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LX4211, a Dual SGLT1/SGLT2 Inhibitor, Improved Glycemic Control in Patients With Type 2 Diabetes in a Randomized, Placebo-Controlled Trial

B Zambrowicz[1], J Freiman[1], PM Brown[1], KS Frazier[1], A Turnage[1], J Bronner[1], D Ruff[2], M Shadoan[1], P Banks[1], F Mseeh[1], DB Rawlins[3], NC Goodwin[3], R Mabon[3], BA Harrison[3], A Wilson[1], A Sands[1] and DR Powell[1]

Thirty-six patients with type 2 diabetes mellitus (T2DM) were randomized 1:1:1 to receive a once-daily oral dose of placebo or 150 or 300 mg of the dual SGLT1/SGLT2 inhibitor LX4211 for 28 days. Relative to placebo, LX4211 enhanced urinary glucose excretion by inhibiting SGLT2-mediated renal glucose reabsorption; markedly and significantly improved multiple measures of glycemic control, including fasting plasma glucose, oral glucose tolerance, and HbA_{1c}; and significantly lowered serum triglycerides. LX4211 also mediated trends for lower weight, lower blood pressure, and higher glucagon-like peptide-1 levels. In a follow-up single-dose study in 12 patients with T2DM, LX4211 (300 mg) significantly increased glucagon-like peptide-1 and peptide YY levels relative to pretreatment values, probably by delaying SGLT1-mediated intestinal glucose absorption. In both studies, LX4211 was well tolerated without evidence of increased gastrointestinal side effects. These data support further study of LX4211-mediated dual SGLT1/SGLT2 inhibition as a novel mechanism of action in the treatment of T2DM.

INTRODUCTION

An estimated 24 million people in the United States have diabetes, and the prevalence is projected to increase to 44 million by 2034.[1] In patients with type 1 and type 2 diabetes mellitus (T2DM), improved glycemic control lowers risk for microvascular complications of renal failure and retinopathy and may also lower risk for macrovascular complications of nonfatal myocardial infarction and coronary heart disease.[2–7] Although metformin and other monotherapies improve glycemic control in patients with T2DM, hemoglobin A_{1c} (HbA_{1c}) levels tend to increase steadily, ultimately requiring additional therapy, which may include insulin.[8–11] Aggressive glycemic control with combination therapy often leads to side effects, most notably weight gain and severe hypoglycemia, which may be associated with increased incidence of cardiovascular (CV) events.[7,10] These concerns underscore the need to develop new agents that safely and effectively treat hyperglycemia without precipitating hypoglycemia in patients with diabetes.

It has been known for decades that inhibiting urinary glucose reabsorption improves glucose homeostasis.[12] Recently, highly selective inhibitors of sodium-glucose transporter-2 (SGLT2), the transporter primarily responsible for renal glucose reabsorption, have been shown to improve glycemic control in preclinical diabetes models and in patients with T2DM.[13–24] Inhibiting SGLT2 in the kidney provides many advantages: (i) glucose is cleared from the circulation without the need for insulin, thereby lowering the demands on pancreatic β-cells; (ii) glucose excretion decreases as blood glucose levels decrease, thereby limiting the risk of severe hypoglycemia; (iii) urinary glucose excretion (UGE) may lower blood pressure; and (iv) UGE may lead to weight loss. All these advantages were observed in recent studies of SGLT2 inhibitors.[14–24] Also, the novel mechanism through which SGLT2 inhibitors lower blood glucose should make them compatible with other glucose-lowering therapies, including insulin.[16]

SGLT1 is the major intestinal glucose transporter, contributing only 10% to renal glucose reabsorption. Patients lacking functional SGLT1 have severe gastrointestinal symptoms due to malabsorption of glucose and galactose.[25] Earlier SGLT2 inhibitors were developed to be highly selective for SGLT2 over SGLT1, primarily because of concerns about the potential for glucose malabsorption secondary to SGLT1 inhibition.[26]

[1]Lexicon Pharmaceuticals, Inc., The Woodlands, Texas, USA; [2]Icon Development Solutions, San Antonio, Texas, USA; [3]Lexicon Pharmaceuticals, Inc., Princeton, New Jersey, USA. Correspondence: DR Powell (dpowell@lexpharma.com)

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However, increased glucose delivery to the distal small intestine and colon after either Roux-en-Y bariatric surgery or ingestion of dietary-resistant starch can improve glucose tolerance in the absence of gastrointestinal symptoms. This effect is possibly mediated by the release of gastrointestinal peptides such as glucagon-like peptide-1 (GLP-1).[27–30] This suggests that an SGLT2 inhibitor that also delays intestinal glucose absorption by inhibiting SGLT1 could have a gastrointestinal safety profile similar to those of selective SGLT2 inhibitors yet offer improved glycemic control.

We have developed LX4211, an orally available L-xyloside[31] that is a potent inhibitor of both SGLT1 and SGLT2 *in vitro*. In the 28-day study presented here, we evaluated the safety and efficacy of LX4211 treatment in patients with T2DM, monitoring UGE and multiple measures of glycemic control. In a follow-up single-dose study that is also presented here, we evaluated the safety and efficacy of LX4211 with a focus on detecting increased levels of GLP-1 and peptide YY (PYY) as indicators of SGLT1 inhibition and delayed glucose absorption.

RESULTS

LX4211 structure and *in vitro* potency

The chemical structure of LX4211 is shown in **Figure 1a**. *In vitro*, LX4211 is a potent dual inhibitor of SGLT1 and SGLT2, with an inhibitory concentration (IC_{50}) of 36 nmol/l against human SGLT1 and 1.8 nmol/l against human SGLT2.

28-day study

The study was conducted at a single center and included 36 patients with T2DM aged 38–64 years. Screening, dosing, and follow-up took place from September to December 2009. The study patients were randomly assigned (1:1:1) to receive 150 or 300 mg of LX4211, or placebo, orally as a liquid formulation, once daily for 28 days. The treatment groups appeared balanced in terms of baseline demographics and disease characteristics (**Table 1**). All patients completed the study in their originally assigned group, except one subject in the placebo group, who discontinued on day 23 because of a family emergency but returned for end-of-study assessments.

Improvements in fasting plasma glucose (FPG) were significant for each of the two treatment groups on days 7, 14, 21, and 28 as compared with the placebo group (**Figure 1b**; **Supplementary Table S1** online). The improvement was rapid, with day 7 FPG reduced from baseline value by 30 and 43 mg/dl in the 150- and 300-mg dose groups, respectively, as compared with a 9 mg/dl increase in the placebo group. By day 28, FPG was reduced from baseline by 52 and 68 mg/dl in the 150- and 300-mg dose groups, respectively, as compared with a 12 mg/dl decrease in the placebo group. Mean homeostasis model assessment of insulin resistance values were also significantly lower on day 27 in both LX4211 groups as compared with placebo (**Supplementary Table S2** online).

By day 28, mean HbA_{1c} was significantly reduced relative to placebo in each of the two treatment groups (**Figure 1c**; **Supplementary Table S3** online). The HbA_{1c} levels were ≤7.0% in 50% of the patients who received LX4211 but in only 18% of patients in the placebo group (**Supplementary Table S4** online). Fructosamine levels were significantly decreased relative to placebo after 14 days in the 300-mg dose group alone, and after 21 and 28 days in both the 150-mg and 300-mg dose groups (**Supplementary Figure S1a** and **Supplementary Table S2** online).

