PPG test performed at Baseline or Week 24 (n=9)

SUPPLEMENTARY DATA

Table 1. Baseline characteristics

Characteristic	Placebo (n=268)	Sotagliflozin 200 mg (n=263)	Sotagliflozin 400 mg (n=262)	Total (N=793)
Age (years)	45.2 (12.72)	46.6 (13.48)	46.4 (13.12)	46.1 (13.11)
Female sex, n (%)	131 (48.9)	137 (52.1)	142 (54.2)	410 (51.7)
Race or ethnic group, n (%)*				
White	244 (91.0)	241 (91.6)	246 (93.9)	731 (92.2)
Black	9 (3.4)	11 (4.2)	8 (3.1)	28 (3.5)
Asian	4 (1.5)	4 (1.5)	2 (0.8)	10 (1.3)
Native American	0	1 (0.4)	0	1 (0.1)
Native Hawaiian or other Pacific Islander	2 (0.7)	2 (0.8)	0	4 (0.5)
Other	9 (3.4)	4 (1.5)	6 (2.3)	19 (2.4)
Hispanic/Latino ethnicity	7 (2.6)	8 (3.0)	15 (5.7)	30 (3.8)
Diabetes duration, years	24.2 (12.38)	25.0 (13.15)	24.0 (12.88)	24.4 (12.80)
A1C (%)	7.54 (0.712)	7.61 (0.735)	7.56 (0.724)	7.57 (0.723)
A1C (mmol/mol)	58.9 (7.80)	59.7 (7.98)	59.1 (7.91)	59.2 (7.90)
A1C <7.0% at baseline, n (%)	51 (19.03)	50 (19.01)	51 (19.47)	152 (19.17)
Fasting plasma glucose (mmol/L) (mg/dL ± SD)	8.53 (3.582) (153.7 ± 64.53)	8.61 (3.814) (155.1 ± 68.71)	8.23 (3.492) (148.2 ± 62.95)	8.45 (3.631) (152.3 ± 65.42)
Weight (kg)	87.30 (17.709)	86.96 (18.539)	86.50 (18.004)	86.92 (18.065)

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Characteristic	Placebo (n=268)	Sotagliflozin 200 mg (n=263)	Sotagliflozin 400 mg (n=262)	Total (N=793)
Body mass index (kg/m^2)	29.55 (5.188)	29.81 (5.686)	29.63 (5.297)	29.66 (5.387)
Body mass index ≥30 kg/m^2, n (%)	114 (42.5)	121 (46.0)	114 (43.5)	349 (44.0)
Blood pressure (mm Hg)	120.9/76.4 (13.47/8.24)	120.0/76.4 (14.84/9.28)	119.5/75.3 (14.73/9.17)	120.1/76.1 (14.35/8.91)
Systolic blood pressure ≥130 mm Hg, n (%)	64 (23.9)	60 (22.8)	60 (22.9)	184 (23.2)
Total daily insulin dose (IU/kg)	0.74 (0.357)	0.72 (0.386)	0.72 (0.335)	0.73 (0.360)
Insulin dose (IU/day)				
Total	66.79 (41.265)	65.11 (42.698)	64.15 (37.636)	65.36 (40.561)
Basal	35.06 (19.733)	34.84 (23.903)	33.39 (18.956)	34.44 (20.958)
Bolus and corrections	31.72 (25.077)	30.27 (23.646)	30.75 (22.832)	30.92 (23.856)
Insulin therapy, n (%)				
MDI	108 (40.3)	107 (40.7)	105 (40.1)	320 (40.4)
CSII	160 (59.7)	156 (59.3)	157 (59.9)	473 (59.6)

Data are mean (SD) unless otherwise indicated.

*Determined according to patient self-report.

Table 2. Primary, Secondary, and Other Prespecified Endpoints.

Characteristic	24 Weeks			52 Weeks		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
A1C (%)*						
No. patients	246	245	242	219	233	224
Baseline, mean ± SD	7.54 ± 0.712	7.61 ± 0.735	7.56 ± 0.724	7.54 ± 0.712	7.61 ± 0.735	7.56 ± 0.724
Difference from baseline, LSM ± SE	-0.07 ± 0.036	-0.43 ± 0.036	-0.48 ± 0.036	-0.01 ± 0.044	-0.26 ± 0.044	-0.32 ± 0.044
95% CI	-0.14 to -0.00	-0.50 to -0.36	-0.56 to -0.41	-0.10 to 0.07	-0.35 to -0.18	-0.41 to -0.24
P value	0.038	<0.001	<0.001	0.80	<0.001	<0.001
Difference from placebo, LSM ± SE		-0.36 ± 0.047	-0.41 ± 0.047		-0.25 ± 0.059	-0.31 ± 0.059
95% CI		-0.45 to -0.27	-0.50 to -0.32		-0.37 to -0.14	-0.43 to -0.20
P value		<0.001	<0.001		<0.001	<0.001
A1C (mmol/mol)						
No. patients	246	245	242	219	233	224
Baseline, mean ± SD	58.9 ± 7.80	59.7 ± 7.98	59.1 ± 7.91	58.9 ± 7.80	59.7 ± 7.98	59.1 ± 7.91
Difference from baseline,	-0.8 ± 0.39	-4.7 ± 0.40	-5.3 ± 0.39	-0.1 ± 0.48	-2.8 ± 0.48	-3.5 ± 0.48

Characteristic	24 Weeks			52 Weeks		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
LSM ± SE						
95% CI	-1.5 to -0.0	-5.5 to -3.9	-6.1 to -4.5	-1.0 to 0.8	-3.8 to -1.9	-4.5 to -2.6
P value	0.046	<0.001	<0.001	0.82	<0.001	<0.001
Difference from placebo, LSM ± SE		-3.9 ± 0.51	-4.5 ± 0.51		-2.7 ± 0.64	-3.4 ± 0.64
95% CI		-4.9 to -2.9	-5.5 to -3.5		-4.0 to -1.5	-4.7 to -2.2
P value		<0.001	<0.001		<0.001	<0.001
FPG (mmol/L)†						
No. patients	245	245	242	219	231	224
Baseline, mean ± SD	8.53 ± 3.582	8.61 ± 3.814	8.23 ± 3.492	8.53 ± 3.582	8.61 ± 3.814	8.23 ± 3.492
Difference from baseline, LSM ± SE	0.21 ± 0.191	-0.34 ± 0.192	-0.78 ± 0.193	0.50 ± 0.227	-0.18 ± 0.222	-0.58 ± 0.225
95% CI	-0.17 to 0.59	-0.72 to 0.04	-1.16 to -0.40	0.05 to 0.94	-0.62 to 0.26	-1.02 to -0.13
P value	0.27	0.08	<0.001	0.028	0.42	0.011
Difference from placebo, LSM ± SE		-0.55 ± 0.259	-0.99 ± 0.260		-0.68 ± 0.308	-1.08 ± 0.311
95% CI		-1.06 to -0.04	-1.50 to -0.48		-1.28 to -0.08	-1.69 to -0.47
P value		0.034	<0.001		0.028	<0.001

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| Characteristic | 24 Weeks | | | 52 Weeks | | |
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
FPG (mg/dL)†						
No. patients	245	245	242	219	231	224
Baseline, mean ± SD	153.7 ± 64.53	155.1 ± 68.71	148.2 ± 62.95	153.7 ± 64.53	155.1 ± 68.71	148.2 ± 62.95
Difference from baseline, LSM ± SE	3.7 ± 3.45	-6.1 ± 3.47	-14.0 ± 3.48	9.0 ± 4.08	-3.2 ± 4.00	-10.4 ± 4.05
95% CI	-3.0 to 10.5	-12.9 to 0.7	-20.9 to -7.2	1.0 to 17.0	-11.1 to 4.6	-18.4 to -2.5
P value	0.28	0.08	<0.001	0.028	0.42	0.010
Difference from placebo, LSM ± SE		-9.8 ± 4.67	-17.8 ± 4.69		-12.2 ± 5.55	-19.4 ± 5.60
95% CI		-19.0 to -0.7	-27.0 to -8.6		-23.1 to -1.3	-30.4 to -8.5
P value		0.036	<0.001		0.028	<0.001
Body weight (kg)†						
No. patients	244	245	242	221	233	224
Baseline, mean ± SD	87.30 ± 17.709	86.96 ± 18.539	86.50 ± 18.004	87.30 ± 17.709	86.96 ± 18.539	86.50 ± 18.004
Difference from baseline, LSM ± SE	0.78 ± 0.187	-1.57 ± 0.188	-2.67 ± 0.188	1.20 ± 0.249	-1.94 ± 0.247	-3.12 ± 0.250
95% CI	0.41 to 1.15	-1.94 to -1.20	-3.04 to -2.30	0.71 to 1.69	-2.42 to -1.45	-3.61 to -2.63
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

