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Weight Change Associated With Telotristat Ethyl in the Treatment of Carcinoid Syndrome

Poster 253

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Background

- Weight loss and malnutrition in patients with malignant tumors are linked to negative outcomes, including excess mortality and morbidity and higher treatment costs.[1–3]
- Telotristat ethyl is a novel, small-molecule tryptophan hydroxylase inhibitor that decreases urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels and bowel movement (BM) frequency in patients with carcinoid syndrome (CS) and is approved by the US Food and Drug Administration and European Commission for the treatment of CS diarrhea in combination with somatostatin analog (SSA) therapy in adults whose symptoms are inadequately controlled by SSA therapy.[4,5]
- Regulatory authorities have suggested that markers of nutritional status should be examined to help explore whether the control of CS-related diarrhea achieved with telotristat ethyl is clinically relevant.

Objective

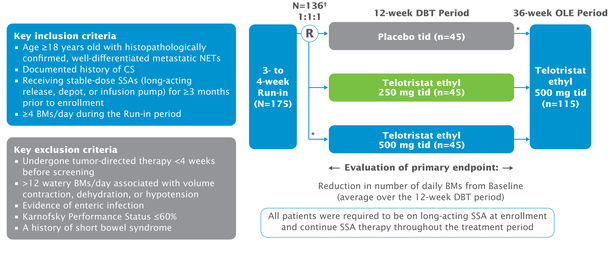
To analyze the effects of telotristat ethyl on changes in body weight, metabolic parameters, adverse events (AEs), and patient-reported outcomes with respect to patients' weight status at the end of the 12-week Double-blind Treatment (DBT) period in the Phase 3 TELESTAR study.

Methods

Study design

- TELESTAR was a Phase 3, randomized, multicenter, parallel-group, double-blind, placebo-controlled study (ClinicalTrials.gov identifier: NCT01677910, **Figure 1**).[6]

FIGURE 1: TELESTAR Study Design



*Including a blinded titration step of 1 week of 250 mg tid
†136 were randomized; 135 were treated.
BMs, bowel movements; CS, carcinoid syndrome; DBT, Double-blind Treatment; NETs, neuroendocrine tumors; OLE, Open-label Extension; R, randomization, SSA, somatostatin analog; tid, 3 times per day

Assessments

- The calculation of the incidence of weight change of ≥3% at Week 12 was prespecified.
- Incidence of treatment-emergent adverse events (TEAEs) and patient-reported outcomes from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) stratified by alterations in body weight
- Statistical tests were conducted post hoc and for descriptive purposes only.

Results

- Out of 135 patients randomly assigned, 120 had data available for analysis (**Table 1**).
- Fifteen patients did not have body weight measured at Baseline (n=2), Week 12 (n=11), or both (n=2).
- Of the 11 patients without Week 12 body weight data, 9 discontinued prior to Week 12 and 2 completed Week 12 but did not have their body weight measured.
- The mean durations of treatment exposure were 12.14, 11.73, and 10.75 weeks among patients with weight gain, stable weight, and weight loss, respectively.

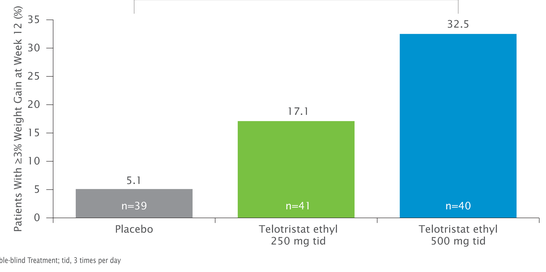
TABLE 1: Patient Demographics

Characteristics	≥3% weight gain (n=22)	Stable weight (n=83)	≥3% weight loss (n=15)	p-value*
Mean age, years (SD)	62.4 (11)	63.4 (8.7)	66.3 (7.7)	0.23
Female, %	54.5	44.6	40	0.66
White, %	95.5	88.0	93.3	
Body weight, kg (SD)	68.6 (17.6)	73.7 (15.7)	69.0 (16.1)	0.31
BMI, kg/m^2 (SD)	24.2 (5.7)	25.3 (4.6)	24.6 (5.0)	0.47
Treatment with SSA, % Octreotide Lanreotide	 63.6 36.4	 78.3 21.7	 93.3 6.7	0.11
u5-HIAA ≤ULN[a], %	22.7	32.5	20.0	0.21

