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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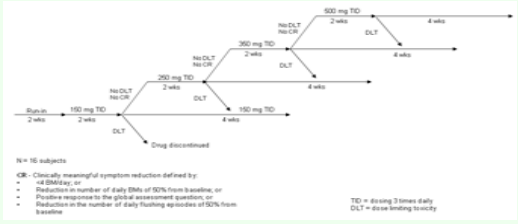
INTRODUCTION

Telotristat etiprate (LX1032 / LX1606), is an orally-delivered serotonin synthesis inhibitor (SSI), affecting the rate-limiting enzyme in 5-HT synthesis, tryptophan hydroxylase (TPH). SSIs represent a novel approach to potentially alleviate symptoms due to excess 5-HT in carcinoid patients. In the U.S., telotristat etiprate is being developed under Fast Track designation from the FDA and has Orphan Drug status in the E.U.

STUDY DESIGN

This is a Phase 2, nonrandomized, multicenter, open-label, serial ascending multiple dose, individual titration, study in patients with symptomatic carcinoid syndrome. This study is being conducted in Germany and the UK.

Eligible patients will be able to continue into an open-label extension phase. The study schema outlines intrapatient dose escalation.



PATIENT SELECTION

- Biopsy-proven metastatic carcinoid tumor of the gastrointestinal (GI) tract with disease extent confirmed by computed tomography, magnetic resonance imaging, or radionuclide imaging
- Symptomatic carcinoid syndrome, defined as experiencing an average of ≥4 bowel movements (BM) per day. Confirmation of eligibility will be determined by measuring the mean number of BM during the run-in period.

OBJECTIVES

Primary

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

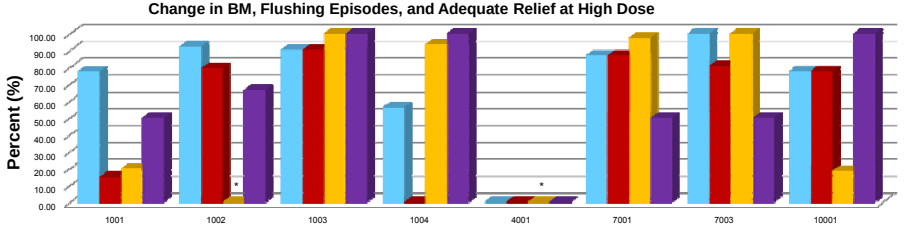
Secondary

- To assess the effects of telotristat etiprate on symptomatic response as determined by changes in the following parameters captured by Interactive Voice Response System [IVRS]):
  - Number of daily BMs
  - Stool form/consistency
  - Sensation of urgency to defecate
  - Sensation/severity of nausea
  - Abdominal pain or discomfort
  - Adequate relief of GI symptoms associated with carcinoid syndrome
- To evaluate the effects of telotristat etiprate on the number of cutaneous flushing episodes
- To assess the proportion of patients achieving clinically meaningful symptom reduction

Additional assessments include: monitoring of adverse events, clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms, physical examinations, determination of 5-HT levels in blood, 5-HIAA levels in urine, and pharmacokinetics (trough drug levels).

CLINICAL AND BIOCHEMICAL RESPONSES

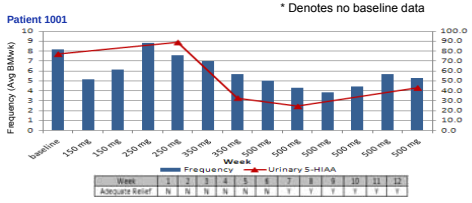
Change in BM, Flushing Episodes, and Adequate Relief at High Dose



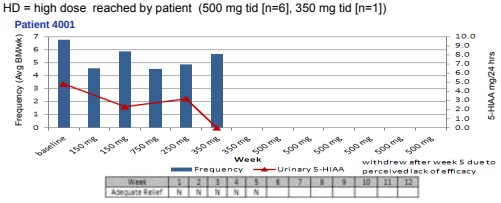
* Denotes no baseline data

HD = high dose reached by patient (500 mg tid [n=6], 350 mg tid [n=1])