		24 Weeks			52 Weeks	
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
Difference from placebo, LSM ± SE		-2.35 ± 0.256	-3.45 ± 0.256		-3.14 ± 0.344	-4.32 ± 0.346
95% CI		-2.85 to -1.85	-3.95 to -2.94		-3.81 to -2.46	-5.00 to -3.64
P value		<0.001	<0.001		<0.001	<0.001
Percent difference from baseline, LSM ± SE	0.92 ± 0.212	-1.87 ± 0.213	-3.10 ± 0.213	1.33 ± 0.280	-2.29 ± 0.278	-3.62 ± 0.280
95% CI	0.50 to 1.33	-2.29 to -1.46	-3.52 to -2.68	0.79 to 1.88	-2.84 to -1.75	-4.17 to -3.07
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Percent difference from placebo, LSM ± SE		-2.79 ± 0.290	-4.02 ± 0.290		-3.63 ± 0.386	-4.96 ± 0.388
95% CI		-3.36 to -2.22	-4.59 to -3.45		-4.39 to -2.87	-5.72 to -4.19
P value		<0.001	<0.001		<0.001	<0.001
Bolus insulin dose (IU)†						
No. patients	241	242	242	216	227	219
Baseline, mean ± SD	31.72 ± 25.077	30.27 ± 23.646	30.75 ± 22.832	31.72 ± 25.077	30.27 ± 23.646	30.75 ± 22.832
Difference from baseline, LSM ± SE	-0.84 ± 0.688	-2.33 ± 0.692	-4.13 ± 0.692	-0.09 ± 0.754	-2.16 ± 0.751	-4.65 ± 0.756
95% CI	-2.19 to 0.51	-3.69 to -0.98	-5.49 to -2.78	-1.57 to 1.39	-3.63 to -0.68	-6.13 to -3.16

	24 Weeks			52 Weeks		
Characteristic	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
P value	0.22	<0.001	<0.001	0.90	0.004	<0.001
Difference from placebo, LSM ± SE		-1.50 ± 0.917	-3.30 ± 0.916		-2.06 ± 1.010	-4.55 ± 1.014
95% CI		-3.30 to 0.30	-5.09 to -1.50		-4.05 to -0.08	-6.54 to -2.57
P value		0.10	<0.001		0.041	<0.001
Percent difference from baseline, LSM ± SE	3.89 ± 2.757	-1.80 ± 2.777	-8.78 ± 2.780	7.01 ± 3.403	1.48 ± 3.398	-8.63 ± 3.423
95% CI	-1.52 to 9.31	-7.25 to 3.65	-14.23 to -3.32	0.33 to 13.69	-5.19 to 8.15	-15.35 to -1.91
P value	0.16	0.52	0.002	0.040	0.66	0.012
Percent difference from placebo, LSM ± SE		-5.70 ± 3.627	-12.67 ± 3.627		-5.53 ± 4.589	-15.63 ± 4.604
95% CI		-12.82 to 1.42	-19.79 to -5.55		-14.54 to 3.48	-24.67 to -6.59
P value		0.12	<0.001		0.23	<0.001
Total daily insulin dose (IU)						
No. patients	241	242	242	216	227	218
Baseline, mean ± SD	66.79 ± 41.265	65.11 ± 42.698	64.15 ± 37.636	66.79 ± 41.265	65.11 ± 42.698	64.15 ± 37.636

Characteristic	24 Weeks			52 Weeks		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Difference from baseline, LSM ± SE	0.81 ± 0.848	-2.17 ± 0.852	-5.54 ± 0.853	2.52 ± 0.988	-2.07 ± 0.984	-6.22 ± 0.991
95% CI	-0.85 to 2.48	-3.84 to -0.50	-7.22 to -3.87	0.58 to 4.46	-4.00 to -0.14	-8.17 to -4.28
P value	0.34	0.011	<0.001	0.011	0.036	<0.001
Difference from placebo, LSM ± SE		-2.98 ± 1.131	-6.36 ± 1.131		-4.59 ± 1.334	-8.74 ± 1.339
95% CI		-5.20 to -0.76	-8.58 to -4.14		-7.21 to -1.97	-11.37 to -6.12
P value		0.009	<0.001		<0.001	<0.001
Percent difference from baseline, LSM ± SE	1.91 ± 1.093	-4.26 ± 1.099	-7.79 ± 1.099	4.15 ± 1.242	-3.87 ± 1.234	-8.50 ± 1.247
95% CI	-0.24 to 4.05	-6.41 to -2.10	-9.95 to -5.63	1.71 to 6.59	-6.29 to -1.45	-10.94 to -6.05
P value	0.08	<0.001	<0.001	<0.001	0.002	<0.001
Percent difference from placebo, LSM ± SE		-6.16 ± 1.450	-9.70 ± 1.450		-8.02 ± 1.663	-12.64 ± 1.672
(95% CI)		-9.01 to -3.32	-12.54 to -6.85		-11.28 to -4.75	-15.93 to -9.36

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Characteristic	24 Weeks			52 Weeks		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
P value		<0.001	<0.001		<0.001	<0.001
Basal insulin dose (IU)						
No. patients	241	243	242	217	228	219
Baseline, mean ± SD	35.06 ± 19.733	34.84 ± 23.903	33.39 ± 18.956	35.06 ± 19.733	34.84 ± 23.903	33.39 ± 18.956
Difference from baseline, LSM ± SE	1.48 ± 0.417	-0.26 ± 0.418	-1.50 ± 0.418	2.44 ± 0.502	-0.36 ± 0.500	-1.91 ± 0.504
95% CI	0.66 to 2.30	-1.08 to 0.56	-2.32 to -0.68	1.45 to 3.43	-1.34 to 0.62	-2.90 to -0.93
P value	<0.001	0.54	<0.001	<0.001	0.47	<0.001
Difference from placebo, LSM ± SE		-1.74 ± 0.558	-2.98 ± 0.558		-2.80 ± 0.681	-4.35 ± 0.684
95% CI		-2.83 to -0.64	-4.08 to -1.89		-4.14 to -1.47	-5.70 to -3.01
P value		0.002	<0.001		<0.001	<0.001
Percent difference from baseline, LSM ± SE	3.77 ± 1.252	-1.73 ± 1.261	-5.35 ± 1.265	5.99 ± 1.467	-1.70 ± 1.464	-5.87 ± 1.478
95% CI	1.31 to 6.23	-4.21 to 0.74	-7.83 to -2.86	3.11 to 8.87	-4.57 to 1.18	-8.77 to -2.97
P value	0.003	0.17	<0.001	<0.001	0.25	<0.001
Percent difference from placebo, LSM ± SE		-5.51 ± 1.633	-9.12 ± 1.634		-7.69 ± 1.950	-11.87 ± 1.959

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| Characteristic | 24 Weeks | | | 52 Weeks | | |
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
95% CI		-8.71 to -2.30	-12.32 to -5.91		-11.52 to -3.86	-15.71 to -8.02
P value		<0.001	<0.001		<0.001	<0.001
SBP, mITT population (mm Hg)						
No. patients (week 12, week 52)	251	247	253	221	233	224
Baseline, mean ± SD	120.9 ± 13.47	120.0 ± 14.84	119.5 ± 14.73	120.9 ± 13.47	120.0 ± 14.84	119.5 ± 14.73
Difference from baseline (week 12, week 52), LSM ± SE	1.0 ± 0.66	-2.5 ± 0.67	-3.2 ± 0.66	1.7 ± 0.74	-1.1 ± 0.73	-2.7 ± 0.74
95% CI	-0.3 to 2.3	-3.8 to -1.2	-4.5 to -1.9	0.3 to 3.1	-2.5 to 0.3	-4.2 to -1.3
P value	0.14	<0.001	<0.001	0.021	0.14	<0.001
Difference from placebo, LSM ± SE		-3.5 ± 0.88	-4.2 ± 0.88		-2.8 ± 0.99	-4.4 ± 0.99
95% CI		-5.2 to -1.8	-5.9 to -2.4		-4.7 to -0.9	-6.4 to -2.5
P value		<0.001	<0.001		0.005	<0.001
DBP, mITT population (mm Hg)						
No. patients (week 12, week 52)	251	247	253	221	233	224

