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Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome

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ORIGINAL REPORT

Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome

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ABSTRACT

Purpose

Preliminary studies suggested that telotristat ethyl, a tryptophan hydroxylase inhibitor, reduces bowel movement (BM) frequency in patients with carcinoid syndrome. This placebo-controlled phase III study evaluated telotristat ethyl in this setting.

Patients and Methods

Patients (N = 135) experiencing four or more BMs per day despite stable-dose somatostatin analog therapy received (1:1:1) placebo, telotristat ethyl 250 mg, or telotristat ethyl 500 mg three times per day orally during a 12-week double-blind treatment period. The primary end point was change from baseline in BM frequency. In an open-label extension, 115 patients subsequently received telotristat ethyl 500 mg.

Results

Estimated differences in BM frequency per day versus placebo averaged over 12 weeks were –0.81 for telotristat ethyl 250 mg ($P < .001$) and –0.69 for telotristat ethyl 500 mg ($P < .001$). At week 12, mean BM frequency reductions per day for placebo, telotristat ethyl 250 mg, and telotristat ethyl 500 mg were –0.9, –1.7, and –2.1, respectively. Responses, predefined as a BM frequency reduction ≥ 30% from baseline for ≥ 50% of the double-blind treatment period, were observed in 20%, 44%, and 42% of patients given placebo, telotristat ethyl 250 mg, and telotristat ethyl 500 mg, respectively. Both telotristat ethyl dosages significantly reduced mean urinary 5-hydroxyindole acetic acid versus placebo at week 12 ($P < .001$). Mild nausea and asymptomatic increases in gamma-glutamyl transferase were observed in some patients receiving telotristat ethyl. Follow-up of patients during the open-label extension revealed no new safety signals and suggested sustained BM responses to treatment.

Conclusion

Among patients with carcinoid syndrome not adequately controlled by somatostatin analogs, treatment with telotristat ethyl was generally safe and well tolerated and resulted in significant reductions in BM frequency and urinary 5-hydroxyindole acetic acid.

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INTRODUCTION

Patients with advanced neuroendocrine tumors (NETs) may develop carcinoid syndrome, a condition associated with tumoral secretion of serotonin and characterized by diarrhea, flushing, bronchial constriction, and the development of cardiac valvular fibrosis, which may lead to heart failure.[1,2] Diarrhea, one of the most prominent symptoms of carcinoid syndrome, negatively affects patients' emotional well-being and social and physical functioning.[3] Serotonin is metabolized into 5-hydroxyindoleacetic acid (5-HIAA), a biomarker measurable in the urine and often used to follow treatment response in patients with carcinoid syndrome.[4,5] High systemic serotonin levels, as reflected by elevated urinary 5-HIAA (u5-HIAA), most often in the setting of widespread tumor metastases, are associated with severe carcinoid syndrome, carcinoid heart disease, and poor prognosis.[2,6,7]

Somatostatin analogs (SSAs), the standard treatment for patients with carcinoid syndrome, are an effective initial treatment, but patients may develop recurrent symptoms during the course of

ASSOCIATED CONTENT

Appendix
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their disease.[4,8] Tryptophan hydroxylase (TPH), the rate-limiting enzyme in serotonin synthesis, converts tryptophan to 5-hydroxytryptophan, which is subsequently converted to serotonin.[5] The hypothesis that inhibiting TPH may reduce symptoms of carcinoid syndrome was tested in 1967 by Engelman et al[9] with parachlorophenylalanine. In that study, symptoms improved and u5-HIAA levels were reduced. However, parachlorophenylalanine crossed the blood-brain barrier, causing severe CNS-related adverse effects, including depression.

Telotristat ethyl is a novel, oral, small-molecule TPH inhibitor that has a high molecular weight and acidic moieties, which inhibit it from crossing the blood-brain barrier.[5,10] Two early studies in patients with carcinoid syndrome suggested that telotristat etiprate, the hippurate salt of telotristat ethyl, reduced bowel movement (BM) frequency and decreased u5-HIAA without overt CNS adverse effects.[11,12] Although the name "telotristat etiprate" was previously granted by the United States Adopted Names Council and has been used in the literature,[11,12] recent guidance from the US Food and Drug Administration recommends using the name of the neutral form rather than the name of the salt for drug products. Therefore, telotristat ethyl is used herein. In this international, multicenter, randomized, double-blind, placebo-controlled phase III trial (TELESTAR), we assessed the safety and efficacy of telotristat ethyl in patients with carcinoid syndrome not adequately controlled with SSA therapy.

PATIENTS AND METHODS

Patients

Eligible patients were ≥18 years of age, had histopathologically confirmed, well-differentiated metastatic NETs, had a documented history of carcinoid syndrome, were experiencing an average of four or more BMs per day, and were receiving stable-dose SSAs (long-acting release [LAR], depot, or infusion pump) for ≥ 3 months before enrollment. Patients with u5-HIAA levels above or below the upper limit of normal (normal: 0 to 15 mg/24 hours[13]) and those with unknown values at baseline were allowed to participate. Because of the risk of acute complications from severe diarrhea, patients experiencing more than 12 watery BMs per day associated with volume contraction, dehydration, or hypotension, or showing evidence of enteric infection were excluded. In addition, patients with a Karnofsky performance status ≤ 60%, a history of short bowel syndrome, or clinically important baseline elevation in liver function tests were excluded. Patients were also excluded if they had recently undergone tumor-directed therapy. Additional exclusion criteria are described in the Data Supplement.

Study Design and Treatment

Patients entered a screening period of 3 or 4 weeks, depending upon their SSA dose schedule (typically administered every 3 to 4 weeks),[14] to establish baseline symptoms. Patients were randomly assigned 1:1:1 to receive oral doses, three times per day for 12 weeks, of telotristat ethyl 250 mg, telotristat ethyl 500 mg, or placebo. Patients continued to receive their baseline SSA therapy for all 12 weeks. Rescue use of short-acting octreotide and antidiarrheal agents was allowed and unrestricted. After this double-blind treatment (DBT) period, all patients were offered treatment with telotristat ethyl 500 mg three times per day in a 36-week open-label extension (OLE). Downward dose adjustment was allowed in cases of intolerability. The OLE is currently ongoing. Conduct of the study was approved by the institutional review board or ethics committee at each center, and the study complied with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Efficacy and Safety Assessments

All primary and secondary efficacy assessments, except u5-HIAA, were self-reported in daily electronic diaries. The primary end point of the study was mean reduction from baseline in daily BMs averaged over 12 weeks. Key secondary end points included change from baseline in u5-HIAA at week 12, the number of daily flushing episodes, and abdominal pain severity (on a scale of 0 to 10) averaged over 12 weeks. Responders were prespecified as patients experiencing a ≥ 30% reduction in BM frequency (relative to baseline) for ≥ 50% of the DBT period. Additional efficacy end points included change from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) scores, rescue short-acting SSA use, stool consistency, and the proportion of days with urgency to defecate (Data Supplement). Patient use of over-the-counter antidiarrheals was not tracked in this study.

