LX1032: A Novel Agent to Reduce Peripheral Serotonin as a Potential Treatment for Carcinoid Syndrome

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INTRODUCTION

LX1032 is a novel, orally delivered, inhibitor of tryptophan hydroxylase (TPH), the rate-limiting enzyme in the biosynthesis of serotonin (5-HT). Elevated 5-HT is a hallmark finding in carcinoid tumors, and in advanced forms of the disease 5-HT is thought to contribute to symptoms associated with carcinoid syndrome (CS), including diarrhea, abdominal pain and cramping, as well as longer-term disease sequelae such as malnutrition and cardiac fibrosis. In advanced tumors, morbidity and mortality often relate as much to the secretion of 5-HT and peptide hormones, as to tumor growth and metastasis.

In humans, as well as in other mammals, there are two distinct TPH genes that encode two isoforms of TPH (TPH1 and TPH2), found predominantly in the enterochromaffin (EC) cells of the GI tract, and TPH1, which is expressed in neuronal cell types and is the predominant isoenzyme in the brain. The vast majority (95%) of 5-HT is produced in the periphery, principally by EC cells.

Prior experience in the 1960s with another TPH inhibitor, para-chlorophenylalanine (pCPA), illustrated that reduction in 5-HT synthesis could provide a significant improvement in symptoms of patients with CS. Further development of pCPA was ultimately curtailed because it crossed the blood-brain-barrier, resulting in depletion of brain 5-HT and subsequent neuro-psychiatric side effects, such as depression. Therefore we developed an agent capable of inhibiting 5-HT production in the periphery without affecting brain 5-HT production that could potentially exert a therapeutic effect on multiple CS symptoms without causing undesired effects in the CNS. Consistent with this approach, TPH1 knockdown mice, which have almost no intestinal 5-HT but normal levels of brain 5-HT, displayed no abnormalities in any neurobehavioral tests.

In preclinical studies, LX1032 was shown to reduce peripheral 5-HT in a dose-dependent fashion without affecting brain 5-HT, recapitulating the TPI knockout mouse phenotype (Figure 2). These important preclinical observations have translated into favorable results in Phase 1 clinical studies involving 111 healthy volunteers. In Phase 1 studies, LX1032 was well tolerated and produced a reduction in peripheral 5-HT levels, suggesting that LX1032 may provide a new approach for the management of many of the symptoms and morbidity experienced by patients with CS, by altering peripheral 5-HT levels without impacting brain 5-HT.

METHODS

LX1032 is a novel oral TPH inhibitor, was designed to modulate peripheral serotonin levels without impacting brain serotonin levels. Dose levels up to 500 mg TID over 14 days were well tolerated in normal healthy volunteers.

In a Phase 2 clinical trial in patients with CS, LX1032 was well tolerated without serious adverse events or dose-limiting toxicities observed up to 2000 mg administered as 500 mg TID. Significant reductions in 24-hour urinary 5-HIAA (Figure 6), as well as whole-blood 5-HT (Figure 6), in the mid to high dose levels indicate inhibition of the target enzyme in the GI tract. These changes in urinary 5-HIAA and whole-blood 5-HT provide initial confirmation of human pharmacodynamics.

The most common occurring AEs were nausea (27%), headache (20%), constipation (20%), diarrhea (10%) and abdominal pain (10%) (Table 1).

No clinically significant changes were observed in standard liver function tests, renal function tests, vital signs, electrocardiograms, or physical examination findings. Laboratory data, including chemistry, hematology, and urinalysis, were evaluated throughout the study. The only finding of any significance was a dose-related increase in total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase.

CONCLUSIONS

Modulating peripheral 5-HT production via inhibition of TPH represents a potential new approach to the management of many of the symptoms experienced by patients with carcinoid syndrome.

LX1032, a novel oral TPH inhibitor, was designed to modulate peripheral serotonin levels without impacting brain serotonin levels.

Modulating peripheral 5-HT levels provides initial confirmation of human pharmacodynamics.

The pharmacokinetic profile for all dose groups was consistent with preclinical predictions. Absorption and conversion to the active moiety through esterase activity was rapid.

The reduction in 5-HT production, coupled with the observed safety profile, supports a potential therapeutic rational for Phase 2 clinical trials in patients with carcinoid syndrome.

A study is ongoing in the U.S. evaluating LX1032 in patients experiencing symptomatic carcinoid syndrome despite maximal stable-dose somatostatin analog therapy.

RESULTS

Table 1. LX1032 MAD Study AE Summary

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Number of Subjects with AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Disorders</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>0</td>
</tr>
<tr>
<td>General Disorders</td>
<td>0</td>
</tr>
<tr>
<td>Administration Site Conditions</td>
<td>0</td>
</tr>
<tr>
<td>Infections, Infestations</td>
<td>0</td>
</tr>
<tr>
<td>Injuries (Job value or physical finding)</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>0</td>
</tr>
</tbody>
</table>

Total subjects with an AE: 6 (9%) 26 (39%)

DISCLOSURE: The authors of this poster are employees of, and have received stock options from, Lexicon Pharmaceuticals, Inc.