Glucose tolerance, as measured by area under the curve (AUC) for glucose concentration from hour 0 to hour 4 of a standard oral glucose tolerance test (OGTT), was significantly improved relative to placebo in both LX4211 groups at all time points measured (**Figure 1d**; **Supplementary Table S5** online). AUC values were lower than those of placebo by 30% on day 2 in both dose groups and by 35 and 36% on day 13 in the 150-mg and 300-mg dose groups, respectively. By day 27, AUC values were 38 and 39% lower in the 150- and 300-mg dose groups, respectively, as compared with the placebo group. To determine whether the lower AUC values reflected decreased glucose excursions in addition to decreased FPG values, we corrected for differences in FPG at hour 0. We found that the glucose excursions above baseline FPG, which were not different between each of the LX4211 dose groups and the placebo group on day −2 (pretreatment), were significantly improved in both the 150-mg and 300-mg dose groups relative to placebo values on study days 2, 13, and 27; on day 27, glucose excursions were 46% lower in both the 150-mg and 300-mg dose groups as compared to the placebo group (**Figure 1e**; **Supplementary Table S6** online). LX4211 treatment also significantly lowered 2-h postprandial glucose (PPG) levels in each treatment group as compared with placebo values on days 1, 7, 21, and 28 (**Supplementary Figure S1b** and **Supplementary Table S2** online).

The 24-h UGE value was significantly increased in both treatment groups as compared with the placebo group on days 1, 14, and 28, and there was a significant increase in 24-h UGE with increasing LX4211 dose on days 1 and 14 (**Figure 1f**; **Supplementary Table S7** online). The net UGE increases in the 150- and 300-mg dose groups relative to the placebo group were 44 and 65 g/day, respectively, on day 1, and trended down over the treatment period to 37 and 48 g/day, respectively, on day 28. In the LX4211-treated groups, the amount of glucose excreted in the first 8 h was comparable to the amount of glucose excreted in the period spanning 8–24 h (**Supplementary Table S8** online).

Mean serum triglyceride (TG) levels in both LX4211-treated groups decreased throughout the study and fell to within the normal range (<151 mg/dl) by day 14. Both doses of LX4211 were associated with statistically significant TG reductions as compared with placebo (**Supplementary Figure S2** and **Supplementary Table S9** online). After 28 days of dosing, there were also trends toward greater reductions in weight and blood pressure in the LX4211-treated groups relative to the placebo group, but these did not attain statistical significance (**Table 2**).

The frequency rates of treatment-emergent adverse events (AEs) were similar among the three groups (**Table 3**). There were no reports of treatment-emergent urinary tract infections, genital infections, episodes of hypoglycemia, or serious AEs, and no CV events or clinically significant electrocardiogram findings were observed.

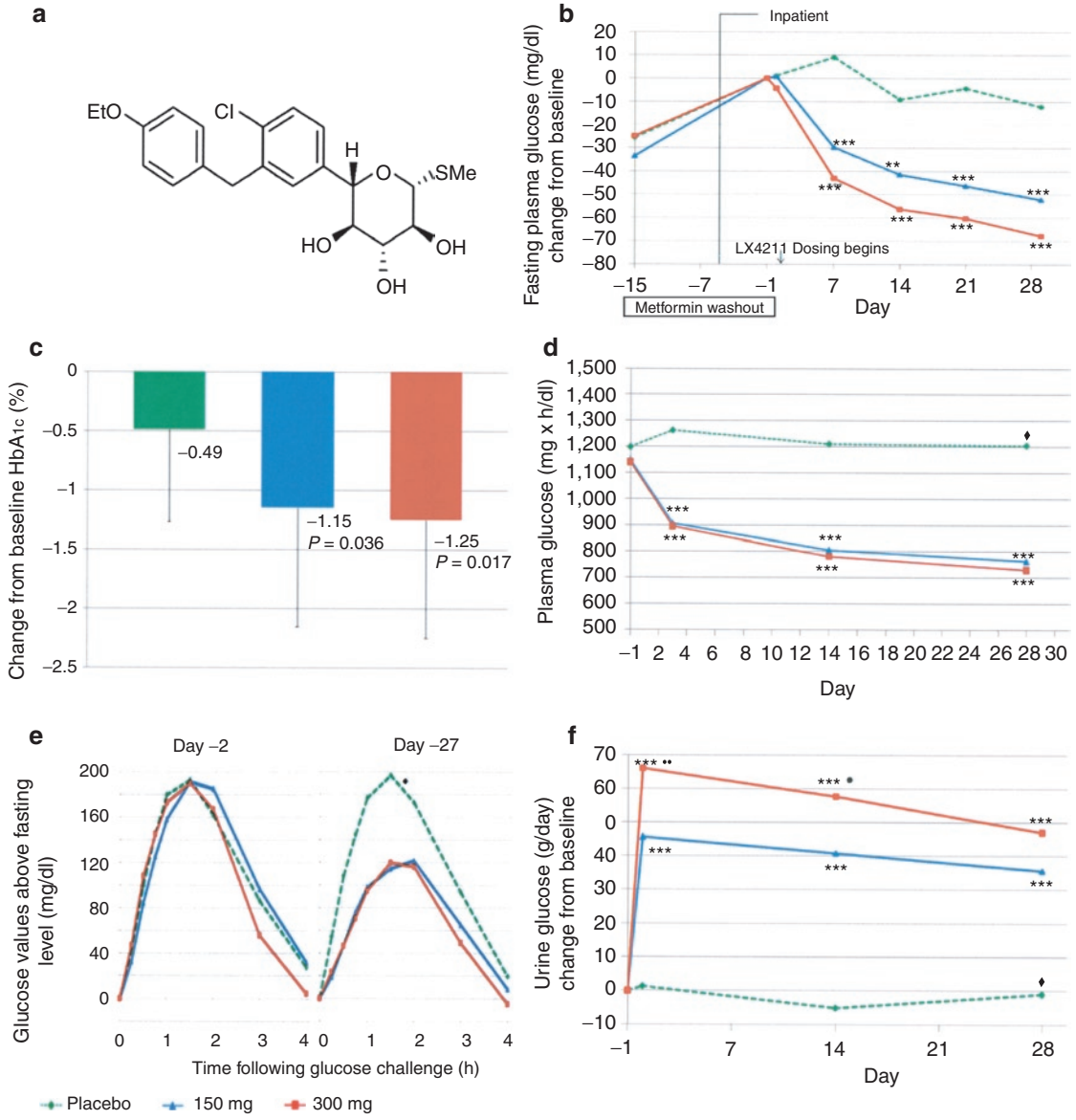

Figure 1 Effect of LX4211 on glycemic parameters and UGE. (**a**) Chemical structure of LX4211, (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol. (**b**) FPG. This schematic representation of the study design depicts mean changes in FPG levels from baseline (day −1) values throughout the study. (**c**) HbA_{1c}. Change in HbA_{1c} levels after 28 days of treatment with LX4211 or placebo. (**d**) OGTT glucose AUCs. AUCs for glucose obtained from OGTTs performed on days −2, 2, 13, and 27. (**e**) OGTT glucose excursions above fasting (hour 0) values. OGTT glucose excursions were plotted after correcting for differences in FPG by adjusting hour 0 glucose values to 0 mg/dl. Left, data from day −2; right, data from day 27. (**f**) UGE. UGE was estimated by measuring the total amount of glucose in 24-h urine samples collected on days −1, 1, 14, and 28; the data shown represent the mean change from baseline (day −1) values. The color key identifying each group in **b**–**f** is at the bottom of the figure. For **d** and **e**, AUC values for each LX4211 treatment group on each day were compared with the AUC values of the placebo group on that day. For **b**,**d**,**f**: different from placebo, ***$P < 0.001$, **$P < 0.01$; different from 150 mg dose group, ••$P < 0.01$, •$P < 0.05$. ♦, $n = 11$ for the placebo group on days 27 and 28. For **e**, AUC values on day 27 were significantly lower for each LX4211 treatment group as compared with placebo, $P < 0.001$. Error bars in **c** represent 1 SD. All the data are presented as arithmetic means except in **c**, in which the data are presented as differences in least squares means. AUC, area under the curve for glucose concentration; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; OGTT, oral glucose tolerance test; UGE, urinary glucose excretion.

