

Telotristat Etiprate Produces Clinical and Biochemical Responses in Patients with Symptomatic Carcinoid Syndrome: Preliminary Results of an Ongoing Phase 2, Multicenter, Open-Label, Serial-Ascending, European Study

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Background: Excess serotonin (5-HT) may contribute to gastrointestinal (GI) symptoms such as diarrhea in carcinoid syndrome (CS) patients. Telotristat etiprate / LX1032/ a.k.a. LX1606, an oral serotonin synthesis inhibitor (SSI), is designed to reduce peripheral 5-HT levels and alleviate GI distress.

Methods: This study evaluates the safety and tolerability of ascending doses (150 mg, 250 mg, 350 mg, and 500 mg tid) of telotristat etiprate in symptomatic CS patients, averaging ≥ 4 bowel movements (BM)/day, either therapy-naïve or receiving somatostatin analogs. Secondary objectives include symptomatic response (change in: number of BM/day, stool form/consistency, sensation of urgency to defecate, sensation/severity of nausea, global assessment of symptoms, assessment of abdominal pain/discomfort, reduction of cutaneous flushing episodes), and assessment of plasma drug concentrations, pharmacokinetics, and pharmacodynamics (urinary 5-hydroxyindolacetic acid [u5-HIAA] and blood 5-HT). All patients began dosing at 150 mg. Dose strength was increased following 2 weeks of therapy with no dose-limiting toxicity. If dose-limiting toxicities occur, the dose will be reduced to prior level. Treatment will continue at

the individual maximum-tolerated dose for 4 weeks; patients can continue in an extension phase.

Results: Currently, 5 patients have completed the ascending dose study and 1 of 3 eligible subjects has enrolled into the long-term extension, up to 48 weeks; 2 more subject are eligible for the long-term extension. Mean age 61 years (range, 51-81), mean BM/day was 6.4 (range, 4-8). Upon completion of 12 weeks dosing, 84% (5/6) had sustained reductions of $\geq 30\%$ in BM/day (50% [3/6] had multiple assessments indicating $\geq 50\%$ BM reductions).

Conclusion: Telotristat etiprate produced biochemical and clinical responses/benefit in refractory CS. No major safety issues were detected. As of 9/2011, 8 patients have been treated with an additional 8 patients required to complete enrollment. Accrual is ongoing.