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Efficacy of Telotristat Etiprate in Refractory Carcinoid Syndrome: Preliminary Results of a Randomized, Placebo-Controlled, Multicenter Study

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Background: Diarrhea associated with carcinoid syndrome has been attributed to excess serotonin. Telotristat etiprate (a.k.a. LX1032, LX1606) is an oral serotonin synthesis inhibitor that decreases peripheral serotonin production. This randomized study assessed the safety, tolerability, and efficacy of telotristat etiprate in carcinoid syndrome associated diarrhea.

Methods: Carcinoid patients with octreotide-refractory diarrhea (>4 bowel movements (BM)/day on stable-dose octreotide) were randomized 3:1 to receive telotristat etiprate or placebo. Patients enrolled in double-blind, placebo-controlled, sequential, escalating dose cohorts of 150, 250, 350, or 500mg tid, with an expansion cohort (500mg tid). Endpoints included safety, reduction in BMs, reduction in 24-hour urinary 5-HIAA (u5-HIAA) and self-reported clinical improvement, as measured by response to a weekly questionnaire. Upon completion of the initial 4-week assessment period, patients could receive open-label telotristat etiprate.

Results: 23 patients enrolled: 16 in the 4 escalating dose cohorts, 7 in the expansion cohort. 18 received telotristat etiprate and 5 received placebo. Patients had a median age of 62 yrs, mean 6.2 BMs/day (range 4-10), and mean u5-HIAA of 64.2 (range 0.03-246 mg). AEs (placebo/telotristat etiprate) included diarrhea (40%/39%), nausea (20%/28%), and abdominal pain (0%/17%); 1 patient was hospitalized with vomiting. Among evaluable telotristat etiprate -treated patients, 5/18 (28%) experienced a clinical (BM) response ($\geq$30% reduction in frequency for $\geq$2 weeks), 9/16 (56%) experienced a biochemical (u5-HIAA) response (reduction of $\geq$50%), and 6/12 (50%) reported subjective relief of bowel symptoms at Week 4. No evaluable placebo patients experienced a BM response (0/5), u5-HIAA response, (0/4) or subjective relief of bowel symptoms at week 4 (0/4).

Conclusion: Treatment with telotristat etiprate was well tolerated and was associated with decreased BM frequency, decreased 24-hour u5-HIAA levels, and a high rate of self-reported subjective clinical improvement in carcinoid patients with octreotide refractory diarrhea. 18 of 19 eligible patients continued treatment under the extension protocol.