On day 1, 24-h urine volume showed a slight but nonsignificant increase in the LX4211-treated groups relative to the placebo group. This was accompanied by modest increases in sodium and chloride excretion relative to placebo, which achieved statistical significance in the group receiving 300 mg (**Supplementary Figure S3** and **Supplementary Table S10** online). By days 14 and 28, all these parameter values in the LX4211 treatment groups were at or below baseline and placebo values. Notably, at no time during the study was urinary calcium excretion increased in the LX4211-treated groups (**Supplementary Figure S3** online). Other clinical laboratory values remained unchanged throughout the study, except blood urea nitrogen and magnesium, which showed slight but significant increases that were within the normal range and rapidly decreased toward placebo levels after treatment ended (**Table 2**).

Table 1 Patient demographics and disease characteristics at baseline in the 28-day study

Parameter	LX4211, 150 mg ($n = 12$)	LX4211, 300 mg ($n = 12$)	Placebo ($n = 12$)
Age (years)			
Mean (SD)	53 (6)	52 (8)	55 (7)
Minimum–maximum	43–61	38–62	40–64
Sex			
Female	6 (50.0%)	4 (33.3%)	6 (50.0%)
Male	6 (50.0%)	8 (66.7%)	6 (50.0%)
Race			
American or Alaskan Native	0 (0%)	2 (16.7%)	0 (0%)
Black or African American	2 (16.7%)	0 (0%)	0 (0%)
White or Caucasian	10 (83.3%)	10 (83.3%)	12 (100.0%)
Height (cm)			
Mean (SD)	166 (8)	170 (10)	164 (8)
Weight (kg)			
Mean (SD)	86 (12)	99 (15)	82 (8)
BMI (kg/m^2)			
Mean (SD)	32 (4)	35 (3)	31 (2)
C-peptide (ng/ml)			
Mean (SD)	2.6 (0.8)	3.4 (0.9)	2.6 (1.0)
Fructosamine (μmol/l)			
Mean (SD)	323 (44)	311 (49)	343 (35)
Fasting plasma glucose (mg/dl)			
Mean (SD)	175 (42)	188 (54)	192 (26)
HbA_{1c} (%)			
Mean (SD)	8.2 (0.8)	8.5 (1.0)	8.2 (0.8)
Fasting plasma insulin (μU/ml)[a]			
Mean (SD)	6.1 (3.9)	6.0 (4.6)	7.8 (5.3)
Triglycerides (mg/dl)			
Mean (SD)	190 (103)	175 (78)	188 (79)
24-h urinary glucose excretion (g/day)			
Mean (SD)	17 (23)	14 (19)	17 (18)

BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}.
[a]Day −2.

Pharmacokinetic parameters and mean plasma concentration–time profiles are summarized in Table 4. For each LX4211 dose, plasma concentrations were detected within 15 min, increased with increasing dose, and decreased in a biphasic pattern. The maximum plasma LX4211 concentration (C_{max}) appeared at 0.5–2.0 h after dosing, and ranged from 82.5–115 ng/ml and 230–307 ng/ml in the 150-mg and 300-mg dose groups, respectively. The increases in C_{max} and AUC for plasma concentration over time curve were slightly more than dose-proportional. The median time to reach C_{max} (i.e., t_{max}) was similar on days 14 and 28 for the two dose groups (1.00–1.50 h), with individual values ranging from 0.48 to 2.02 h. Mean plasma LX4211 concentrations at the end of the dosage interval (C_{min}) were similar on days 7, 14, 21, and 28, and all were higher than values on day 1, in both the 150- and 300-mg dose groups (Table 4; **Supplementary Table S11** online). C_{max} and AUC_{0-tau} values, as determined on days 1, 14, and 28, were similar on days 14 and 28, and each was higher than values on day 1 in both dose groups. Collectively, these data support the view that steady state was reached by day 14, and possibly even by day 7, based on the C_{min} value. Apparent total clearance of LX4211 from plasma after oral administration (CL/F) and CL/F at steady state (CL/F_{ss}) were similar across dose groups. After multiple doses, CL/F_{ss} was lower on days 14 and 28 than the value observed after a single dose. CL/F on day 1 and CL/F_{ss} on days 14 and 28 were higher than the sum of hepatic blood flow and renal blood flow, suggesting the possibility of unabsorbed LX4211 in the gastrointestinal tract. Mean ± SD values for $t_{1/2}$ (half-life) were 20.7 ± 13.7 and 13.5 ± 5.3 h in the 150-mg and 300-mg dose groups, respectively.

The dual inhibition of SGLT1 and SGLT2 by LX4211 *in vitro* suggested that LX4211 might work not only by increasing UGE but also by triggering intestinal release of GLP-1. We performed a *post hoc* analysis of GLP-1 levels in samples collected on days 1 and 28. On day 1, total GLP-1 levels showed a nonsignificant increase after meals in the LX4211-treated groups; similar results were noted on day 28 (**Supplementary Figure S4** and **Supplementary Table S12** online). This led us to carry out a prospective test to investigate whether LX4211 increased the levels of gastrointestinal peptides. This was performed as part of a single-dose study that compared the effects of liquid and solid oral formulations of LX4211.

Single-dose study assessing GLP-1 and PYY response to liquid and tablet oral formulations of LX4211

The study was conducted in 12 LX4211-naive inpatients with T2DM, 44–65 years of age. Screening, dosing, and follow-up took place from 7 October 2010 through 31 October 2010. The study had a three-way crossover design (Figure 2a), with patients randomly assigned to one of three treatment-sequence groups; at different times, each patient received 300 mg LX4211 administered as a single dose of two 150-mg tablets, six 50-mg tablets, or a 300-mg liquid formulation (300 ml). The baseline demographics and disease characteristics of these patients are shown in **Supplementary Table S13** online.

As compared with pretreatment day (day −1) values, a single 300-mg dose of any of the LX4211 formulations significantly increased UGE over the next 24 h (Figure 2b, **Supplementary Table S14** online), significantly increased total GLP-1 and total PYY between 0 and 13 h (which encompassed the three scheduled meals) (Figure 2c,e, **Supplementary Table S15** online), and significantly decreased plasma glucose and insulin between 0 and 13 h (**Supplementary Figure S5** and **Supplementary Table S15** online). Both tablet formulations were also associated with an increase in active GLP-1 between 0 and 13 h, whereas glucagon values were not altered (Figure 2d,

