Greater Dose-Ranging Effects on A1C Levels Than on Glucosuria With LX4211, a Dual Inhibitor of Sodium Glucose Transporters SGLT1 and SGLT2, in Type 2 Diabetes on Metformin Monotherapy

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OBJECTIVE

To assess the dose-ranging efficacy and safety of LX4211, a dual inhibitor of sodium glucose cotransporter 1 (SGLT1) and SGLT2, in type 2 diabetes.

RESEARCH DESIGN AND METHODS

Type 2 diabetic patients inadequately controlled on metformin were randomly assigned to 75 mg once a day, 200 mg once daily, 200 mg twice daily, or 400 mg once daily of LX4211 or placebo. Primary end point was A1C change from baseline to week 12. Secondary end points included changes in blood pressure (BP) and body weight.

RESULTS

Baseline characteristics in 299 patients randomly assigned to LX4211 or placebo in this 12-week dose-ranging study were similar: mean age 55.9 years, A1C 8.1% (65 mmol/mol), BMI 33.1 kg/m^2, and BP 124/79 mmHg. LX4211 significantly reduced A1C to week 12 in a dose-dependent manner by 0.42% (4.6 mmol/mol), 0.52% (5.7 mmol/mol), 0.80% (8.7 mmol/mol), and 0.92% (10.0 mmol/mol), respectively ($P <$ 0.001 each), compared with 0.09% (1.0 mmol/mol) for placebo. Greater A1C reductions were produced by 400 mg once a day than 200 mg once a day LX4211 without higher urinary glucose excretion, suggesting a contribution of SGLT1 inhibition. Significant reductions were seen in body weight (−1.85 kg; $P < 0.001$) and systolic BP (−5.7 mmHg; $P < 0.001$), but diastolic BP was unchanged (−1.6; $P = 0.164$). Adverse events with LX4211 were mild to moderate and similar to placebo, including urinary tract infections and gastrointestinal-related events; genital infections were limited to LX4211 groups (0–5.0%). No hypoglycemia occurred.

CONCLUSIONS

Dual inhibition of SGLT1/SGLT2 with LX4211 produced significant dose-ranging improvements in glucose control without dose-increasing glucosuria and was associated with reductions in weight and systolic BP in metformin-treated type 2 diabetes.

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Defects in insulin secretion, reduced peripheral insulin action, and incretin system dysfunction are known pathophysiological defects of type 2 diabetes addressed by currently available antidiabetic agents, including insulin, which can reduce the endogenous glucose load by acting on hepatic glucose production and peripheral glucose uptake. Further attempts to reduce glucose load have been largely limited to providing patients with dietary guidance to restrict caloric intake.

Early pharmacology studies in the dog and rat (1,2), utilizing parenteral administration of phlorizin, a potent dual sodium glucose cotransporter (SGLT) 1 and SGLT2 inhibitor, suggested inhibition of intestinal and renal glucose reabsorption could provide a benefit in type 2 diabetes. However, the potential for severe diarrhea due to the rapid conversion in the small intestine of phlorizin to phloretin, which nonspecifically inhibits multiple targets including GLUT2, necessitated the development of alternative selective SGLT2 inhibitors to focus on the renal glucose-lowering effects (3). SGLT2 is the primary transporter involved in glucose reabsorption by the kidney and selective SGLT2 inhibitors available and in development have produced glucose-lowering effects through an insulin independent mechanism by enhancing urinary glucose excretion (UGE) (4). This enhanced UGE translates in increased elimination of calories in the urine resulting in modest weight loss. In addition, SGLT2 inhibition leads initially to renal sodium excretion and has been shown to reduce blood pressure (BP) without electrolyte imbalances (5).