*p-values refer to Kruskal–Wallis test of group differences (≥3% weight gain, stable weight, or ≥3% weight loss groups) and are descriptive.
†The reference range for u5-HIAA was 0–10 mg per 24 hours prior to June 27, 2013, and 0–15 mg per 24 hours on and after June 27, 2013.
Patients were stratified into 3 groups, according to alteration of their body weight during the DBT period.
BMI, body mass index; DBT, Double-blind Treatment; SD, standard deviation; SSA, somatostatin analog; u5-HIAA, urinary 5-hydroxyindoleacetic acid; ULN, upper limit of normal

- Weight gain ≥3% at Week 12 was observed in 2/39 (5.1%) patients on placebo, 7/41 (17.1%) patients on telotristat ethyl 250 mg 3 times per day, and 13/40 (32.5%) patients on telotristat ethyl 500 mg 3 times per day.
- The trend in weight gain incidence was significantly different across groups (Cochran–Armitage test, p = 0.0017) (**Figure 2**).
- Among 20 patients with a ≥3% weight gain on telotristat ethyl, 10 experienced a reduction of at least 30% in BM frequency at Week 12.
- Among patients with ≥3% weight gain and ≥3% weight loss, the mean percent changes in weight from Baseline to Week 12 were 4.9% and –7.2%, respectively.

FIGURE 2: Weight Gain of ≥3% During the DBT Period, by Treatment Group



DBT, Double-blind Treatment; tid, 3 times per day

- Increases in serum cholesterol, along with unchanged serum creatinine clearance, suggest that the observed weight gain is not solely related to rehydration and could represent true metabolic improvement (**Table 2**).

TABLE 2: Mean Changes in Metabolic Parameters Related to Nutritional Status

Mean change from Baseline to Week 12	≥3% weight gain (n=22)	Stable weight (n=83)	≥3% weight loss (n=15)	p-value*
Albumin, g/L	0.6	0.2	–2.5	0.020
Cholesterol, mmol/L	0.431	0.239	–0.411	0.001
Creatinine clearance, mL/min	2.2	8.0	–1.8	0.24
Triglycerides, mmol/L	0.295	0.095	0.018	0.59

*p-values refer to Kruskal–Wallis test of group differences (≥3% weight gain, stable weight, or ≥3% weight loss groups) and are descriptive.
Patients were stratified into 3 groups, according to alteration of their body weight during the DBT period.
DBT, Double-blind Treatment

- Patients with weight gain showed a trend toward lower rates of AEs (**Table 3**).
- AEs of decreased appetite, cachexia, and performance status decreased were reported during the DBT period among those with weight loss but not those with weight gain.

TABLE 3: Patients With Adverse Events During the DBT Period

Category, n (%)	≥3% weight gain (n=22)	Stable weight (n=83)	≥3% weight loss (n=15)
Any TEAE	17 (77.3%)	73 (88.0%)	15 (100%)
Severe TEAE	0	8 (9.6%)	8 (53.3%)
Serious TEAE	1 (4.5%)	9 (10.8%)	6 (40.0%)
Study drug discontinuation due to TEAE	0	5 (6.0%)	2 (13.3%)
Study discontinuation due to TEAE[a]	0	3 (3.6%)	2 (13.3%)
TEAE resulting in death	0	0	0

Patients were stratified into 3 groups, according to alteration of their body weight during the DBT period.
[a]TEAEs leading to study discontinuation were anemia, cardiac arrest, nausea, vomiting, eructation, dyspepsia, chills, fatigue, general health deterioration, dehydration, disease progression (5 patients), sepsis, rash, and increased gamma-glutamyl transferase.
DBT, Double-blind Treatment; TEAE, treatment-emergent adverse event

- More favorable mean improvements in patient-reported outcomes were identified on the EORTC QLQ-C30 items relating to global status/quality of life, physical function, and gastrointestinal function for patients who had experienced weight gain during the 12-week DBT period (**Table 4**).