Adverse events (AEs) were graded as mild, moderate, or severe (Data Supplement). Depression-related AEs were events of special interest, and a validated two-question case-finding instrument was administered to all patients at each study visit.[15] A pharmacokinetic analysis substudy was performed in 40 patients (Data Supplement). The planned efficacy analyses were based on the intent-to-treat population. However, a single patient initially randomly assigned to receive telotristat ethyl 500 mg was subsequently deemed a screen failure and was not treated. This same patient was subsequently re-evaluated, found to meet all eligibility criteria, randomly assigned a second time to telotristat ethyl 250 mg, and included in the telotristat ethyl 250 mg group for analysis of efficacy and safety. The safety population consisted of all patients who received at least one dose of the study drug.

Statistical Analysis

A blocked Wilcoxon rank sum statistic (stratified by baseline u5-HIAA levels) was used to evaluate the primary efficacy end point. The nonparametric Hodges-Lehmann estimator was used to describe the magnitude of the treatment effect. Parallel analyses were used for additional efficacy end points, including change from baseline in u5-HIAA level, number of flushing episodes, abdominal pain severity, EORTC QLQ-C30 scores, stool consistency, and the proportion of days with urgency to defecate. A Bonferroni-based multiple comparison procedure with restrictions on the order of testing treatment group hypotheses was applied to control the local and overall type I error probabilities ($\alpha = .05$) for the primary and secondary efficacy end points. A more detailed description of the statistical methods used in this study is provided in the Data Supplement.

RESULTS

Patient Characteristics

From January 31, 2013, to March 4, 2015, 135 patients from 12 countries were randomly assigned to receive telotristat ethyl 250 mg or 500 mg three times per day or placebo three times per day (Fig 1). Demographic and baseline characteristics were similar among groups (Table 1); 43% of patients were receiving above-label doses of SSAs, defined as a cumulative dose of > 30 mg octreotide LAR or > 120 mg lanreotide over the course of 4 weeks.[8,16] At baseline, mean daily BM frequency ranged from 5.2 to 6.1 counts per day and mean u5-HIAA levels ranged from 81.0 to 92.6 mg/24 hours across all treatment groups. More than 57% of patients had u5-HIAA levels above the upper limit of normal.

Patient Disposition

In this study (N = 135), 45 patients received treatment in each study arm. A total of 136 random assignments occurred; one

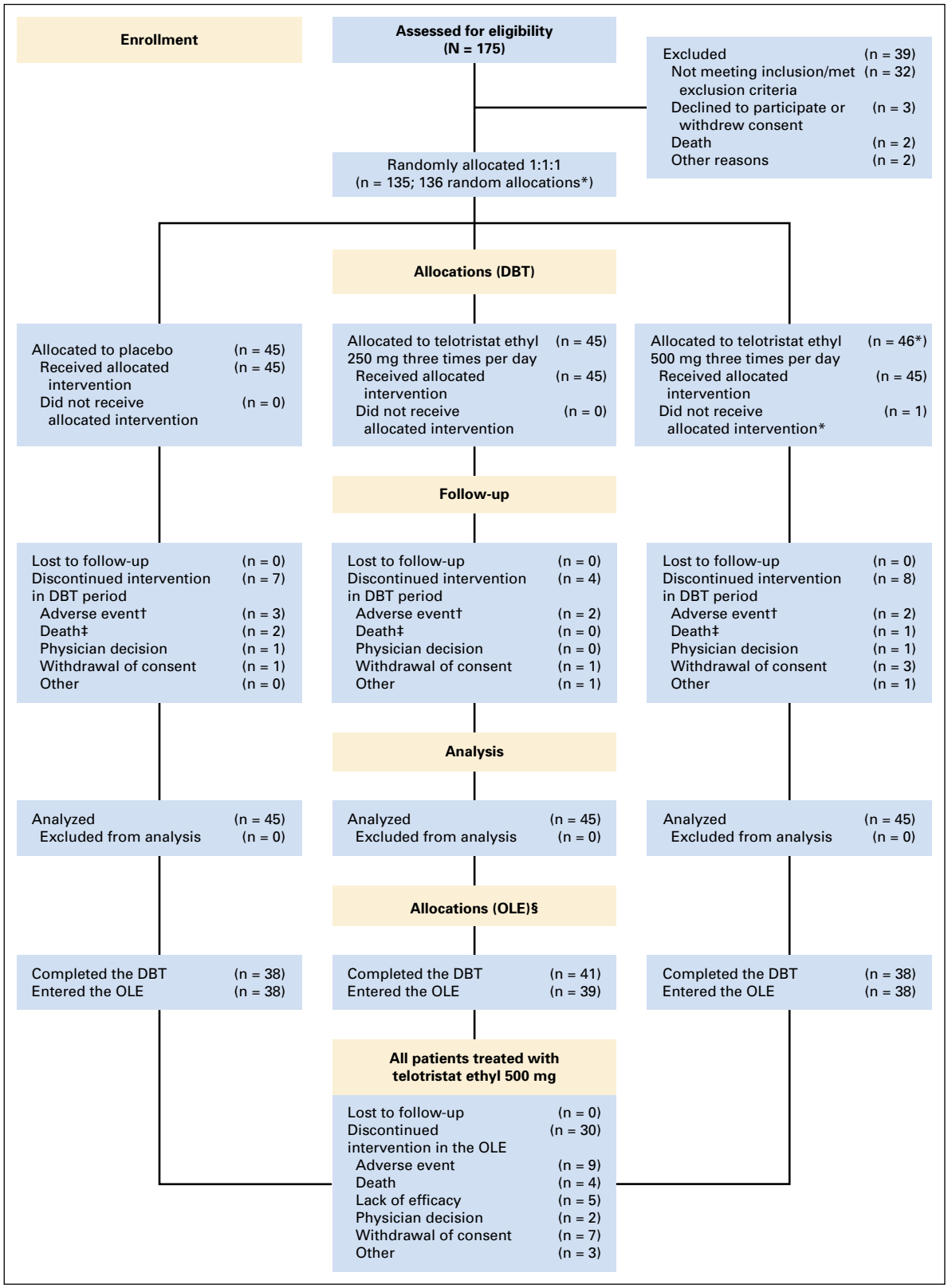

Fig 1. CONSORT diagram. Patient flow in the double-blind treatment (DBT) period of the TELESTAR study. (*) One patient initially randomly assigned to receive telotristat ethyl 500 mg was designated a screen failure because of bruising found during physical examination. This patient was subsequently rescreened, met all eligibility criteria, and was subsequently randomly assigned a second time to telotristat ethyl 250 mg. This patient was included in the telotristat ethyl 250 mg group for both efficacy and safety analyses. (†) Additional adverse events leading to study discontinuation are fully described in Table 3. (‡) A total of five deaths occurred after random assignment, but two patients (one each receiving placebo and telotristat ethyl 250 mg three times per day) previously withdrew from the study because of adverse events. (§) Patient flow into the open-label extension (OLE) reflects data extracted from the interim clinical study report.