LX4211 is a dual inhibitor of SGLT1 and SGLT2, with half-maximal inhibitory concentration values of 36 and 1.8 nm for these two transporters, respectively (6). LX4211 is nearly identical in potency at SGLT2 inhibition compared with the selective SGLT2 inhibitors dapagliflozin and canagliflozin, but >10-fold more potent than these agents at inhibiting SGLT1 (7). Since SGLT1 is the primary transporter for glucose uptake from the diet by the gastrointestinal (GI) tract, it is expected that postprandial blood glucose (PPG) will be reduced by SGLT1 inhibition. This is supported by multiple lines of evidence demonstrating decreased PPG levels associated with mutations in SGLT1 or pharmacologic inhibition of SGLT1. Such evidence comes from SGLT1 knockout mice (8,9), humans with loss-of-function mutations in the SGLT1 gene (10), SGLT inhibitors attached to nonabsorbable polymers that can only inhibit glucose transport in the GI tract (11,12), pharmacologic effects of selective SGLT1 inhibitors (13,14), and preclinical and clinical studies with LX4211 (6,15–17). Preclinical studies also indicate that SGLT1 inhibition with LX4211, or a selective SGLT1 inhibitor, results in elevated glucose in the cecum and increased postprandial blood levels of GLP-1 and peptide YY (PYY), hormones involved in glucose homeostasis and appetite control. Of note, these postmeal SGLT1-mediated effects on cecal glucose, GLP-1, and PYY levels are only observed in SGLT1 knockout mice, but not in SGLT2 knockout mice.

In mechanistic clinical studies, SGLT1 inhibition by LX4211 has also been associated with lower PPG, lower insulin levels, and elevations of GLP-1 and PYY (18–20). Through its insulin-independent mechanism of action of dual inhibition of SGLT1 and SGLT2, resulting in reductions of intestinal glucose absorption while promoting glucosuria. In a short-term type 2 diabetes pilot study, LX4211 produced significant improvements in fasting plasma glucose (FPG), PPG, and A1C levels (6).

The goal of the current study was to further examine the dose-ranging efficacy and safety of LX4211 in a larger type 2 diabetic population on background metformin monotherapy. It was designed to provide greater precision of the impact of LX4211 on A1C and other glycemic parameters as well as on BP and body weight. The sample size and duration of therapy were also intended to provide a better evaluation of GI tolerability and overall safety, with the goal of selecting a dose of LX4211 for the clinical development program.

RESEARCH DESIGN AND METHODS

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study to assess the dose ranging safety, tolerability, and efficacy of four oral-dose regimens of LX4211 in patients with type 2 diabetes inadequately controlled on metformin (A1C 7–10.5% [53.0–91.3 mmol/mol]). The primary objective of this study was to evaluate the change from baseline to week 12 in A1C for four different dosing regimens of LX4211 (75 mg once daily, 200 mg once daily, and 200 mg twice daily and 400 mg once daily) versus placebo. Secondary objectives were to determine the proportion of patients achieving A1C <7% at week 12 and to determine the change from baseline to week 12 in FPG, oral glucose tolerance test, body weight, BP, and triglycerides. Throughout the trial, a urinary glucose substudy, comprised of 24-h urine glucose measurements in addition to spot glucosuria/creatinine ratio, was conducted in 100 patients at day 1 and week 12 (~20/treatment group).

A minimum of 285 patients were planned for enrollment. Patients were to be randomly assigned to one of the following five treatment arms (n = 57/group) with equal assignment probability (1:1:1:1:1): 75 mg once daily, 200 mg once daily, 200 mg twice daily, 400 mg once daily of LX4211 or matching placebo once daily.

The study consisted of a screening period (2 to 3 weeks), 12-week treatment period, and a 2-week follow-up period. LX4211 dose adjustments were not permitted during the study. At screening, patients were counseled to follow American Diabetes Association–recommended diet and exercise guidelines. Full inclusion/exclusion criteria are provided in the Supplementary Data.

Safety was assessed throughout the study, and all adverse events (AEs) were followed for at least 30 days following the last dose of study drug. Additional information was collected for AEs deemed to be of special interest: hypoglycemia, genitourinary (GU) infections, and cardiovascular events. An independent masked committee adjudicated cardiovascular events.

The study was conducted according to Good Clinical Practices and the principles of the Declaration of Helsinki. All study participants provided written consent prior to screening for the study that was approved by the Institutional Review Board providing oversight for each particular study center. The study was registered on clinicaltrials.gov (NCT01376557).