Table 2 Efficacy and safety parameters in the 28-day study

Variable[a]	Treatment	Day −1 (baseline)	Day 28 (end of treatment)	Day 36 (1-week post-treatment)
Body weight (kg)	150 mg	86 ± 12	83 ± 11	85 ± 10
	300 mg	99 ± 15	95 ± 14	98 ± 15
	Placebo	82 ± 8	80 ± 8	81 ± 7
Systolic BP (mm Hg, seated)	150 mg	124 ± 17	114 ± 13	ND
	300 mg	121 ± 13	108 ± 15	ND
	Placebo	118 ± 8	114 ± 8	ND
Diastolic BP (mm Hg, seated)	150 mg	80 ± 9	73 ± 8	ND
	300 mg	77 ± 10	72 ± 11	ND
	Placebo	77 ± 10	77 ± 8	ND
Hematocrit (%)	150 mg	41 ± 2	40 ± 2	37 ± 3
	300 mg	43 ± 3	43 ± 3	40 ± 3
	Placebo	43 ± 4	40 ± 6	39 ± 5
Serum sodium (mEq/l)	150 mg	136 ± 3	136 ± 4	137 ± 2
	300 mg	136 ± 1	138 ± 2	138 ± 2
	Placebo	135 ± 2	135 ± 3	137 ± 3
Serum potassium (mEq/l)	150 mg	4.4 ± 0.3	4.4 ± 0.5	4.2 ± 0.3
	300 mg	4.4 ± 0.3	4.4 ± 0.2	4.2 ± 0.3
	Placebo	4.5 ± 0.4	4.5 ± 0.2	4.4 ± 0.4
Serum chloride (mEq/l)	150 mg	102 ± 2	103 ± 3	104 ± 2
	300 mg	102 ± 4	105 ± 2	105 ± 3
	Placebo	101 ± 2	102 ± 2	103 ± 3
Serum calcium (mg/l)	150 mg	9.2 ± 0.2	9.1 ± 0.4	8.9 ± 0.3
	300 mg	8.9 ± 0.4	8.9 ± 0.4	8.9 ± 0.4
	Placebo	9.1 ± 0.3	9.1 ± 0.2	9.1 ± 0.4
Serum magnesium (mg/l)	150 mg	1.9 ± 0.1	2.1 ± 0.1**	1.8 ± 0.1
	300 mg	2.0 ± 0.2	2.2 ± 0.1**	2.0 ± 0.2
	Placebo	2.0 ± 0.2	2.0 ± 0.2	1.9 ± 0.1
Serum LDL (mg/dl, calculated)	150 mg	100 ± 30	94 ± 27	93 ± 23
	300 mg	106 ± 27	91 ± 29	87 ± 25
	Placebo	129 ± 37	107 ± 28	111 ± 27
Serum HDL (mg/dl)	150 mg	37 ± 6	36 ± 6	41 ± 6
	300 mg	36 ± 3	37 ± 6	42 ± 5
	Placebo	42 ± 6	43 ± 7	47 ± 8
Serum BUN (mg/dl)	150 mg	17 ± 6	20 ± 7**	14 ± 3
	300 mg	17 ± 3	19 ± 3*	16 ± 4
	Placebo	19 ± 3	18 ± 4	15 ± 3
Serum creatinine (mg/dl)	150 mg	0.78 ± 0.19	0.84 ± 0.20	0.78 ± 0.19
	300 mg	0.83 ± 0.09	0.91 ± 0.09	0.87 ± 0.12
	Placebo	0.80 ± 0.13	0.86 ± 0.08	0.79 ± 0.12
eGFR (ml/min/1.73 m^2)	150 mg	129 ± 28	114 ± 25	ND
	300 mg	139 ± 36	124 ± 35	ND
	Placebo	114 ± 18	103 ± 11	ND
Urine potassium (mEq/day)	150 mg	83.3 ± 22.7	81.1 ± 25.3	ND
	300 mg	80.1 ± 25.6	78.1 ± 26.8	ND
	Placebo	86.5 ± 18.0	86.9 ± 22.1	ND
Urine magnesium (mg/day)	150 mg	143 ± 41	126 ± 46	ND
	300 mg	158 ± 30	137 ± 47	ND
	Placebo	140 ± 43	124 ± 39	ND
Urine creatinine (g/day)	150 mg	1.75 ± 0.56	1.56 ± 0.56	ND
	300 mg	1.91 ± 0.45	1.66 ± 0.54	ND
	Placebo	1.71 ± 0.37	1.69 ± 0.36	ND
Urine protein (mg/day)	150 mg	219 ± 192	227 ± 236	ND
	300 mg	213 ± 192	198 ± 94	ND
	Placebo	129 ± 72	146 ± 51	ND
Urine β2-microglobulin (μg/l)	150 mg	37 ± 29	24 ± 18	ND
	300 mg	34 ± 29	45 ± 39	ND
	Placebo	36 ± 26	28 ± 41	ND

BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ND, not determined.

[a]All results presented as arithmetic mean ± SD. *$P < 0.05$, **$P < 0.01$, change from baseline value different from placebo.

Supplementary Table S15 online). Because the no-treatment control was not concurrently implemented across treatment periods, we tested for evidence of a period effect to ensure that any inference based on comparisons with day −1 values was valid. The levels of GLP-1, PYY, and insulin were not associated with a significant period effect, suggesting that results based on within-treatment comparisons with day −1 values were informative and that LX4211 might have played a role in the changes. By contrast, a significant period effect was found for glucose ($P < 0.05$), suggesting that the changes relative to day −1 may be only partially explained by LX4211 treatment, because they were confounded with time. No significant sequence effect was observed in the analysis for any of these parameters.

The occurrence of treatment-emergent AEs was reported at similar rates among the three groups (**Supplementary Table S16** online). There were no serious AEs, or withdrawals attributable to AEs during this study. Most of the AEs were mild in intensity. There were no episodes of hypoglycemia and no clinically significant changes in other laboratory values or vital signs.

The pharmacokinetic parameters derived for plasma LX4211 are summarized in **Table 5**. The absorption rate for the LX4211 liquid formulation was approximately threefold faster than for the tablets, with the median T_{max} being 3.00 h for each tablet treatment group and 0.875 h for the liquid treatment group (**Figure 2f**). Also, the mean C_{max} was 2- to 2.5-fold lower for the tablet treatments than for the liquid formulation. Although the AUC values associated with each tablet treatment group were similar, both were lower than that of the liquid formulation; this finding suggests that the tablet formulation has lower bioavailability. The mean ± SD values for $t_{1/2}$ were 13.2 ± 2.8, 19.8 ± 8.8, and 17.9 ± 9.0 h for the 2 × 150-mg tablets, 6 × 50-mg tablets, and liquid formulation, respectively, consistent with once-daily dosing of LX4211.

Table 3 Treatment-emergent adverse events (TEAEs) reported by >1 patient in the 28-day study

Preferred term	LX4211, 150 mg (*n* = 12)	LX4211, 300 mg (*n* = 12)	Placebo (*n* = 12)
	Number and percentage (%) of patients		
Number of patients with at least one TEAE	9 (75.0%)	8 (66.7%)	8 (66.7%)
Gastrointestinal disorders			
Abdominal pain	1 (8.3%)	1 (8.3%)	2 (16.7%)
Constipation	3 (25.0%)	2 (16.7%)	2 (16.7%)
Diarrhea	1 (8.3%)	1 (8.3%)	0 (0.0%)
Flatulence	1 (8.3%)	1 (8.3%)	0 (0.0%)
Nausea	2 (16.7%)	1 (8.3%)	2 (16.7%)
Infections and infestations			
Upper respiratory tract infection	1 (8.3%)	1 (8.3%)	0 (0.0%)
Nervous system disorder	5 (41.7%)	1 (8.3%)	3 (25.0%)
Dizziness	3 (25.0%)	0 (0.0%)	2 (16.7%)
Headache	5 (41.7%)	1 (8.3%)	2 (16.7%)
Renal and urinary disorders			
Pyuria	1 (8.3%)	1 (8.3%)	0 (0.0%)

DISCUSSION

LX4211 treatment rapidly improved multiple measures of glycemic control in patients with T2DM. After 28 days, the decreases in FPG from baseline were 39 and 55 mg/dl in the 150- and 300-mg LX4211 dose groups, respectively, after correcting for changes in placebo values. This magnitude of improvement in FPG, and the fact that it was largely achieved by day 7, is entirely consistent with decreases from baseline HbA_{1c} values of 0.76 and 0.66 on day 28 in the 300- and 150-mg dose groups, respectively, after correcting for changes in placebo values.[32] In addition, the improvement in glucose tolerance observed with LX4211 treatment suggests that LX4211 might lower HbA_{1c} levels not only by decreasing FPG but also by decreasing PPG excursions. The LX4211-mediated decrease in HbA_{1c} after 4 weeks in our inpatient study was comparable to decreases in HbA_{1c} after 12 weeks of treatment with dapagliflozin, canagliflozin, or empagliflozin in an outpatient setting.[14–18,24] This degree of HbA_{1c} reduction suggests that LX4211 merits further study in a 12-week outpatient trial.

