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

Matthew Kulke[1], Thomas O'Dorisio[2], Alexandria Phan[3], Robert Langdon Jr[4], Billie Marek[5], Nadeem Iklaque[6], Emily Bergsland[7], Joel Freiman[8], Linda Law[8], Phillip Banks[8], Kenny Frazier[8], Jessica Jackson[8], Brian Zambrowicz[8].
[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; [4]Nebraska Methodist Hospital System, Omaha, NE; [5]Texas Oncology, P.A., McAllen, TX; [6]St. Francis Hospital, Grove Beach, IN; [7]University of California – San Francisco Cancer Center, San Francisco, CA; [8]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. Reducing 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.

STUDY OVERVIEW

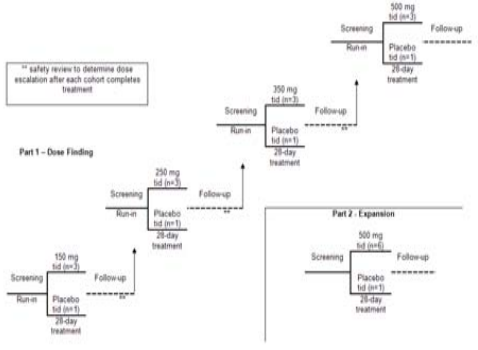
This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, ascending multidose study in patients with symptomatic carcinoid syndrome despite stable-dose octreotide long-acting release (LAR) depot therapy.

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



Number of Patients
Part 1, 16 patients enrolled
Part 2, 7 patients enrolled
Randomization was conducted centrally

OBJECTIVES

Primary Objective
- 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

ASSESSMENTS

Efficacy
The primary efficacy measure was the reduction in the number of daily bowel movements.
Secondary efficacy measurements included:
- Description of the average stool form for bowel movements
- Sensation of urgency to defecate
- Subjective global assessment of symptoms associated with carcinoid syndrome
- Description of abdominal pain or discomfort
- Chromogranin-A
- Number of cutaneous flushing episodes
- Frequency of rescue, short-acting octreotide dosing

Safety
Safety assessments included monitoring of adverse events, clinical laboratory parameters, vital signs,12-lead electrocardiograms, and physical examinations.

Pharmacokinetics
Telotristat etiprate and LP-778902 (active moiety) concentrations in plasma were measured at baseline (predose Day 1), at each weekly visit (Weeks 1, 2, 3, and 4), then periodically throughout the extension period.

Pharmacodynamics
Pharmacodynamic assessments included determinations of 5-HT levels in blood and 5-HIAA levels in urine.

PATIENT SELECTION/DEMOGRAPHICS

- Biopsy-proven metastatic carcinoid tumor with disease extent confirmed by computed tomography, magnetic resonance imaging, or radionuclide imaging
- Refractory to octreotide therapy, defined as experiencing ≥4 bowel movements per day despite stable-dose octreotide LAR depot therapy (and supplemental rescue, short-acting octreotide therapy, as needed).
  - For the purposes of this study, stable-dose octreotide therapy was defined as octreotide LAR depot therapy or a continuous subcutaneous infusion of octreotide therapy via pump at the same dose level for at least 3 months prior to the run-in period.
- Confirmation of eligibility was determined by mean number of bowel movements measured during the run-in period.

DEMOGRAPHICS	N=23
Mean Age yrs (range)	62 (44-83)
Sex (M%: F%)	10 (43%):12 (57%)
Mean BM Frequency, #/day (range)	6.3 (4-10)
Octreotide dose:	
30 mg q 4 wks	4
30 mg q 3 wks	2
40 mg q 2-4 wks	15
60 mg q 3 wks	1
Octreotide infusion pump	1
Mean u5-HIAA, mg/24h (range)	65.4 (0.3-246)

RESPONDER DEFINITION

Clinical Response
≥30% reduction from baseline in the daily mean number of bowel movements per week and/or achieving a mean ≤3 bowel movements/day for the week for 2 weeks*

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

Responder rates assessed among patients who had u5-HIAA at both baseline and ≥1 post dosing time point.

Adequate Relief
Weekly response 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?"

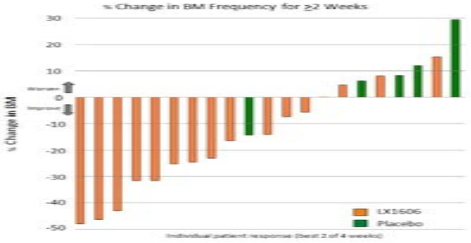
**excluding weeks with short-term octreotide rescue*

PRIMARY OUTCOMES

	Placebo		Telotristat etiprate	
	n	Responder	n	Responder
Clinical Response: (at least 30% reduction in bowel movements for at least 2 weeks)	5	0 %	18	5 (28%)
Biochemical Response: (at least 50% reduction or normalization in u5-HIAA)	5	0 %	16	9 (56%)
Adequate Relief: (at Week 4)	4	0 %	12	6 (50%)

REDUCTION IN BM FREQUENCY

	Placebo n=5	150 mg tid n=3	250 mg tid n=3	350 mg tid n=3	500 mg tid n=9	Pooled Telotristat n=18
Clinical Response	0 (0%)	1 (33%)	2 (67%)	0 (0%)	2 (22%)	5 (28%)
Change in BM frequency (#/day)	+0.7	-1.4	-2.2	-1.2	-0.9	-1.25



ADEQUATE RELIEF

	Placebo n=4	150 mg tid n=2	250 mg tid n=3	350 mg tid n=2	500 mg tid n=5
Week 4 (Patients that have responded "Yes")	0	1 (50%)	2 (67%)	1 (50%)	2 (40%)

CHANGE IN u5-HIAA

	Placebo n=5	150 mg tid n=3	250 mg tid n=3	350 mg tid n=2	500 mg tid n=8	Pooled Telotristat N=16
Baseline Mean u5-HIAA, mg/24h (Range)	100.28 (0.3-246.0)	51.53 (4.6-117.0)	2.4 (1.7-3.6)	3.6 (3.3-3.9)	92.34 (2.3-217.0)	65.4 (1.7-217.0)
At least 50% reduction or normalization of u5-HIAA	0 (0%)	2 (67%)	1 (33%)	0 (0%)	6 (75%)	9 (56%)

SAFETY

- 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 at all doses and demonstrated a favorable safety profile over 28 days.
- Preliminary evidence of efficacy observed across several endpoints:
  - o Reduced bowel movement frequency
  - o Decreased u5-HIAA
  - o Patient-reported relief of symptoms
- Further evaluation of telotristat etiprate in patients with carcinoid syndrome is warranted.

To view this poster online, snap a photo of this QR code with your smart phone (QR reader required).

Presented at the North American NeuroEndocrine Tumor Society (NANETS) Meeting – Minneapolis, MN – October 20-22, 2011

Disclosure: Authors who are employees of Lexicon Pharmaceuticals , Inc., may own stock or may have been given stock options.