Table 1. Demographic and Baseline Characteristics of the Patient Population

Characteristic	Placebo (n = 45)			Telotristat Ethyl (three times per day) 250 mg (n = 45)			500 mg (n = 45)			Total
	No. (%)	Mean	SD	No. (%)	Mean	SD	No. (%)	Mean	SD	No. (%)
Age, years		63.3	8.7		62.4	9.1		64.9	9.0	
Males	24 (53.3)			21 (46.7)			25 (55.6)			
Daily BM frequency		5.2	1.4		6.1	2.1		5.8	2.0	
Minimum, maximum		3.5-9.0			3.5-13.0			3.6-12.5		
SSA therapy at study entry*										
Octreotide LAR	30 (66.7)			40 (88.9)			33 (73.3)			
Lanreotide depot	15 (33.3)			5 (11.1)			12 (26.7)			
SSA use above labeled dose†	18 (40.0)			19 (42.2)			21 (46.7)			
u5-HIAA										
≤ ULN (0-15 mg/24 hours)	12 (26.7)			12 (26.7)			12 (26.7)			
> ULN (> 15 mg/24 hours)	26 (57.8)			26 (57.8)			26 (57.8)			
Unknown	7 (15.6)			7 (15.6)			7 (15.6)			
Baseline values, mg/24 hours		81.0 (n = 44)			92.6 (n = 42)			89.5 (n = 44)		
CgA at baseline, μg/L		885.7 (n = 42)			503.2 (n = 43)			1,203.4 (n = 43)		
Cutaneous flushing episodes per day		1.8	1.9		2.8	3.7		2.7	3.4	
Total No. of patients with ≥ 2 episodes per day										52 (38.5)
Abdominal pain score		2.5	2.3		2.6	2.3		2.6	2.2	
≥ 3 of 10	17 (37.8)			17 (37.8)			18 (40.0)			
No. of patients with severe abdominal pain, score of ≥ 3 of 10										52 (38.5)

Abbreviations: BM, bowel movement; CgA, chromogranin-A; LAR, long-acting release; SD, standard deviation; SSA, somatostatin analog; u5-HIAA, urinary 5-hydroxyindoleacetic acid; ULN, upper limit of normal.

*At study entry, patients received a minimum SSA dose of octreotide LAR 30 mg or lanreotide depot 120 mg once every 4 weeks or the highest tolerated dose. Includes patients who received SSA therapy via a subcutaneous continuous infusion pump.

†Above-label dosing was defined as a cumulative dose of > 30 mg octreotide LAR or > 120 mg lanreotide over the course of 4 weeks.[8,16]

patient initially randomly assigned to the telotristat ethyl 500 mg group and deemed a screen failure was rescreened and subsequently randomly assigned a second time to receive telotristat ethyl 250 mg (Data Supplement). Forty-one patients (91.1%) and 38 patients (82.6%) in the telotristat ethyl 250 mg and 500 mg groups, respectively, and 38 patients (84.4%) in the placebo group completed the DBT period. Compliance, defined as receipt of 75% to 125% of planned doses, was 93.3% and 86.7% in the telotristat ethyl 250 mg and 500 mg groups, respectively, and 86.7% in the placebo group. Use of short-acting rescue octreotide was slightly higher in the placebo group than in patients receiving telotristat ethyl (Appendix Fig A1, online only). At the time this article was prepared, 115 patients entered the OLE, 56 completed it, and 29 were currently receiving treatment. Mean treatment exposure was 26.7 weeks (range, 1.7 to 38.3 weeks).

Efficacy

BM frequency. Treatment with telotristat ethyl at either dosage was associated with statistically significant reductions in BM frequency over time compared with placebo (Fig 2A). The Hodges-Lehmann estimator for patients receiving telotristat ethyl 250 mg was −0.81 and −0.69 for those receiving telotristat ethyl 500 mg ($P < .001$). The arithmetic mean reduction in daily BM frequency from baseline to week 12 was –1.7 –and –2.1 with the telotristat ethyl 250 mg and 500 mg, respectively, and –0.9 for the placebo (Fig 2B). Individual patient responses during the DBT period are shown in Figures 2C and 2D. In total, 44% and 42% of participants who received telotristat ethyl 250 mg and 500 mg, respectively, were classified as BM responders versus 20% of patients who received the placebo. The odds ratios (ORs) were 3.49 (95% CI, 1.33 to 9.16) and 3.11 (95% CI, 1.20 to 8.10) for telotristat ethyl 250 mg and 500 mg, respectively (Table 2). In the OLE, BM reductions were consistent with results from the DBT period (Fig 2A).

u5-HIAA. In patients who were evaluable at baseline and week 12, treatment with telotristat ethyl at either dosage was associated with statistically significant reductions in u5-HIAA levels compared with placebo. The Hodges-Lehmann estimator was –30.1 mg/24 hours and –33.8 mg/24 hours for telotristat ethyl 250 mg and 500 mg, respectively ($P < .001$ for both). At week 12, arithmetic mean u5-HIAA levels decreased by 40.1 mg/24 hours and by 57.7 mg/24 hours in the telotristat ethyl 250 mg and 500 mg groups, respectively. The mean u5-HIAA levels increased in the placebo group by 11.5 mg/24 hours at week 12. Individual patient responses during the DBT period are shown in Figures 3A and 3B. In a post hoc analysis of patients treated with telotristat ethyl, 78% (n = 25) and 87% (n = 26) of patients in the 250 mg and 500 mg groups, respectively, experienced a ≥ 30% decrease in u5-HIAA levels compared with 10% (n = 3) in the placebo group.

Flushing and abdominal pain. Relatively few patients reported having two or more flushing episodes per day or abdominal pain (rating of ≥3 of 10 in severity) at baseline (Table 1), and changes in these end points did not reach statistical significance (Appendix Table A1).