LX4211 administered once daily resulted in an immediate, dose-dependent increase in UGE which was spread throughout the day. This increase in daily UGE became less pronounced by the end of the study, probably because of improved glycemic control in LX4211-treated patients. The loss of glucose calories in urine during LX4211 treatment contributed to the additional weight lost by these patients but cannot account for the entire placebo-corrected weight loss. LX4211 treatment was associated with (i) increases in the excretion of sodium and chloride in urine as well as increases in the volume of urine on day 1, returning to baseline levels by day 14, and (ii) a 1- to 2-mg/dl increase in serum blood urea nitrogen on day 28, which reversed after treatment ended. These findings are consistent with a glucose-mediated diuresis in LX4211-treated patients. This early diuretic effect could explain some of the weight loss and also some of the trend toward decreased blood pressure. Dapagliflozin treatment also lowers weight and blood pressure, in association with modest increases in urine volume and serum blood urea nitrogen,[15–17] suggesting that the osmotic diuresis induced by SGLT2 inhibitors is an on-target mechanism that contributes to lowering of weight and blood pressure.

Partial inhibition of intestinal SGLT1 by LX4211 may contribute to the improvement in glycemic control. This is consistent with the following: (i) human SGLT1 is potently inhibited *in vitro* by LX4211 (IC_{50} = 36 nmol/l); (ii) SGLT inhibitors covalently attached to nonabsorbable polymers remain in the rat gastrointestinal tract after oral delivery, where they inhibit intestinal SGLT1 and improve glycemic control by lowering glucose excursions during OGTTs; and (iii) our pharmacokinetic data that suggest limited absorption of LX4211 from the gastrointestinal tract.[33,34] Partial inhibition of intestinal SGLT1 may improve glycemic control through a physiologic mechanism similar to the one thought to contribute to improved control after Roux-en-Y bariatric surgery or ingestion of dietary-resistant starch, namely, increased glucose delivery to the distal small intestine and colon. When Roux-en-Y surgery or ingestion of dietary-resistant starch increases glucose delivery to the distal gut, glucose tolerance improves in association with, and possibly mediated by, increased levels of GLP-1.[27–30] PYY levels also rise, consistent with increased production of both PYY and GLP-1 by intestinal L cells in response to glucose and/or short-chain fatty acid metabolites of glucose.[27,29,35–38] The release of GLP-1 and PYY from L cells, their normal site of release in the gastrointestinal tract, may enhance their beneficial effect as compared with systemic delivery through parenteral administration or systemic accumulation of GLP-1 induced by dipeptidyl peptidase-4 inhibitors. This suggestion is based on the expression of GLP-1 and PYY receptors on afferent vagal nerves that innervate the gastrointestinal tract, as well as on animal studies demonstrating that GLP-1- and PYY-mediated inhibition of food intake, GLP-1–mediated increased glucose disposal, and GLP-1–mediated delayed gastric emptying all require direct signaling to the brainstem via these vagal circuits for maximal effect.[39–44] We therefore hypothesize that partial inhibition of intestinal SGLT1 by LX4211 results in delayed glucose uptake, which triggers the release of GLP-1 and PYY by L cells, and that the increased levels of active GLP-1 may contribute to the improved glycemic control noted in LX4211-treated patients.

Concerns regarding the tolerability of pharmacologic SGLT1 inhibition are based on historical observations of gastrointestinal side effects in individuals receiving oral doses of the nonselective SGLT inhibitor phlorizin and in patients with glucose/galactose malabsorption (OMIM #606824) due to lack of functional SGLT1. Also, theoretical safety concerns have been based on SGLT1 expression in the heart.[25,45] Phlorizin,

Table 4 Pharmacokinetic parameters after single and multiple doses of LX4211 in the 28-day study

Day	Dose	Statistic	C_{max}	t_{max}[a]	$AUC_{0-\infty}$	AUC_{0-tau}	$t_{1/2}$[b]	C_{min}	CL/F[c]
	(mg)		(ng/ml)	(h)	(ng × h/ml)	(ng × h/ml)	(h)	(ng/ml)	(l/h)
1		*n*	12	12	5	12	ND	ND	5
	150	Mean	82.5	1.00	417	403	ND	ND	395
		SD	36.4	0.48–1.50	145	188	ND	ND	136
		n	12	12	6	11	ND	ND	6
	300	Mean	230	1.00	1,061	1,082	ND	ND	350
		SD	99.4	0.75–1.50	665	637	ND	ND	138
14		*n*	12	12	ND	12	ND	12	12
	150	Mean	113	1.50	ND	732	ND	14.7	241
		SD	43.3	0.75–1.50	ND	322	ND	8.78	93.9
		n	12	12	ND	12	ND	12	12
	300	Mean	291	1.00	ND	1,752	ND	33.6	228
		SD	123	0.75–1.52	ND	1,009	ND	20.3	131
28		*n*	12	12	ND	12	9	12	12
	150	Mean	115	1.25	ND	833	20.7	16.7	228
		SD	77.5	0.75–2.02	ND	486	13.7	15.3	93.2
		n	12	12	ND	12	8	12	12
	300	Mean	307	1.00	ND	1,974	13.5	36.1	202
		SD	105	0.50–1.0	ND	1,303	5.30	24.7	114

$AUC_{0-\infty}$, AUC for plasma concentration from time 0 to infinity; AUC_{0-tau}, AUC for plasma concentration from time 0 to the end of the dosing period; CL/F, apparent clearance; CL/F_{ss}, CL/F at steady state; C_{max}, maximum plasma LX4211 concentration; C_{min}, mean plasma LX4211 concentrations at the end of the dosage interval; F, bioavailability; ND, not determined; t_{max}, median time to reach C_{max}; $t_{1/2}$, half-life.

