SUPPLEMENTARY DATA

Supplementary Table 1. Summary of treatment-emergent adverse events

System Organ Class **Preferred term**	**Placebo** **(N=17)**	**Sotagliflozin** **(N=16)**
Any event	12 (71%)	14 (88%)
TEAEs Reported for >1 Patient		
Infections and Infestations	7 (41%)	8 (50%)
Nasopharyngitis	2 (12%)	2 (13%)
Gastroenteritis	0	2 (13%)
Upper respiratory tract infection	1 (6%)	1 (6%)
Sinusitis	1 (6%)	1 (6%)
Gastrointestinal Disorders	3 (18%)	8 (50%)
Nausea	1 (6%)	4 (25%)
Vomiting	1 (6%)	2 (13%)
Flatulence	1 (6%)	1 (6%)
Nervous System Disorders	2 (12%)	5 (31%)
Headache	2 (12%)	3 (19%)
Sinus headache	0	2 (13%)
Skin and Subcutaneous Disorders	3 (18%)	2 (13%)
Skin irritation	2 (12%)	0
Metabolic and Nutrition Disorders	0	3 (19%)
Decreased appetite	0	2 (13%)
Diabetic ketoacidosis*	0	2 (13%)
Investigations	2 (12%)	0
Blood creatine phosphokinase increased	2 (12%)	0
Additional Mechanism-related TEAEs Reported for 1 Patient		
Infections and Infestations		
Cystitis	1 (6%)	0
Fungal skin infection	1 (6%)	0
Lice infestation	1 (6%)	0
Localized infection	1 (6%)	0
Nail infection	0	1 (6%)
Skin infection	0	1 (6%)
Gastrointestinal Disorders		
Abdominal discomfort	0	1 (6%)
Abdominal distension	0	1 (6%)
Abdominal pain	0	1 (6%)
Abdominal pain upper	1 (6%)	0
Abnormal faeces	1 (6%)	0
Colitis	0	1 (6%)
Diarrhoea	0	1 (6%)
Dyspepsia	0	1 (6%)
Faeces hard	0	1 (6%)
Renal and Urinary Disorders		
Acute prerenal failure	0	1 (6%)
Nephrolithiasis	0	1 (6%)
Nocturia	1 (6%)	0
Pollakiuria	0	1 (6%)

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Patients experiencing multiple incidents of the same AE were counted once.
SOC=system organ class
TEAEs were defined as any event occurring after the first dose of LX4211 (or placebo) and prior to a patient's termination, withdrawal, or completion of the study.
* In both cases blood glucose levels were classically elevated at the time of diagnosis and both patients first attempted self-treatment by increasing insulin doses through their pumps without inspecting or altering the infusion set or site of insertion. The first patient had a 5% decrease in bolus and 6% decrease in basal insulin and presented with symptoms of gastroenteritis and laboratory glucose of 553 mg/dL. The insulin infusion set was documented to be crimped. The second patient had a 34% decrease in bolus and a 4% increase in basal insulin and presented with nausea, vomiting and abdominal pain, SMBG of 381 mg/dL and laboratory glucose of 376 mg/dL. The investigator attributed DKA to either infusion set crimping or insulin did not deliver due to shallow insertion. Study drug was interrupted for 2 and 3 days, respectively, and after appropriate treatment and correction of insulin pump delivery issues, both patients recovered and resumed study drug.