Quality of life and other end points. EORTC QLQ-C30 diarrhea subscale scores, which were averaged over the DBT period, improved by 19.2 points (on a scale of 0 to 100) and by 21.6 points in the telotristat ethyl 250 mg and 500 mg groups, respectively, and by only 8.5 points in the placebo group ($P = .039$ and $P = .051$ for

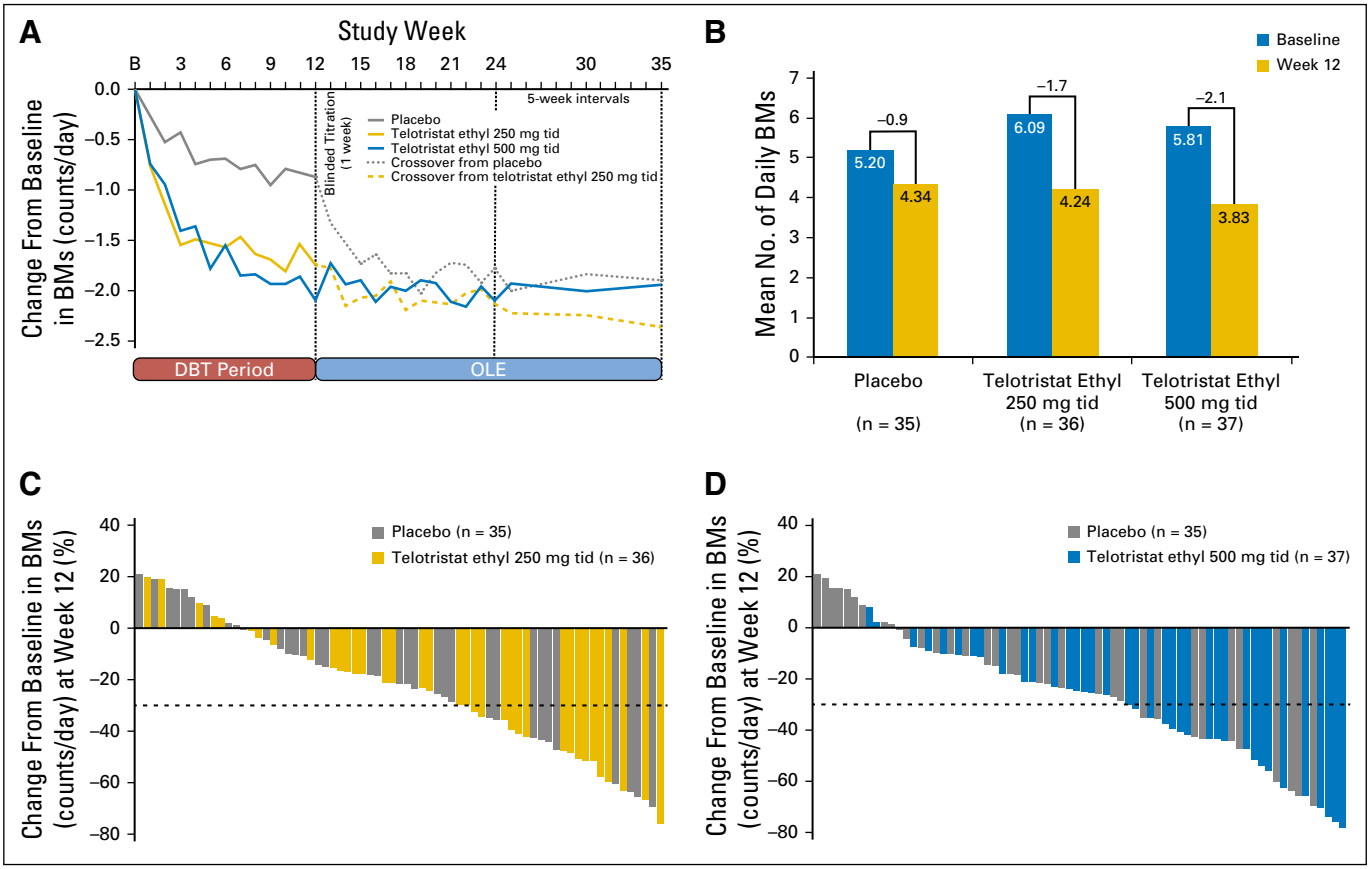

Fig 2. Change from baseline in frequency of bowel movements (BMs) in patients receiving placebo or telotristat ethyl (250 mg or 500 mg) three times per day (tid). (A) Reduction in mean daily BM frequency from baseline over the double-blind treatment (DBT) period and open-label extension (OLE). The 36-week OLE is currently ongoing; thus, an interim analysis up to week 35 is presented. (B) Reduction in mean daily BM frequency at baseline and week 12. The Hodges-Lehmann estimator, a nonparametric measure used to describe the magnitude of treatment effect, was −0.81 BMs per day for telotristat ethyl 250 mg three times per day (tid) and −0.69 BMs per day for telotristat ethyl 500 mg three times per day ($P < .001$). The arithmetic mean reduction in daily BM frequency from baseline to week 12 was –1.7 with telotristat ethyl 250 mg three times per day, –2.1 with telotristat ethyl 500 mg three times per day, and –0.9 with placebo. Data include only patients for whom both baseline and week 12 assessments were available. (C and D) The distribution of individual patient responses as the percentage change from baseline in daily BM frequency at week 12 for (C) telotristat ethyl 250 mg three times per day and (D) telotristat ethyl 500 mg three times per day. The dashed line represents the prespecified cutoff of ≥ 30% reduction in BM frequency used in the responder analysis.

telotristat ethyl 250 mg and 500 mg, respectively.). No significant treatment group differences were observed in the nausea and vomiting subscale. No overall differences in the global health status subscale were observed between treatment arms, although patients classified as BM responders reported modest improvements in overall quality of life compared with nonresponders in all three treatment arms (Appendix Table A2). Some evidence that telotristat ethyl may also improve stool consistency, reduce the urgency to defecate, and reduce rescue short-acting octreotide use was observed (Appendix Table A1; Appendix Fig A1). Pharmacokinetic models also support a dose response to treatment of both u5-HIAA and BM frequency (Data Supplement).

Safety

The overall incidence of treatment-emergent adverse events (TEAEs) across the three treatment arms was similar (Table 3; Appendix Table A3). A higher incidence of nausea was noted in patients in the telotristat ethyl 500 mg group (31.1%) compared with patients in the telotristat ethyl 250 mg group or the placebo group (13.3% and 11.1%, respectively). One patient receiving placebo discontinued the study drug because of nausea; however, no patients receiving telotristat ethyl discontinued because of nausea. Dose-related increases in hepatic enzymes, particularly gamma-glutamyl transferase, were observed in both telotristat ethyl groups (Table 3). In the DBT period, depression-related AEs, including depression, depressed mood, and decreased interest, occurred during treatment in 6.7%, 6.7%, and 15.6% of patients in the placebo, telotristat ethyl 250 mg, and 500 mg groups, respectively. However, no patient reporting depression required initiation of new antidepressant therapy, and no cases of depression resulted in treatment discontinuation. In the OLE, among patients who crossed over from placebo to telotristat ethyl 500 mg, there was only one new report of decreased interest, but no new reports of depression or depressed mood were made between weeks 12 and 24 (Appendix Table A4).

