Single Doses of LX4211, a Dual Inhibitor of SGLT1 and SGLT2, Improves Parameters of Glycemic Control and Increases GLP-1 and PYY in Patients with Type 2 Diabetes (T2D).

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BACKGROUND

Inhibiting the sodium glucose cotransporters SGLT1 and SGLT2 is a unique approach to achieving glycemic control in patients with Type 2 Diabetes Mellitus (T2DM). Lexicon Pharmaceuticals has developed LX4211, an orally-administered small molecule dual inhibitor of SGLT1 and SGLT2, with the goal of improving glycemic parameters by reducing glucose absorption and transport. LX4211 blocks glucose reabsorption by the kidney by inhibiting SGLT2, thereby increasing urinary glucose excretion. It is believed that LX4211 also blocks glucose absorption in the small intestine by inhibiting SGLT1, thereby triggering the release of incretins and other gastrointestinal peptides.

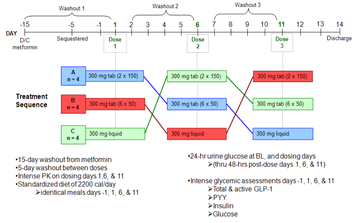
In our Phase 1 study in healthy individuals and our Phase 2a study in patients with T2DM, LX4211 delivered as a liquid formulation was well tolerated with a favorable safety profile at the doses and schedule given, and showed a dose-dependent increase in glucosuria. In addition, the T2DM patients treated with LX4211 over 28 days in our Phase 2a study showed statistically and clinically significant improvements in all glycemic parameters assessed, including highly significant improvements in hemoglobin A1c, fasting plasma glucose and oral glucose tolerance. A trend toward increases in total glucagon-like peptide-1 (GLP-1) levels with meals among LX4211-treated T2DM patients was also noted; this may have resulted from LX4211 inhibition of SGLT1-mediated glucose absorption in the small intestine, which likely stimulates GLP-1 release.

Presented here are results of a second Phase 1 trial which compared the pharmacokinetics, safety and pharmacodynamics of LX4211 delivered as oral liquid or solid (tablet) formulations to patients with T2DM; this was performed in anticipation of using the tablet formulation in future clinical trials. In addition to presenting pharmacokinetic and safety data, we emphasize our observation that each LX4211 formulation significantly decreases circulating glucose and insulin levels while significantly increasing circulating levels of GLP-1 and peptide YY (PYY) compared to baseline (day -1) values.

STUDY DESIGN

This was a single-center, open-label, randomized-sequence, 3-way crossover study to assess the pharmacokinetic (PK), safety and pharmacodynamic (PD) effects of LX4211 in both solid (tablet) and liquid form in patients with T2DM. After a 14-day washout of metformin, patients received single 300 mg oral doses of LX4211 before breakfast as two (2) 150 mg tabs, six (6) 50 mg tabs, or 300 mg solution (10 mg/mL), with a 5-day washout between doses. PK and PD endpoints were assessed on days -1 (baseline [BL] untreated control), 1, 6, and 11. A schematic representation of the study design is presented in Figure 1.

Figure 1. Study design



PATIENT DEMOGRAPHICS

Table 1. Patient demographics at baseline

Demographic or Baseline Characteristic	Treatment Sequence A* (n=4)	Sequence B* (n=4)	Sequence C* (n=4)	Total (N=12)
Age (years)				
n	4	4	4	12
Mean (SD)	54.8 (6.90)	51.8 (5.74)	62.0 (3.16)	56.2 (6.70)
Median	53.0	53.0	62.5	56.5
Minimum, Maximum	49, 64	44, 57	58, 65	44, 65
Sex, n (%)				
Male	3 (75.0)	1 (25.0)	2 (50.0)	6 (50.0)
Female	1 (25.0)	3 (75.0)	2 (50.0)	6 (50.0)
Body mass index (kg/m^2)				
n	4	4	4	12
Mean (SD)	33.35 (4.371)	31.38 (3.526)	33.75 (4.291)	32.83 (3.847)
Median	32.00	32.35	34.30	32.35
Min, Max	29.8, 39.6	26.7, 34.1	28.7, 37.7	26.7, 39.6