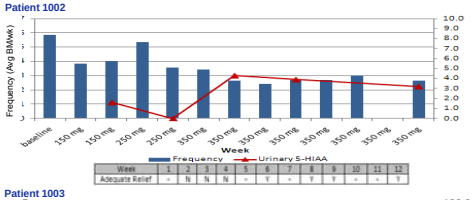
Patient 1001



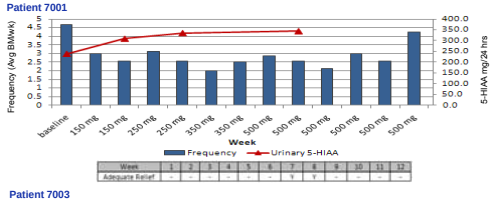
Patient 4001



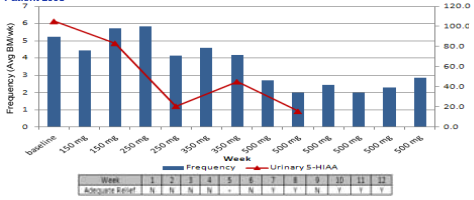
Patient 1002



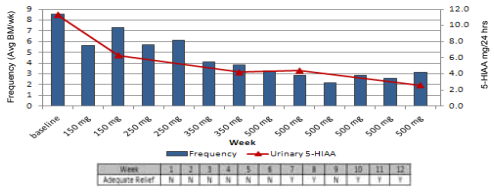
Patient 7001



Patient 1003



Patient 7003



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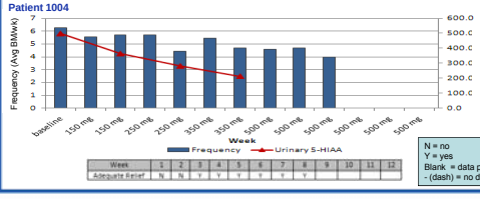
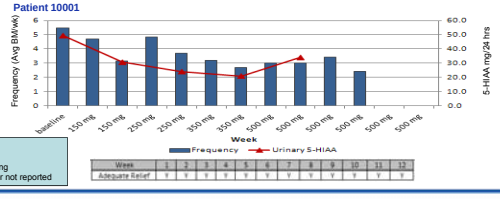


Patient 10001



N = no
Y = yes
Blank = data pending
- (dash) = no data or not reported

DEMOGRAPHICS

	Study Population
Mean Age, yrs (range)	61 (51-81)
Mean BM Frequency, #/day (range)	6.4 (4-8)
Mean u5-HIAA, mg/24h* (range)	140.9 (4.8-500)
Sex (% female)	50%

* 7 of 8 included

DISCUSSION

Data shown represents preliminary unaudited data.

- Graphs depict the clinical and biochemical responses for patients with up to 12 weeks of treatment. There is a general trend to clinically relevant decreases in BM frequency over time and with increasing dose. This clinical response is associated with a decrease in u5-HIAA levels. Patients most commonly reported experiencing adequate relief of their GI carcinoid symptoms at higher doses.
- Currently, 6 of 8 patients have achieved a 30% reduction in BM for at least 70% of days while on highest dose.
- Five of 8 patients experienced ≤3 BM/day during 70% of the days while on highest dose.
- Six of 8 patients have progressed to the highest dose tested (500 mg tid). One patient remained at 350 mg tid due to scheduling conflicts and 1 patient discontinued early due to reporting inadequate relief.
- Four out of 5 eligible patients have enrolled into the long-term extension, up to 48 additional weeks.
- LX1606.203 is an ongoing clinical trial. To date, 6 SAEs have occurred. All events were assessed as unrelated to study drug.

CONCLUSIONS

- Data from this ongoing clinical study indicate telotristat etiprate, a serotonin synthesis inhibitor, is safe and well-tolerated with no dose-limiting toxicities, drug-related SAEs, or discontinuations due to AEs.
- In patients with CS, telotristat etiprate is producing biochemical and clinical benefit, including improvements in:
  - Daily BM frequency
  - Flushing episode frequency
  - Urinary 5-HIAA levels
  - Adequate relief of GI symptoms
- As of October 2011, 8 patients have been treated; 7 patients have completed the ascending dose study. Accrual is ongoing and open through December 2011.

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

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