DISCUSSION

In this randomized, double-blind, placebo-controlled phase III study in patients with carcinoid syndrome not adequately

Table 2. Efficacy Assessments in the DBT Period

Variable	Placebo (n = 45)			Telotristat Ethyl (three times per day)									
				250 mg (n = 45)					500 mg (n = 45)				
	No. (%)	Mean (SD)	OR	No. (%)	Mean (SD)	*P*	OR	95% CL	No. (%)	Mean (SD)	*P*	OR	95% CL
BM frequency													
Daily reduction averaged over 12 weeks		−0.62 (0.83)			−1.43 (1.36)					−1.46 (1.31)			
Arithmetic mean treatment difference		—			−0.81					−0.83			
Hodges-Lehmann estimator*		—			−0.81	< .001				−0.69	< .001		
Responder analysis													
Responders†	9 (20)		—	20 (44)		.011	3.49	1.33 to 9.16	19 (42)		.020	3.11	1.20 to 8.10
Change from baseline in BM frequency at week 12													
BM responders‡	9	−1.9 (0.8)		16	−2.6 (1.6)				16	−3.1 (2.1)			
BM nonresponders	26	−0.5 (1.1)		20	−1.0 (1.5)				21	−1.3 (1.4)			
u5-HIAA‡	29			32					31				
Absolute change from baseline levels at week 12, mg/24 h		11.5 (35.6)			−40.1 (84.8)					−57.7 (82.2)			
Arithmetic mean treatment difference		—			−51.6				−69.2				
Hodges-Lehmann estimator*		—			−30.1	< .001			−33.8		< .001		

Abbreviations: BM, bowel movement; CL, confidence limit; DBT, double-blind treatment; OR, odds ratio; SD, standard deviation; u5-HIAA, urinary 5-hydroxyindoleacetic acid.
*Nonparametric measure derived as the median of all possible differences between the groups.
†Responders were defined as having ≥ 30% reduction in BM frequency for ≥ 50% of study period.
‡Data include only patients for whom both baseline and week 12 assessments were available.

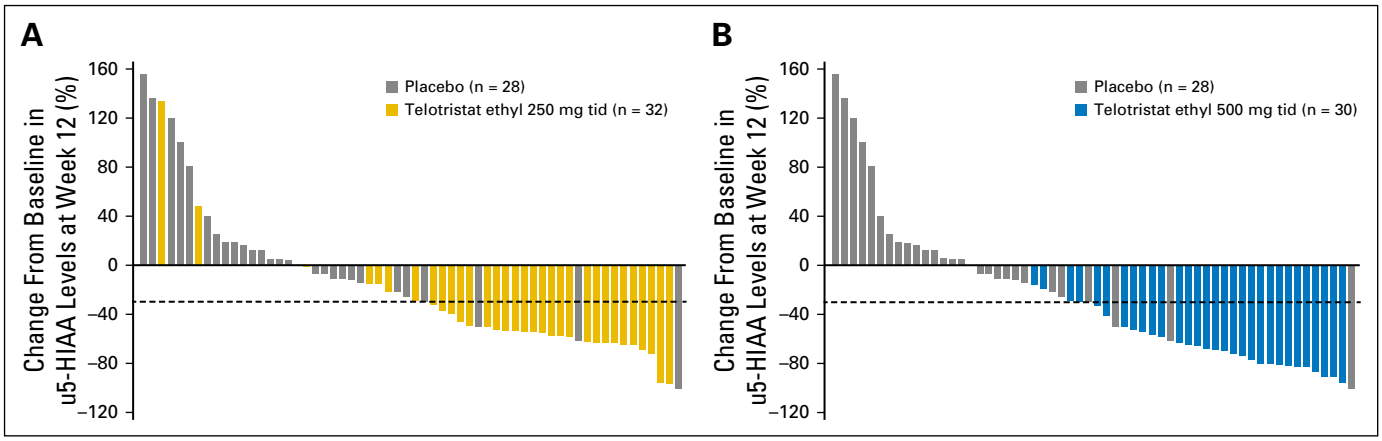

Fig 3. Percentage change from baseline in urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels at week 12. (A and B) Distribution of individual patient responses as percentage change from baseline in u5-HIAA levels at week 12 for (A) telotristat ethyl 250 mg 3 times per day (tid) and (B) telotristat ethyl 500 mg three times per day. In patients treated with telotristat ethyl, 78% (n = 25) and 84% (n = 26) of patients in the 250 mg and 500 mg groups, respectively, experienced a ≥ 30% decrease in u5-HIAA levels compared with 10% (n = 3) in the placebo group. The dashed line represents a commonly used cutoff of ≥ 30% reduction in secretory biomarkers of carcinoid syndrome.[27]

controlled on SSA therapy, treatment with the oral TPH inhibitor telotristat ethyl was associated with statistically significant reductions in BM frequency compared with placebo. Marked decreases in u5-HIAA were also associated with treatment. Although the overall incidence of TEAEs was similar across all treatment groups, nausea and elevated gamma-glutamyl transferase were reported more often in patients receiving telotristat ethyl. In patients receiving subsequent treatment in the OLE, reductions in BM frequency seemed to be sustained, and no new safety signals were observed. To our knowledge, this study represents one of the largest randomized placebo-controlled studies conducted to date to assess symptom control in patients with carcinoid syndrome.

SSAs, including octreotide and lanreotide, are widely used for the treatment of carcinoid syndrome, but not all patients achieve complete symptom control.[4,17,18] Moreover, patients with carcinoid syndrome often live for years and may develop recurrent symptoms.[4,6] There are few other treatment options, and the development of new treatments for carcinoid syndrome has proved challenging, in part because of the rarity of the condition and the lack of new drug candidates.[19-21]

BM frequency is a useful end point in carcinoid syndrome studies because of its impact on patient function[3] and well-being. A decrease of approximately three BMs per day (from a baseline of five to six BMs per day) was reported with octreotide LAR in patients with carcinoid syndrome.[17] In this study, in patients experiencing diarrhea despite concomitant SSA therapy, BM frequency decreased by approximately two BMs per day with telotristat ethyl.

We performed a prespecified responder analysis, defining responders as patients experiencing ≥ 30% decrease in BM frequency for ≥ 50% of the DBT period, thereby measuring both magnitude and duration of response.[10,11] More than 40% of patients treated with telotristat ethyl were responders versus 20% of patients treated with placebo.