Statistical Analysis

The primary measure of efficacy was the mean absolute change from baseline to

week 12 in A1C. This end point was used to derive the sample size to determine if at least one of the LX4211 treatment groups differed from the placebo control group by ≥0.60%. The statistical test for each comparison was sized at α = 0.05, powered at 80%, and assumed a common SD of 1.0%. These assumptions along with a conservative correction for early withdrawal patients netted a sample size target of 57 patients per group.

Primary analyses of the efficacy data were based on the intent-to-treat patient population and comprised of all patients as randomized; the per-protocol population (patients who received study drug and had at least one postbaseline measurement, ≥80% compliance, and no major protocol violations) was used in an exploratory manner to assess treatment effects for the efficacy parameters. The safety population included all randomized patients who had received any study drug dose. Patients in this population were assigned to the treatment group as to how they were treated on day 1.

Continuous efficacy and safety variables were summarized descriptively by the number of patients with nonmissing data, mean and SD, median, minimum, and maximum values. Categorical variables were summarized descriptively by their counts and associated percentages. Time to event end points were summarized by Kaplan-Meier statistics (21).

Demographic data, baseline disease characteristics, prior and concomitant medications, final disposition, and safety data were summarized descriptively only.

Analysis of continuous efficacy measures was based on use of ANCOVA statistics with a fixed-effect model including treatment group, the baseline value of the dependent variable serving as the covariate, and a residual error term. Treatment contrasts were conducted using a per comparison α-level = 0.05. Analyses based on individual time points other than just week 12 adopted a similar method of analysis, but included additional fixed terms of time and a treatment-by-time interaction in the model. Individual treatment contrasts of each LX4211 treatment group versus the placebo control were based on testing differences in least squares means. Statistical significance for each of these contrasts was established at α = 0.05. Logistic regression tests were applied to evaluate the effect of treatment on the proportion of patients achieving an A1C <7.0% (53 mmol/mol) at week 12; the baseline value of A1C served as a covariate in the analysis. Treatment effects for time to rescue were assessed by use of the log-rank test.

Efficacy end points with missing observations employed the last observation carried forward (LOCF) method to derive a full dataset. Efficacy data collected after initiation of rescue therapy were excluded from analysis and subjected to the LOCF algorithm as needed. Additional analyses were conducted to assess the robustness of using the LOCF rule. These sensitivity analyses include the following: use of baseline carried observations forward for missing data, linear mixed model repeated-measures analysis with observed data, and implementation of a pattern mixture model.

RESULTS

Screening was conducted in 614 patients, and 299 were enrolled and randomized from 52 sites in the U.S. (Supplementary Fig. 1). In general, treatment groups were well balanced. Mean age was 55.9 years (range 30–75), the majority of patients (54.8%) were female, mean weight was 93.7 kg (range 45.8–149.2), mean BMI at baseline was 33.1 kg/m^2 (range 18.5–46.1), and mean A1C was 8.1% (range 6.6–10.8). The majority (84.3%) of patients were white. Full demographics are summarized in Table 1.

LX4211 decreased A1C in a dose-dependent manner throughout the 12-week study (Fig. 1). Maximum efficacy was achieved in the 400-mg once daily dose group with a −0.92% (10 mmol/mol) absolute reduction of A1C ($P < 0.001$) from a baseline of 8.1% (65 mmol/mol) to a final A1C at week 12 of 7.1% (54 mmol/mol) as compared with −0.09% (−1.0 mmol/mol) in the placebo group (P = 0.403) from a baseline of 7.9% (63 mmol/mol) to a final A1C of 7.8% (62 mmol/mol). LX4211 significantly increased the proportion of patients achieving A1C control, <7% (53 mmol/mol), at week 12 (P = 0.022) and also reduced FPG with a maximum placebo-subtracted reduction of 29 mg/dL (1.6 mmol/L) at the 400-mg once daily dose ($P < 0.001$).

