

Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Sotagliflozin After Multiple Ascending Doses in Chinese Healthy Subjects

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Background: Sotagliflozin (LX4211) is a dual inhibitor of sodium-glucose cotransporter (SGLT)1 and SGLT2 being investigated to improve glycemic control in adults with diabetes. This study was firstly conducted to assess the pharmacokinetic (PK), pharmacodynamic (PD) profiles, safety and tolerability in Chinese healthy subjects after administration of sotagliflozin.

Methods: This was a Phase I, randomized, double-blind, placebo-controlled, ascending multiple-dose study. Healthy subjects received 200mg or 400mg of sotagliflozin or placebo once daily for 8 days, respectively. PK parameters of sotagliflozin and LX4211-GLU (main metabolite), as measured by blood samples collected pre/postdose on Day 1/predose on Day 2-Day 8/postdose on Day 8, and PD parameters of absolute urinary glucose excretion (UGE) were determined. Treatment-emergent adverse events (TEAEs) were evaluated.

Results: Overall, 24 subjects were enrolled and randomized to sotagliflozin 200 mg (N = 9), sotagliflozin 400 mg (N = 9), or placebo (N = 6) group, and all subjects completed the study. Sotagliflozin was rapidly absorbed with dose-proportional systemic exposure and a moderate degree (less than 2-fold) of accumulation. Sotagliflozin plasma concentrations peaked at 1.0 h post dose. On Day 8, the estimated increases for C_{max} and AUC_{tau} were 1.89-fold and 1.70-fold. The pooled accumulation ratio of sotagliflozin was 1.57 for C_{max} and 1.84 for AUC_{tau} . LX4211-GLU had similar PK features. UGE was significantly elevated in both sotagliflozin groups relative to the placebo group. All TEAEs were mild and resolved without sequelae. There were no serious AEs or other significant TEAEs.

Conclusion: Sotagliflozin was rapidly absorbed with dose-proportional systemic exposure and a moderate degree of accumulation. Both 200 mg and 400 mg sotagliflozin per day were well tolerated in Chinese healthy subjects.

Keywords: diabetes mellitus, sotagliflozin/LX4211, sodium-glucose cotransporter, pharmacokinetics, pharmacodynamics, safety

Introduction

Diabetes mellitus (DM) is a global epidemic posing a significant health threat to people around the world.¹ According to the International Diabetes Federation (IDF), the global diabetes prevalence in 2021 is estimated to be 537 million people, rising to 643 million by 2030 and 784 million by 2045. China has the largest population of patients with diabetes in a single country.² In the past 10 years (2011–2021), people with diabetes in China increased from 90 million to 140 million, with a rapid increase of 56%. It is estimated that in the next 20 years, although the incidence of diabetes in China might tend to decrease, the total number of patients would increase to 164 million in 2030 and 174 million in 2045.²

DM is a metabolic disease characterized by persistent hyperglycaemia, which is associated with increased risk of long-term microvascular and macrovascular complications. The most serious consequences of DM are heart and kidney diseases, which represent one of the greatest pandemics of chronic disease in the world today.^{3,4} Approximately 6.7 million adults between the age of 20–79 were estimated to die from diabetes or its associated complications in 2021 (1 every 5 seconds). This corresponds to 12.2% of global deaths from all causes in this age group.² Although there are multiple therapeutic options for DM, there is an unmet need for treatments that can lower glucose with a low incidence of hypoglycemia, avoid

weight gain, and reduce the risk of complications including nephropathy and cardiovascular disease.^{5,6} In recent years, much attention has focused on sodium-glucose cotransporter (SGLT) inhibitors.

SGLT is a membrane protein that regulates sodium and glucose transport across cell membranes. SGLT2 is responsible for the bulk ($\approx 90\%$) of glucose reabsorption from the proximal renal tubule under normal physiologic conditions.^{7,8} SGLT1 mediates the absorption of glucose in the small intestine and accounts for the remaining glucose reabsorption.⁹ SGLT2 inhibitors (SGLT2i) increase urinary glucose excretion (UGE), with little risk for hypoglycemia with an insulin-independent mechanism. More importantly, SGLT2i has been shown to possess a favorable metabolic profile and significantly reduce weight, blood pressure, uric acid, atherosclerotic events, hospitalization for heart failure, cardiovascular and total mortality, and progression of chronic kidney disease.^{4,10,11} First-in-class of dual SGLT1 and SGLT2 inhibitor sotagliflozin, also known as LX4211, is proved to inhibit both SGLT1 and SGLT2 thus blunting and delaying absorption of glucose from the gastrointestinal tract and blocking reabsorption of glucose by the proximal renal tubule^{12,13}

Sotagliflozin has 20-fold higher selectivity for SGLT2 than that for SGLT1.¹⁴ The effectiveness of sotagliflozin in inhibiting SGLT2 is similar to that of the selective SGLT2 inhibitors, while it is more potent than the latter molecules in inhibiting SGLT1.^{14–16} In a study of SGLT1 genetic variants that were examined for missense variations in SGLT1, researchers found that reduced intestinal glucose uptake, as measured by lower postprandial glucose, was shown to be associated with less obesity, diabetes, heart failure, and mortality.¹⁷ Moreover, in the recent Phase III SOLOIST-WHF and SCORED clinical trials, sotagliflozin resulted in a lower total number of deaths from cardiovascular causes, hospitalizations, and urgent visits for heart failure compared to placebo in high-risk patients with type 2 diabetes mellitus (T2DM).^{18,19} The results in chronic kidney disease stage 3 (CKD3) overall showed a statistical reduction in HbA1c, which was the primary endpoint.²⁰ Sotagliflozin may be a potential option for adults who are suffering from worsening heart failure or additional risk of heart failure, by reducing the risk of cardiovascular death, and hospitalization for heart failure.^{18,19} However, sotagliflozin is associated with the following adverse reactions including diarrhoea, genital mycotic infections, urinary tract infections, hypotension/volume depletion, increased serum creatinine and decreased estimated glomerular filtration rate (eGFR) occurred after initiating sotagliflozin, and especially diabetic ketoacidosis (in patients with type 1 diabetes).^{13,19,21,22} The safety profile of sotagliflozin is generally consistent with that observed with selective SGLT2 inhibitors, except for an increased incidence of diarrhea likely associated with partial SGLT1 inhibition.²³