* Sequence A=300 mg (2 x 150 mg tablets) → 300 mg (6 x 50 mg tablets) → 300 mg (liquid)
Sequence B=300 mg (6 x 50 mg tablets) → 300 mg (liquid) → 300 mg (2 x 150 mg tablets)
Sequence C=300 mg (liquid) → 300 mg (2 x 150 mg tablets) → 300 mg (6 x 50 mg tablets)

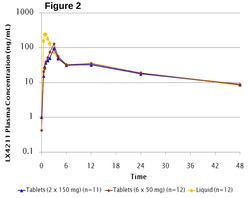
Mean (SD) fasting plasma glucose for all subjects was 183.0 mg/dL (27.87) at day-1.

RESULTS

Pharmacokinetics

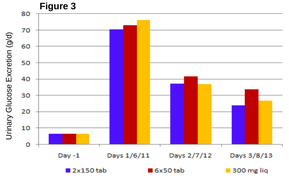
Figure 2. Time course of plasma LX4211 levels after oral administration of liquid or tablet LX4211 formulations.

- The absorption rate for the liquid formulation was 3-fold faster than for the tablets.
- Mean C_{max} was significantly greater for the liquid formulation compared to the tablets.
- AUC values of both tablet strengths were similar to each other but were about 25% less than the liquid formulation, suggesting a lower relative bioavailability of the tablet formulation.
- The mean half-life values were similar between liquid and tablet forms.



Pharmacodynamics

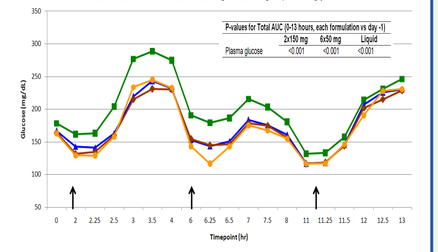
Figure 3. Single 300 mg doses of LX4211 increase UGE. UGE was estimated by measuring the total amount of glucose present in 24-hour urine samples collected on day -1 (baseline) and after a single dose of an LX4211 formulation administered on days 1, 6, and 11.



RESULTS (cont.)

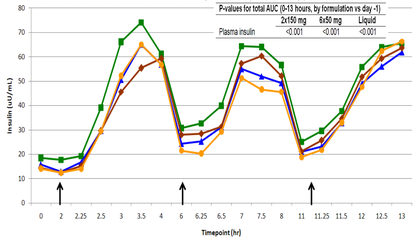
Pharmacodynamics (cont.)

Figure 4. Single 300 mg doses of LX4211 lower glucose and insulin levels while increasing GLP-1 and PYY levels. Blood was collected immediately before (at hour 0) and at multiple time points after administration of an LX4211 formulation on days 1, 6 and 11; blood was collected at the identical time points on day -1. After plasma samples were assayed for the relevant analyte, AUC values were calculated for the time interval between hours 0 and 13. The effect of each LX4211 formulation on each analyte was compared to day -1 baseline values. Analytes analyzed were: (A) Plasma glucose, (B) Plasma insulin, (C) Total GLP-1, (D) Active GLP-1, and (E) Total PYY.

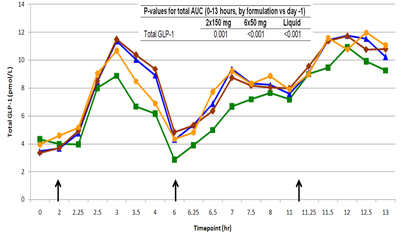


A) Plasma Glucose: Each LX4211 formulation significantly decreased plasma glucose levels between 0 and 13 hours after dosing, indicating improved glycemic control.