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Characteristic	24 Weeks			52 Weeks		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Baseline, mean ± SD	76.4 ± 8.24	76.4 ± 9.28	75.3 ± 9.17	76.4 ± 8.24	76.4 ± 9.28	75.3 ± 9.17
Difference from baseline (week 12, week 52), LSM ± SE	0.8 ± 0.41	-1.0 ± 0.42	-1.1 ± 0.41	0.9 ± 0.46	-0.6 ± 0.46	-1.4 ± 0.46
95% CI	-0.0 to 1.6	-1.8 to -0.2	-1.9 to -0.3	-0.0 to 1.8	-1.5 to 0.3	-2.3 to -0.5
P value	0.051	0.019	0.009	0.06	0.22	0.003
Difference from placebo, LSM ± SE		-1.8 ± 0.54	-1.9 ± 0.54		-1.4 ± 0.61	-2.3 ± 0.62
95% CI		-2.8 to -0.7	-2.9 to -0.8		-2.6 to -0.2	-3.5 to -1.0
P value		0.001	<0.001		0.020	<0.001
SBP, patients with baseline SBP ≥130 mm Hg (mm Hg)						
No. patients (week 12, week 52)	58	54	60	51	55	56
Baseline, mean ± SD	139.1 ± 7.98	140.7 ± 9.92	139.8 ± 9.35	139.1 ± 7.98	140.7 ± 9.92	139.8 ± 9.35
Difference from baseline (week 12, week 52), LSM ± SE	-4.4 ± 1.64	-9.9 ± 1.72	-11.0 ± 1.61	-7.3 ± 1.70	-9.5 ± 1.69	-11.0 ± 1.64
95% CI	-7.7 to -1.2	-13.2 to -6.5	-14.2 to -7.8	-10.6 to -3.9	-12.8 to -6.1	-14.3 to -7.8

Characteristic	24 Weeks			52 Weeks		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
P value	0.008	<0.001	<0.001	<0.001	<0.001	<0.001
Difference from placebo, LSM ± SE		-5.4 ± 2.25	-6.6 ± 2.18		-2.2 ± 2.28	-3.7 ± 2.26
(95% CI)		-9.9 to -1.0	-10.9 to -2.3		-6.7 to 2.3	-8.2 to 0.7
P value		0.017	0.003		0.34	0.10
Urine ACR (mg/mmol)						
No. patients	243	244	237	214	232	215
Baseline, mean ± SD	3.2261 ± 13.68241	4.3769 ± 19.55254	1.8873 ± 5.58182	3.2261 ± 13.68241	4.3769 ± 19.55254	1.8873 ± 5.58182
Difference from baseline, LSM ± SE	-0.2516 ± 0.44128	0.1500 ± 0.44482	-0.0233 ± 0.44983	0.4133 ± 1.25487	1.9187 ± 1.20947	0.1968 ± 1.25465
95% CI	-1.1178 to 0.6145	-0.7231 to 1.0231	-0.9062 to 0.8597	-2.0507 to 2.8772	-0.4561 to 4.2934	-2.2667 to 2.6603
P value	0.57	0.74	0.96	0.74	0.11	0.88
Difference from placebo, LSM ± SE		0.4016 ± 0.58174	0.2284 ± 0.58623		1.5054 ± 1.73043	-0.2165 ± 1.75905
95% CI		-0.7404 to 1.5437	-0.9225 to 1.3793		-1.8924 to 4.9032	-3.6705 to 3.2376
P value		0.49	0.70		0.38	0.90

Characteristic	24 Weeks			52 Weeks		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
eGFR (mL/min/1.73 m^2)						
No. patients	244	243	239	217	233	223
Baseline, mean ± SD	87.58 ± 18.465	87.04 ± 20.182	86.58 ± 18.933	87.58 ± 18.465	87.04 ± 20.182	86.58 ± 18.933
Difference from baseline,[‡] LSM ± SD	-0.20 ± 0.684	-2.18 ± 0.690	-2.35 ± 0.694	-1.06 ± 0.722	-2.46 ± 0.713	-2.16 ± 0.722
95% CI	-1.54 to 1.14	-3.53 to -0.82	-3.71 to -0.99	-2.48 to 0.36	-3.86 to -1.06	-3.58 to -0.74
P value	0.77	0.002	<0.001	0.14	<0.001	0.003
Difference from placebo, LSM ± SD		-1.98 ± 0.904	-2.15 ± 0.906		-1.40 ± 0.951	-1.10 ± 0.957
95% CI		-3.75 to -0.20	-3.93 to -0.37		-3.27 to 0.46	-2.98 to 0.78
P value		0.029	0.018		0.14	0.25
Documented blood glucose ≤3.9 mmol/L (≤70 mg/dL) (events/patient/day)						
No. patients	249	244	239	238	245	237
Baseline, mean ± SD	0.339 ± 0.3489	0.341 ± 0.3407	0.334 ± 0.3368	0.339 ± 0.3489	0.341 ± 0.3407	0.334 ± 0.3368
Difference from baseline,	-0.057 ±	-0.096 ±	-0.095 ±	-0.130 ±	-0.163 ±	-0.167 ±

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Characteristic	24 Weeks			52 Weeks		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
LSM ± SD	0.0198	0.0200	0.0202	0.0166	0.0164	0.0167
95% CI	-0.096 to -0.018	-0.136 to -0.057	-0.135 to -0.056	-0.163 to -0.098	-0.195 to -0.131	-0.200 to -0.134
P value	0.004	<0.001	<0.001	<0.001	<0.001	<0.001
Difference from placebo, LSM ± SD		-0.039 ± 0.0269	-0.038 ± 0.0270		-0.033 ± 0.0222	-0.037 ± 0.0224
95% CI		-0.092 to 0.014	-0.091 to 0.015		-0.076 to 0.011	-0.081 to 0.007
P value		0.15	0.16		0.14	0.10
Documented blood glucose ≤3.9 mmol/L (≤70 mg/dL) (event rate)						
No. patients	268	263	262	268	263	262
Patients with events, n (%)	265 (98.9)	260 (98.9)	257 (98.1)	266 (99.3)	260 (98.9)	258 (98.5)
Events per person-year	102.0	93.1	99.4	96.1	84.1	90.0
Event rate	90.23	82.57	87.81	86.44	75.66	80.52
95% CI	81.47 to 99.93	74.30 to 91.76	79.07 to 97.51	78.18 to 95.56	68.22 to 83.90	72.66 to 89.24

Characteristic		24 Weeks			52 Weeks	
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Relative rate		0.92	0.97		0.88	0.93
95% CI		0.80 to 1.04	0.85 to 1.11		0.77 to 0.99	0.82 to 1.06
P value vs placebo		0.18	0.68		0.040	0.28
Documented blood glucose ≤3.0 mmol/L (≤55 mg/dL) (events/patient/day)						
No. patients	249	244	239	238	245	237
Baseline, mean ± SD	0.070 ± 0.1600	0.068 ± 0.1372	0.065 ± 0.1407	0.070 ± 0.1600	0.068 ± 0.1372	0.065 ± 0.1407
Difference from baseline, LSM ± SD	-0.011 ± 0.0069	-0.024 ± 0.0070	-0.021 ± 0.0071	-0.017 ± 0.0060	-0.037 ± 0.0059	-0.041 ± 0.0060
95% CI	-0.025 to 0.002	-0.038 to -0.010	-0.035 to -0.007	-0.028 to -0.005	-0.049 to -0.026	-0.053 to -0.030
P value	0.10	<0.001	0.003	0.005	<0.001	<0.001
Difference from placebo, LSM ± SD		-0.012 ± 0.0095	-0.010 ± 0.0095		-0.020 ± 0.0080	-0.025 ± 0.0081
95% CI		-0.031 to 0.006	-0.028 to 0.009		-0.036 to -0.005	-0.041 to -0.009
P value		0.20	0.31		0.011	0.002

Characteristic	24 Weeks			52 Weeks		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Documented blood glucose ≤3.0 mmol/L (≤55 mg/dL) (event rate)						
No. patients	268	263	262	268	263	262
Patients with events, n (%)	238 (88.8)	237 (90.1)	228 (87.0)	248 (92.5)	250 (95.1)	244 (93.1)
Events per person-year	18.8	16.6	17.4	18.1	14.9	15.8
Event rate	17.35	15.08	16.06	17.10	13.72	14.82
95% CI	14.95 to 20.13	12.91 to 17.62	13.78 to 18.71	14.85 to 19.69	11.85 to 15.88	12.83 to 17.12
Relative rate		0.87	0.93		0.80	0.87
95% CI		0.72 to 1.05	0.77 to 1.12		0.67 to 0.96	0.72 to 1.04
P value vs placebo		0.15	0.42		0.016	0.12
DTSQs score[†§]						
No. patients	237	240	233	—	—	—
Baseline, mean ± SD	28.9 ± 4.66	28.4 ± 5.29	29.2 ± 4.80	—	—	—
Difference from baseline, LSM ± SE	-0.4 ± 0.30	2.1 ± 0.31	2.1 ± 0.31	—	—	—
95% CI	-1.0 to 0.2	1.5 to 2.7	1.5 to 2.8	—	—	—