Sotagliflozin is a new class of medication for the treatment of DM with the unique dual inhibiting effects of both SGLT1 and SGLT2, which has its approval in the European Union (EU) as an adjunct to insulin in patients with T1DM with a body mass index (BMI) ≥ 27 kg/m² who have failed to achieve adequate glycaemic control despite optimal insulin therapy. The pharmacokinetic (PK) profiles of sotagliflozin and its key plasma metabolites LX4211-GLU (LX4211-glucuronide, sotagliflozin-3-O-glucuronide or M19) have been examined in European-American populations,^{24–26} while data from Asian population are still lacking. This is the first study to determine the PK, PD profiles and the safety and tolerability of sotagliflozin in Chinese healthy subjects to make a preliminary evaluation in this population.

Methods

Study Design

This was a Phase I, single-center, randomized, double-blind, placebo-controlled, ascending multiple-dose clinical pharmacology study in Chinese healthy subjects. The study design is shown in [Figure 1](#). Subjects were randomly assigned 3:1 (sotagliflozin: placebo) among the following two sotagliflozin treatment groups: (1) sotagliflozin 200 mg vs placebo once daily (qd) or (2) sotagliflozin 400 mg vs placebo qd. Daily dose was administered prior to the first meal for 8 consecutive days. Both 200 mg and 400 mg are the authorised doses for use in the EU. This study was registered at ClinicalTrials.gov (<https://ClinicalTrials.gov>, identifier: NCT03909451) and conducted at a single study site, Beijing Hospital, Beijing, People's Republic of China. The first subject was enrolled on April 28, 2019, and the last subject completed the study on August 19, 2019.

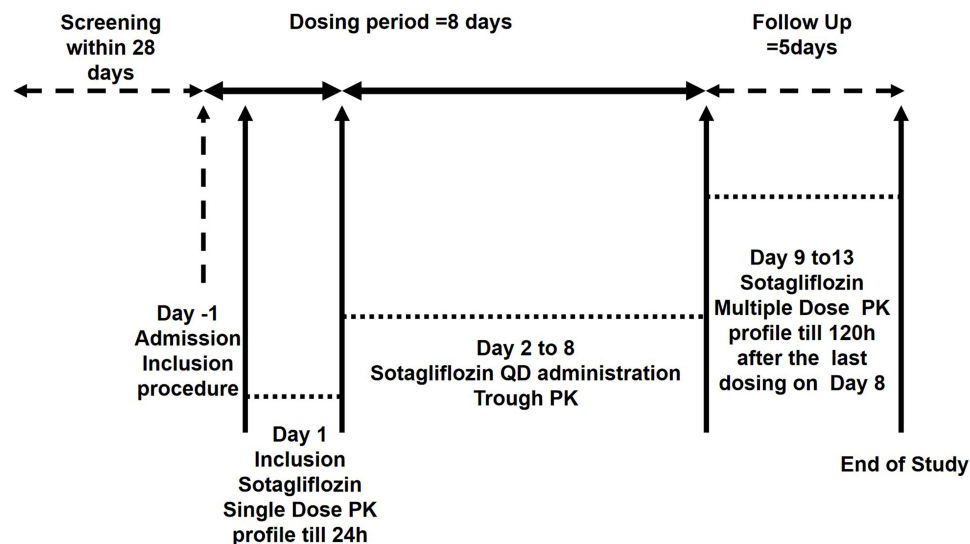


Figure 1 Study design.

Study Population

The study population consisted of Chinese healthy subjects (≥ 18 to ≤ 45 years of age) with body weight between 50.0 and 95.0 kg, body mass index between 18.5 and 27.9 kg/m²; systolic blood pressure (SBP) < 140 mmHg or diastolic blood pressure (DBP) < 90 mm Hg; heart rate > 50 and < 100 beats per minute (BPM); 12-lead electrocardiogram (ECG) QTc (Fridericia algorithm) ≤ 450 ms and normal ECG tracing or abnormal ECG tracing to be not clinically relevant; laboratory parameters within the normal range or an abnormality to be clinically irrelevant; however, serum creatinine, alkaline phosphatase, hepatic enzymes (aspartate aminotransferase, alanine aminotransferase), total bilirubin (unless the subject had documented Gilbert syndrome), and pancreatic enzymes (amylase and lipase) should not have exceeded the upper laboratory limit of normal.

Study Parameters

Primary PK parameters were maximum plasma concentration (C_{\max}) and area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (τ) (AUC_{τ}) for both sotagliflozin and its primary metabolite LX4211-GLU both on Day 1 and Day 8. Secondary PK parameters were time to reach C_{\max} (t_{\max}) for both sotagliflozin and LX4211-GLU in Day 1, plasma concentration observed just before treatment administration during repeated dosing (C_{trough}) for both sotagliflozin and LX4211-GLU from Day 2 to Day 8 and t_{\max} , terminal half-life associated with the terminal slope (λ_z) ($t_{1/2z}$), area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real-time t_{last} (AUC_{last}), area under the plasma concentration versus time curve extrapolated to infinity AUC (AUC), AUC_{τ} accumulation ratio (R_{ac}), C_{\max} accumulation ratio ($R_{\text{ac}}^{C_{\max}}$) for both sotagliflozin and LX4211-GLU; apparent volume of distribution during the terminal (λ_z) phase (V_z/F) and apparent total body clearance of a drug from the plasma (CL/F) for sotagliflozin only on Day 8. PD parameters were absolute UGE as measured by 24-hour urine collection captured in fractions of 0–8 h and 8–24 h on Day 1 and Day 8.

Safety and tolerability measurements included treatment-emergent adverse events (TEAE), clinical laboratory evaluations, vital signs and ECG. TEAE is defined as an adverse event that started, worsened, or became serious during the time between the first dose and the end of study (inclusive).