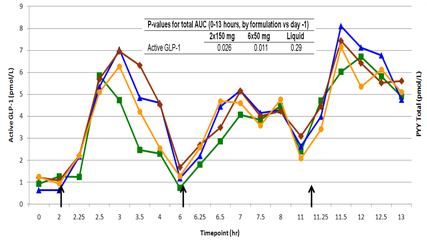
B) Plasma Insulin: Each LX4211 formulation significantly decreased plasma insulin levels between 0 and 13 hours after dosing, indicating improved glycemic control.



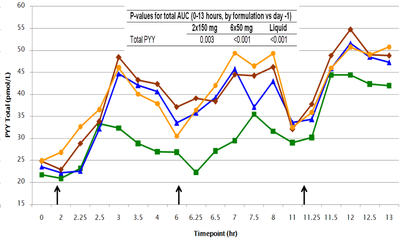
C) Total GLP-1: Each LX4211 formulation significantly increased circulating levels of total GLP-1 between 0 and 13 hours after dosing.



D) Active GLP-1: Both tablet formulations significantly increased circulating levels of active GLP-1 between 0 and 13 hours after dosing.



E) Total PYY: Each LX4211 formulation significantly increased circulating levels of total PYY between 0 and 13 hours after dosing.



SAFETY

Body System / Preferred Term	Treatment: Tablets, 2 x 150 mg (N=12)	Tablets, 6 x 50 mg (N=12)	Liquid, 300 mg (N=12)	Overall (N=12)
	Number and percentage (%) of subjects			
Number of subjects with at least 1 TEAE	3 (25.0)	3 (25.0)	4 (33.3)	6 (50.0)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)
Gastrointestinal disorders	1 (8.3)	1 (8.3)	4 (33.3)	5 (41.7)
Abdominal pain	0 (0.0)	1 (8.3)	1 (8.3)	2 (16.7)
Constipation	1 (8.3)	0 (0.0)	2 (16.7)	2 (16.7)
Diarrhea	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)
General disorders and administration site conditions	1 (8.3)	1 (8.3)	0 (0.0)	2 (16.7)
Chest pain	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)
Non-cardiac chest pain	0 (0.0)	1 (8.3)	0 (0.0)	1 (8.3)
Nervous system disorders	2 (16.7)	1 (8.3)	1 (8.3)	3 (25.0)
Headache	2 (16.7)	1 (8.3)	1 (8.3)	3 (25.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)
Dysuria	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)
Vulvovaginal pruritus	0 (0.0)	0 (0.0)	1 (8.3)	1 (8.3)

There were no SAEs, deaths, or discontinuations due to adverse events. All events were mild in severity, with the exception of 1 headache in the 6 x 50 mg tablet group (moderate severity).

SUMMARY

- In this study, LX4211 was well tolerated with a favorable safety profile at the doses and schedule given in patients with T2DM.
- PK data supports once a day dosing with the solid dose formulation.
- Each LX4211 formulation resulted in a clinically significant increase in 24-hour UGE.
- Each LX4211 formulation significantly decreased plasma glucose and insulin levels between 0 and 13 hours after dosing, indicating improved glycemic control.
- Each LX4211 formulation significantly increased circulating levels of total GLP-1 and PYY between 0 and 13 hours after dosing.
- Both tablet formulations significantly increased circulating levels of active GLP-1 between 0 and 13 hours after dosing.

CONCLUSIONS

These data support the hypothesis that LX4211, a dual SGLT1/SGLT2 inhibitor, increases UGE by inhibiting renal SGLT2 and increases circulating GLP-1 and PYY by inhibiting intestinal SGLT1. Both effects may contribute to the improved glycemic control that accompanies LX4211 treatment in patients with T2DM.

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Disclosure: Authors who are employees of Lexicon Pharmaceuticals , Inc., may own stock or may have been given stock options.