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Characteristic	24 Weeks			52 Weeks		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
P value	0.20	<0.001	<0.001	—	—	—
Difference from placebo, LSM ± SE		2.5 ± 0.40	2.5 ± 0.40	—	—	—
95% CI		1.7 to 3.3	1.8 to 3.3	—	—	—
P value		<0.001	<0.001	—	—	—
DDS2 score[†]						
No. patients	243	244	242	217	228	222
Baseline, mean ± SD	5.0 ± 2.18	5.1 ± 1.97	4.9 ± 2.15	5.0 ± 2.18	5.1 ± 1.97	4.9 ± 2.15
Difference from baseline, LSM ± SE	0.3 ± 0.11	-0.4 ± 0.11	-0.5 ± 0.11	0.1 ± 0.11	-0.3 ± 0.11	-0.4 ± 0.11
95% CI	0.1 to 0.5	-0.6 to -0.2	-0.7 to -0.3	-0.1 to 0.3	-0.6 to -0.1	-0.6 to -0.2
P value	0.010	<0.001	<0.001	0.37	0.002	<0.001
Difference from placebo, LSM ± SE		-0.7 ± 0.14	-0.8 ± 0.14		-0.4 ± 0.15	-0.5 ± 0.15
95% CI		-0.9 to -0.4	-1.0 to -0.5		-0.7 to -0.2	-0.8 to -0.2
P value		<0.001	<0.001		0.003	<0.001

*Primary endpoint.

[†]Secondary endpoint.

[‡]The mean ± SD change from baseline in eGFR at week 53 was -3.87 ± 10.047 mL/min/1.73 m^2 for the placebo group, 0.67 ± 9.329 mL/min/1.73 m^2 for the sotagliflozin 200 mg group, and -1.35 ± 9.539 mL/min/1.73 m^2 for the sotagliflozin 400 mg group.

[§]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.

Table 3. Changes in CGM values at week 24.

	Placebo (n=45)	Sotagliflozin 200 mg (n=44)	Sotagliflozin 400 mg (n=47)
Mean daily glucose, mmol/L ± SD (mg/dL ± SD)			
No. patients	36	37	37
Mean baseline	9.45 ± 1.56 (170.31 ± 28.184)	9.57 ± 1.80 (172.42 ± 32.347)	9.54 ± 1.39 (171.84 ± 25.050)
Difference from baseline, LSM ± SE	0.11 ± 0.25 (1.93 ± 4.455)	-0.17 ± 0.25 (-2.97 ± 4.450)	-0.86 ± 0.25 (-15.57 ± 4.517)
95% CI	-0.38 to 0.60 (-6.89 to 10.75)	-0.65 to 0.32 (-11.78 to 5.83)	-1.36 to -0.37 (-24.50 to -6.63)
P value	0.67	0.51	<0.001
Difference from placebo		-0.27 ± 0.32 (-4.91 ± 5.810)	-0.97 ± 0.32 (-17.50 ± 5.821)
95% CI		-0.91 to 0.37 (-16.42 to 6.61)	-1.61 to -0.33 (-29.04 to -5.96)
P value		0.40	0.003
MAGE, mmol/L ± SD (mg/dL ± SD)			
No. patients	36	37	37

	Placebo **(n=45)**	**Sotagliflozin 200 mg** **(n=44)**	**Sotagliflozin 400 mg** **(n=47)**
Mean baseline	8.90 ± 1.84 (160.32 ± 33.146)	9.07 ± 1.84 (163.43 ± 33.086)	8.74 ± 1.89 (157.40 ± 34.113)
Difference from baseline, LSM ± SE	-0.24 ± 0.32 (-4.29 ± 5.762)	-0.49 ± 0.32 (-8.79 ± 5.782)	-1.44 ± 0.32 (-25.86 ± 5.849)
95% CI	-0.87 to 0.40 (-15.70 to 7.12)	-1.12 to 0.15 (-20.23 to 2.65)	-2.08 to -0.79 (-37.43 to -14.29)
P value	0.46	0.13	<0.001
Difference from placebo		-0.25 ± 0.41 (-4.50 ± 7.409)	-1.20 ± 0.41 (-21.57 ± 7.418)
95% CI		-1.06 to 0.57 (-19.19 to 10.19)	-2.01 to -0.38 (-36.27 to -6.86)
P value		0.54	0.004
Percent time in range (3.9-10.0 mmol/L [70 to 180 mg/dL]), per 24 h			
No. patients	36	37	37
Mean baseline	54.19 ± 12.941	53.95 ± 14.963	53.18 ± 13.892
Difference from baseline, LSM ± SE	-1.83 ± 2.230	1.21 ± 2.231	8.56 ± 2.269
(95% CI)	-6.25 to 2.58	-3.21 to 5.62	4.08 to 13.05

	Placebo (n=45)	Sotagliflozin 200 mg (n=44)	Sotagliflozin 400 mg (n=47)
Hours per day corresponding to percent time per day ± SE	-0.44 ± 0.54	0.29 ± 0.54	2.05 ± 0.54
P value	0.41	0.59	<0.001
Difference from placebo		3.04 ± 2.882	10.40 ± 2.885
(95% CI)		-2.67 to 8.75	4.68 to 16.12
Hours per day corresponding to percent time per day ± SE		0.73 ± 0.69	2.50 ± 0.69
P value		0.29	<0.001
Standard deviation, mmol/L ± SD (mg/dL ± SD)			
No. patients	36	37	37
Mean baseline	3.51 ± 0.72 (63.28 ± 12.905)	3.58 ± 0.71 (64.55 ± 12.814)	3.43 ± 0.72 (61.87 ± 13.032)
Difference from baseline, LSM ± SE	-0.08 ± 0.13 (-1.37 ± 2.359)	-0.13 ± 0.13 (-2.39 ± 2.360)	-0.44 ± 0.13 (-7.97 ± 2.387)
95% CI	-0.33 to 0.18 (-6.04 to 3.30)	-0.39 to 0.13 (-7.06 to 2.28)	-0.70 to -0.18 (-12.69 to -3.24)
P value	0.56	0.31	0.001

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	Placebo (n=45)	Sotagliflozin 200 mg (n=44)	Sotagliflozin 400 mg (n=47)
Difference from placebo		-0.06 ± 0.17 (-1.03 ± 3.048)	-0.37 ± 0.17 (-6.60 ± 3.055)
95% CI		-0.39 to 0.28 (-7.07 to 5.02)	-0.70 to -0.03 (-12.66 to -0.55)
P value		0.74	0.033
2-h PPG, mmol/L ± SD (mg/dL ± SD)[†]			
No. patients (per-protocol population)	28	28	30
Mean baseline	13.15 ± 5.386 (236.8 ± 97.04)	11.99 ± 4.662 (215.8 ± 83.87)	11.16 ± 3.708 (200.9 ± 66.85)
Difference from baseline, LSM ± SE	-1.03 ± 0.812 (-18.5 ± 14.62)	-1.99 ± 0.845 (-35.7 ± 15.21)	-2.24 ± 0.833 (-40.2 ± 14.99)
95% CI	-2.64 to 0.59 (-47.5 to 10.6)	-3.67 to -0.31 (-66.0 to -5.4)	-3.90 to -0.58 (-70.0 to -10.4)
P value	0.21	0.021	0.009
Difference from placebo		-0.96 ± 1.018 (-17.3 ± 18.32)	-1.21 ± 1.011 (-21.7 ± 18.20)
95% CI		-2.99 to 1.06 (-53.7 to 19.2)	-3.23 to 0.80 (-58.0 to 14.5)

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|	Placebo (n=45)	Sotagliflozin 200 mg (n=44)	Sotagliflozin 400 mg (n=47)
P value		0.35	0.24

CGM, continuous glucose monitoring; CI, confidence interval; LSM, least squares mean;

MAGE, mean amplitude of glucose excursions PPG, postprandial glucose.

