Supplementary Data

Inclusion and Exclusion Criteria

Inclusion criteria

Patients had to meet all of the following criteria to be considered eligible to participate in the study:

(1) Patient had given written informed consent to participate in the study in accordance with local regulations.
(2) Adult patients 18–30 years with confirmed diagnosis of type 1 diabetes (T1D) made at least 1 year before informed consent.
(3) Patients treated with insulin(s) or insulin analog(s) alone, delivered via continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDI); the method of insulin delivery must not have had changed from CSII to MDI or vice versa in the 3 months before the screening visit.
(4) A1C ≥9.0% at screening.
(5) Patient had to be willing and able to perform self-monitored blood glucose and complete the study diary as required per protocol.
(6) Females of childbearing potential had to use an adequate method of contraception to avoid pregnancy throughout the duration of the study and for 30 days after the last dose of the study drug. Females of childbearing potential included any female who had experienced menarche and who had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or was not postmenopausal. Postmenopause was defined as no menses for ≥12 months without another cause. For females with questionable menopausal history (e.g., irregular menstrual periods and age >40 years), a documented serum follicle-stimulating hormone level must have been ≥30 mIU/mL.
(7) Females of childbearing potential had to have a negative serum or urine pregnancy test before the start of the study drug. In the case of positive urine pregnancy testing, a negative serum sample for pregnancy testing, to confirm that the patient is not pregnant, must be obtained before start of the study.

Exclusion criteria

Patients who met any of the following criteria were to be excluded from participating in the study:

(1) Therapies and/or medications:
  (a) Any prior use of sotagliflozin
  (b) Use of antidiabetic agent other than insulin(s) or insulin analog(s) at the time of screening (any medication other than insulin or insulin analogs used for treatment of T1D must have been washed out for at least 8 weeks before the screening visit)
  (c) Use of sodium-glucose cotransporter (SGLT) inhibitors within 8 weeks before screening. Note: Patients taking an SGLT inhibitor could have that prohibited medication stopped and could be considered for entry into the study if they had not been taking the prohibited medication for at least 8 weeks before screening.
  (d) Chronic systemic corticosteroid use, defined as any dose of systemic corticosteroid taken for more than four consecutive weeks within 6 months before screening visit. Note: Topical, inhaled, ocular, or nasal sprays corticosteroids were allowed.
(2) Diabetes-related conditions:
  (a) T2D, or severely uncontrolled T1D as determined by the Investigator
  (b) History of diabetic ketoacidosis (DKA) or nonketotic hyperosmolar state within 6 months of screening
  (c) History of severe hypoglycemic event within 1 month before the screening visit
  (d) Active proliferative diabetic retinopathy with treatment planned during the study period
(3) Laboratory results:
  (a) At screening, eGFR <45 mL/min/1.73 m^2 as determined by the 4-variable modification of diet in renal disease equation
  (b) Fasting triglycerides >600 mg/dL (>33.3 mmol/L). Note: Patients who failed screening based on this criterion had to have their fasting status verified and could have TG-lowering medications adjusted and be rescreened during the screening window.
  (c) Abnormal liver function at screening defined as any of the following: aspartate aminotransferase >2×upper limit of the normal reference range (ULN), ALT >2×ULN, serum total bilirubin >1.5×ULN. Note: If it was the opinion of the investigator and the medical monitor that an increase in bilirubin was due to Gilbert's syndrome, then the patient could participate.
  (d) Screening β-hydroxybutyrate (BHB) >0.6 mmol/L
(4) Reproductive status:
  (a) Females who were pregnant or breastfeeding or intended to be during the course of the study
(5) Gastrointestinal (GI)/hepatic:
  (a) By known history, serologic evidence of current infectious liver disease (hepatitis A, B, or C), including antihepatitis A virus (immunoglobulin M), hepatitis B surface antigen, or antihepatitis C virus. Note: Patients with isolated positive hepatitis B surface antibody could have been included.
  (b) Difficulty swallowing such that the patient could not take the study drug
  (c) History of pancreatitis within 12 months of screening, or any prior history of recurrent pancreatitis
(6) Renal:
  (a) Initiation of chronic dialysis within 30 days before the screening visit or expected to occur within 180 days after the screening visit

(b) Renal disease that required treatment with immunosuppressive therapy or renal transplant
(c) History of glucose-galactose malabsorption or primary renal glucosuria

