C39

Telotristat Etiprate in a Subset of Carcinoid Syndrome Patients who have High Levels of Urinary 5-hydroxyindoleacetic Acid and Frequent Flushing

Darren Wheeler[1]; Dieter Hörsch[2]; Juan Valle[3]; Pablo Lapuerta[1]; Brian Zambrowicz[1]; Arthur Sands[1]; Douglas Fleming[1]

[1]Lexicon Pharmaceuticals, Inc, The Woodlands, TX 77381, USA
[2]Zentralink Bad Berka GmbH, 99437 Bad Berka, Germany
[3]The University of Manchester / The Christie NHS Foundation Trust, Manchester, Department of Medical Oncology, Manchester M13 9NT, UK

Background: Serotonin is a key mediator of carcinoid syndrome (CS), which includes gastrointestinal symptoms and flushing. High levels of urinary 5-hydroxyindoleacetic acid (u5-HIAA, a serotonin metabolite) have been linked with carcinoid heart disease (CaHD). Additionally, CS patients having >3 flushing episodes/day have a 5-fold risk of developing CaHD. Telotristat etiprate is an oral inhibitor of serotonin synthesis in Phase 3 development for the treatment of CS. There is limited information on the potential benefits of serotonin reduction in patients who may be at higher risk for CaHD.

Methods: We retrospectively reviewed data on all patients who received telotristat etiprate in a Phase 2 trial for CS. In patients with identified risk factors for developing CaHD (elevated u5-HIAA and >3 flushing episodes/day), we assessed baseline characteristics, reductions in u5-HIAA, improvements in daily bowel movements (BMs), and flushing frequency, as well as adverse events while on telotristat etiprate.

Results: Of the 15 enrolled patients, 5 patients (33%) met the criteria and had complete 12-week data available, including a patient diagnosed with CaHD 1 month before entering study. At baseline, these 5 patients had elevated u5-HIAA levels (mean 97 mg/24 hrs, range 11 to 282 mg/24 hrs) despite use of somatostatin analogs (SSAs) (3/5 patients), as well as inadequately controlled CS (≥4 daily BMs and ≥3 episodes of flushing/day). At week 12, u5-HIAA levels were reduced (mean reduction 67%, range 44 to 97%). There was also reduction in BM frequency (mean reduction 52%, range 32 to 72%) and daily flushing (mean reduction 45%, range -3 to 86%). There was 1 SAE of gastroenteritis, not considered drug-related.

Conclusions: In CS patients with CaHD or at risk for CaHD, u5-HIAA levels, flushing, and BM frequency all decreased substantially within 12 weeks of telotristat etiprate treatment.

Patient	u5-HIAA (mg/24 hour)			Average daily BM frequency			Average daily flushing frequency		
	Baseline	12 wks TE	Change (%)	Baseline	9-12 wks TE	Change (%)	Baseline	9-12 wks TE	Change (%)
A	77.0	43.0	-44	8.2	4.9	-40	11.4	11.7	+3
B	11.3	2.6	-77	8.5	2.7	-68	3.0	0.5	-83
C	282.0	150.0	-47	4.0	2.7	-32	6.2	3.8	-39
D	67.9	2.1	-97	5.0	1.4	-72	3.6	0.5	-86
E	49.4	15.6	-68	5.5	2.9	-47	3.9	3.1	-21
Mean			-67			-52			-45