Consistent with these observations, we also observed improvements in quality of life using the EORTC QLQ-C30 diarrhea subscale. No differences in the EORTC QLQ-C30 global health scores were observed. In fact, these scores were similar across all three treatment arms, suggesting that no quality of life detriment was associated with treatment. Interestingly, only minimal changes in overall EORTC QLQ-C30 global health scores were observed in previous studies in patients with NETs who received SSAs, suggesting that this domain may not be particularly sensitive in this patient population.[22-24]

The BM response rate of 20% in the placebo group was a somewhat unexpected observation in our study. Although the placebo effect is well documented in clinical trials,[25,26] BM frequency is a relatively robust and objective end point and, in theory, should not be susceptible to subjective reporting. Use of short-acting rescue SSA therapy was somewhat more common in the placebo arm of this study and may have partially accounted for our observations. In addition, variability in the absorption of long-acting SSAs, differences in use of other antidiarrheal medications, and dietary changes may have contributed to the responses observed in the placebo group.

Treatment with telotristat ethyl significantly reduced u5-HIAA levels, suggesting effective TPH inhibition. u5-HIAA levels may vary for other reasons, and in prior studies of patients with NETs, ≥ 30% reduction in secretory biomarkers has been used as a measure of treatment efficacy to reduce the risk of capturing natural variability.[27] In this study, > 78% of patients treated with telotristat ethyl (at either dosage) experienced a ≥ 30% decrease in u5-HIAA levels versus 10% in the placebo group. The broader clinical significance of decreasing systemic serotonin levels, as determined by u5-HIAA levels, in patients with carcinoid syndrome has not been fully established. However, serotonin stimulates fibroblast proliferation and has been linked to cardiac valvular fibrosis in patients with carcinoid syndrome.[28] Serotonin may also mediate mesenteric fibrosis often observed in patients with small intestine NETs.[29] Future studies examining whether these complications of carcinoid syndrome can be prevented by reducing serotonin production with telotristat ethyl are warranted.

Similar reductions in BM frequency were observed at both telotristat ethyl dosages; however, over time, numerically greater reductions in BM frequency were observed with telotristat ethyl

Table 3. TEAEs Reported in the DBT Period

Category	Placebo (n = 45)	Telotristat Ethyl (three times per day) 250 mg (n = 45)	500 mg (n = 45)
Any TEAE	39 (86.7)	37 (82.2)	42 (93.3)
Study discontinuation as a result of TEAE*	6 (13.3)	3 (6.7)	3 (6.7)
TEAE resulting in death†	3 (6.7)	1 (2.2)	1 (2.2)
Selected AEs occurring in ≥ 5% of patients in any study arm by system organ class and preferred term‡			
GI disorders			
Nausea	5 (11.1)	6 (13.3)	14 (31.1)
Abdominal pain	8 (17.8)	5 (11.1)	10 (22.2)
Vomiting	4 (8.9)	2 (4.4)	5 (11.1)
Abdominal distension	3 (6.7)	2 (4.4)	1 (2.2)
Diarrhea	3 (6.7)	3 (6.7)	0
Dyspepsia	3 (6.7)	1 (2.2)	1 (2.2)
General disorders and administration site conditions			
Fatigue	4 (8.9)	4 (8.9)	7 (15.6)
Infections and infestations			
Nasopharyngitis	1 (2.2)	2 (4.4)	3 (6.7)
Pneumonia	0	0	3 (6.7)
AEs relating to investigations			
Increased gamma-glutamyl transferase§	0	4 (8.9)	4 (8.9)
Increased ALT‖	0	1 (2.2)	3 (6.7)
Increased alkaline phosphatase¶	0	0	3 (6.7)
Metabolism and nutrition disorders			
Decreased appetite	2 (4.4)	3 (6.7)	7 (15.6)
Hypokalemia	3 (6.7)	3 (6.7)	5 (11.1)
Nervous system disorders			
Headache	2 (4.4)	5 (11.1)	4 (8.9)
Dizziness	2 (4.4)	0	4 (8.9)
Memory impairment	3 (6.7)	0	1 (2.2)
Psychiatric disorders			
Depression-related#	3 (6.7)	3 (6.7)	7 (15.6)
Confusional state	0	0	3 (6.7)
Respiratory, thoracic, and mediastinal disorders			
Dyspnea	0	2 (4.4)	4 (8.9)
Cough	1 (2.2)	1 (2.2)	3 (6.7)
Vascular disorders (new or worsening)			
Flushing	2 (4.4)	3 (6.7)	3 (6.7)

NOTE. All data are presented as No. (%).
Abbreviations: AE, adverse event; DBT, double-blind treatment; TEAE, treatment-emergent adverse event.
*TEAEs leading to study discontinuation were anemia, cardiac arrest, nausea, vomiting, eructation, dyspepsia, chills, fatigue, general health deterioration, dehydration, disease progression (five patients), sepsis, rash, and increased gamma-glutamyl transferase.
†All deaths occurred in the setting of advanced metastatic disease.
‡AEs were graded according to a standard severity grading scheme as mild, moderate, or severe.
§Mean changes from baseline at week 12 in gamma-glutamyl transferase (U/L ± standard deviation [SD]) for all patients studied were 4.4 ± 31.6 in the placebo group, 130.0 ± 204.4 in the telotristat ethyl 250 mg three times per day group, and 242.4 ± 358.1 in the telotristat ethyl 500 mg three times per day group.
‖Mean changes from baseline to week 12 in ALT (U/L ± SD) for all patients studied were –0.1 ± 6.2 in the placebo group, 7.1 ± 16.4 in the telotristat ethyl 250 mg three times per day group, and 17.4 ± 42.6 in the telotristat ethyl 500 mg three times per day group.
¶Mean changes from baseline to week 12 in alkaline phosphatase (U/L ± SD) for all patients studied were 16.1 ± 57.6 in the placebo group, 22.8 ± 41.8 in the telotristat ethyl 250 mg three times per day group, and 57.5 ± 140.8 in the telotristat ethyl 500 mg three times per day group.
#Depression-related AEs include depression, depressed mood, and decreased interest.

500 mg from weeks 7 to 12. Reductions in u5-HIAA levels and in the EORTC QLQ-C30 diarrhea subscale, the proportion of days with the urgency to defecate, and improvements in stool consistency were also numerically greater with telotristat ethyl 500 mg. Telotristat ethyl 500 mg demonstrated a favorable long-term tolerability profile, suggesting that this dose may be beneficial to patients not adequately responding to initial treatment with telotristat ethyl 250 mg.