[†]In order to assess the change in PPG under standardized conditions, the per-protocol population

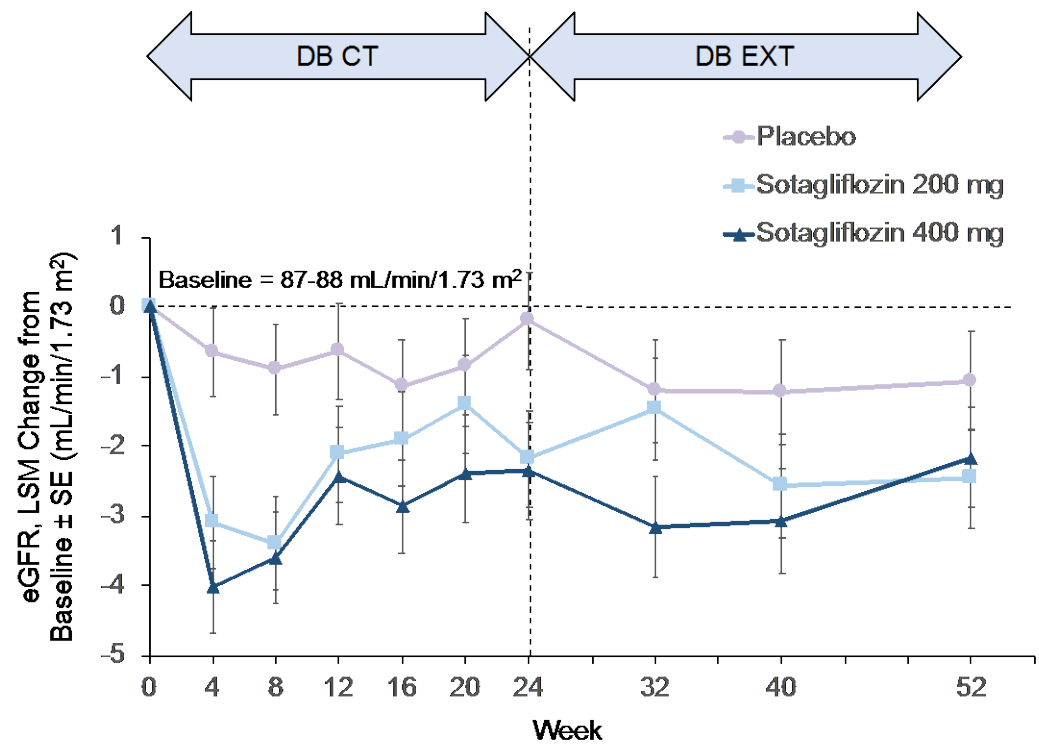was selected; 2-h PPG values were obtained after a standardized mixed meal.

Figure 2. LSM percent (A) and absolute (B) change from baseline in insulin dose at 24 and 52 weeks. Baseline values are IU/day.
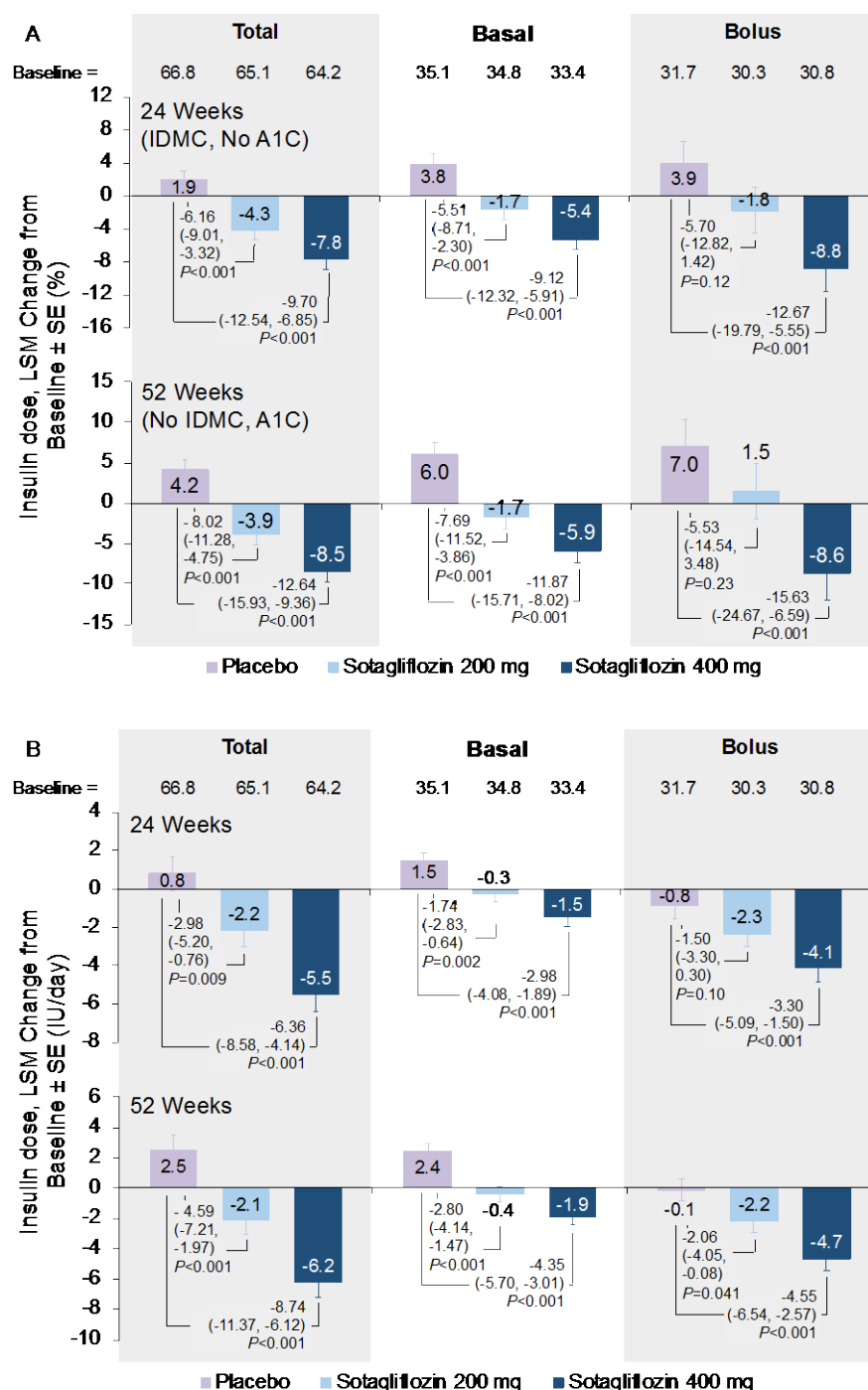
Figure 3. Least squares mean (LSM) change from baseline in estimated glomerular filtration rate (eGFR) over 52 weeks. Error bars represent standard error (SE).
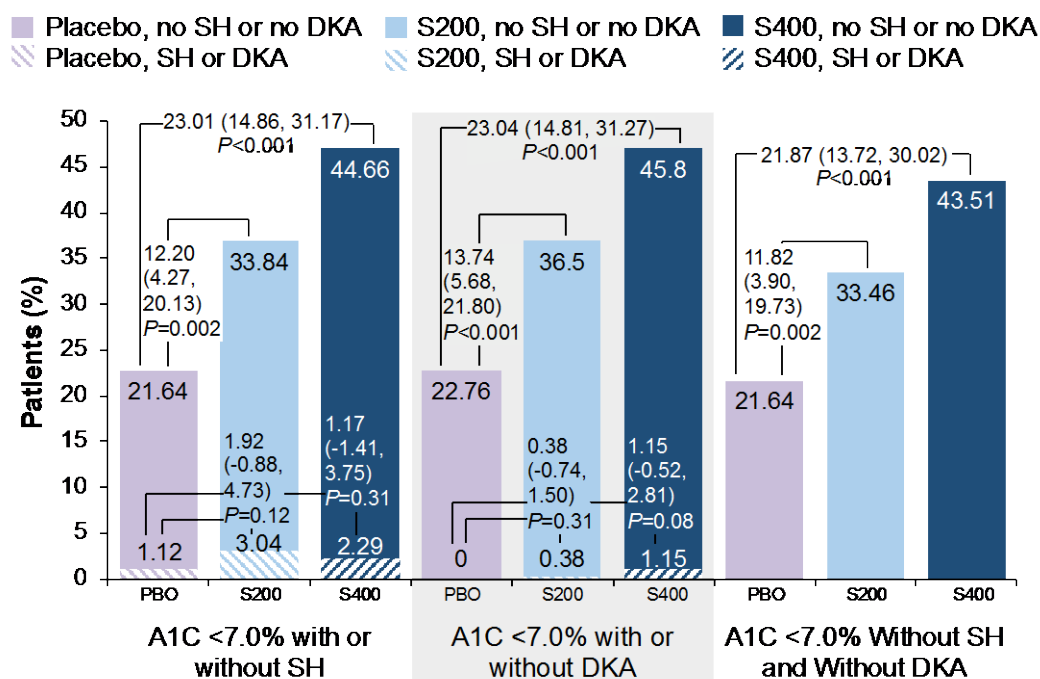
Figure 4. Overall summary of composite endpoints showing proportions of patients with A1C <7.0% who did not experience severe hypoglycemia (SH), diabetic ketoacidosis (DKA), weight gain, either weight gain or SH, or documented hypoglycemia ≤3.0 mmol/L at 24 weeks. *P<0.05 vs placebo.
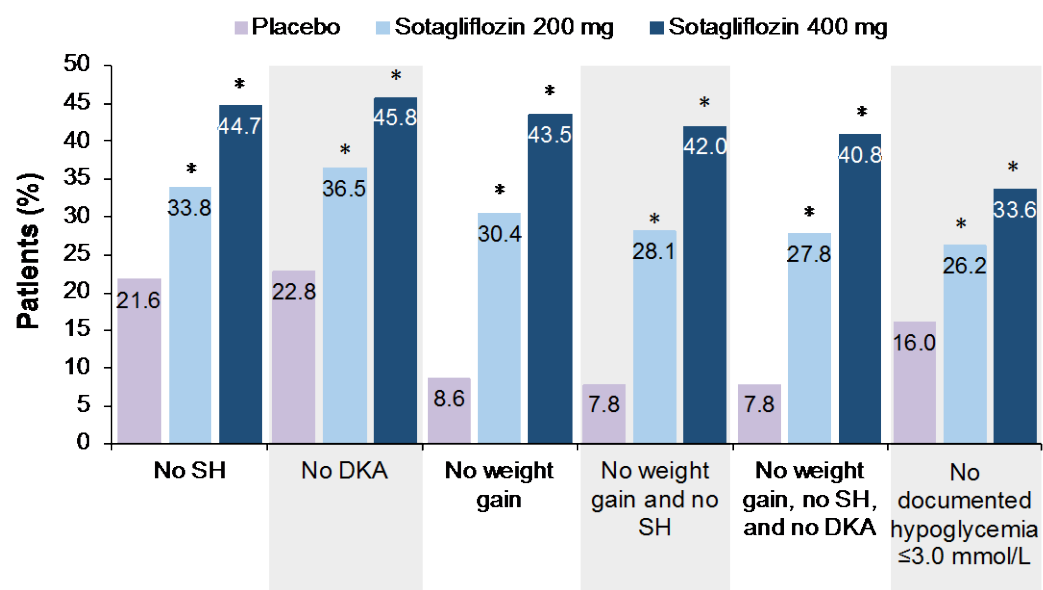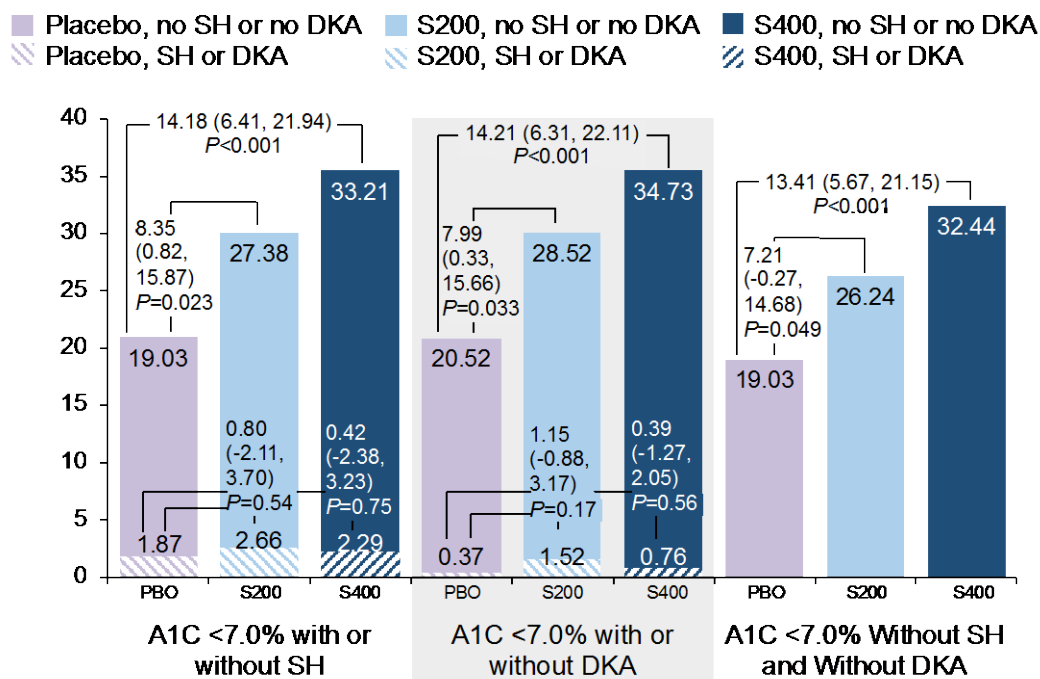
Figure 5. Proportions of patients with A1C <7.0%, severe hypoglycemia (SH), and/or diabetic ketoacidosis (DKA) at 24 weeks (*A*) and 52 weeks (*B*) and proportions of patients with a change in A1C ≥0.5%, severe hypoglycemia (SH), and/or diabetic ketoacidosis (DKA) at 24 weeks (*C*) and 52 weeks (*D*). 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.