UGE was measured as glucose/creatinine ratio in all patients as spot checks and as glucose/creatinine ratio and total daily UGE in a substudy that included 24-h urine collections. Results from the three measurements consistently showed an apparent plateau of UGE reached at the 200 mg once daily LX4211 dose with no further increments in glucosuria with higher LX4211 doses (Fig. 1).

Weight loss began gradually and continued over time with mean loss of ~2 kg or more in the top three dose groups (Fig. 1). A ≥5% weight loss was achieved in 10.7% of patients with LX4211 treatment, while only 1.7% on placebo achieved such a change.

In a population with a mean baseline systolic BP of 125 mmHg, LX4211 reduced systolic BP in a dose-dependent manner, with the greatest change of −6 mmHg observed in the 400-mg dose group ($P < 0.001$). Reductions in diastolic BP were also observed, but those were of a lesser magnitude on average (Table 2). Additional BP data are summarized in Supplementary Table 1.

There were no significant differences in HDL, LDL, or triglyceride changes for LX4211 versus placebo. There was marked variability in the triglyceride data in the current study, potentially due to high baseline values and intrapatient fluctuations (Supplementary Table 2).

Trough plasma drug concentration levels were measured during the study and increased roughly dose proportionally (Supplementary Fig. 2).

AEs were generally mild or moderate, self-limited, and evenly distributed across the placebo and LX4211 treatment groups; there were no apparent AE dose relationships.

The incidence of GI AEs was similar among all of the LX4211 dose groups and placebo. The proportion of patients with any GI AE was 22 and 20% on LX4211 400 mg once daily and placebo, respectively. There were five patients with diarrhea on LX4211 400 mg once daily compared with four on placebo and one patient with constipation on LX4211 400 mg once daily compared with four on placebo.

Extended AE terms indicative of specific clinical diagnoses of GU infections were examined to maximize capture of GU AEs (Table 3). Urinary tract infections were reported in four women and

Table 1—Patient demographics at baseline

Characteristic (statistics/category)	LX4211				Placebo	Total
	75 mg once daily (*N* = 59)	200 mg once daily (*N* = 60)	200 mg twice daily (*N* = 60)	400 mg once daily (*N* = 60)	(*N* = 60)	(*N* = 299)
Age (years)						
Mean (SD)	56.1 (9.6)	55.6 (9.3)	56.4 (8.8)	56.1 (9.5)	55.1 (9.8)	55.9 (9.3)
Sex						
Male	34 (57.6%)	17 (28.3%)	29 (48.3%)	29 (48.3%)	26 (43.3%)	135 (45.2%)
Female	25 (42.4%)	43 (71.7%)	31 (51.7%)	31 (51.7%)	34 (56.7%)	164 (54.8%)
Race						
Black/African American	5 (8.5%)	9 (15.0%)	5 (8.3%)	6 (10.0%)	6 (10.0%)	31 (10.4%)
White	48 (81.4%)	51 (85.0%)	53 (88.3%)	51 (85.0%)	49 (81.7%)	252 (84.3%)
Other*	6 (10.2%)	0	2 (3.3%)	3 (5.0%)	5 (8.3%)	16 (5.4%)
Weight (kg)						
Mean (SD)	96.2 (19.3)	95.6 (19.4)	95.0 (22.2)	91.4 (18.6)	90.6 (20.7)	93.7 (20.1)
BMI (kg/m^2)						
Mean (SD)	33.4 (5.2)	34.2 (5.8)	32.9 (5.6)	32.7 (5.8)	32.2 (5.8)	33.1 (5.7)
FPG (mg/dL)						
Mean (SD)	168.5 (44.1)	179.5 (53.6)	181.0 (43.3)	168.3 (39.2)	167.1 (45.4)	172.2 (45.3)
Hemoglobin A1C (%)						
Mean (SD)	8.0 (0.9)	8.3 (1.0)	8.4 (0.9)	8.1 (1.0)	7.9 (0.9)	8.1 (1.0)

*Other is comprised of American Indian, Alaska Native, Asian, or patients specified as "other" or "multiple."

distributed evenly among treatment groups including placebo (75 mg once daily, *n* = 1; 200 mg once daily, *n* = 1; 400 mg once daily, *n* = 1; and placebo group, *n* = 1). All of the urinary tract infections and GU infections resolved with treatment; none led to study drug discontinuation. Table 3 summarizes all AEs reported in ≥3% of LX4211-treated patients including AEs of special interest.