Telotristat ethyl was generally well tolerated in this patient population. Increases in transaminases and nausea were observed in previous studies of telotristat ethyl.[11,12] In this study, these events did not result in treatment discontinuation in patients randomly assigned to receive telotristat ethyl. Telotristat ethyl did not appear to be associated with an increased incidence of serious TEAEs. Preclinical studies suggest that telotristat ethyl does not have significant CNS penetration.[5] In this study, a higher incidence of depression-related events was observed in patients who received telotristat ethyl 500 mg than in patients who received placebo; however, incidences in patients who received telotristat ethyl 250 mg and placebo were nearly identical. Most events resolved on study, and no new antidepressant therapies were initiated. In the current interim analysis of the OLE, rates of depression-related events have been relatively low. However, these data may be subject to some degree of selection bias and should be interpreted with caution. Additional follow-up in the

ongoing OLE and evaluation of safety data in a separate ongoing phase III study (clinical trial information: NCT02063659) are planned.

In conclusion, treatment with the oral TPH inhibitor telotristat ethyl (250 mg or 500 mg three times per day) was generally safe and well tolerated and was associated with a significant decrease in BM frequency in patients with carcinoid syndrome receiving treatment with SSAs. The associated decreases in u5-HIAA provide evidence that telotristat ethyl effectively decreases serotonin production and has the potential to mitigate serotonin-mediated complications in this patient population. These observations suggest that telotristat ethyl represents a potential new treatment approach for patients with carcinoid syndrome.

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Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome

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Appendix

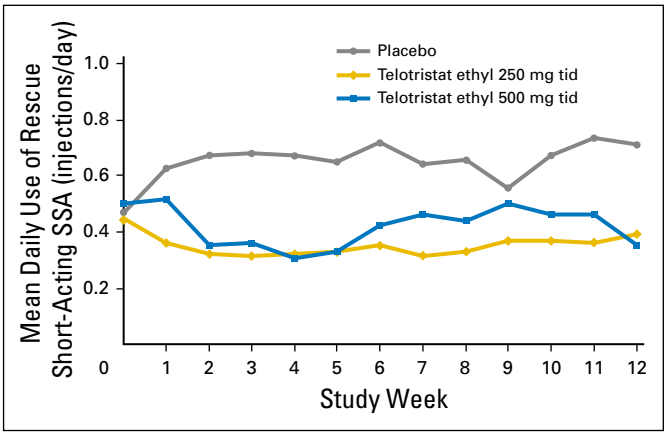

Fig A1. Mean daily use of rescue short-acting somatostatin analog (SSA) therapy in the double-blind treatment period. Some evidence that treatment with telotristat ethyl decreased the use of rescue short-acting SSA therapy was observed during the double-blind treatment period.

Table A1. Additional Secondary End Points of the DBT Period

Variable	Placebo (n = 45)		Telotristat Ethyl (three times per day) 250 mg (n = 45)		500 mg (n = 45)	
	Mean (SD)	*P*	Mean (SD)	*P*	Mean (SD)	*P*
Flushing						
Change from baseline in daily flushing episodes averaged over 12 weeks, counts per day	−0.16 (1.16)		−0.30 (1.31)		−0.53 (1.34)	
Arithmetic mean treatment difference	—		−0.13		−0.36	
Hodges-Lehmann estimator*	—	—	0.036	.39	0.00	.84
Abdominal pain						
Change from baseline in abdominal pain averaged over 12 weeks, points†	−0.23 (1.16)		−0.49 (1.44)		−0.33 (1.18)	
Arithmetic mean treatment difference	—		−0.26		−0.11	
Hodges-Lehmann estimator*	—	—	−0.17	.28	−0.05	.87
Daily rescue short-acting SSA use						
Change from baseline in use of short-acting SSAs, averaged over 12 weeks, injections per day	0.18		−0.11		0.03	
Arithmetic mean treatment difference	—		−0.30		−0.15	
Hodges-Lehmann estimator*	—	—	0	.19	0	.16
Stool consistency						
Change from baseline in stool consistency averaged over 12 weeks, points	−0.22 (0.48)		−0.26 (0.47)		−0.36 (0.41)	
Arithmetic mean treatment difference	—		−0.05		−0.15	
Hodges-Lehmann estimator*	—	—	−0.09	.57	−0.15	.052
Urgency to defecate						
Proportion of days	0.75 (0.29)		0.67 (0.34)		0.60 (0.31)	
Arithmetic mean treatment difference	—		−0.09		−0.15	
Hodges-Lehmann estimator*	—	—	−0.02	.35	–0.13	.006

Abbreviations: DBT, double-blind treatment; SD, standard deviation; SSA, somatostatin analog.
*Nonparametric measure derived as the median of all possible differences between the groups.
†Abdominal pain based on patient rating using an 11-point scale: 0, no pain; 10, worst pain ever experienced.

Table A2. Quality-of-Life Outcomes During the DBT Period

EORTC QLQ-C30 Subscale	Placebo (n = 45)		Telotristat Ethyl (three times per day) 250 mg (n = 45)		500 mg (n = 45)	
	No. of Patients	Mean (SD)	No. of Patients	Mean (SD)	No. of Patients	Mean (SD)
Global health status/QoL*	39	−2.0 (18.3)	39	1.7 (19.1)	37	−2.1 (21.4)
BM responders†	9	3.7 (30.4)	16	7.8 (20.5)	14	1.2 (17.9)
BM nonresponders†	25	−5.0 (18.0)	20	−6.2 (20.8)	20	0.8 (22.8)
Diarrhea‡	39	−8.5 (21.9)	39	−19.2 (29.3)	37	−21.6 (27.2)
BM responders†	9	−22.2 (33.3)	16	−22.9 (35.9)	14	−33.3 (34.6)
BM nonresponders†	25	−8.0 (27.7)	20	−20.0 (29.4)	20	−8.3 (18.3)
Nausea and vomiting‡	39	−2.4 (13.5)	39	−2.4 (20.3)	38	−0.9 (21.0)
Insomnia‡	39	−7.7 (25.9)	40	3.3 (18.9)	38	4.4 (33.3)
Physical functioning*	39	−1.2 (13.3)	40	−0.2 (11.1)	38	−2.1 (11.8)
Role functioning*	39	−1.3 (16.8)	39	7.7 (28.8)	38	1.1 (26.9)
Emotional functioning*	39	0.5 (13.7)	39	0.7 (16.4)	37	1.6 (15.5)
Cognitive functioning*	39	0.0 (20.8)	39	−2.4 (13.2)	37	−0.7 (12.6)
Social functioning*	39	0.4 (15.8)	39	2.6 (23.4)	37	−3.2 (20.8)
Fatigue‡	39	0.4 (18.7)	40	−2.4 (22.2)	38	−2.9 (20.1)
Pain‡	39	1.7 (19.6)	40	−5.2 (28.4)	38	−4.4 (29.5)
Dyspnea‡	39	1.7 (18.7)	40	−1.7 (20.9)	38	4.4 (24.4)
Appetite loss‡	38	−7.5 (25.9)	40	1.3 (25.7)	38	−0.9 (23.2)
Constipation‡	38	0.9 (3.8)	39	2.6 (7.2)	38	5.7 15.6)
Financial difficulties‡	38	−1.3 (19.1)	39	−5.1 (15.4)	36	2.8 (18.5)

NOTE. EORTC QLQ-C30 subscales show mean change from baseline averaged over 12 weeks (points), unless otherwise specified.
Abbreviations: BM, bowel movement; DBT, double-blind treatment; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; QoL, quality of life; SD, standard deviation.
*For all total/domain scores, a higher functional score indicates a more favorable outcome.
†Change from baseline at week 12 (points).
‡For all individual/symptom scores, a higher score indicates a less favorable patient outcome.