(7) Cardiovascular:
(a) Congestive heart failure with ejection fraction <40% and/or New York Heart Association Class III or IV heart failure within 3 months before the screening visit
(b) Patients with arrhythmia or heart block that was life-threatening or symptomatic. Note: Asymptomatic atrial fibrillation is not considered to be life-threatening, and patients with asymptomatic atrial fibrillation were to be permitted to enter the study. Patients with arrhythmias at screening were to be allowed to be rescreened and randomly assigned if there was documented resolution of the arrhythmia within the screening period.
(c) . Patient had any of the following within 3 months before the screening visit:
(i) Hospitalization due to unstable angina
(ii) Myocardial infarction
(iii) Coronary artery bypass graft or percutaneous transluminal coronary angioplasty
(iv) Transient ischemic attack or significant cerebrovascular disease
(v) Previously undiagnosed or unstable angina

(8) Hematologic:
(a) History of hemoglobinopathies (sickle cell anemia, thalassemia major, sideroblastic anemia) or other disorder that might interfere with A1C determination
(b) Donation or loss of >400 mL of blood or blood product within 8 weeks before screening

(9) Immune system:
(a) Known severe immunocompromised status, including, but not limited to, patients who had undergone organ transplantation. Note: Patients with human immunodeficiency virus (HIV) could have participated if the investigator considered them otherwise suitable candidates for the study.

(10) Malignancy or active treatment for malignancy (i.e., radiation or chemotherapy) within 5 years before the screening visit. Note: Patients with squamous or basal cell carcinomas of the skin, carcinomas in situ of the cervix or uterus, ductal breast cancer in situ, resected low-grade prostate cancer, or other malignancies, which in the opinion of the investigator and the study medical monitor were considered cured, could have participated.

(11) Current eating disorder or increase or decrease of body weight 12 weeks before screening by more than 10%

(12) Known allergies, hypersensitivity, or intolerance to sotagliflozin or any inactive component of sotagliflozin (i.e., microcrystalline cellulose, croscarmellose sodium [disintegrant], talc, silicone dioxide, and magnesium stearate [nonbovine]), unless the reaction was deemed irrelevant to the study by the investigator

(13) Administration of any other investigational drug or participation in an interventional clinical research study within 30 days or five half-lives (whichever is longer) of the planned screening visit

(14) History of alcohol or illicit drug abuse (using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition; American Psychiatric Association, 2013) within 12 months before the screening visit

(15) Patient was a study coordinator, employee of an Investigator, or immediate family member of any of the aforementioned

(16) Any condition that, in the opinion of the investigator, might render the patient unable to complete the study

(17) The presence of a clinically significant medical history, physical examination, or laboratory finding that, in the opinion of the investigator or the sponsor, might interfere with any aspect of study conduct or interpretation of results. The investigator or the sponsor was to have supplied justification for exclusion, if applicable.

Procedure for Assessment of Postprandial Glucose

A 2-h postprandial glucose (PPG) sample was obtained after a standardized mixed meal[S1,S2] on day 1 and at the week 12 visit (or earlier for patient terminating study participation before week 12). Patients with hypersensitivity or dietary restrictions to the contents of the standardized mixed meal omitted it, and the reason for omission was recorded in source documents.

For both the day 1 and week 12 scheduled mixed meal, patients took their usual/prescribed basal insulin before coming to the site for the visit. Patients did not to take any short-acting (bolus) insulin on the day of the mixed meal until instructed to do so by study staff.

The last dose of single-blind placebo was administered on the day before day 1. The first dose of the double-blind study drug on day 1 of the standardized mixed meal was given after completion of the 2-h PPG collection. For the week 12 standardized mixed meal, the patient took the dose of the double-blind study drug immediately after the fasting blood samples were obtained and bolus insulin was administered, and approximately 15 min before ingestion of the standardized mixed meal began.

Standard meal for mixed meal

The standard (breakfast) meal was provided as a liquid nutrition drink (Boost®, Ensure®, or similar), with ∼40 g carbohydrate and ∼240 calories per bottle (∼8 ounces). The caloric composition of the meal was ∼65% carbohydrate, ∼15% protein, and ∼20% fat. The amount given was 6 mL/kg body weight up to a maximum of 360 mL. Therefore, for patients ≥60 kg, the standard meal consisted of ∼60 g carbohydrate and 360 calories. Efforts were made to provide the same mixed-meal product for the baseline and week 12 standardized mixed meal.