There were fewer reports of hyperglycemia or worsening diabetes on LX4211 400 mg once daily compared with placebo (1 vs. 6, respectively), and there were no hypoglycemia events; two hypotension episodes were reported, one each in the 75 mg once daily and placebo groups.

There were four serious AEs, none of which were assessed as being related to study treatment, including bile duct stone (200 mg once daily, *n* = 1, with previous medical history), pulmonary embolus (400 mg once daily, *n* = 1, with previous medical history), lower limb fracture (400 mg once daily, *n* = 1, work-related accident), and myocardial infarction (placebo, *n* = 1).

A cardiovascular adjudication committee reviewed all potential cardiovascular events and read all electrocardiograms, including the patient randomized to placebo who had a confirmed myocardial infarction. There were no deaths.

Thirty-two patients discontinued therapy over the 12-week treatment and 2-week follow-up period (*n* = 30 and *n* = 2, respectively). Of these, four discontinued because of an AE (75 mg once daily, *n* = 1; 200 mg once daily, *n* = 1; 400 mg once daily, *n* = 1; and placebo, *n* = 1), including headache, diarrhea, pulmonary embolus, and myocardial infarction, respectively. The remaining 28 discontinuations were due to the following: withdrawn consent (*n* = 17), lost to follow-up evaluation (*n* = 6), protocol noncompliance (*n* = 4), and withdrawn by the investigator (*n* = 1).

CONCLUSIONS

LX4211 provided significant improvements in glycemic control with meaningful reductions in A1C and FPG levels in inadequately controlled type 2 diabetic patients on background metformin monotherapy and also decreased BP and body weight. Overall, LX4211 treatment was well tolerated, and the greatest efficacy was achieved with LX4211 400 mg once daily with no apparent dose-related increase in AEs, providing support for further exploration of this dose level in clinical development.

Of note, LX4211 400 mg once daily produced greater reduction of A1C than 200 mg once daily despite similar amounts of UGE. The A1C numerical difference was relatively large, an absolute reduction of 0.92% (10.0 mmol/mol) from baseline versus 0.52% (3.3 mmol/mol), respectively, while the mean glucose/creatinine ratios at week 12 were similar at 48 and 45 g/g, for 400 mg once daily and 200 mg once daily dose groups, respectively, and despite significantly increased systemic exposure in the 400 mg group (Supplementary Fig. 2). Similarly, the 400 mg once daily dosage decreased FPG more than the 200 mg once daily. These improvements in glycemic control in the absence of corresponding increases in UGE are highly suggestive that part of the efficacy observed in the 400 mg once daily dose group is achieved through clinically meaningful SGLT1 inhibition in the GI tract. Indeed, GI SGLT1 inhibition is consistent with the results of prior studies of LX4211, in which significant reductions in PPG and elevations of GLP-1 and PYY have been observed (6,15–17). In patients with type 2 diabetes and healthy subjects, LX4211 has produced sustained reductions in PPG after an oral glucose challenge or meal, indicating intestinal SGLT1 inhibition.

The placebo-subtracted reduction in A1C of 0.83% obtained with LX4211 400 mg once daily after 3 months of treatment, to a final A1C of 7.1%, is encouraging; however, it is unclear whether it is significantly different from that of selective SGLT2 inhibitors. Dapagliflozin, empagliflozin, and canagliflozin produced placebo-subtracted reductions in A1C of 0.67, 0.70, and