[a]t_{max} is presented as median (minimum–maximum). [b]For $t_{½}$, the terminal elimination phase could not be sufficiently resolved for all individuals; only data for which the terminal phase could be accurately calculated are presented. [c]CL/F is CL/F_{ss} on days 14 and 28.

the earliest SGLT inhibitor tested in humans, induces nausea when taken orally at high doses.[46] However, phlorizin is rapidly converted to phloretin in the small intestine.[47,48] Phloretin inhibits multiple proteins, including the facilitative glucose transporters, and can uncouple mitochondrial oxidative phosphorylation. However, it does not inhibit SGLT1, suggesting that phlorizin-induced nausea may well result from inhibition of intestinal proteins other than SGLT1.[48–51] Patients with glucose/galactose malabsorption cannot absorb glucose in the gastrointestinal tract, and as little as 6 g of glucose taken orally can trigger diarrhea and other gastrointestinal side effects. This inability to absorb glucose also results in flat blood glucose curves during OGTTs.[25,52] We did not observe an increase in the frequency of gastrointestinal side effects in patients treated with LX4211 relative to placebo even after they were challenged with 75 g of glucose during OGTTs. The absence of more frequent gastrointestinal side effects, the presence of decreased but not absent blood glucose excursions during OGTTs, and the elevated GLP-1 and PYY levels noted during LX4211 treatment are consistent with partial inhibition of SGLT1, sufficient to allow glucose to reach the distal small intestine and colon but insufficient to completely prevent glucose absorption. Finally, the risk of CV toxicity seems remote. Patients with glucose–galactose malabsorption are not reported to be at increased risk for CV problems despite complete absence of functional SGLT1.[52] Also, keeping in mind that LX4211 inhibits SGLT1 with an IC_{50} of 36 nmol/l, systemic LX4211 levels achieved with the tablet forms do not appear high enough to significantly inhibit SGLT1 in the heart, kidney, or other organs.

LX4211 was safe and well tolerated at the doses and schedule employed. There were no treatment-emergent urinary tract infections, genital infections, CV events, or episodes of hypoglycemia, and laboratory data provided no evidence of renal toxicity. Importantly, gastrointestinal AEs were mild and equally divided among the LX4211 and placebo groups. Serum magnesium rose slightly with LX4211 treatment but remained within the normal range, as was observed with dapagliflozin,[15] and urinary calcium excretion did not increase in LX4211-treated patients.

The significantly decreased TG levels observed in T2DM patients receiving LX4211 were not observed with dapagliflozin treatment[15,17,18] but have been reported for treatment with GLP-1 analogs; in addition, sitagliptin may also lower TGs.[53,54] This suggests that TG lowering, if confirmed in future studies, may be related to LX4211-mediated increases in GLP-1. Because T2DM is associated with an increased risk for CV events, it is crucial that new compounds that improve glycemic control in patients with T2DM do not further increase CV risk.[4–6,55] The possibility that LX4211 may lower body weight, blood pressure, and TGs, all of which are associated

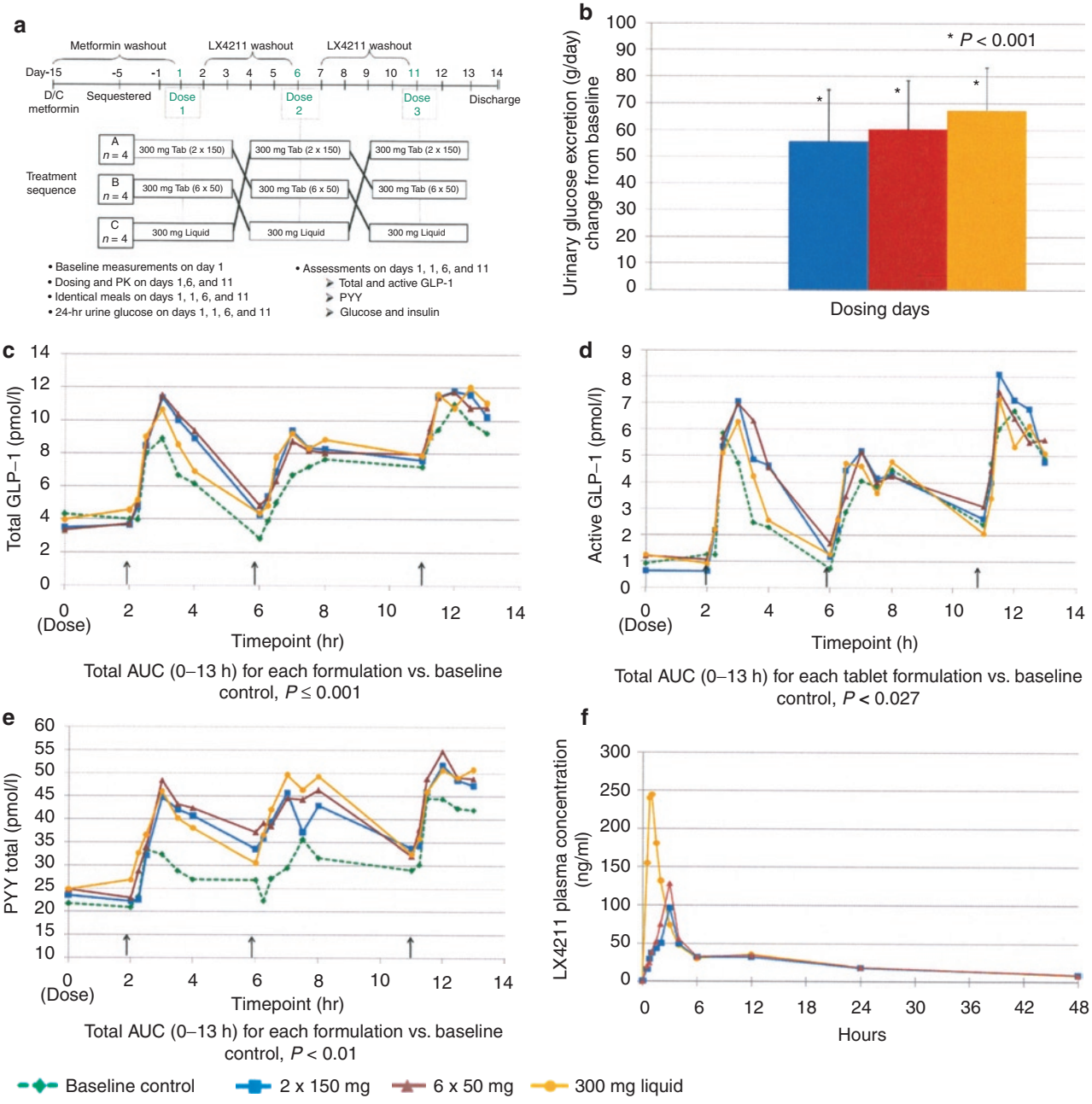

Figure 2 Effects of single doses of liquid or solid forms of oral LX4211 on UGE and on circulating levels of GLP-1, PYY, and LX4211. (**a**) Study design. This schematic representation depicts the treatment sequence; each of three groups of patients ($n = 4$ per group) received each of three LX4211 formulations on days 1, 6, and 11. Metformin was washed out before day 1, and LX4211 formulations administered on days 1 and 6 were washed out over the 5 days following each of the doses. The levels of UGE, GLP-1, PYY, and LX4211 measured on the day when the LX4211 formulation was administered to 12 patients with type 2 diabetes mellitus (T2DM) were compared with those on day −1 (baseline control levels) measured in the same 12 patients. (**b**) UGE. UGE was estimated by measuring the total amount of glucose present in 24-h urine samples collected at baseline (day −1) and on the days when each LX4211 formulation was administered; the data shown represent mean changes from baseline values. (**c**–**e**) Circulating GLP-1 and PYY. These were measured at the same time points on day −1 and on the days when each LX4211 formulation was administered. In **c**–**e**, arrows show the time points at which meals were provided, and *P* values are presented at the bottom of each of these panels. (**c**) Total GLP-1. (**d**) Active GLP-1. (**e**) Total PYY. (**f**) Time course of plasma LX4211 levels after oral administration of liquid or tablet LX4211 forms. The color key identifying each group in **b**–**f** is at the bottom of the figure. Error bars in **b** represent 1 SD. All data are presented as arithmetic means. AUC, area under the curve; D/C, discontinue; GLP-1, glucagon-like peptide-1; PK, pharmacokinetic analysis; PYY, peptide YY; UGE, urinary glucose excretion.

with decrease in CV risk,[56] suggests that LX4211 is unlikely to increase, and may indeed decrease, CV risk in the T2DM population.