Table A3. All AEs Occurring in ≥ 5% of Patients in Any Study Arm in the DBT Period

AE (system organ class preferred term)	Placebo (n = 45)	Telotristat Ethyl (three times per day) 250 mg (n = 45)	500 mg (n = 45)	Total (N = 135)
GI disorders				
Nausea	5 (11.1)	6 (13.3)	14 (31.1)	25 (18.5)
Abdominal pain	8 (17.8)	5 (11.1)	10 (22.2)	23 (17.0)
Vomiting	4 (8.9)	2 (4.4)	5 (11.1)	11 (8.1)
Upper abdominal pain	0	2 (4.4)	5 (11.1)	7 (5.2)
Abdominal distension	3 (6.7)	2 (4.4)	1 (2.2)	6 (4.4)
Diarrhea	3 (6.7)	3 (6.7)	0	6 (4.4)
Flatulence	1 (2.2)	3 (6.7)	2 (4.4)	6 (4.4)
Dyspepsia	3 (6.7)	1 (2.2)	1 (2.2)	5 (3.7)
General disorders and administration site conditions				
Fatigue	4 (8.9)	4 (8.9)	7 (15.6)	15 (11.1)
Asthenia	3 (6.7)	2 (4.4)	1 (2.2)	6 (4.4)
Peripheral edema	1 (2.2)	3 (6.7)	1 (2.2)	5 (3.7)
Pyrexia	2 (4.4)	3 (6.7)	0	5 (3.7)
Infections and infestations				
Nasopharyngitis	1 (2.2)	2 (4.4)	3 (6.7)	6 (4.4)
Pneumonia	0	0	3 (6.7)	3 (2.2)
AEs relating to investigations				
Increased gamma-glutamyl transferase*	0	4 (8.9)	4 (8.9)	8 (5.9)
Increased ALT†	0	1 (22.2)	3 (6.7)	4 (3.0)
Increased alkaline phosphatase‡	0	0	3 (6.7)	3 (2.2)
Metabolism and nutrition disorders				
Decreased appetite	2 (4.4)	3 (6.7)	7 (15.6)	12 (8.9)
Hypokalemia	3 (6.7)	3 (6.7)	5 (11.1)	11 (8.1)
Nervous system disorders				
Headache	2 (4.4)	5 (11.1)	4 (8.9)	11 (8.1)
Dizziness	2 (4.4)	0	4 (8.9)	6 (4.4)
Memory impairment	3 (6.7)	0	1 (2.2)	4 (3.0)
Psychiatric disorders				
Depression-related§	3 (6.7)	3 (6.7)	7 (15.6)	13 (9.6)
Confusional state	0	0	3 (6.7)	3 (2.2)
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	0	2 (4.4)	4 (8.9)	6 (4.4)
Cough	1 (2.2)	1 (2.2)	3 (6.7)	5 (3.7)
Epistaxis	0	0	3 (6.7)	3 (2.2)
Vascular disorders (new or worsening)				
Flushing	2 (4.4)	3 (6.7)	3 (6.7)	8 (5.9)

NOTE. Adverse events (AEs) were graded according to a standard severity grading scheme as mild, moderate, or severe. All data are presented as No. (%).
Abbreviation: DBT, double-blind treatment.
*Mean changes from baseline at week 12 in gamma-glutamyl transferase (U/L ± standard deviation [SD]) for all patients studied were 4.4 ± 31.6 in the placebo group, 130.0 ± 204.4 in the telotristat ethyl 250 mg three times per day group, and 242.4 ± 358.1 in the telotristat ethyl 500 mg three times per day group.
†Mean changes from baseline to week 12 in ALT (U/L ± SD) for all patients studied were –0.1 ± 6.2 in the placebo group, 7.1 ± 16.4 in the telotristat ethyl 250 mg three times per day group, and 17.4 ± 42.6 in the telotristat ethyl 500 mg three times per day group.
‡Mean changes from baseline to week 12 in alkaline phosphatase (U/L ± SD) for all patients studied were 16.1 ± 57.6 in the placebo group, 22.8 ± 41.8 in the telotristat ethyl 250 mg three times per day group, and 57.5 ± 140.8 in the telotristat ethyl 500 mg three times per day group.
§Depression-related AEs include depression, depressed mood, and decreased interest.

Table A4. Summary of TEAEs Reported During the OLE

Category	OLE* (n = 115)	
	No.	%
Any TEAE	105	91.3
Any serious TEAE†	36	31.3
Study discontinuation as a result of TEAE‡	14	12.2
TEAE resulting in death§	8	7.0
Selected key AEs		
Any depression-related AE¶	17	15.0
Nausea	23	20.0
Increased gamma-glutamyl transferase	7	6.1
Increased alanine aminotransferase	4	3.5
Increased alkaline phosphatase	5	4.3

Abbreviations: AE, adverse event; OLE, open-label extension; TEAE, treatment-emergent adverse event.

*Patients were initiated at 500 mg telotristat ethyl three times per day. Mean treatment exposure was 11.3 weeks in the double-blind treatment period and 26.7 weeks in the OLE.

†AEs were considered serious if they involved death, a life-threatening AE, inpatient hospitalization, a persistent or significant incapacity, substantial disruption in the ability to conduct normal life function, or a congenital anomaly or birth defect.

‡TEAEs leading to study discontinuation in the OLE were supraventricular tachycardia, disease progression (five patients), abdominal distension, constipation, GI hemorrhage, hematemesis, large intestine perforation, asthenia, fatigue, general physical health deterioration, hepatomegaly, peritonitis, sepsis, increased liver enzymes, decreased weight, decreased appetite, dehydration, mental confusion, cognitive disorder, renal failure, and urticaria.

§None of the deaths occurring during the OLE were considered related to study drug. The deaths were generally attributable to the progression or complication of the underlying disease.

¶Depression-related AEs include depression, depressed mood, and decreased interest.