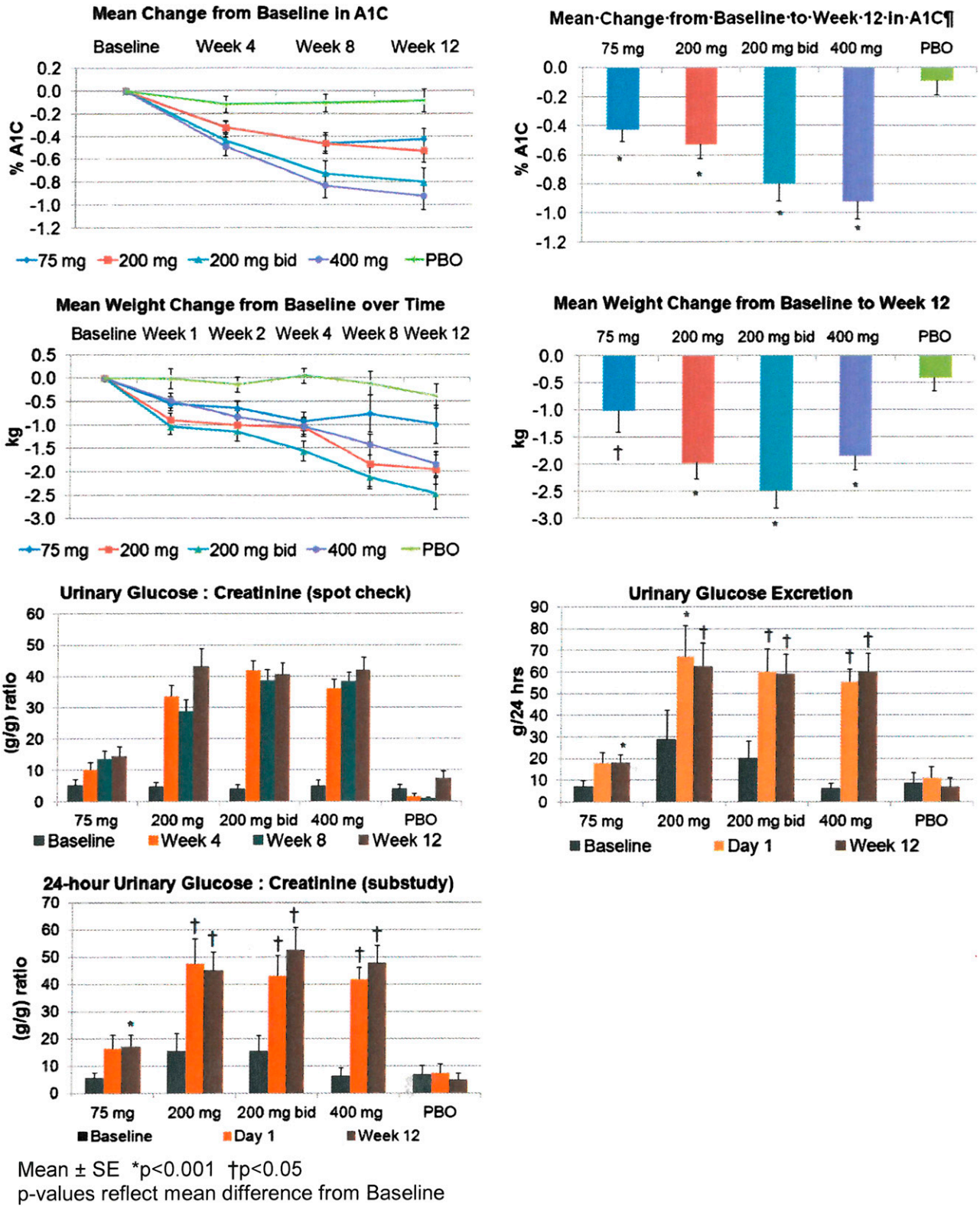

Figure 1—A1C, weight, and UGE changes. bid, twice daily; PBO, placebo.

0.72%, respectively, after 12 weeks at dose levels that were advanced into phase 3 clinical trials (22–24). Further clinical studies will be necessary to fully characterize the potential added effects of SGLT1 inhibition on the efficacy of LX4211 ideally versus active comparators such as selective SGLT2 inhibitors.