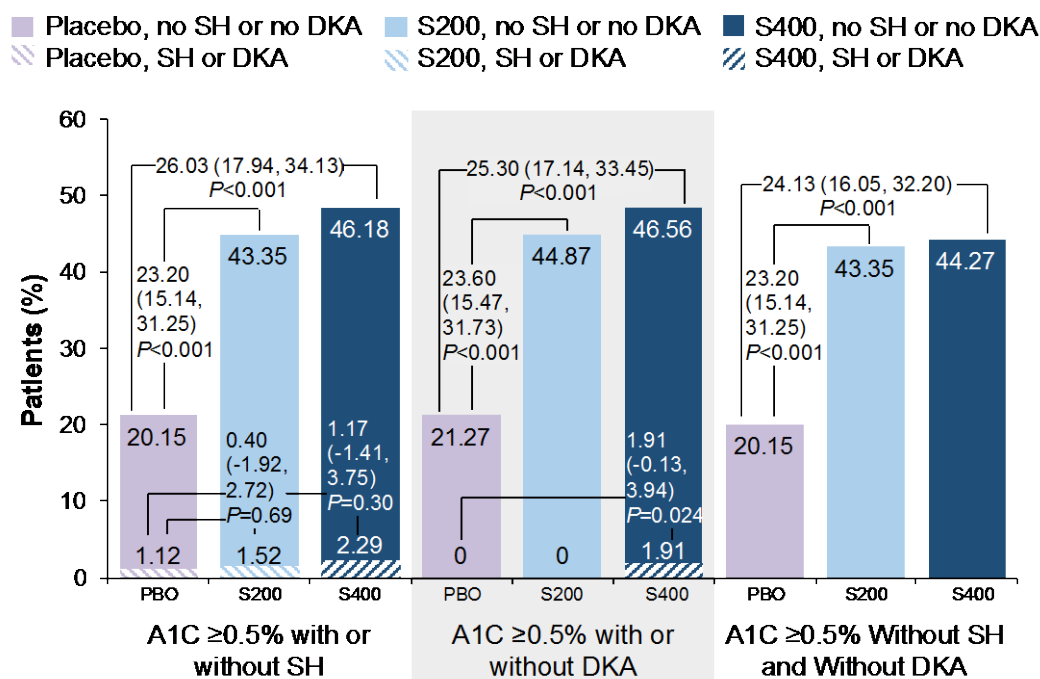A. Patients with A1C <7.0% with and without SH and DKA at 24 weeks

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

Legend:
- Placebo, no SH or no DKA
- Placebo, SH or DKA
- S200, no SH or no DKA
- S200, SH or DKA
- S400, no SH or no DKA
- S400, SH or DKA

