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CARCINOIOD 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 CARCINOIOD SYNDROME. LX1606 IS AN ORALLY-DELIVERED INHIBITOR OF THE RATE-LIMITING ENZYMES IN 5-HT SYNTHESIS, TRYPTOPHAN HYDROXYLASE (TPH) and 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. LX1606 (aka LX1032), offers a potentially novel therapeutic approach to CS palliation.

Current enrollment: 16 patients have been treated in the dose escalation phase. LX1606 500 mg TID has been identified as the optimal dose. As of May 2011, enrollment is ongoing in the expansion phase.

ClinicalTrials.gov registry: NCT00853047

STUDY OVERVIEW

This study is evaluating the safety, tolerability, and preliminary efficacy of LX1606 in patients with CS. Endpoints included: reduction in daily bowel movements (BM), cutaneous flushing episodes, abdominal discomfort, and use of rescue short-acting octreotide or other rescue medication. Pharmacokinetics and pharmacodynamics (including whole blood 5-HT and urinary 5-HIAA) will also be assessed.

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, ascending multidose study in patients with symptomatic carcinoid syndrome despite stable-dose octreotide and/or placebo/LAR depot therapy. This study is being conducted in the U.S.

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).

LX1606 is an orally-delivered inhibitor of the rate-limiting enzymes in 5-HT synthesis, tryptophan hydroxylase (TPH). LX1606 has been shown in preclinical, as well as clinical studies, to reduce peripheral 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. LX1606 (aka LX1032), offers a potentially novel therapeutic approach to CS palliation.

LX1606 has been granted “Fast Track” designation by the FDA for the treatment of gastrointestinal symptoms associated with CS in refractory patients (those who no longer respond to standard therapy), and has orphan drug status in the E.U. for treatment of carcinoid tumors in certain patients.

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STUDY DESIGN

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Two-part study:
Part 1: Dose-escalation
Part 2: Confirmation of dose selection

The study consists of:
- Pre-treatment period (up to 6 months, including screening and run-in, i.e., a 28-day period to establish baseline symptoms).
- Treatment period (28 days)
- Follow-up period (14 days)

Patients who complete the Treatment Period are allowed to participate in an optional 24-month, open-label extension period.

Number of Patients:
- Part 1: 16 patients
- Part 2: up to 8 patients

A total of up to 24 patients

Randomization is being conducted centrally.

OBJECTIVES

Primary
To evaluate the safety and tolerability of orally administered LX1606 in patients with symptomatic carcinoid syndrome

Secondary
- To assess the effects of LX1606 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 LX1606 in patients with carcinoid syndrome by evaluating a change from baseline in:
  - Stool form
  - The sensation of urgency to defecate
- Subjective global assessment of symptoms associated with carcinoid syndrome
- Subjective assessment of abdominal pain or discomfort
- Cutaneous flushing episodes
- To evaluate effects on the frequency of rescue, short-acting octreotide use
- To assess the pharmacodynamic effects of LX1606 by assessing 5-HT levels in blood over time versus baseline
- To assess the pharmacodynamic effects of LX1606 by assessing 5-HIAA levels in urine over time versus baseline

PATIENT SELECTION

Patients are eligible if they meet all inclusion and no exclusion criteria. Inclusion criteria:
1. Age 18 years or older
2. Male or female; males and females of childbearing potential must study in patients with metastatic carcinoid tumors may reduce many of the symptoms and sequelae commonly associated with carcinoid syndrome. LX1606 (aka LX1032), offers a potentially novel therapeutic approach to CS palliation.

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This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, ascending multidose study in patients with symptomatic carcinoid syndrome despite stable-dose octreotide and/or other rescue medication. Pharmacokinetics and pharmacodynamics (including whole blood 5-HT and urinary 5-HIAA) will also be assessed.


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ASSESSMENTS

Efficacy
The primary efficacy measure will be the number of daily bowel movements. Secondary efficacy measures will include:
- 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 will include monitoring of adverse events, clinical laboratory parameters (hematology, blood chemistry, and urinalysis), vital signs (blood pressure, heart rate, pulse, and oral temperature), 12-lead electrocardiograms, and physical examinations.

Pharmacokinetics
Blood samples for the purposes of determining LX1606 (produg) and LP-779902 (active moiety) concentrations in plasma will be collected at baseline (predose Day 1), and at each weekly visit thereafter (Weeks 1, 2, 3, and 4), then periodically throughout the extension period.

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

DISCUSSION

Carcinoid syndrome represents a variable symptom complex that emerges following metastasis of neuroendocrine tumors. These tumor cells are well known for their ability to secrete large amounts of neuroendocrine mediators; of these, 5-HT is one of the best characterized. Excessive 5-HT is one of the hallmarks of carcinoid syndrome and is thought to be responsible for many of the symptoms associated with carcinoid syndrome.

Somatostatin analogues (SA) have been shown to be effective at ameliorating many of the symptoms clinically associated with carcinoid syndrome. However, over time, patients with carcinoid syndrome may develop refractory symptoms.

LX1606 potentially represents a novel approach to symptom control and is being tested in patients with carcinoid syndrome. Its mechanism of action is to inhibit TPH, the rate-limiting enzyme in 5-HT biosynthesis, and thereby reduce the amount of 5-HT secreted by the tumors. As it focuses on a different target than the SA, it potentially may offer symptom management for patients refractory to SA. In addition, LX1606 is an orally-delivered agent, it may offer enhanced convenience to the patient. By lowering the amount of 5-HT secreted by these tumors, longer-term sequelae of carcinoid syndrome attributable to excess 5-HT may be delayed.

Ongoing proof-of-concept studies are directed at evaluating the influence of LX1606 on symptoms of carcinoid syndrome as well as determining its impact on disease progression. Currently, an open-label study is accruing carcinoid syndrome patients in the UK and Germany. Future studies will focus on signals identified in these ongoing exploratory evaluations.

Presented at the American Society of Clinical Oncology Annual Meeting – Chicago, IL June 3-7, 2011

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