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

Matthew Kulke 1, Thomas O’Donisio 2, Alexandria Phani 3, Robert Langdon Jr. 4, Billie Marek 5, Nadeem Iklae 6, Emily Berglind 7, Joel Freiman 8, Linda Law 9, Philip Banks 10, Kenny Frazier 11, Jessica Jackson 12, Brian Zambrowicz 13

1 Dana-Farber Cancer Institute, Boston, MA; 2 University of Iowa Hospitals and Clinics, Iowa City, IA; 3 The University of Texas M.D. Anderson Cancer Center, Houston, TX; Nebraska Methodist Hospital System, Omaha, NE; 5 Texas Oncology, PA, McAllen, TX; 3 St. Francis Hospital, Grove Beach, IN; 4 University of California – San Francisco Cancer Center, San Francisco, CA; Lexicon Pharmaceuticals, Inc., The Woodlands, TX.

BACKGROUND
Carcinoid tumors are associated with serotonin (5-HT) secretion. High levels of serotonin are thought to contribute to the diarrhea and abdominal discomfort observed in patients with carcinoid syndrome (CS). Telotristat etiprate (aka LX1606/LX1032) is an orally-delivered inhibitor of the rate-limiting enzyme in 5-HT synthesis, tryptophan hydroxylase (TPH). Telotristat etiprate has been shown in preclinical, as well as studies in healthy volunteers and carcinoid syndrome patients, to reduce peripheral 5-HT production. In humans this is evidenced by reductions in 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) and blood 5-HT concentrations. Reductions of the amount of 5-HT produced by metastatic carcinoid tumors may reduce many of the symptoms and sequelae commonly associated with carcinoid syndrome. Telotristat etiprate offers a potentially novel therapeutic approach to CS palliation.

OBJECTIVES
• To evaluate the safety and tolerability of orally administered telotristat etiprate in patients with carcinoid syndrome

SECONDARY OBJECTIVES
• To assess the effects of telotristat etiprate by measuring symptomatic response over time versus baseline, as determined by number of daily bowel movements.
• To assess the effects of a range of multiple oral doses of telotristat etiprate on signs and symptoms of carcinoid syndrome.

STUDY OVERVIEW
This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, ascending multidose study in patients with symptomatic carcinoid syndrome despite stable-dose octreotide long-acting release (LAR) depot therapy. Cohorts of patients with octreotide-refractory CS were sequentially assigned to receive 4 weeks of telotristat etiprate or placebo in a 3:1 ratio. Oral telotristat etiprate or placebo were administered 3 times daily for the dose cohorts of 150 mg, 250 mg, 350 mg, 500 mg. All patients continued stable-dose octreotide LAR for the duration of the study. After completing the 4-week blinded portion of the study, patients were eligible to receive open-label treatment at the 500 mg dose level. Treatment in the placebo-controlled portion of the study has been completed and patients continue in the open-label, long-term extension phase.

STUDY DESIGN
Two-part study: Part 1: Dose-escalation Part 2: Expansion cohort at highest dose

PATIENT SELECTION/DEMOGRAPHICS

Clinical Response: ≥30% reduction from baseline in the daily mean number of bowel movements per week and/or achieving a mean CS bowel movement/day for the week for 2 weeks.

Biochemical Response: Complete response: ≥50% reduction from baseline or normalization in u5-HIAA

Responders rates assessed among patients who had u5-HIAA at both baseline and 21 post dosing time point.

Safety
Weekly responders to question: “In the past 7 days, have you had adequate relief of your carcinoid syndrome bowel complaints such as diarrhea, urgent need to have a bowel movement, abdominal pain or discomfort?”

Telotristat etiprate was well tolerated and adverse events in the study were usually mild to moderate and overall with similar frequencies between treatment groups and placebo.

Most common AEs (placebo/telotristat etiprate) included diarrhea (40%/39%), nausea (20%/28%), and abdominal pain (0%/17%).

There was 1 treatment-emergent serious adverse event assessed as possibly related to study drug; a patient in the 350 mg dose group with a history of nausea and vomiting was hospitalized for exacerbation of nausea and vomiting.

CONCLUSIONS
Telotristat etiprate was well tolerated and adverse events in the study were usually mild to moderate and overall with similar frequencies between treatment groups and placebo.

Most common AEs (placebo/telotristat etiprate) included diarrhea (40%/39%), nausea (20%/28%), and abdominal pain (0%/17%).

There was 1 treatment-emergent serious adverse event assessed as possibly related to study drug; a patient in the 350 mg dose group with a history of nausea and vomiting was hospitalized for exacerbation of nausea and vomiting.

Telotristat etiprate was well tolerated at all doses and demonstrated a favorable safety profile over 28 days.

Clinical response evidence of efficacy observed across several endpoints:
- Reduced bowel movement frequency
- Decreased u5-HIAA
- Patient-reported relief of symptoms

Further evaluation of telotristat etiprate in patients with carcinoid syndrome is warranted.