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LX1032: A Novel Agent to Reduce Serotonin In Carcinoid Syndrome

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Background: Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the biosynthesis of serotonin (5-HT). TPH1, the isoform located in enterochromaffin cells, is responsible for the majority of systemic 5-HT production. Patients with carcinoid syndrome (CS) commonly have gastrointestinal symptoms, due to increased 5-HT produced by metastatic GI tumor cells. LX1032 is an oral TPH inhibitor which represents a new mechanism for potentially managing GI symptoms associated with CS by reducing 5HT production.

Methods: Single (n=47 subjects) and multiple (n=40 subjects) ascending dose studies with LX1032 have been completed in normal volunteers. Twenty four hour urinary 5-HIAA and blood 5-HT were measured as biomarkers of pharmacodynamic activity.

Results: LX1032 produced a significant dose-dependent reduction in urinary 5-HIAA and blood 5-HT levels, with maximal reductions observed at doses ≥500 mg, once daily, in the 14 day multiple ascending dose (MAD) study. Single doses up to 500 mg were well tolerated with no evidence of dose-limiting toxicity or tolerability; GI related adverse events (nausea, emesis, and diarrhea) started to emerge at the 1000 mg dose level and became dose-limiting at the 1500 mg single dose level. Multiple doses were well tolerated at all dose levels up to 1500 mg (500 mg TID). Adverse events (AEs) were mild to moderate and no serious AEs occurred; a dose-dependent, mild increase in hepatic transaminase levels was observed in the MAD study.

Conclusion: Inhibiting TPH, and thereby reducing peripheral 5-HT production, represents a potential new approach for managing GI symptoms in CS patients. LX1032 is a novel, orally bioavailable TPH inhibitor that significantly reduces 5-HT production and is well tolerated. The favorable safety profile and observed decrease in urinary 5-HIAA and blood 5-HT levels indicate that LX1032 could be used to lower 5-HT as a potential new approach for managing hyperserotonemia-related complications of CS.