Supplementary Table 2. Mean CGM glucose for the 3-hour period after meals

Mean CGM Glucose 3-hours after meals	Study Drug	Baseline	Treatment	Change from Baseline	p-value Change from Baseline	p-value Sotagliflozin vs Placebo
Breakfast	Placebo	177.2 (39.0)	172.6 (33.5)	-4.2 (32.8)	0.94	---
	Sotagliflozin	168.0 (54.7)	151.8 (22.3)	-16.7 (39.4)	0.004	0.034
Lunch	Placebo	166.6 (39.4)	178.0 (37.1)	+7.8 (40.3)	0.42	---
	Sotagliflozin	180.2 (56.2)	161.6 (29.0)	-18.8 (31.6)	0.08	0.07
Dinner	Placebo	171.3 (46.5)	175.7 (28.9)	+2.1 (32.1)	0.50	---
	Sotagliflozin	173.5 (61.8)	162.9 (29.5)	-8.5 (52.4)	0.41	0.28

P-values are calculated from least squares mean analyses.
The baseline analysis period consists of Days -6 to -2, the treatment analysis period consists of Days 3 to 27.
Data are reported as the arithmetic Mean (SD), unless otherwise indicated.

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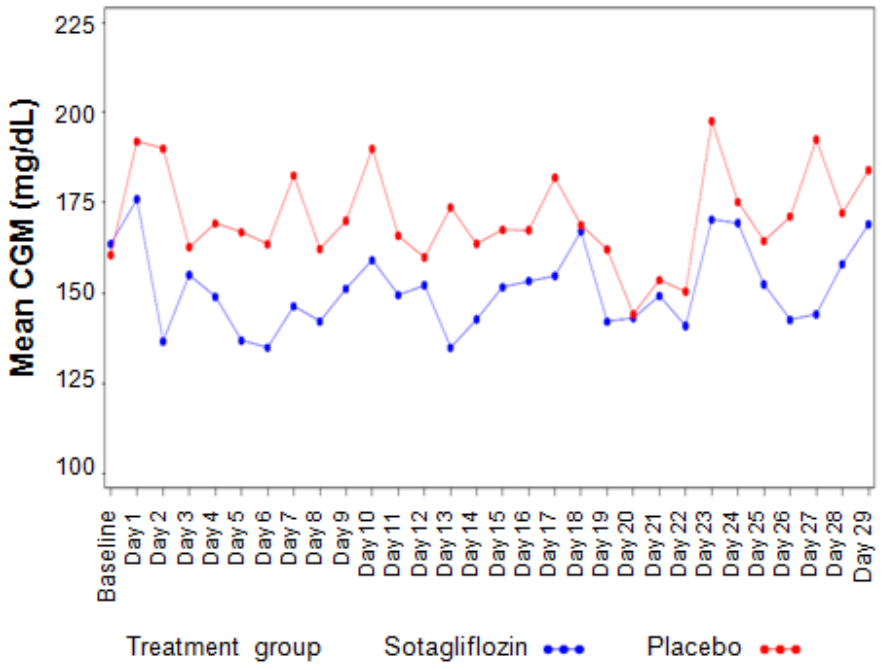
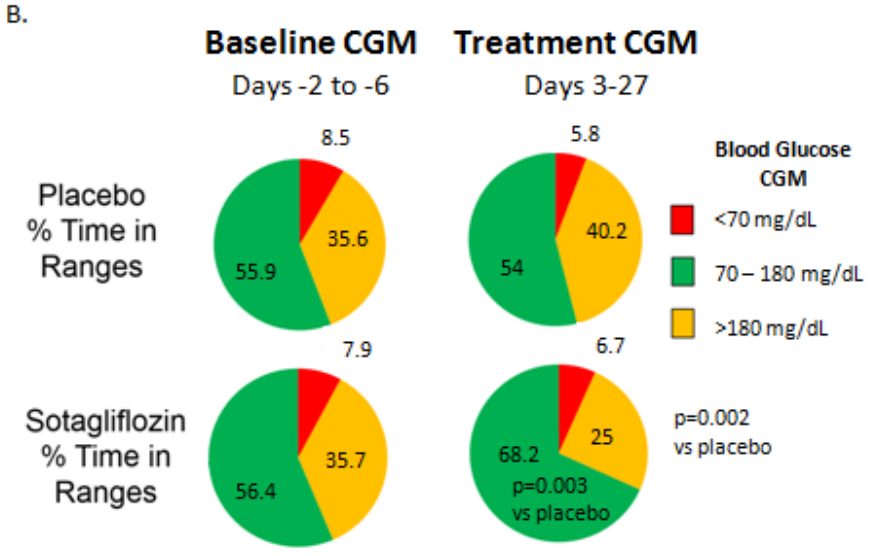
Supplementary Figure 1. Mean glucose by CGM (A) and percentage of time in target ranges, hyperglycemia, and hypoglycemia (B).

