Efficacy and Safety Results of Telotristat Ethyl in Patients with Carcinoid Syndrome During the Double-blind Treatment Period of the TELECAST Phase 3 Clinical Trial

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Background: Serotonin overproduction by neuroendocrine tumors is a feature of carcinoid syndrome (CS), which is characterized by diarrhea, flushing, and valvular heart disease. In a previous pivotal Phase 3 trial (TELESTAR) in patients with CS experiencing on average ≥4 bowel movements (BMs)/day despite stable-dose somatostatin analog (SSA) therapy, the tryptophan hydroxylase inhibitor telotristat etiprate (TE) reduced BM frequency and urinary 5-hydroxyindoleacetic acid (u5-HIAA), a serotonin metabolite. TELECAST was another double-blind, placebo-controlled, Phase 3 study evaluating safety and efficacy of TE in SSA-treated and SSA-naïve patients with less-severe gastrointestinal symptoms than TELESTAR patients.

Methods: All eligible patients (N=76) were experiencing ≥1 prespecified CS-associated symptom; SSA-treated patients were required to have <4 BMs/day. Patients were randomly assigned (1:1:1) to receive placebo (n=26), TE 250 mg (n=25), or TE 500 mg (n=25) orally 3x/day for 12 weeks. Safety and change from baseline in u5-HIAA at Week 12 were co-primary endpoints. Responders were predefined as patients experiencing ≥30% reduction in BM frequency for ≥50% of days.

Results: At baseline, across all groups, mean BM frequency was 2.5 BMs/day (range: 2.2–2.8) and mean u5-HIAA was 78 mg/day (range: 66–86); ≥92% of patients were receiving SSA therapy. Estimated treatment differences in mean u5-HIAA compared with placebo were –30 mg/day (–54%; P<0.001) for TE 250 mg and –41 mg/day (–90%; P<0.001) for TE 500 mg.

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On each TE dosage, 10 (40%) patients were BM responders versus 0 on placebo.
Serious adverse events and study discontinuations were infrequent (Table 1). The incidence of gastrointestinal-related adverse events (AEs) was similar across groups. Mild or moderate hepatic enzyme elevations were observed in TE-treated patients, and depression-related AEs occurred in 2 placebo and 2 TE patients (1/dosage); none of these AEs led to study discontinuation.

Conclusion: TE significantly reduced u5-HIAA and BM frequency and was well tolerated.

Table 1: Key safety results of the double-blind treatment period of the TELECAST study

	Placebo (n=26)	TE 250 mg tid (n=25)	TE 500 mg tid (n=25)
≥1 serious AE, n (%)*	5 (19.2)	1 (4.0)	2 (8.0)
Treatment discontinuations due to AEs, n (%)	1 (3.8)	2 (8.0)	
Depression-related AEs, n (%)†	2 (7.7)	1 (4.0)	1 (4.0)
Hepatic enzyme elevations, n (%)		2 (8.0)	3 (12.0)
Elevated GGT, n (%)		1 (4.0)	1 (4.0)
Elevated ALT, n (%)		1 (4.0)	
Any GI-related AE, n (%)	15 (57.7)	16 (64.0)	9 (36.0)
Abdominal pain, n (%)	4 (15.4)	8 (32.0)	
Nausea, n (%)‡	4 (15.4)	3 (12.0)	2 (8.0)

*The following serious AEs were reported: placebo – disease progression, cerebrovascular accident, bronchiectasis, dyspnea, urethral stent insertion; TE 250 mg – disease progression; TE 500 mg – ascites and disease progression. No deaths occurred during the double-blind treatment period. †All cases of depression-related AEs, including depression, depressed mood, and decreased interest, were mild or moderate in intensity, and none led to treatment discontinuation. ‡All cases of nausea were mild or moderate in intensity, and none led to treatment discontinuation. AE, adverse event; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; GI, gastrointestinal; TE, telotristat etiprate; tid, 3x/day.