A1C <7.0% with or without SH

Values: PBO 19.03 / 1.87, S200 27.38 / 2.66, S400 33.21 / 2.29
14.18 (6.41, 21.94) P<0.001
8.35 (0.82, 15.87) P=0.023
0.80 (-2.11, 3.70) P=0.54
0.42 (-2.38, 3.23) P=0.75

A1C <7.0% with or without DKA

Values: PBO 20.52 / 0.37, S200 28.52 / 1.52, S400 34.73 / 0.76
14.21 (6.31, 22.11) P<0.001
7.99 (0.33, 15.66) P=0.033
1.15 (-0.88, 3.17) P=0.17
0.39 (-1.27, 2.05) P=0.56

A1C <7.0% Without SH and Without DKA

Values: PBO 19.03, S200 26.24, S400 32.44
13.41 (5.67, 21.15) P<0.001
7.21 (-0.27, 14.68) P=0.049

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

Legend:
- Placebo, no SH or no DKA
- Placebo, SH or DKA
- S200, no SH or no DKA
- S200, SH or DKA
- S400, no SH or no DKA
- S400, SH or DKA

Patients (%)

A1C ≥0.5% with or without SH

Values: PBO 20.15 / 1.12, S200 43.35 / 1.52, S400 46.18 / 2.29
26.03 (17.94, 34.13) P<0.001
23.20 (15.14, 31.25) P<0.001
0.40 (-1.92, 2.72) P=0.69
1.17 (-1.41, 3.75) P=0.30

A1C ≥0.5% with or without DKA

Values: PBO 21.27 / 0, S200 44.87 / 0, S400 46.56 / 1.91
25.30 (17.14, 33.45) P<0.001
23.60 (15.47, 31.73) P<0.001
1.91 (-0.13, 3.94) P=0.024

A1C ≥0.5% Without SH and Without DKA

Values: PBO 20.15, S200 43.35, S400 44.27
24.13 (16.05, 32.20) P<0.001
23.20 (15.14, 31.25) P<0.001

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

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, no severe hypoglycemia, and no 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. [†]P<0.05 vs placebo. See Table 4 for LSM differences between treatment groups. PBO, placebo. S200, sotagliflozin 200 mg. S400, sotagliflozin 400 mg.
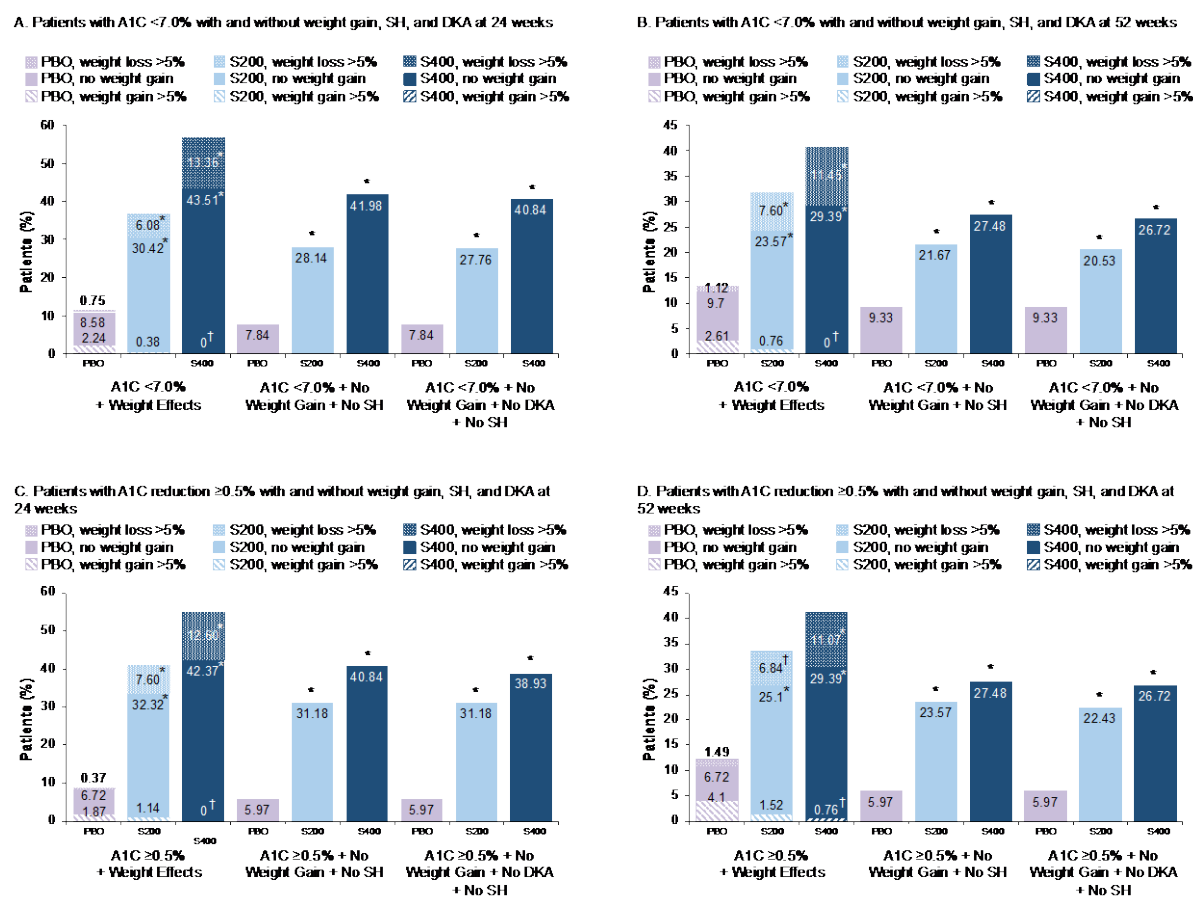
Table 4. Proportions of patients achieving selected composite outcomes.

Characteristic	Placebo (n=268) n (%)	Sotagliflozin 200 mg (n=263) n (%)	Percent difference from placebo (95% CI) *P* value	Sotagliflozin 400 mg (n=262) n (%)	Percent difference from placebo (95% CI) *P* value
Patients achieving A1C <7.0% at 24 weeks and:					
Weight gain >5%	6 (2.24)	1 (0.38)	-1.86 (-4.16 to 0.44) 0.06	0	-2.24 (-4.39 to -0.09) 0.014
No weight gain	23 (8.58)	80 (30.42)	21.84 (14.97 to 28.71) <0.001	114 (43.51)	34.93 (27.68 to 42.18) <0.001
Weight loss >5%	2 (0.75)	16 (6.08)	5.34 (1.89 to 8.78) <0.001	35 (13.36)	12.61 (7.99 to 17.24) <0.001
No severe hypoglycemia or weight gain	21 (7.84)	74 (28.14)	20.30 (13.61 to 26.99) <0.001	110 (41.98)	34.15 (26.98 to 41.31) <0.001

Characteristic	Placebo (n=268) n (%)	Sotagliflozin 200 mg (n=263) n (%)	Percent difference from placebo (95% CI) *P* value	Sotagliflozin 400 mg (n=262) n (%)	Percent difference from placebo (95% CI) *P* value
No severe hypoglycemia, DKA, or weight gain	21 (7.84)	73 (27.76)	19.92 (13.25 to 26.59) <0.001	107 (40.84)	33.00 (25.86 to 40.15) <0.001
Patients achieving A1C reduction ≥0.5% at 24 weeks and:					
Weight gain >5%	5 (1.87)	3 (1.14)	-0.72 (-3.17 to 1.72), 0.50	0	-1.87 (-3.86 to 0.13) 0.027
No weight gain	18 (6.72)	85 (32.32)	25.60 (18.83 to 32.38) <0.001	111 (42.37)	35.65 (28.58 to 42.72) <0.001
Weight loss >5%	1 (0.37)	20 (7.60)	7.23 (3.57 to 10.89) <0.001	33 (12.60)	12.22 (7.76 to 16.68) <0.001
No severe hypoglycemia or weight gain	16 (5.97)	82 (31.18)	25.21 (18.56 to 31.86) <0.001	107 (40.84)	34.87 (27.90 to 41.84) <0.001