A.

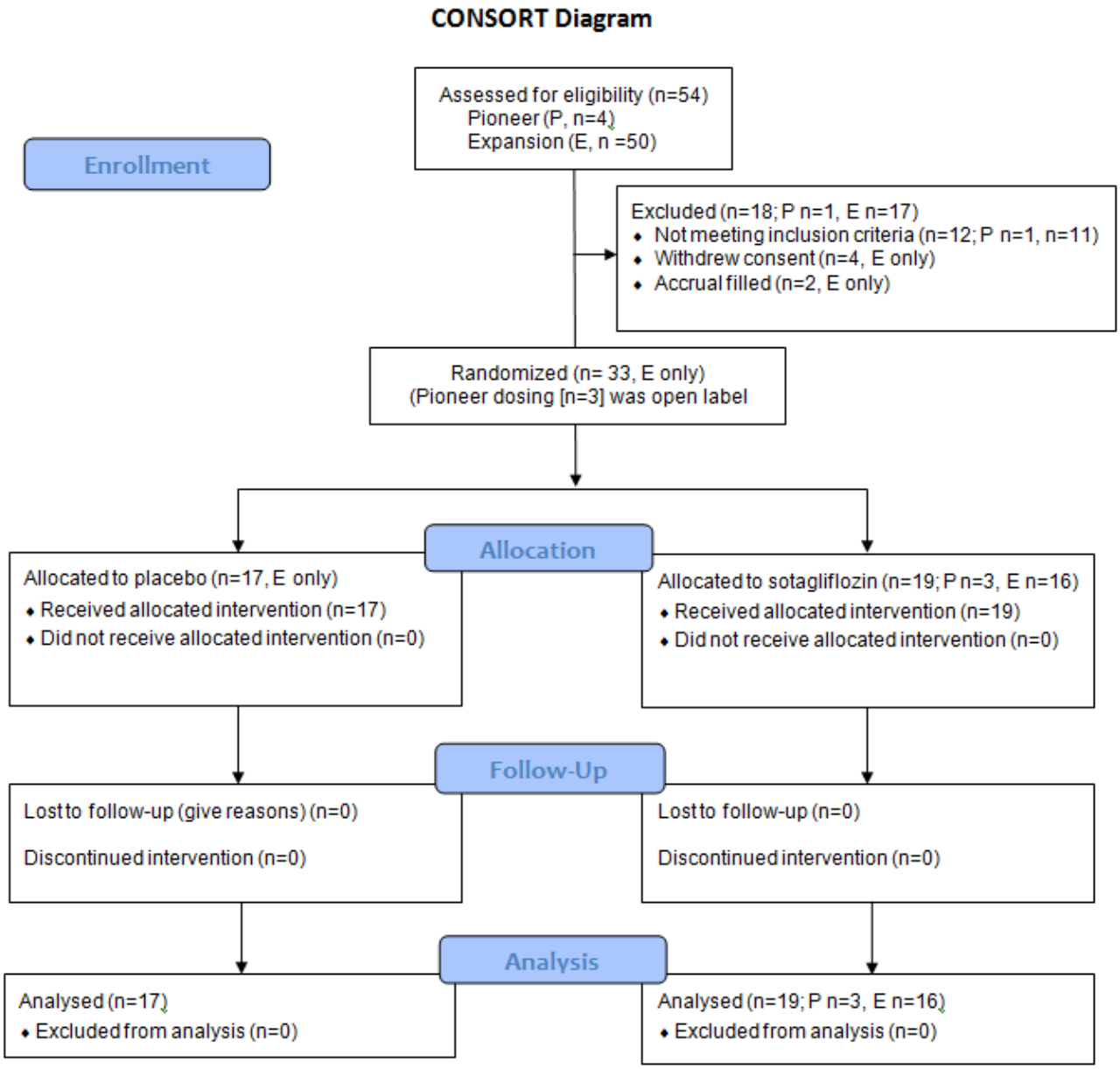


B.