These studies demonstrate that a 28-day regimen of once-daily oral LX4211, a dual SGLT1/SGLT2 inhibitor, was safe and well tolerated in T2DM patients. LX4211 significantly improved several measures of glycemic control in these individuals, accompanied by increases in the circulating levels of GLP-1 and PYY, decreases in TG levels, and trends toward lower weight and blood pressure. The major limitations of

Table 5 Pharmacokinetic parameters of LX4211 liquid and tablet forms, single-dose study

TRT	Statistic	C_{max} (ng/ml)	t_{max} (h)	AUC_{0-last} (ng × h/ml)	AUC_{0-24} (ng × h/ml)	$AUC_{0-\infty}$ (ng × h/ml)	$t_{1/2}$ (h)	CL/F (l/h)
Tablets (2 × 150 mg)	*n*	11	11	11	11	8	8	8
	Mean	105	3.00	1,066	762	1,104	13.2	340
	SD	52.4	1.00–3.00	622	361	567	2.76	167
Tablets (6 × 50 mg)	*n*	12	12	12	12	12	12	12
	Mean	135	3.00	1,166	855	1,471	19.8	275
	SD	106	0.50–3.00	639	445	940	8.83	148
Liquid	*n*	12	12	12	12	12	12	12
	Mean	276	0.875	1,385	1,078	1,680	17.9	239
	SD	160	0.50–1.50	729	512	1,193	9.00	113

AUC_{0-last}, AUC for plamsa concentration from time 0 to the last time point of measurable concentration; AUC_{0-24}, AUC for plasma concentration from time 0 to 24 h; $AUC_{0-\infty}$, AUC for plasma concentration from time 0 to infinity; CL/F, apparent clearance; C_{max}, maximum plasma LX4211 concentration; TRT, treatment; t_{max}, median time to reach C_{max}; $t_{1/2}$, half-life.

these initial studies of LX4211 in patients with T2DM were the short study duration, the inpatient setting, and the small number of patients enrolled. Nevertheless, the results clearly indicate the need for further studies of LX4211 in a larger sample size of patients with diabetes so as to evaluate the effects of long-term dual SGLT1 and SGLT2 inhibition on safety, metabolic parameters, and glycemic control.

METHODS

These studies were conducted at a single center (ICON Development Solution Phase I Center, San Antonio, TX) and carried out in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review board with jurisdiction over that site, and all patients gave written informed consent before being enrolled in the study.

28-day study

Study design. The study was a randomized, placebo-controlled, double-blind study conducted at a single center and included both male and female patients, 38–64 years of age and with an established diagnosis of T2DM, either naive to therapy or not well controlled on metformin monotherapy. The inclusion criteria at screening were FPG ≤240 mg/dl, HbA_{1c} 7–11%, C-peptide ≥1 ng/ml, and body mass index <42 kg/m^2. The patients were screened for adequate renal function and excluded from the study if the estimated glomerular filtration rate was <80 ml/min/1.73 m^2. (ref. 57) A complete list of inclusion and exclusion criteria is provided in the **Supplementary Materials and Methods** online. The study was registered with ClinicalTrials.gov (NCT00962065).

Metformin washout, which included daily glucometer assessments and instructions on dietary guidelines and restrictions, was performed over a 14-day period starting on day −15. Patients were instructed to return to the clinic if their FPG was >280 mg/dl on 2 consecutive days; they were to be discontinued from the study if laboratory tests confirmed an FPG >280 mg/dl.

All patients who successfully completed metformin washout entered the inpatient facility 5 days before the scheduled randomization (day −5) for diet stabilization. They were placed on one of two low-glycemic-index diets containing 6 g of sodium chloride; those with body mass index ≤35 kg/m^2 at entry received a 2,500-calorie daily diet, and those with body mass index ≥36 kg/m^2 received a 2,800-calorie daily diet. All subjects received diets containing ~50% calories as carbohydrates. A baseline OGTT was carried out 2 days before randomization (day −2). Additional baseline parameters measured on day −1 included weight, vital signs, electrocardiogram, 24-h urine collection, FPG, plasma fructosamine, and HbA_{1c}.

The patients were randomly and equally assigned to receive either 150 mg or 300 mg of LX4211 (Lexicon Pharmaceuticals, Princeton, NJ; IC_{50} values were measured using an assay described previously)[31] or placebo, once daily for 28 days. The methods used to generate and implement the random allocation sequence, and to blind and unblind the study, are described in the **Supplementary Materials and Methods** online. For this proof-of-concept study in patients with T2DM, 12 patients were assigned to each group; no formal sample size calculation was made. Both active drug and placebo were administered as oral solutions at 8:00 AM, 1 h before breakfast; the placebo was composed of identical ingredients except that it lacked LX4211. Doses were selected based on the earlier observation that the 300-mg dose was well tolerated and produced a maximal glycosuric effect in healthy volunteers enrolled in a phase I trial (data not shown). The inpatient active treatment interval of 28 days was followed by 7 days of outpatient follow-up and end-of-study sample collection.

The primary objective was to establish the safety profile for the two doses of LX4211 in patients with T2DM. The secondary objective was to evaluate the efficacy of the two LX4211 doses as compared with placebo, using the following measures: UGE, response to OGTT, FPG, fructosamine levels, homeostatic model assessment of insulin resistance, 2-h PPG, and LX4211 pharmacokinetics.

Assessments. A complete schedule of study assessments is provided as **Supplementary Table S17** online. UGE was collected for 24 h beginning at 8:00 AM. The OGTT was performed beginning at 8:00 AM after an 8-h fast. For the OGTT, the patients received a 75 g oral glucose solution (Glucola; Ames Laboratories, Elkhart, IN); OGTT glucose AUC values were calculated using linear-log trapezoidal summations. Homeostasis model assessment of insulin resistance was calculated as (fasting glucose (mg/dl) × fasting insulin (μU/ml))/405.[58] The 2-h PPG was measured after the patients had consumed an entire standardized shake for lunch. HbA_{1c} was measured as an exploratory end point. A *post hoc* analysis of total GLP-1 levels in retained plasma samples was performed by Pacific Biomarkers (Seattle, WA). Blood samples were obtained to measure LX4211 concentrations for pharmacokinetic analyses (see below). Safety assessments included weight, vital signs, electrocardiogram, clinical laboratory tests, physical examination, and AE assessments; AEs were coded and listed according to the relevant body system and preferred terms based on the Medical Dictionary for Regulatory Activities (MedDRA), version 12.0.

Quantitation of LX4211 in plasma. Blood samples for determining LX4211 plasma concentrations were collected before administration of the dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after the dose on days 1, 14, and 28. Additional blood samples were collected immediately before dosing on days 7 and 21, and a single sample was collected on day 36. Immediately after collection, the blood samples were placed in an ice/water bath; plasma was then separated by centrifugation at 2,000*g* for 15 min at 4 °C. Within 90 min of collection, plasma samples were stored at −70 °C. Plasma LX4211 levels were quantitated using liquid chromatography with tandem mass spectrometric detection.

Noncompartmental pharmacokinetic analysis. LX4211 pharmacokinetic parameters were calculated from the concentration–time data using a noncompartmental model 200 of the WinNonlin (WinNonlin

Professional Network Edition, version 5.2 or higher; Pharsight, Palo Alto, CA). The $t_{1/2}$ during the log linear terminal phase was calculated from the elimination rate constant (λ) determined by linear regression analysis of the log-linear part of the plasma concentration–time curve (i.e., ln2/λ). All calculations used the actual sampling time points.