We hypothesize that dual inhibition of SGLT1 and SGLT2 may provide A1C reduction with less dependence on renal glucose excretion than SGLT2 inhibition alone, which may prove to be effective in type 2 diabetes with renal compromise. In the current study,

Table 2—Systolic and diastolic sitting BP, change from baseline to week 12

Study week/statistics	LX4211 75 mg qd (*N* = 59)	LX4211 200 mg qd (*N* = 60)	LX4211 200 mg bid (*N* = 60)	LX4211 400 mg qd (*N* = 60)	Placebo (*N* = 60)
Sitting systolic BP mm Hg change from baseline to week 12					
N	57	60	59	59	60
Mean (SD)	−0.1 (12.7)	−3.9 (12.1)	−4.5 (12.1)	−5.7 (12.4)	−0.3 (13.6)
P value [1]	0.942	0.017	0.007	<0.001	0.872
Least significant mean (SE)	0.5 (1.5)	−3.2 (1.5)	−5.4 (1.5)	−5.9 (1.5)	−0.5 (1.5)
Least significant mean difference from placebo (SE)	1.1 (2.2)	−2.7 (2.1)	−4.8 (2.1)	−5.4 (2.1)	—
95% CI for mean difference from placebo	(−3.2, 5.3)	(−6.9, 1.5)	(−9.0, −0.6)	(−9.6, −1.2)	—
P value vs. placebo	0.624	0.202	0.024	0.012	—
Sitting diastolic BP mm Hg change from baseline to week 12					
N	57	60	59	59	60
Mean (SD)	−0.6 (8.8)	−2.8 (7.9)	−2.2 (7.9)	−1.6 (8.9)	−0.5 (9.1)
P value [1]	0.598	0.007	0.035	0.164	0.697
Least significant mean (SE)	−0.2 (1.0)	−2.1 (1.0)	−2.8 (1.0)	−2.0 (1.0)	−0.7 (1.0)
Least significant mean difference from placebo (SE)	0.5 (1.4)	−1.4 (1.4)	−2.2 (1.4)	−1.3 (1.4)	—
95% CI for mean difference from placebo	(−2.4, 3.3)	(−4.2, 1.4)	(−5.0, 0.6)	(−4.1, 1.5)	—
P value vs. placebo	0.748	0.327	0.130	0.355	—

patients had normal renal function (serum creatinine <1.4 mg/dL for females, <1.5 mg/dL for males, and glomerular filtration rate >60 mL/min). A pilot clinical trial of LX4211 in the setting of renal impairment and type 1 diabetes has recently been completed (25).

In terms of safety, SGLT1 inhibition was previously believed to have the potential for glucose-galactose malabsorption and diarrhea or other GI symptoms based on individuals with loss of function mutations in SGLT1 (7,26,27). However, GI tolerance of carbohydrates appears possible even in patients with glucose-galactose malabsorption with homozygous mutations in SGLT1. Most of the 33 individuals in an Amish cohort with loss of function mutations in SGLT1 were reported to tolerate a normal carbohydrate-containing diet by the

Table 3—Treatment-emergent AEs reported in >3% of all LX4211-treated patients, regardless of causality, and AEs of special interest