Patients were instructed to completely consume the meal within 15–20 min. Water or noncaffeinated, zero-calorie beverages were allowed ad libitum. No other food could be consumed until the 2-h PPG sample was collected. If the patient was unable to consume at least 50% of the standard

meal at baseline, the standardized mixed meal was not completed, and the subsequent 12-week standardized mixed meal was not be performed. If the patient consumed >50% of the standardized mixed meal, the approximate amount was recorded and an equivalent amount was consumed at the subsequent, 12-week standardized mixed meal.

Staff at study centers received the following instructions for the standardized mixed meal:

Baseline visit (day 1)

(1) Record the amount and brand name of the standard meal liquid nutrition drink the patient is instructed to consume in the source documents.
(2) Fasting blood samples are obtained, including fasting plasma glucose (FPG).
(3) Record the time of blood sample collection in the source documents.
(4) Immediately after the fasting blood samples are collected, the patient takes the meal-time amount of bolus insulin that is appropriate for the carbohydrate content of the standard meal. Because the endpoint is glucose change from time zero glucose, no additional ''high blood glucose correction'' (sliding scale) insulin should be given at this meal. The amount of insulin and time of administration are recorded in the source documents.
(5) Fifteen minutes after the bolus insulin is administered, the patient starts consuming the standard meal.
(6) Record the time the meal ingestion starts in the source documents.
(7) The 2-h countdown for the 2-h plasma PPG starts immediately after the patient begins ingestion of the standard meal.
(8) The patient is instructed to ingest the prescribed amount of the standard meal within 15–20 min.
(9) Record the time ingestion is completed, measure the portion of the meal not ingested (if any), and record the assessed percent of prescribed amount ingested in the source documents.
(10) No blood samples for pharmacokinetics are collected at this visit.
(11) Two hours after the meal ingestion starts, the 2-h plasma PPG is collected.
(12) Record the time that the 2-h plasma PPG is collected in the source documents.
(13) Double-blind study drug is administered AFTER the blood sample is drawn at 120 min.
(14) Record the time the double-blind study drug is administered in the source documents.

Week 12 visit

(1) Record the amount and brand name of the standard meal liquid nutrition drink that the patient is instructed to consume in the source documents.
(2) Fasting blood samples are obtained, including FPG and PK samples.
(3) Record the time of blood sample collection in the source documents.
(4) Immediately after the fasting blood samples are collected, the patient takes the meal-time amount of bolus insulin that is appropriate for the carbohydrate content of the standard meal. Because the endpoint is glucose change from time zero glucose, no additional ''high blood glucose correction'' (sliding scale) insulin should be given at this meal. The amount of insulin and time of administration are recorded in the source documents.
(5) Double-blind study drug is administered immediately AFTER the bolus insulin is administered.
(6) Record the time that the double-blind study drug is administered in the source documents.
(7) Fifteen minutes after the meal-time insulin is administered, the patient starts consuming the standard meal.
(8) Record the time the meal ingestion starts in the source documents.
(9) The 2-h countdown for the 2-h PPG starts immediately after the patient begins ingestion of the standard meal.
(10) The patient is instructed to ingest the prescribed amount of the standard meal within 15–20 min.
(11) Record the time that ingestion is completed, measure the portion of the meal not ingested (if any), and record the assessed percent of prescribed amount ingested in the source documents.
(12) Two hours after the meal ingestion starts, the 2-h postprandial plasma glucose and PK samples are collected.
(13) Record the time that the 2-h postprandial blood samples are collected in the source documents.

Patient and Provider Instructions to Mitigate DKA and Other Adverse Events

Patient communication card text

The following list may help you to recognize 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 drugs. In such cases, your study doctor may advise you not to take your

study drug from the day before the procedure or surgery until after the procedure or surgery is complete, and you are taking food and liquids as you usually do.

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 urine analysis 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 DKA. 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 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 h 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 g of carbohydrate each hour provided by a glucose-containing sports drink or oral rehydration fluid. The site will evaluate whether an assessment for metabolic acidosis is appropriate. If laboratory testing confirms the presence of metabolic acidosis, then the ''Possible diabetic ketoacidosis'' electronic case report form will be completed. If nausea and vomiting are present and the patient is unable to retain liquids, the patient should be evaluated in an Emergency Room.

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

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

Supplementary References

S1. Greenbaum CJ, Mandrup-Poulson T, McGee PF, et al.: Mixed-meal tolerance test versus glucagon stimulation test for the assessment of beta-cell function in therapeutic trials in type 1 diabetes. Diabetes Care 2008;31:1966–1971.

S2. Lane JD, Barkauskas CE, Surwitt RS, Feinglos MN: Caffeine impairs glucose metabolism in type 2 diabetes. Diabetes Care 2004;27:2047–2048.