SUPPLEMENTARY DATA

Supplementary Figure 2. Patient disposition



SUPPLEMENTARY DATA

Inclusion Criteria

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

1. Adults between the ages of 18 to 55 years (inclusive) at the time of Screening:
    a. All patients of childbearing potential had to agree to use an adequate method of contraception during the study, and for 30 days after the last dose of study drug. Adequate methods of contraception for patient or partner included condoms with spermicide gel, diaphragm with spermicide gel, coil (intrauterine device), surgical sterilization, vasectomy, oral contraceptive pill, depot progesterone injections, progesterone implant, NuvaRing®, Ortho Evra®, and abstinence.
2. Confirmed diagnosis of T1DM, diagnosed prior to age 40 years, and for at least 6 months prior to Screening
    a. Current treatment with rapid-acting insulin (ie, Humalog®, NovoLog®, or Apidra®) using CSII, with stable basal dose (defined as no greater than a 20% change) within 2 weeks of Screening
    OR
    b. Combination of rapid-acting insulin-analog with long acting insulin-analog (ie, Lantus® or Levemir®) using multiple daily injections (MDI) with stable basal dose (defined as no greater than a 20% change) within 2 weeks of Screening. **Note**: Short-acting regular insulin (ie, regular Humulin® or Velosulin®) were not allowed in this study and had to be converted to rapid acting insulin in order for the patient to participate in the study.
3. Screening with the following laboratory values:
    a. FPG ≤270 mg/dL
    b. Body mass index (BMI) ≤32 kg/m^2
    c. A1C value ≥7.0% to ≤9.0%
    d. Fasting C-peptide ≤0.7 ng/mL
    e. Triglycerides ≤600 mg/dL at Screening and at Baseline
4. Willing and able to wear and operate a continuous glucose monitor
5. Willing and able to self-assess blood glucose
6. Willing and able to provide written informed consent