System organ class	LX4211 75 mg once daily (*N* = 57)	LX4211 200 mg once daily (*N* = 60)	LX4211 200 mg twice daily (*N* = 60)	LX4211 400 mg once daily (*N* = 59)	Placebo (*N* = 60)	Total (*N* = 296)
Number of patients with at least one TEAE	38 (66.7)	36 (60.0)	37 (61.7)	34 (57.6)	40 (66.7)	185 (62.5)
Infections and infestations						
Upper respiratory tract infection	2 (3.5)	2 (3.3)	3 (5.0)	1 (1.7)	3 (5.0)	11 (3.7)
Nasopharyngitis	4 (7.0)	2 (3.3)	1 (1.7)	2 (3.4)	1 (1.7)	10 (3.4)
Sinusitis	3 (5.3)	3 (5.0)	0	1 (1.7)	1 (1.7)	8 (2.7)
GI disorders						
Diarrhea	2 (3.5)	6 (10.0)	4 (6.7)	5 (8.5)	4 (6.7)	21 (7.1)
Nausea	5 (8.8)	3 (5.0)	2 (3.3)	6 (10.2)	3 (5.0)	19 (6.4)
Constipation	1 (1.8)	5 (8.3)	1 (1.7)	1 (1.7)	4 (6.7)	12 (4.1)
Nervous system disorders						
Headache	6 (10.5)	6 (10.0)	2 (3.3)	3 (5.1)	1 (1.7)	18 (6.1)
AEs of special interest						
GU events*						
Vulvovaginal mycotic infection	0	1 (1.7)	1 (1.7)	1 (1.7)	0	3 (1.0)
Vaginal infection	0	1 (1.7)	0	1 (1.7)	0	2 (0.7)
Vaginitis bacterial	0	0	1 (1.7)	0	0	1 (0.3)
Vulvovaginal candidiasis	0	0	0	1 (1.7)	0	1 (0.3)
Vulvovaginitis	0	1 (1.7)	0	0	0	1 (0.3)
Urinary tract infection	1 (1.8)	1 (1.7)	1 (1.7)	1 (1.7)	1 (1.7)	4 (1.4)
GU events in female patients [*n* = female patients]	1 (4.0) [25]	3 (7.0) [43]	3 (9.7) [31]	3 (9.7) [31]	1 (2.9) [34]	11 (6.5) [164]
Hypoglycemia	0	0	0	0	0	0

Data are *n* (%) unless otherwise noted. *Each incidence of vaginal infection represents one patient each (*n* = 8).

age of 20 years (28). Overall, LX4211 produced no evidence of GI intolerance with a GI safety profile that was similar to placebo. It may be possible that greater SGLT1 inhibition with even higher doses of LX4211 may produce GI symptoms, but the results of this and other studies support the presence of a therapeutic window in which efficacy can be achieved with acceptable tolerability.

Glucosuria has been associated with urinary tract infections and fungal genital infections (4,29,30). In this study, there were only five urinary tract infections, one on placebo and one each in four of the LX4211 dose groups. There were three reports of vaginal yeast infection on LX4211 400 mg once daily and none on placebo. There were no reports of balanitis. There were no discontinuations due to any of these events. While these incidences appear relatively low, larger studies and longer follow-up will be necessary to fully characterize glucosuria and its potential effects on rates of GU infection.

Lipid changes were not significant in this study, but were not expected with the relatively small number of patients. The variability in triglycerides was too large to perform a reliable comparison of treatment groups. There were small, nonsignificant increases in HDL and LDL in all treatment groups, including placebo. Small increases in HDL and LDL have been reported with canagliflozin (30) and dapagliflozin (31) in phase 3 clinical studies.

BP changes with LX4211 treatment were of a magnitude comparable to approved antihypertensive agents (32), and they were obtained without hypotension in a normotensive population. Patients were instructed to not take their study medication (LX4211 or placebo) the morning of their last visit, so the week 12 BP assessments reflect drug trough level effects.

Significant weight loss was observed, and it was gradual over the 12 weeks, consistent with caloric loss, but further study is needed to quantify in terms of water or fat loss. SGLT2 inhibition with dapagliflozin has been associated with weight loss primarily through the loss of fat mass (4). DEXA will be helpful to characterize weight change in future studies.

The current study had several limitations. The duration of treatment was likely inadequate to capture the full glycemic efficacy of LX4211 and long-term weight reduction. A1C was reduced over time during the study and had not appeared to reach a plateau by week 12. Final assessments were performed at trough drug levels (12–24 h after last dose), which was appropriate for an examination of BP change (33), but perhaps not ideal for other parameters.

In summary, LX4211, a dual inhibitor of SGLT1 and SGLT2, produced beneficial effects in glycemic parameters, BP, and body weight with an overall incidence of AEs that was similar to placebo except for a small increase in genital infections. The results suggest the potential for a clinically relevant SGLT1 inhibition with lower reliance on glucosuria and a favorable therapeutic window. The potential for a dual-acting inhibition of SGLT1 and SGLT2 oral treatment appears feasible, and further studies are needed to better understand the impact of LX4211 in the management of type 2 diabetes.

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