LX1033, a Second Generation Locally-acting Serotonin Synthesis Inhibitor, Demonstrates Increased Potency and Favorable Safety Profile in Preclinical Studies
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BACKGROUND

Serotonin (5-HT) mediates gastrointestinal (GI) mobility, secretion, inflammation and sensation and may play an important role in irritable bowel syndrome (IBS).

Serotonin synthesis inhibition with LX1031 has been shown to improve symptoms in non-conspiring IBS patients in correlation with decreases in urinary 5-hydroxyindoleacetic acid (5-HIAA).

We now report that a second generation, locally-acting, novel serotonin synthesis inhibitor (SSI), LX1033 has exhibited improved in vitro inhibition of tryptophan hydroxylase (TPH) and greater pharmacokinetic effects on 5-HT synthesis in rodents.

OBJECTIVES

These exploratory studies were designed to:

- delineate the in vitro and in vivo characteristics of LX1033, and
- compare its potency and safety profile to the first-generation serotonin synthesis inhibitor, LX1031.

METHODS

In vitro, comparisons were made for LX1033 vs. LX1031 for the half maximum inhibition concentration (IC50); human TPH inhibition was assessed spectrophotometrically and cellular TPH1 inhibition was assessed by measuring 5-HT in intact cells using the RBL-2H3 cell line. In RBL-2H3 cells, SSI was tested at different concentrations with each cell for 3 days to delineate the IC50 of 5-HT in the cells. In the proximal colon, LX1033 decreased 5-HT levels by 71% (jejunum), 76% (ileum), 65% (proximal colon), and 61% (distal colon).

RESULTS (continued)

• After being administered in the diet for 10 consecutive days, LX1033 significantly reduced 5-HT levels in whole blood, duodenum, jejunum, ileum, and colon in 30 and 100 mg/kg/day dose levels.

LX1033 caused 33% decrease of whole blood 5-HT at 30 mg/kg/day and 49% decrease at 100 mg/kg/day.

TABLE 1: Comparison of in vitro potency of LX1033 and LX1031: TPH inhibition

**Table 2: Comparison of LX1033 vs. LX1031 in jejunal and distal colon 5-HT reduction in rats**

**DISCUSSION**

• In a head-to-head study, LX1030 demonstrated better reduction of tissue 5-HT than LX1031 in various regions of the GI tract, while maintaining a low exposure profile.

• Studies in mice also demonstrated that LX1033 was effective in reducing peripheral 5-HT, while showing no evidence of crossing the blood-brain barrier.

• Results from genetic and animal toxicology studies confirmed that LX1033 was safe and well tolerated (data not shown).

CONCLUSIONS

• LX1033 proved to be 5-10x more potent than LX1031 on in vitro enzyme and cell-based assays.

• Preclinical in vitro and in vivo studies in rodents demonstrate that LX1033 inhibits 5-HT synthesis in a greater extent than LX1031.

• LX1033 has demonstrated a favorable safety profile in preclinical studies and may be a novel therapeutic agent for IBS-darrean predispersed (IBS-D) and other GI disorders.

Enrollment is ongoing in a placebo-controlled, 4-week Phase 2 trial of LX1033 in 350 patients with IBS-D.

Reference:
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Presented at Digestive Disease Week – San Diego, CA – May 19-22, 2012

**RESULTS**

• Enrollment is ongoing in a placebo

In the Sprague-Dawley study, LX1033 was formulated in 0.25% methylcellulose plus 0.1% Tween 80 and orally administered at 0, 5, 15, 50, or 150 mg/kg/day (total daily dose of 0, 10, 30, 100, or 300 mg/kg/day) for 4 consecutive days. Animals were sacrificed approximately 16-18 hours after their last dose. Whole blood and various intestinal segments (mesentry-fat removed, gut lumen opened and blotted dry) were collected, oven dried and stored at -20°C. Tissue weights were taken prior to 5-HT analysis.

In the LX1030 mouse dietary study, female C57BL/6J mice were acclimatized to single housed and purified low fat diet (LFD; D12451B, Research Diet Inc.), which provides 10 kcal as fat (lard). LX1033 was mixed in LFD and fed to the treated mice for 10 consecutive days to achieve dose levels of 30 and 100 mg/kg/day. Whole blood, brain, and GI tissues were collected and stored frozen prior to 5-HT analysis.

In the proximal colon, LX1033 decreased 5-HT levels by 71% (jejunum), 76% (ileum), 65% (proximal colon), and 61% (distal colon).

**RESULTS (continued)**

• In a head to-head study in rats, vehicle, LX1031 and LX1033 were orally administered for 5 consecutive days. LX1033 showed a dose-dependent reduction of 5-HT in the jejenum, ileum, proximal, colon, and distal colon, with the greatest reduction at 200 mg/kg/day (71%, jejenum; 76%, ileum; 65% (proximal colon); and 61% (distal colon)). LX1033 demonstrated better reduction of 5-HT than LX1031 in these various GI segments in rats.