Pharmacokinetic/Pharmacodynamic Sampling

For both sotagliflozin and LX4211-GLU concentration measurements, blood samples were collected within 1h before dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12h after dosing on Day 1, predose on Day 2–Day 8. After the last dose on Day 8, blood

samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120h. Sotagliflozin and LX4211-GLU plasma concentrations were analyzed using liquid chromatography with tandem mass spectrometry detection (LC-MS/MS), a validated method. Sotagliflozin, metabolite LX4211-GLU, and the internal standard (IS), which was stable isotope label ([D5]-sotagliflozin, [D5]- LX4211-GLU), were extracted by supported protein precipitation using 96-well deep well plates (Axygen, USA), and separated by a column of Xbridge C18, 3.5 μ m, 50 \times 2.1 mm (Waters, USA). Detection was performed via API5500 mass spectrometer (AB Sciex, USA) using multiple reaction monitoring. The quantification was performed using multiple reaction monitoring of the transitions m/z 483.0 \rightarrow 315.0 and m/z 599.2 \rightarrow 357.1 for sotagliflozin and metabolite LX4211-GLU. The lower limit of quantification (LLOQ) for sotagliflozin and metabolite LX4211-GLU were 2.00 ng/mL and 10.0 ng/mL, respectively, when 50 μ L of plasma was used. Calibration curves for sotagliflozin and metabolite LX4211-GLU in human plasma were linear over the concentration range 2.00–2000 ng/mL and 10.0–10,000 ng/mL. The inter-run accuracy of sotagliflozin varied between –3.0% and 0.1%, while the metabolite LX4211-GLU ranged between 2.2% and 8.2%. The PK parameters were calculated, using noncompartmental methods from plasma sotagliflozin and LX4211-GLU concentrations.

To investigate urinary glucose excretion increased by sotagliflozin dosing, 24-hour urine samples were collected on both Day 1 and Day 8. Post-dose accumulative urine sample was collected for 24h in fractions of 0–8 h and 8–24h. All urine glucose concentrations were measured in the central lab, and the results were not sent back to investigators for blinding purpose.

Safety and Tolerability Assessments

During and following dosing, safety and tolerability were assessed through the reporting of TEAEs, vital signs, electrocardiogram and clinical laboratory evaluations (including hematology, coagulation, biochemistry, serology, urinalysis, and pregnancy test), and review of concomitant medications throughout the study at the local laboratory of the clinical center. TEAEs' severity was graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Statistical Methods

Pharmacokinetic Analysis

PK parameters of sotagliflozin and its primary metabolite (LX4211-GLU) were summarized by descriptive statistics in PK population. All subjects with no major or critical deviations related to investigational medicinal product (IMP), and for whom PK data were considered sufficient and interpretable, were included in the PK population. Subjects received only placebo were not part of the pharmacokinetic population. For ease of presentation, mean values will be arithmetic mean unless specified. Concentration values below the plasma assay limit were treated as zero in calculating mean values. AUC values extrapolated by more than 20% were excluded from any pharmacokinetic statistical analysis. CL/F and Vz/F were calculated using AUC_{τ} . R_{ac} and $R_{ac}^{C_{max}}$ were calculated as the ratio of the AUC_{τ} and C_{max} on day 8 to the AUC_{τ} and C_{max} on day 1. Statistical analysis of pharmacokinetic parameters was performed using Phoenix WinNonlin (Certara USA, Inc.).

Pharmacodynamic Analysis

All PD parameters were summarized by treatment and visit using descriptive statistics in the PD population. PD population included subjects with no major or critical deviations related to IMP and/or PD measurements, for whom the PD data were considered sufficient.

Safety and Tolerability Analysis

Analyses of the safety data were based on the Safety Population, which was defined as all randomized subjects who received at least one dose of double-blind treatment. Subjects were analyzed for safety analyses according to the treatment actually received. All safety summaries were descriptive, and no statistical significance tests were performed on the safety data.

Results

Demographics and Baseline Characteristics

The demographic characteristics of the subjects are shown in Table 1. A total of 24 subjects were randomized to placebo (N = 6), sotagliflozin 200 mg (N = 9), and sotagliflozin 400 mg (N = 9) groups. All subjects were Asian (not Hispanic or Latino). All subjects (100%) completed the study.

Pharmacokinetic Results

Pharmacokinetics of Sotagliflozin

Following single and multiple administration, sotagliflozin was rapidly absorbed at both 200 and 400 mg dose levels with a median t_{max} of 1.00 h postdose (0.50–1.50 h). On Day 8, sotagliflozin mean $t_{1/2z}$ was 20.5 h and 22.4 h for 200 mg and 400 mg dose levels, CL/F was 267 L/h and 307 L/h for 200 mg and 400 mg dose levels, respectively.

Mean accumulation ratios (R_{ac} and $R_{ac-C_{max}}$) ranged from 1.45 to 2.05, indicating a moderate degree of accumulation of sotagliflozin following multiple dosing. The pooled accumulation ratio of sotagliflozin 200 mg and 400 mg after 8 days of qd administration were 1.57 (90% CI: 1.38 to 1.78) for C_{max} and 1.84 (90% CI: 1.69 to 2.01) for AUC_{tau} , respectively.

Systemic exposure of sotagliflozin increased in an approximately dose proportional manner. For a 2-fold increase between doses on Day 8, the estimated increases for C_{max} and AUC_{tau} were 1.89-fold (90% CI: 1.47 to 2.43) and 1.70-fold (90% CI: 1.27 to 2.29), respectively. Over the same dose range, the estimated increases in C_{max} and AUC_{tau} on Day 1 were similar (1.56-fold [90% CI: 1.07 to 2.26] and 2.02-fold [90% CI: 1.50 to 2.73], respectively).

