LX1033, a Serotonin Synthesis Inhibitor (SSI), Decreases Levels of Urinary 5-HIAA: Results of a Phase 1 Study
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BACKGROUND

• LX1033, a locally acting, oral, small molecule, is a potent serotonin synthesis inhibitor (SSI).
• Decreasing GI serotonin is associated with clinical improvement in patients experiencing non-constipating irritable bowel syndrome (IBS-D).
• An earlier generation SSI, LX1031, produced a significant improvement in the weekly global assessment of IBS-related pain and discomfort.
• In preclinical studies, LX1033 demonstrated similar ability to reduce local tissue serotonin levels as compared to LX1031 preclinical activity, using lower dose.

KEY INCLUSION / EXCLUSION CRITERIA

Inclusion:
- Healthy volunteers
- Age 18-50 years
- No known history of hepatic disease or abnormal liver function tests
- No concurrent condition that could have interfered with the analysis of safety or tolerability

Exclusion:
- Any surgical or medical condition that could have interfered with absorption, distribution, metabolism, or excretion of LX1033
- Must not have received any investigational agent or selective serotonin reuptake inhibitor within 30 days prior to study entry
- Prior exposure to LX1031 was not permitted

STUDY DESIGN

Primary Objective
To evaluate the safety and tolerability of LX1033 over a range of multiple oral doses in healthy subjects

Secondary Objectives
- To evaluate the pharmacokinetics of LX1033 over a range of multiple oral doses in healthy subjects
- To assess the pharmacodynamic effects of LX1033 by assessing whole blood 5-HT levels over time versus baseline
- To assess the pharmacodynamic effects of LX1033 by assessing urinary 5-HIAA (u5-HIAA) levels over time versus baseline

OBJECTIVES

• To assess the pharmacodynamic effects of LX1033 by assessing urinary 5-HIAA levels over time versus baseline
• To assess the pharmacodynamic effects of LX1033 by assessing whole blood 5-HT levels over time versus baseline

STUDY DESIGN

Primary Objective
- To evaluate the safety and tolerability of LX1033 over a range of multiple oral doses in healthy subjects

Secondary Objectives
- To assess the pharmacokinetics of LX1033 over a range of multiple oral doses in healthy subjects
- To assess the pharmacodynamic effects of LX1033 by assessing whole blood 5-HT levels over time versus baseline
- To assess the pharmacodynamic effects of LX1033 by assessing urinary 5-HIAA levels over time versus baseline

STATISTICAL METHODS

Data were summarized descriptively by treatment group. The placebo subsets were pooled for data reporting. Continuous variables were summarized as the number of nonmissing observations, mean, standard deviation, median, minimum, and maximum. Categorical data were summarized as counts and their relative percentages. Data summaries and tables reflected observed cases and not all subjects treated.

DISCUSSION

- LX1033 was well tolerated across all dose levels studied.
- Adverse events were mostly mild in intensity and evenly distributed across cohorts.
- The most frequent AEs were GI disorders experienced across all treatment groups.
- AE discontinuation due to transient increase in ALT and AST occurred in 1 subject with cholelithiasis and fatty liver infiltrate.

CONCLUSIONS

- In healthy subjects, LX1033 produced similar reductions in u5-HIAA, compared to the first generation SSI, LX1031, at lower doses.
- Rapid and sustained reduction in mean urinary and plasma 5-HIAA concentrations from baseline was observed with all LX1033 dose levels over 14 days.
- Good correlation between plasma and urinary 5-HIAA levels was seen.
- Doses up to 750 mg tid, when dosed for 14 days, were safe and well tolerated. A subsequent Phase 1 study, utilizing tablet formulation of LX1033, confirmed similar safety, pharmacokinetic, and pharmacodynamic results.