Statistics. Analyses were carried out in accordance with a detailed statistical analysis plan. Continuous variables were summarized by the number of patients with nonmissing data, mean, SD, median, minimum, and maximum values. Categorical variables were summarized by their counts and associated percentages. All tests of treatment effects were two-sided at the 0.05 level of significance, with no adjustments made for multiple comparisons. SAS (version 9.1.3; SAS Institute, Cary, NC) was used to make all statistical comparisons and summarize the data descriptively.

Imputation or any other data-assignment rule was not used to substitute values for missing observations. All data analyses and summaries were based on observed cases. Unless stated otherwise, all statistical analyses presented in this paper were based on a repeated-measures general linear mixed model using change from baseline data, with baseline defined as day −1 for all calculations. This statistical model was saturated and contained fixed effects of treatment, study day, and a treatment × study day interaction. Techniques were implemented to provide tests of simple contrasts (i.e., differences among the treatment groups) at each study day. TG reduction was analyzed *post hoc* using similar statistical methods.

Single-dose study assessing GLP-1 and PYY response to LX4211 liquid and tablet oral formulations

Study design. The study was conducted at the same center and included both male and female patients, 44–65 years of age with an established diagnosis of T2DM; inclusion and exclusion criteria were identical to those described for the 28-day study, except that patients with a positive test for glutamic acid decarboxylase were excluded in the 28-day study. All participants provided written informed consent. The study was approved by the institutional review board at the investigational clinic.

Metformin was washed out over a 14-day period, if applicable, and monitored as in the 28-day study. All the patients who successfully completed metformin washout were housed in the clinic beginning 5 days prior to randomization (day −5) for diet stabilization. The participants were placed on a 2,200 calorie, high-glycemic-index daily diet containing 6 g of sodium chloride and ~50% of calories as carbohydrates.

Patients were randomly assigned in a 1:1:1 ratio among treatment-sequence groups, where they received single oral 300-mg doses of LX4211, as either a liquid formulation (30 ml of solution prepared at 10 mg/ml) or a solid formulation (two 150-mg tablets or six 50-mg tablets), in three successive treatment periods (doses on days 1, 6, and 11) separated by a 5-day washout period between doses (**Figure 2a**). The methods used to generate and implement the random allocation sequence are described in the **Supplementary Materials and Methods** online. The patients remained in house until study day 14. Four patients were assigned to each group; no formal sample size calculation was made. LX4211 was administered at 7:00 AM, 2 h before breakfast. On days −1, 1, 6, and 11, all the patients received identical meals, which they completely consumed within 30 min.

The primary objective was to evaluate the pharmacokinetics of LX4211 in both solid (tablet) and liquid oral dosage forms in patients with T2DM. The secondary objectives were to evaluate these oral dosage forms of LX4211 for their safety and for their pharmacodynamic effects on 24-h UGE, FPG, insulin, glucagon, total GLP-1, active GLP-1, and total PYY. The study was registered at ClinicalTrials.gov (NCT01188863).

Assessments. A complete schedule of study assessments is provided as **Supplementary Table S18** online. Safety and efficacy assessments were performed as in the 28-day study. Total and active GLP-1, glucose, PYY, and insulin were measured by Pacific Biomarkers.

Quantitation of LX4211 in plasma. Blood samples for determining plasma LX4211 concentrations were collected before administration of the dose on days 1, 6, and 11 and then at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 12, 24, and 48 h after LX4211 administration. LX4211 levels were quantitated using liquid chromatography/mass spectrometry as in the 28-day study.

Noncompartmental pharmacokinetic analysis. Noncompartmental analysis was performed as described for the 28-day study.

Statistics. Analyses were conducted in accordance with a detailed statistical analysis plan. Continuous and categorical variables were summarized using methods identical to those described for the 28-day study. Imputation or any other data assignment rule was not used to substitute values for missing observations. All data analyses and summaries were based on observed cases. The lone exception was for the pharmacodynamic variables whereby values reported below the lower limit of quantification were assigned a value of lower limit of quantification/2. The baseline was defined as day −1 for all calculations of change from baseline, unless noted otherwise.

The statistical model partitioned fixed effects of sequences, study days, assessment time within a study day, treatments, and a random term of patients with sequences to test differences among the different formulations of LX4211. First-order interactions were included as needed.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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AUTHOR CONTRIBUTIONS

B.Z. wrote the manuscript, designed research, and analyzed data. J.F. wrote the manuscript and analyzed data. P.M.B. designed research and analyzed data. K.S.F. wrote the manuscript, designed research, and analyzed data. A.T. wrote the manuscript and analyzed data. J.B. analyzed data. D.R. performed research. M.S. designed research. P.B. designed research and analyzed data. F.M. designed research, performed research, and contributed new reagents/analytical tools. D.B.R. designed research and contributed new reagents/analytical tools. N.C.G. designed research and contributed new reagents/analytical tools. R.M. designed research and contributed new reagents/analytical tools. B.A.H. designed research and contributed new reagents/analytical tools. A.W. analyzed data. A.S. wrote the manuscript, designed research, and analyzed data. D.R.P. wrote the manuscript, designed research, and analyzed data.

CONFLICT OF INTEREST

B.Z. is the chief scientific officer of Lexicon Pharmaceuticals and owns stock. J.F. is an employee of Lexicon Pharmaceuticals and owns stock. P.M.B. was an employee of Lexicon Pharmaceuticals at the time the studies were conducted and owns stock. K.S.F. is an employee of Lexicon Pharmaceuticals and owns stock. A.T. is an employee of Lexicon Pharmaceuticals and owns stock. J.B. is an employee of Lexicon Pharmaceuticals and owns stock. M.S. was an employee of Lexicon Pharmaceuticals at the time the studies were conducted. P.B. is an employee of Lexicon Pharmaceuticals and owns stock. F.M. is an employee of Lexicon Pharmaceuticals and owns stock. D.B.R. is an employee of Lexicon Pharmaceuticals and owns stock. N.C.G. is an employee of Lexicon Pharmaceuticals and owns stock. R.M. is an employee of Lexicon Pharmaceuticals and owns stock. B.A.H. is an employee of Lexicon Pharmaceuticals and owns stock. A.W. is an employee of Lexicon Pharmaceuticals and owns stock. A.S. is the president and chief executive officer of Lexicon Pharmaceuticals and owns stock. D.R.P. is an employee of Lexicon Pharmaceuticals and owns stock. D.R. declared no conflict of interest.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ This is the first report of a clinical trial with a dual SGLT1 and SGLT2 inhibitor in patients with T2DM. Multiple SGLT2-selective inhibitors are currently in clinical development.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ Is dual SGLT1 and SGLT2 inhibition a safe and potentially beneficial treatment for T2DM?

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ Dual SGLT1 and SGLT2 inhibition produced good glycemic control over 4 weeks of inpatient treatment, reduced triglyceride levels, and produced trends toward decrease in body weight and blood pressure.

✓ Reductions in intestinal glucose uptake and release of postprandial GLP-1 and PYY by the gastrointestinal tract were consistent with intestinal SGLT1 inhibition.

✓ Inhibition of SGLT1 appeared to be safe, with no increase in episodes of diarrhea in the treatment arms relative to placebo. This contrasts with theoretical concerns that have resulted in a focus on SGLT2-selective compounds.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ SGLT1 inhibition and concomitant reduction in intestinal glucose uptake, along with elevations in GLP-1 and PYY levels, could provide benefits additional to those of SGLT2 inhibition alone.

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