Table 1 Demographic and Baseline Characteristics

Characteristics	Statistic	Placebo (N = 6)	Sotagliflozin 200 mg (N = 9)	Sotagliflozin 400 mg (N = 9)	Overall (N = 24)
Age (years)	n	6	9	9	24
	Mean (SD)	27.0 (9.21)	31.9 (4.01)	36.3 (5.10)	32.3 (6.84)
	SEM	3.76	1.34	1.7	1.40
	Min, Max	19, 42	25, 37	28, 43	19, 43
	Median	23.5	33.0	38.0	33.0
Sex, n (%)	Male	6 (100.0)	7 (77.8)	7 (77.8)	20 (83.3)
	Female	0	2 (22.2)	2 (22.2)	4 (16.7)
Race, n (%)	Asian	6 (100)	9 (100)	9 (100)	24 (100)
Height (cm)	Mean (SD)	170.7 (7.81)	167.8 (5.29)	169.9 (8.30)	169.3 (6.96)
	SEM	3.19	1.76	2.77	1.42
	Min, Max	158, 178	159, 176	156, 184	156, 184
	Median	173.0	167.0	168.0	169.0
Weight (kg)	Mean (SD)	67.27 (9.243)	66.48 (8.146)	66.83 (5.890)	66.81 (7.336)
	SEM	3.774	2.715	1.963	1.497
	Min, Max	58.9, 81.5	57.7, 76.0	60.0, 75.5	57.7, 81.5
	Median	64.30	63.70	64.6	64.15
BMI (kg/m ²)	Mean (SD)	23.03 (2.036)	23.59 (2.348)	23.20 (2.072)	23.30 (2.090)
	SEM	0.831	0.783	0.691	0.427
	Min, Max	20.1, 25.7	20.0, 26.9	19.8, 25.7	19.8, 26.9
	Median	23.10	24.00	23.70	23.85

Abbreviations: n, number of subjects with valid observations; N, number of subjects, SD standard deviation; SEM, standard error of the mean; %, percentage of subjects with valid observations (n/N×100); BMI, body weight (kg)/height (m)².

Within-subject variability was approximately 22% [90% CI: 17.0%, to 30.8%] for C_{\max} and 15% [90% CI: 11.4% to 20.6%] for AUC_{τ} , and between-subject variability in exposure (based on C_{\max} and AUC_{τ}) was moderate to high for both dose levels and on both days with coefficient of variation% (CV%), estimates ranging from 31% to 57%.

Summary statistics of sotagliflozin PK parameters following single and multiple dosing of 200 mg and 400 mg are presented in Table 2.

The mean sotagliflozin plasma concentration–time profiles following single and multiple dosing are presented in Figure 2.

Pharmacokinetics of LX4211-GLU

Following single and multiple dose administration of sotagliflozin, LX4211-GLU appeared rapidly in the systemic circulation at both dose levels with a median t_{\max} between 1.00 and 1.50 h postdose (1.00–4.00 h). On Day 8, LX4211-GLU mean $t_{1/2z}$ was 24.8 h and 22.0 h for 200 and 400 mg dose levels, respectively.

Table 2 Plasma Pharmacokinetic Parameters of Sotagliflozin Following Single and Multiple Dose Administration of 200 Mg and 400 Mg Sotagliflozin

PK Parameters	Sotagliflozin 200mg		Sotagliflozin 400mg	
	Day 1	Day 8	Day 1	Day 8
N	9	9	9	9
C_{\max} (ng/mL)	90.9 ± 33.0 (85.5) [36]	127 ± 39.9 (122) [31]	151 ± 85.8 (133) [57]	241 ± 81.3 (230) [34]
C_{trough} (ng/mL)	NA	18.8 ± 11.0 (16.2) [58]	NA	25.5 ± 13.4 (22.7) [52]
t_{\max} (h)	1.00 (0.50–1.50)	1.00 (0.50–1.00)	1.00 (0.50–1.50)	1.00 (0.50–1.50)
AUC_{τ} (ng h/mL)	422 ± 150 (398) [35]	859 ± 363 (799) [42]	855 ± 321 (805) [38]	1420 ± 463 (1360) [32]
AUC_{last} (ng h/mL)	NA	1610 ± 1100 (1350) [68]	NA	2290 ± 873 (2130) [38]
AUC (ng h/mL)	NA	1420 ± 680 ^a (1290) [48]	NA	2450 ± 970 (2270) [40]
$t_{1/2z}$ (h)	NA	20.5 ± 7.03 ^a (19.5) [34]	NA	22.4 ± 10.4 (20.3) [47]
CL/F (L/h)	NA	267 ± 94.8 (250) [35]	NA	307 ± 93.8 (294) [31]
V_z/F (L)	NA	7880 ± 2650 ^a (7500) [34]	NA	9450 ± 4460 (8590) [47]
R_{ac}	NA	2.05 ± 0.450 (2.01) [22]	NA	1.72 ± 0.326 (1.69) [19]
$R_{ac} \cdot C_{\max}$	NA	1.45 ± 0.283 (1.43) [19]	NA	1.85 ± 0.764 (1.73) [41]

Notes: Data are shown as mean ±SD (geometric mean) [CV %], except t_{\max} which is as median (Min–Max). ^aN = 8, since a regression analysis could not be applied for sotagliflozin for one subject.

Abbreviations: SD, standard deviation; CV%, coefficient of variation%; NA, not applicable; C_{\max} , maximum plasma concentration observed; C_{trough} , plasma concentration observed just before treatment administration during repeated dosing; t_{\max} , time to reach C_{\max} ; AUC_{τ} , area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (τ); AUC_{last} , area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time t_{last} ; AUC, area under the plasma concentration versus time curve extrapolated to infinity (values with percentage of extrapolation >20% will not be reported); $t_{1/2z}$, terminal half-life associated with the terminal slope (λ_z); CL/F, apparent total body clearance of a drug from the plasma; V_z/F , apparent volume of distribution during the terminal (λ_z) phase; R_{ac} , AUC_{τ} accumulation ratio; $R_{ac} \cdot C_{\max}$, C_{\max} accumulation ratio.