TABLE 4: Patient-reported Outcomes Based on EORTC QLQ-C30 Items[a]

	≥3% weight gain (n=22)	Stable weight (n=83)	≥3% weight loss (n=15)	p-value*
Domains where higher values reflect worsening				
Appetite loss	–7.5	–3.3	4.8	0.06
Diarrhea	–18.4	–14.3	–7.8	0.27
Nausea and vomiting	–7.1	–1.9	4.4	0.09
Fatigue	–5.6	–2.6	2.2	0.39
Domains where higher values reflect improvement				
Physical function	1.2	0.7	–7.8	0.08
Global status/quality of life	4.6	1.9	–20.6	<0.001

*p-values refer to Kruskal–Wallis test of group differences (≥3% weight gain, stable weight, or ≥3% weight loss groups) and are descriptive.
[a]Relating to global status/quality of life, physical function, and items relating to gastrointestinal function. The presented scores reflect mean changes from Baseline, averaged over the 12-week DBT period.
Patients were stratified into 3 groups, according to alteration of their body weight during the DBT period.
DBT, Double-blind Treatment; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

Summary and Conclusions

- Among patients with CS, the use of telotristat ethyl in the TELESTAR trial was associated with a significant increase in the incidence of at least 3% weight gain from Baseline.
  - The incidence of weight gain on telotristat ethyl was dose related and greater than the incidence of weight gain on placebo.
  - Weight gain may have been related to reduced incidence of diarrhea.
- Patients with weight gain showed evidence of increased serum cholesterol, which could indicate an improvement in nutritional status.
- Patients with weight gain had lower rates of serious AEs and mean improvements in patient-reported outcomes compared with patients with stable weight or weight loss.

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DISCLOSURES

MOW: Ipsen, Novartis Pharmaceuticals, and Pfizer. DH: Lexicon Pharmaceuticals, Inc., Ipsen Bioscience, Novartis Pharmaceuticals, and Pfizer. PL, RF, AK, KA, and QMY: employees of Lexicon Pharmaceuticals, Inc. Authors who are employees of Lexicon Pharmaceuticals, Inc., may have common stock or may have been granted stock options or other equity incentive awards. MP: Lexicon Pharmaceuticals, Inc., and Ipsen. JWV: Ipsen, Novartis Pharmaceuticals, Pfizer, and Advanced Accelerator Applications. MEC: Lexicon Pharmaceuticals, Inc., Novartis Pharmaceuticals, and Ipsen Biopharmaceuticals. EB: Lexicon Pharmaceuticals, Inc. PLK: Lexicon Pharmaceuticals, Inc., Advanced Accelerator Applications, Dicerna, Esanex, Genentech, Merck, Oxigene, Ipsen, and Novartis Pharmaceuticals. LBA: Lexicon Pharmaceuticals, Inc., Novartis Pharmaceuticals, AbbVie Pharmaceuticals, Inc., Mateon Pharmaceuticals, Inc., Markey Cancer Foundation, Helsinn Pharmaceuticals, Inc., and Entrinsic Health Solutions, LLC. KO: Novartis Pharmaceuticals and Ipsen. RRPW: Lexicon Pharmaceuticals, Inc. MHK: Lexicon Pharmaceuticals, Inc., Ipsen Bioscience, and Novartis Pharmaceuticals. GK, EG, SW, and CLB: nothing to disclose.

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