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Exclusion Criteria

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

1. History of any of the following: T2DM or diabetes resulting from secondary diabetes (ie, acromegaly, Cushing's disease, chronic pancreatitis, or pancreatectomy)
2. Two or more severe episodes of hypoglycemia that required assistance by a third party within 3 months prior to Screening
3. Use of premixed insulin (ie, Humulin® 70/30, Novolin® 70/30, NovoLog® 70/30, Humulin® 50/50 or Humalog® 75/25). **Note**: patients on premixed insulin could be allowed to switch to MDI or CSII per Investigator's discretion.
4. History of diabetic ketoacidosis (DKA) within 1 year of Screening
5. Glomerular filtration rate (GFR) <60 mL/min as calculated using the Modification of Diet in Renal Disease (MDRD) equation at Screening as follows, with Pcr being serum or plasma creatinine in mg/dL:
   GFR (mL/min/1.73 m^2) = 186 x (Pcr)-1.154 x (age)-0.203 x (0.742 if female) x (1.210 if African American)
6. Presence of active hepatic disease or clinically significant abnormal liver function tests (LFTs): (aspartate transaminase [AST] or alanine transaminase [ALT] >2.0 times the upper limit of normal [ULN])
7. History of chronic pancreatitis
8. History of myocardial infarction, severe/unstable angina, or coronary revascularization procedure within 6 months prior to Screening
9. History of clinically significant cardiac arrhythmias (ie, supraventricular tachycardia, ventricular tachycardia, or atrial fibrillation) within 6 months prior to Screening
10. Congestive heart failure with ejection fraction <40% and/or New York Heart Association [NYHA] class III or IV symptoms of heart failure within 6 months prior to Screening
11. Patients with uncontrolled stage III hypertension (defined as systolic blood pressure [SBP] ≥180 mmHg or diastolic blood pressure [DBP] ≥110 mmHg)
12. The presence of any clinically significant physical, laboratory, or electrocardiogram (ECG) findings at Screening that, in the opinion of the Investigator and/or Sponsor, might have interfered with any aspect of study conduct or interpretation of results
13. History of human immunodeficiency virus (HIV) or hepatitis C antibody (HCV Ab)
14. History of illicit drug or alcohol abuse, as defined by DSM IV, within 12 months prior to Screening
15. Use of any investigational agent or device within 30 days prior to Screening or any therapeutic protein or antibody within 90 days prior to Screening
16. Use of any medication (prescription or over the counter) or herbal supplements taken for the purpose of weight loss, including sibutramine and orlistat, within 2 weeks of Screening
17. Chronic use of any antidiabetic therapy other than insulin within 2 months prior to Screening
18. Use of systemic corticosteroids within 4 weeks prior to Screening. **Note**: intra-nasal, intra-ocular, intra-articular, topical, and inhaled steroid preparations were permitted.
19. Had undergone major surgery within 6 months prior to Screening, or was planning any surgery during the course of the study
20. >20 cm of bowel resection, any malabsorptive disorder, severe gastroparesis, any gastrointestinal procedure for the purpose of weight loss (including LAPBAND™), which would slow gastric emptying
21. Inability or difficulty swallowing whole tablets or capsules
22. Women who were pregnant or breastfeeding, or who intended to become pregnant during the course of the study or within 30 days of last dose of study drug
23. Inability or unwillingness to communicate or cooperate with the Investigator for any reason

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Statistical Methodology

Treatment group differences for the primary efficacy variable and related insulin-based endpoints were tested by analysis of covariance (ANCOVA) statistics with a model including a fixed effect for treatment, the baseline factor used in the randomization process, and the baseline value of the dependent variable as a covariate (if applicable). Point estimates and confidence limits of treatment effect were derived from least squares adjusted means. Distribution-free methods were used to supplement the ANCOVA modeling. Descriptive methods were used to summarize data from the pioneer and, placebo-controlled expansion groups. For continuous variables, this included N, mean, standard deviation, median, minimum, and maximum value. Categorical variables were tabulated using patient counts and percentages. Change from baseline data were presented wherever appropriate.

Statistical analyses of treatment differences for the blood glucose data collected at multiple time points were made by using mixed linear models with random patient effects. Where appropriate, the models reflected change from baseline and were parameterized for repeated measures such that changes over time within each treatment group and between treatment groups could be tested. The models also included an effect reflecting the baseline factor used in the randomization process and a baseline value of the dependent variable as a covariate (if applicable). Simple effects were abstracted from the treatment-by-time interaction to test treatment group differences at specific time points.. Graphical methods and mixed linear models were used to facilitate analysis of the CGM data.

Safety analyses involved examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Summaries were prepared by study group (pioneer, expansion) and within the expansion group by treatment group, and as needed, by study visit. Treatment-emergent adverse event summaries included the overall incidence (by system organ class and preferred term), events by maximum intensity, event by relationship to study treatment, events leading to discontinuation of study drug, and serious adverse events. The incidence and pattern of hypoglycemic events were summarized.

Vital signs, ECG, SMBG, and laboratory parameters (hematology, chemistry, and urinalysis) were summarized descriptively at each time point. Actual and change from baseline data were calculated and summarized; shift table analysis was applied to the laboratory data.

All statistical analyses were based on the observed data sets. For the case that at least 15% of the observations were missing for a particular variable, the last observation carried forward method was to be used to assign data to missing observations. No imputation methods were applied to the safety data. The category of reportable events of special interest included major adverse cardiovascular events (MACE), breast cancer, bladder cancer, bone fractures, urogenital infections, and hypoglycemia.