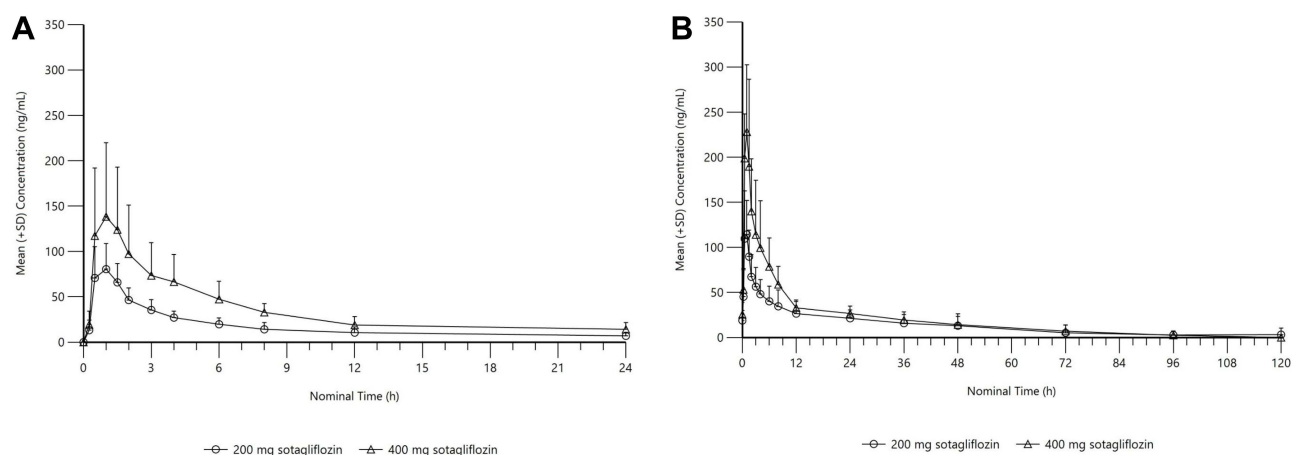


Figure 2 Mean (+SD) sotagliflozin plasma concentration-time profiles following (A) single dose (Day 1) and (B) multiple qd dose (Day 8) of 200 mg and 400 mg of sotagliflozin.

There was evidence of some accumulation of LX4211-GLU at both 200 mg and 400 mg dose levels with mean R_{ac} and $R_{ac}^{C_{max}}$ ranging from 1.23 to 1.85.

Systemic exposure of LX4211-GLU showed a dose-dependent increase with mean AUC_{tau} and C_{max} approximately 1.85- and 2.40-fold higher at 400 mg dose level compared to 200 mg dose level on Day 8.

Between-subject variability in exposure (based on C_{max} and AUC_{tau}) was moderate for both dose levels and on both days with CV% estimates ranging from 30% to 39%, with the exception of AUC_{tau} on Day 1 at 400 mg dose level, where variability was low, with a CV% of 19%.

Summary statistics of LX4211-GLU PK parameters following single and multiple dosing of 200 mg and 400 mg are presented in Table 3.

The mean LX4211-GLU plasma concentration-time profiles following single and multiple dosing are presented in Figure 3

Pharmacodynamic Results

Urine samples were collected for the assessment of UGE on Day 1 and 8. The mean (\pm SD) 24-hour UGE (mmol) values of sotagliflozin 200 mg, sotagliflozin 400 mg and placebo groups were 188.17 (\pm 51.957), 250.18 (\pm 38.063) and 0.47 (\pm 0.063) on Day 1, and 213.02 (\pm 67.216), 263.90 (\pm 56.665) and 0.45 (\pm 0.105) on Day 8, respectively. After unit conversion (1mol to 180 grams), on day 1 mean (\pm SD) 24-hour UGE (gram) values were 33.87 (\pm 9.352), 45.03 (\pm 6.851) and 0.08 (\pm 0.011) for sotagliflozin 200 mg, sotagliflozin 400 mg, and placebo treatment groups. And on day 8, 24-hour UGE (gram) were 38.34 (\pm 12.099), 47.50 (\pm 10.200) and 0.08 (\pm 0.019), respectively. UGE was elevated relative to the placebo group in the 200 mg and 400 mg groups over both Day 1 and Day 8, and increased slightly between Day 1 and Day 8 in both groups. UGE was increased slightly in the 400mg group relative to the 200 mg group (Figure 4).

Safety and Tolerability

Brief Summary of Treatment-Emergent Adverse Events

Overall, 24 subjects completed the treatment period and were included in the safety population. An overview of TEAEs is presented in Table 4.

No deaths, serious AEs (SAEs), or TEAEs leading to treatment discontinuation were observed in this study. In general, the proportions of subjects who experienced any TEAEs in the study were higher following administration of sotagliflozin compared to placebo. All TEAEs were of grade 1 intensity, which did not require corrective treatment (except for topical iodophor for folliculitis) and resolved without sequelae. Nearly half of the TEAEs reported for the sotagliflozin groups (44.4%) were considered treatment-related by the Investigator.

Table 3 Plasma Pharmacokinetic Parameters of LX4211-GLU Following Single and Multiple Dose Administration of 200 Mg and 400 Mg Sotagliflozin

