Efficacy and Safety of Telotristat Ethyl in Patients With Carcinoid Syndrome Inadequately Controlled by Somatostatin Analogs: Analysis of the Completed TELESTAR Extension Period

Background

Carcinoid syndrome (CS) affects 1 in 2000 patients with neuroendocrine tumors (NETs) and is characterized by an increased production of serotonin, which causes diarrhea, flushing, and a variety of cardiovascular symptoms. Somatostatin analogs (SSAs) are the standard treatment for patients with CS, but patients may develop intolerance to these agents.

Telotristat ethyl (TEL) is a novel, oral, selective indole-3-propionic acid hydroxylase inhibitor that decreases serotonin production. TEL was previously studied in NETs and failed to reach the phase III clinical trial endpoint for urinary 5-hydroxyindoleacetic acid (u5-HIAA) reductions in the TELESTAR trial. In this study, we evaluated the pharmacodynamic profile and safety of TEL in patients who failed to achieve adequate u5-HIAA reduction with SSA therapy during the placebo-controlled phase of TELESTAR.

Methods

Study design

This was a single-centre, double-blind, placebo-controlled, parallel-group study consisting of a 12-week double-blind treatment (DBT) period and a 12-week open-label extension (OLE) period. All patients entered the OLE period after completing the DBT period. Patients were randomized 1:1 to receive placebo or TEL 500 mg tid. The primary endpoint was the reduction in u5-HIAA from baseline to week 12 of the DBT period.

Key inclusion criteria

Patients with CS due to a NET of any type, who had previously enrolled in the TELESTAR DBT period and had no u5-HIAA reductions ≥50% from baseline at the end of the DBT period. Patients were enrolled in the OLE period if they were not asymptomatic and had a baseline u5-HIAA level ≥5 mg/day.

Key exclusion criteria

Patients who were taking any investigational or non-investigational drug within 14 days prior to study entry or who were planning to take any investigational or non-investigational drug during the study. Patients with a history of severe asthma or chronic obstructive pulmonary disease were also excluded.

Results

The study enrolled 115 patients who crossed over from placebo to TEL 500 mg tid. The mean baseline u5-HIAA level was 64.9 mg/day. During the 12-week DBT period, the mean reduction in u5-HIAA was 34 mg/day (57.2%) for patients treated with TEL 500 mg tid compared to 4.4 mg/day (7.1%) for placebo. A total of 111 patients entered the OLE period, and the mean cumulative exposure to TEL was 38.4 weeks (standard deviation 11.4 weeks).

Throughout the OLE period, the overall incidences of treatment-emergent adverse events (TEAEs) and incidences of TEAEs leading to study discontinuation were similar to those of patients who remained on telotristat ethyl (631 incidences in 73/77 patients) during the OLE period.

Safety assessments

TELESTAR was a double-blind, placebo-controlled study, and there were no unexpected adverse events. The most common TEAEs were diarrhea (26.7%), abdominal pain (23.3%), and increased appetite (23.3%). The incidences of TEAEs were similar between the placebo and TEL groups during both the DBT and OLE periods.

Summary and Conclusions

Significantly greater reductions in u5-HIAA were observed at Week 12 for both telotristat ethyl 250 mg tid and telotristat ethyl 500 mg tid, and reductions persisted through Week 44. Statistically significant reductions in u5-HIAA levels for both telotristat ethyl 250 mg tid and telotristat ethyl 500 mg tid were evident 12 weeks after treatment was discontinued through Week 44. Improvements in EORTC QLQ-C30 subscale scores observed with telotristat ethyl at Week 12 were maintained through Week 44. Safety data from the 48-week study suggest that telotristat ethyl was well tolerated, with few discontinuations due to adverse events. There was no notable increase in the incidence of TEAEs in patients who crossed over from placebo to telotristat ethyl, and TEAE incidence during the OLE period was similar to that in the DBT period.

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