Characteristic	Placebo (n=268) n (%)	Sotagliflozin 200 mg (n=263) n (%)	Percent difference from placebo (95% CI) *P* value	Sotagliflozin 400 mg (n=262) n (%)	Percent difference from placebo (95% CI) *P* value
No severe hypoglycemia, DKA, or weight gain	16 (5.97)	82 (31.18)	25.21 (18.56 to 31.86) <0.001	102 (38.93)	32.96 (26.03 to 39.89) <0.001
Patients achieving A1C <7.0% at 52 weeks and:					
Weight gain >5%	7 (2.61)	2 (0.76)	-1.85 (-4.41 to 0.70) 0.10	0	-2.61 (-4.90 to -0.33) 0.008
No weight gain	26 (9.70)	62 (23.57)	13.87 (7.26 to 20.48) <0.001	77 (29.39)	19.69 (12.75 to 26.62) <0.001
Weight loss >5%	3 (1.12)	20 (7.60)	6.49 (2.67 to 10.30) <0.001	30 (11.45)	10.33 (5.90 to 14.76) <0.001
No severe hypoglycemia or weight gain	25 (9.33)	57 (21.67)	12.34 (5.89 to 18.80) <0.001	72 (27.48)	18.15 (11.35 to 24.96) <0.001

Characteristic	Placebo (n=268) n (%)	Sotagliflozin 200 mg (n=263) n (%)	Percent difference from placebo (95% CI) P value	Sotagliflozin 400 mg (n=262) n (%)	Percent difference from placebo (95% CI) P value
No severe hypoglycemia, DKA, or weight gain	25 (9.33)	54 (20.53)	11.20 (4.83 to 17.58) <0.001	70 (26.72)	17.39 (10.62 to 24.16) <0.001
Patients achieving A1C reduction ≥0.5% at 52 weeks and:					
Weight gain >5%	11 (4.10)	4 (1.52)	-2.58 (-5.76 to 0.59) 0.08	2 (0.76)	-3.34 (-6.32 to -0.37) 0.015
No weight gain	18 (6.72)	66 (25.10)	18.38 (11.97 to 24.79) <0.001	77 (29.39)	22.67 (16.02 to 29.33) <0.001
Weight loss >5%	4 (1.49)	18 (6.84)	5.35 (1.60 to 9.11) 0.002	29 (11.07)	9.58 (5.13 to 14.02) <0.001
No severe hypoglycemia or weight gain	16 (5.97)	62 (23.57)	17.60 (11.37 to 23.84) <0.001	72 (27.48)	21.51 (15.03 to 27.99) <0.001

Characteristic	Placebo (n=268) n (%)	Sotagliflozin 200 mg (n=263) n (%)	Percent difference from placebo (95% CI) P value	Sotagliflozin 400 mg (n=262) n (%)	Percent difference from placebo (95% CI) P value
No severe hypoglycemia, DKA, or weight gain	16 (5.97)	59 (22.43)	16.46 (10.30 to 22.62) <0.001	70 (26.72)	20.75 (14.31 to 27.19) <0.001

*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).

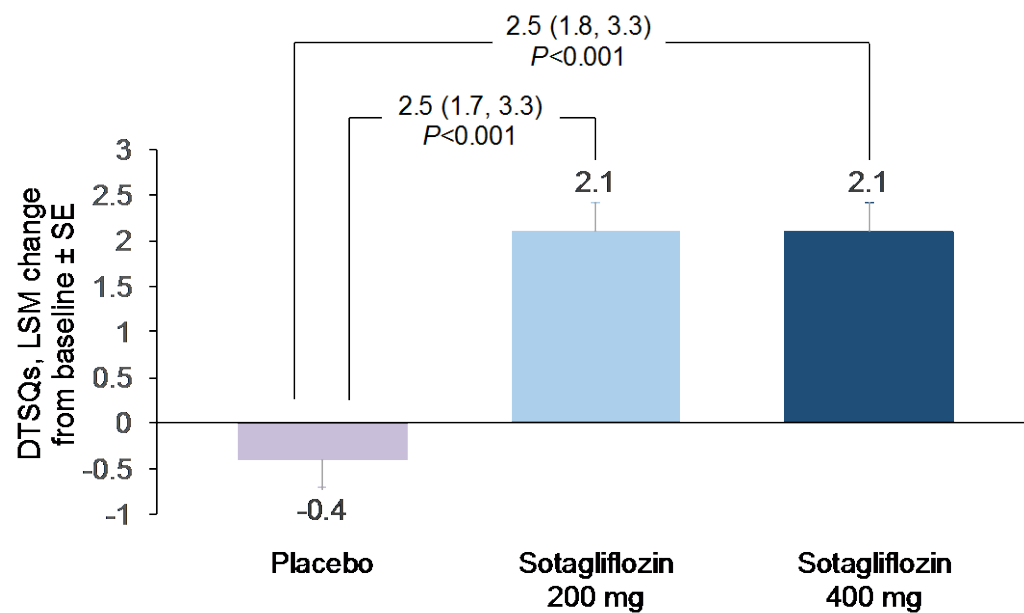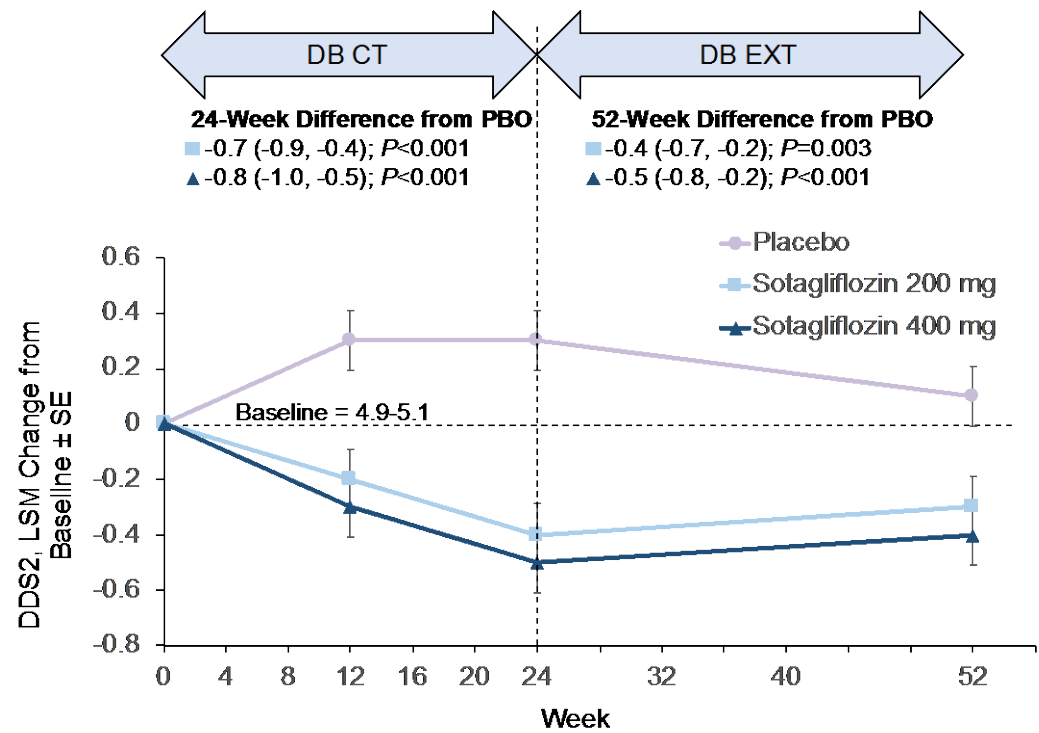Figure 7. LS Mean change from baseline in DTSQs total score at week 24.

Figure 8. Mean change from baseline in DDS2 total score by study visit.

Table 5. Acidosis-related events (baseline to 52 weeks).

Events, no. patients (%)	Placebo (n=268)	Sotagliflozin 200 mg (n=263)	Sotagliflozin 400 mg (n=262)
Acidosis-related adverse events	11 (4.1)	28 (10.6)	43 (16.4)
Nonserious acidosis-related adverse events	8 (3.0)	15 (5.7)	31 (11.8)
Serious acidosis-related adverse events	3 (1.1)	13 (4.9)	14 (5.3)
Positively adjudicated metabolic acidosis	3 (1.1)	10 (3.8)	12 (4.6)
Positively adjudicated metabolic acidosis that was also diabetic ketoacidosis	1 (0.4)	9 (3.4)	11 (4.2)
Adjudicated diabetic ketoacidosis events* occurring at			
BG >13.9 mmol/L (>250 mg/dL)	1	5	9
BG ≥8.3-13.9 mmol/L (≥150-250 mg/dL)	0	5	2
BG <8.3 mmol/L (<150 mg/dL)	0	0	0

BG = blood glucose.

*A total of 22 DKA events occurred in 21 patients. One patient in the sotagliflozin 200 mg group had 2 events.

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. All medians were <0.2 mmol/L at the end of double-blind treatment, and the means reflected an increase of ~0.1 mmol/L from baseline.