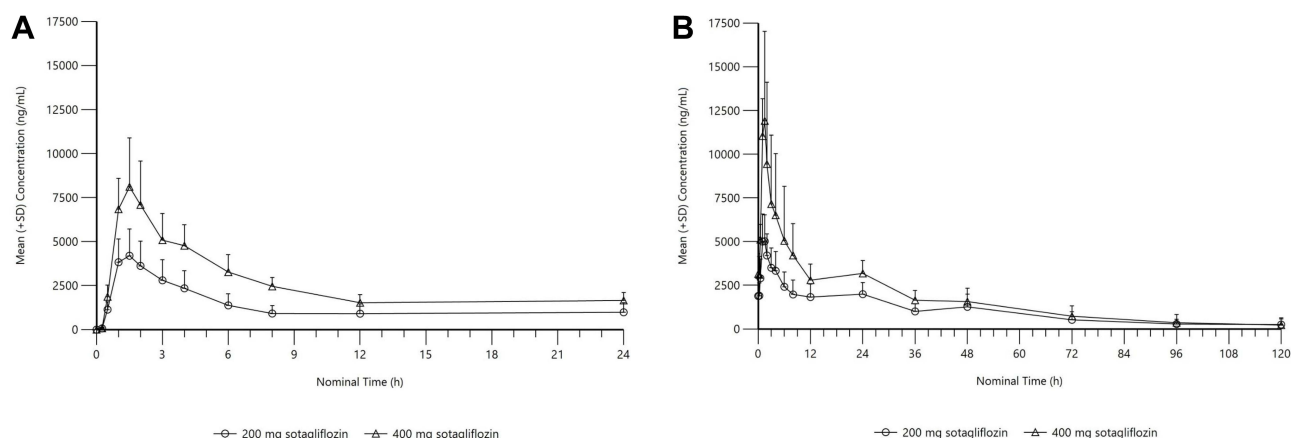
PK Parameters	Sotagliflozin 200mg		Sotagliflozin 400mg	
	Day 1	Day 8	Day 1	Day 8
N	9	9	9	9
C _{max} (ng/mL)	4300 ± 1420 (4030) [33]	5210 ± 1560 (4940) [30]	8250 ± 2750 (7920) [33]	12,500 ± 4750 (11,900) [38]
C _{trough} (ng/mL)	NA	1890 ± 726 (1750) [39]	NA	3150 ± 1150 (2970) [37]
t _{max} (h)	1.50 (1.00–1.50)	1.00 (1.00–2.00)	1.50 (1.00–4.00)	1.50 (0.50–1.50)
AUC _{tau} (ng h/mL)	32,000 ± 12,600 (28,600) [39]	55,800 ± 17,900 (52,200) [32]	61,700 ± 11,600 (60,800) [19]	103,000 ± 37,900 (98,400) [37]
AUC _{last} (ng h/mL)	NA	125,000 ± 51,900 (114,000) [42]	NA	198,000 ± 64,400 (189,000) [32]
AUC (ng h/mL)	NA	120,000 ± 44,200 ^a (111,000) [37]	NA	191,000 ± 60,400 ^b (182,000) [32]
t _{1/2z} (h)	NA	24.8 ± 11.2 ^a (22.7) [45]	NA	22.0 ± 15.6 (18.3) [71]
R _{ac}	NA	1.85 ± 0.362 (1.83) [20]	NA	1.65 ± 0.375 (1.62) [23]
R _{ac} ·C _{max} ^{ac}	NA	1.23 ± 0.139 (1.23) [11]	NA	1.52 ± 0.222 (1.50) [15]

Notes: Data are shown as mean ±SD (geometric mean) [CV %], except t_{max} which is as median (Min–Max). ^aN = 8, since a regression analysis could not be applied for LX4211-GLU for one subject; ^bN = 8, since one subject was excluded due to AUC_{extrap} >20% for LX4211-GLU.

Abbreviations: SD, standard deviation; CV%, coefficient of variation%; NA, not applicable; C_{max}, maximum plasma concentration observed; C_{trough}, plasma concentration observed just before treatment administration during repeated dosing; t_{max}, time to reach C_{max}; AUC_{tau}, area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (τ); AUC_{last}, area under the plasma concentration versus time curve extrapolated to infinity (values with percentage of extrapolation >20% will not be reported); t_{1/2z}, terminal half-life associated with the terminal slope (λ_z); R_{ac}, AUC_{tau} accumulation ratio; R_{ac}·C_{max}^{ac}, C_{max} accumulation ratio.

Analysis of Adverse Events

The number and percentage of subjects with TEAEs by primary System Organ Class (SOC) and Preferred Term (PT) are summarized in Table 5.

**Figure 3** Mean (+SD) LX4211-GLU plasma concentration-time profiles following (A) single dose (Day 1) and (B) multiple qd dose (Day 8) of 200 mg and 400 mg of sotagliflozin.

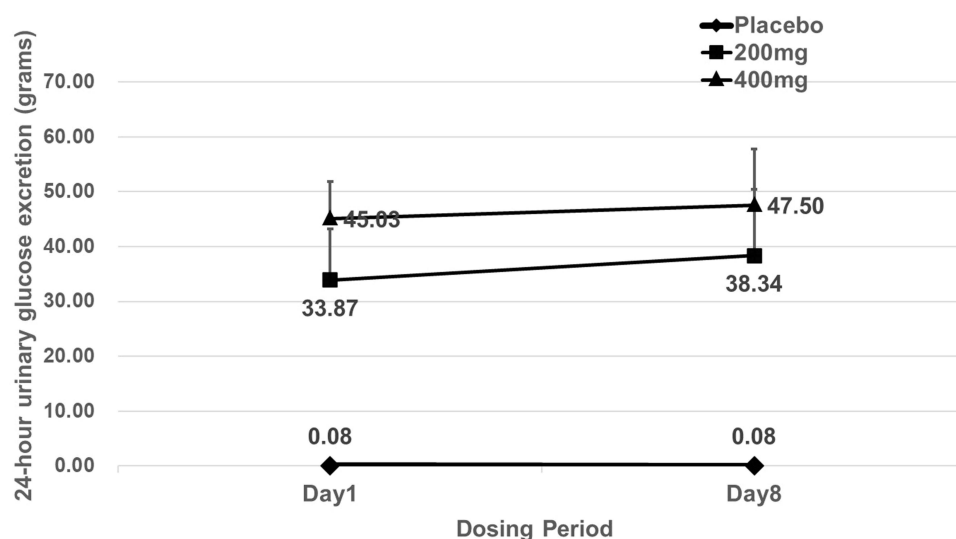


Figure 4 Mean (+SD) 24-hour UGE (grams) for placebo, sotagliflozin 200 mg and 400 mg treatment groups on Days 1 and 8. 1 mmol = 0.18 g of glucose (1 mol = 180 g).

In the sotagliflozin 200 mg group, TEAEs of folliculitis, anemia, dizziness, petechiae, proteinuria, chest discomfort, increased blood phosphorus and decreased white blood cell count were reported, with each TEAE reported in 1 (11.1%) subject. In the sotagliflozin 400 mg group, TEAEs of dizziness, headache, constipation, haemorrhoidal haemorrhage, mouth ulceration, dermatitis, asthenia, increased ALT, increased blood ketone body (0.61 mmol/L), and blood urine were

Table 4 Overview of Treatment-Emergent Adverse Events (TEAEs) for All Subjects

	Placebo	Sotagliflozin 200mg	Sotagliflozin 400mg	Sotagliflozin Overall
	nS (%) [nE]	nS (%) [nE]	nS (%) [nE]	nS (%) [nE]
N	6	9	9	18
Overall	1 (16.7%) [2]	5 (55.6%) [8]	5 (55.6%) [10]	10 (55.6%) [18]
SAE	0	0	0	0
Leading to study discontinuation	0	0	0	0
Leading to permanent treatment discontinuation	0	0	0	0
Leading to death	0	0	0	0
Severity				
Grade 1	1 (16.7%) [2]	5 (55.6%) [8]	5 (55.6%) [10]	10 (55.6%) [18]
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Relationship to treatment				
Not related	1 (16.7%) [1]	3 (33.3%) [3]	1 (11.1%) [1]	4 (22.2%) [4]
Related	1 (16.7%) [1]	4 (44.4%) [5]	4 (44.4%) [9]	8 (44.4%) [14]

Abbreviations: N, number of subjects; nS, number of subjects with an adverse event; %, percentage of subjects with an adverse event (nS/N×100); nE, number of adverse events; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 5 Summary of TEAEs by Primary SOC and PT for All Subjects

Primary System Organ Class Preferred Term [n (%)] (MedDRA22.0)	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400mg
N	6	9	9
Any class	1 (16.7%)	5 (55.6%)	5 (55.6%)
Infections and infestations	1 (16.7%)	1 (11.1%)	0
Folliculitis	1 (16.7%)	1 (11.1%)	0
Blood and lymphatic system disorders	0	1 (11.1%)	0
Anaemia	0	1 (11.1%)	0
Nervous system disorders	0	1 (11.1%)	1 (11.1%)
Dizziness	0	1 (11.1%)	1 (11.1%)
Headache	0	0	1 (11.1%)
Gastrointestinal disorders	1 (16.7%)	0	2 (22.2%)
Constipation	1 (16.7%)	0	1 (11.1%)
Haemorrhoidal haemorrhage	0	0	1 (11.1%)
Mouth ulceration	0	0	1 (11.1%)
Skin and subcutaneous tissue disorders	0	1 (11.1%)	1 (11.1%)
Dermatitis	0	0	1 (11.1%)
Petechiae	0	1 (11.1%)	0
Renal and urinary disorders	0	1 (11.1%)	0
Proteinuria	0	1 (11.1%)	0
General disorders and administration site conditions	0	1 (11.1%)	1 (11.1%)
Asthenia	0	0	1 (11.1%)
Chest discomfort	0	1 (11.1%)	0
Investigations	0	2 (22.2%)	2 (22.2%)
Alanine aminotransferase increased	0	0	1 (11.1%)
Blood ketone body increased	0	0	1 (11.1%)
Blood urine present	0	0	1 (11.1%)
Blood phosphorus increased	0	1 (11.1%)	0
White blood cell count decreased	0	1 (11.1%)	0

Abbreviations: N, number of subjects treated within each group; n (%), number and % of subjects with at least one TEAE in each category; TEAE, treatment-emergent adverse event; SOC, system organ class; PT, Preferred term.

reported, with each TEAE in 1 (11.1%) subject. In the pooled placebo group, folliculitis and constipation were each reported in 1 (16.7%) subject.

The only TEAEs by preferred term that were reported in more than 1 subject across treatment groups in the study were dizziness (2 on sotagliflozin), folliculitis (1 on sotagliflozin and 1 on placebo) and constipation (1 on sotagliflozin and 1 on placebo). All the other TEAEs were reported in 1 single subject.

Several reported TEAEs were related to abnormal laboratory test values (anemia, proteinuria, increased blood phosphorus, decreased white blood cell count, increased ALT, increased blood ketone body and blood urine present) that were considered clinically significant by the Investigator; however, all these laboratory test-related TEAEs were asymptomatic, mild in intensity, did not require corrective treatment or consultation, and did not lead to IMP discontinuation or modification. The AE of asymptomatic alanine aminotransferase (ALT) increase was $<2 \times$ upper limit of normal (ULN). There were no trends in changes of biochemistry (including hypoglycemia), hematology, and urinalysis observed during the TEAE period.

Potentially clinically significant abnormalities (PCSAs) of QRS interval >110 ms were reported in 4 subjects (2 on 200mg sotagliflozin and 2 on placebo), but none increased from baseline $\geq 25\%$ or was considered clinically relevant by the Investigator. There were no other PCSAs observed in vital signs or other ECG parameters.

Discussion

Sotagliflozin/Lx4211, an orally administered small molecule, is the unique dual inhibitor of SGLT1 and SGLT2 approved for marketing up to now and has its approval in the EU since 2019. Previous researches about the pharmacokinetic, pharmacodynamic profiles, safety and tolerability of sotagliflozin were almost performed in European-American populations.^{24–26} This is the first study conducted in Chinese healthy subjects to obtain the corresponding data after multiple ascending doses of sotagliflozin.

According to the publicly available data from European Medicines Agency (EMA),¹³ the median t_{\max} following a single-dose of sotagliflozin (400–2000 mg) ranged from 1.25 to 3 h. After administration of multiple doses (400 and 800 mg), the median t_{\max} ranged from 2.5 to 4 h. While in the present study, the C_{\max} values of both 200 and 400 mg qd doses were rapidly achieved with the median t_{\max} of 1.00 (0.50–1.50) h following either single or multiple administration of sotagliflozin. In the initial studies in healthy subjects from the United States, after multiple-dose qd administration of up to 500mg sotagliflozin in a liquid formulation, the maximum circulating concentration of sotagliflozin on Day 7 was 165 ng/mL, and the total exposure ($AUC_{0-\tau}$) was 1172 ng h/mL.²⁷ In the present study, the maximum circulating concentration of sotagliflozin was 241 ng/mL on Day 8, with the $AUC_{0-\tau}$ of 1420 ng h/mL. It seemed that sotagliflozin was absorbed faster and the systemic exposure was slightly higher in Chinese healthy subjects.

Based on a previous population PK analysis, race had no clinically meaningful effect on the PK of sotagliflozin. In addition to population differences, systemic exposure was affected by body weight, renal impairment, and hepatic impairment.^{13,28} Hence, for healthy subjects with normal liver and kidney function, body weight should be a considerable factor. In the previous studies based on European-American population in clinical trials LX4211.206/LX4211.309/LX4211.310/LX4211.312, the mean baseline body weight values were 81.08–87.30 kg, with the mean BMI of 27.50–29.55 kg/m².²⁶ While the baseline body weight of the subjects from the present study was only 66.48–67.27 kg, and the mean BMI was 23.03–23.59 kg/m². The differences in exposure between our results and those of previous European–American studies were not considered to have clinical significance, therefore no dose adjustment is required based on weight according to previous population PK analysis.¹³

The exposure of sotagliflozin was increased when co-administered with food (high fat/high caloric), the C_{\max} was ca 2.5-fold and total exposure ca 1.5-fold higher compared to under fasted condition.²⁶ Dosing of sotagliflozin immediately before breakfast maximized the PD effects of both SGLT1 and SGLT 2 inhibition and provided a convenient dosing schedule.²⁹ Thus, the recommended sotagliflozin medication time is once daily before the first meal of the day.¹³ Chinese diet is very different from European–American diet. As sotagliflozin is taken just before the meal, diet may affect the pharmacokinetic profiles. This needs to be clarified in future studies.

The major metabolite of sotagliflozin is LX4211-GLU, representing 94% of the total plasma radioactivity.²⁶ LX4211-GLU was shown to have an in vitro potential to inhibit CYP3A4 and CYP2D6 and also to induce CYP3A4, but no clinically important interaction was demonstrated in studies with metoprolol (CYP2D6 substrate) or midazolam (CYP3A4 substrate). However, LX4211-GLU is a very poor inhibitor for both SGLT2 and SGLT1 transporters with IC50s of $>10,000$ nM.²⁶

Dose-proportional increases of plasma sotagliflozin concentration were observed, and the accumulation index at steady state was about 2, according to the publicly available data from EMA based on European-American populations.²⁶ Mean terminal $T_{1/2}$ ranged from 21 to 35 h for sotagliflozin and from 19 to 26 h for LX4211-GLU.^{13,25} In healthy volunteers, mean CL/F of sotagliflozin ranged from 261 to 374 L/hr.¹³ In consistent with these findings, dose-proportional increases in C_{\max} and AUC_{τ} were also observed for sotagliflozin and LX4211-GLU with a moderate degree of accumulation in the current study. Mean $t_{1/2z}$ of sotagliflozin and LX4211-GLU was approximately 20.5–22.4h and 22.0–24.8h, respectively, supporting the once daily dosing strategy. Mean CL/F of sotagliflozin was 267L/h for 200mg dose and 307L/h for 400mg dose, respectively. Taken together, sotagliflozin and its main metabolite LX4211-GLU show similar PK features, and the overall pharmacokinetic characteristics of Chinese healthy subjects were comparable to those of European-American populations.

Pharmacodynamic results showed significant increase of UGE in the two sotagliflozin groups when compared with placebo group, which was consistent with the previous studies.²⁶ In healthy volunteers in the United States, after a single dose of 400 mg sotagliflozin, the amount of UGE over 24 hours ranged between 40 and 45 g glucose in clinical trial LX4211.111. The initial single-dose and multiple-dose studies of sotagliflozin (LX4211-1-101) performed in healthy subjects, showed the maximum 24 h UGE was 44g achieved at the 300mg dose, and further increasing the dose did not provide greater UGE despite increased systemic exposure of sotagliflozin.²⁷ In the present study, UGE was increased in both sotagliflozin groups relative to placebo over Day 1 and Day 8, and the added efficacy of 400mg qd was increased slightly in UGE compared with 200 mg qd. It might suggest that in Chinese population, the increasement of sotagliflozin to 400mg qd or even higher dose may lead to greater treatment efficacy; meanwhile, the safety issues such as genitourinary infections and hypovolaemia should be concerned. This is worth investigating in the future study.

Overall, sotagliflozin was well tolerated in Chinese healthy subjects at 200mg and 400mg when given orally qd for 8 days in the study. Although a slight increasement of TEAEs was observed in the sotagliflozin groups compared to placebo, all TEAEs were grade 1 intensity, with no deaths or TEAEs that led to discontinuation. No new safety concerns were identified.

Studies showed that genital mycotic infections, diarrhoea, and volume depletion events are increased with sotagliflozin compared to placebo.^{19,30} An increased risk of diabetic ketoacidosis has only been observed with sotagliflozin, specifically in patients with type 1 diabetes.²¹ The adverse event profile is generally consistent with other SGLT inhibitors. In the present study, none of these AEs was observed in Chinese healthy subjects. However, if sotagliflozin is approved to be used in patients with diabetes in China, attention should also be paid to the adverse events listed above.

This study had several limitations that should be considered. First, the healthy subjects were different from the target population for oral sotagliflozin, although this could prevent the potential confounding effect of concomitant medications and comorbidities. Second, the 8 d administration is not sufficient to characterize the safety and tolerability of sotagliflozin in a Chinese population. Last, even though a small number of subjects per treatment group are generally acceptable for Phase I trials, the sample size of the present study was relatively small. Future studies in the larger target population may provide more convincing data.

Conclusion

In conclusion, this study firstly assessed the pharmacokinetics, pharmacodynamics, safety and tolerability of sotagliflozin following multiple ascending doses in Chinese healthy subjects. Sotagliflozin was rapidly absorbed at both 200 and 400 mg dose levels. Systemic exposure of sotagliflozin increased in an approximately dose proportional manner. UGE was increased in the sotagliflozin 200 mg and 400 mg groups over Day 1 and Day 8. Analyses of clinical safety data from this study demonstrated that sotagliflozin was well tolerated, and no significant safety findings were identified in Chinese healthy subjects when given orally qd for 8 days. These results may support further clinical investigation of sotagliflozin in the Chinese population.

Data Sharing Statement

The original data of this study will not be openly shared due to confidentiality concerns.

Ethics Approval

The study was approved by the Ethics Committee of Beijing Hospital. This study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), all applicable laws, rules and regulations.

Informed Consent

All study participants provided written informed consent before enrollment in the study and could withdraw from the study at any time.

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Disclosure

The authors report no conflicts of interest in this work.

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