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Long-Term Safety Experience with Telotristat Ethyl Across Five Clinical Studies in Patients with Carcinoid Syndrome

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Malignant carcinoid syndrome • Tryptophan hydroxylase • Telotristat ethyl • Serotonin • Diarrhea • Neuroendocrine tumors

ABSTRACT

Background. Patients with neuroendocrine tumors (NETs) and carcinoid syndrome experience considerable morbidity and mortality; carcinoid syndrome may be associated with shorter survival. Carcinoid syndrome is linked to tumoral secretion of serotonin and other bioactive substances. The subsequent debilitating diarrhea and urgency to defecate pose significant health risks. In previous studies, telotristat ethyl, a tryptophan hydroxylase inhibitor, was effective and well tolerated in treating carcinoid syndrome diarrhea. We present pooled safety data from five clinical trials with telotristat ethyl in patients with carcinoid syndrome.

Subjects, Materials, and Methods. Adverse events reported during telotristat ethyl treatment were pooled from two phase II and three phase III clinical trials in 239 patients with carcinoid syndrome. Long-term safety of telotristat ethyl and

causes of hospitalization and death were reviewed; overall survival was estimated.

Results. Mean (median; range) duration of exposure and follow-up was 1.3 years (1.1 years; 1 week to 5.7 years), with 309 total patient-years of exposure. Leading causes of hospitalization were gastrointestinal disorders or were related to the underlying tumor and related treatment. Survival estimates at 1, 2, and 3 years were 93%, 88%, and 77%. Nearly all deaths were due to progression or complication of the underlying disease; none were attributable to telotristat ethyl. There was one death in year 4.

Conclusion. Based on long-term safety data, telotristat ethyl is well tolerated and has a favorable long-term safety profile in patients with carcinoid syndrome. *The Oncologist* 2019;24:e662–e670

Implications for Practice: Carcinoid syndrome can cause persistent diarrhea, even in patients treated with somatostatin analogs. Across five clinical trials in patients with carcinoid syndrome, telotristat ethyl has been well tolerated and efficacious, providing clinicians with a new approach to help control carcinoid syndrome diarrhea, in addition to somatostatin analog therapy. By reducing the stool frequency in patients with carcinoid syndrome whose diarrhea is refractory to anticholinergics, such as loperamide and atropine/diphenoxylate, and somatostatin analog dose escalation, improvement in quality of life becomes an achievable goal.

INTRODUCTION

Between 1973 and 2012, the incidence of neuroendocrine tumors (NETs) increased 6.4-fold, with an estimated prevalence of >100,000 cases in the U.S. [1]. Patients with advanced NETs may develop carcinoid syndrome, a condition

associated with tumoral secretion of serotonin and other bioactive substances and characterized by diarrhea, flushing, bronchial constriction, and the development of cardiac valvular fibrosis [2–4]. Diarrhea, one of the most prominent symptoms

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Table 1. Overview of studies and number of patients included in the pooled analysis

Study, n ^a	Study design	Telotristat ethyl dosing arms	Key inclusion criteria	Key exclusion criteria
U.S. phase II study [31] (NCT00853047) n = 22	Phase II, 4-week, double-blind, placebo-controlled, with OLE	<ul style="list-style-type: none"> • 150 mg t.i.d. • 250 mg t.i.d. • 350 mg t.i.d. • 500 mg t.i.d. 	<ul style="list-style-type: none"> • ≥4 BMs per day 	<ul style="list-style-type: none"> • Karnofsky performance status ≤70% • Previous use of TPH inhibitor
European phase II study [32] (NCT01104415) n = 15	Phase II, 12-week, open label with optional 124-week extension	<ul style="list-style-type: none"> • 150 mg t.i.d. • 250 mg t.i.d. • 350 mg t.i.d. • 500 mg t.i.d. 	<ul style="list-style-type: none"> • ≥4 BMs per day 	<ul style="list-style-type: none"> • Karnofsky performance status ≤70%
TELESTAR [29] (NCT01677910) n = 128	Phase III, 12-week, double-blind, placebo-controlled, with 36-week OLE	<ul style="list-style-type: none"> • 250 mg t.i.d. • 500 mg t.i.d. 	<ul style="list-style-type: none"> • ≥4 BMs per day • Receiving stable-dose SSAs 	<ul style="list-style-type: none"> • Karnofsky performance status ≤60% • Previous exposure to telotristat ethyl
TELECAST [30] (NCT02063659) n = 74 ^b	Phase III, 12-week, double-blind, placebo-controlled, with 36-week OLE	<ul style="list-style-type: none"> • 250 mg t.i.d. • 500 mg t.i.d. 	<ul style="list-style-type: none"> • <4 BMs per day if on SSAs and have at least one additional sign of carcinoid syndrome • If not on SSAs, at least one sign or symptom of carcinoid syndrome 	<ul style="list-style-type: none"> • Karnofsky performance status ≤60%
TELEPATH [42] (NCT02026063) n = 92 ^c	Phase III, open label	<ul style="list-style-type: none"> • 250 mg t.i.d. • 500 mg t.i.d. 	<ul style="list-style-type: none"> • Ongoing participation in U.S. phase II study, European phase II study, TELECAST, or TELESTAR 	<ul style="list-style-type: none"> • Major protocol violation or tolerability concern in U.S. phase II study, European phase II study, TELECAST, or TELESTAR

^an values represent the number of patients in this analysis from each study.

^bThe TELECAST study enrolled 8 patients who were not on SSA therapy at baseline [30] and 23 patients who did not report diarrhea at baseline; these patients met other eligibility criteria for carcinoid syndrome (data on file).

^cThe TELEPATH study is a long-term extension study that includes patients from the U.S. phase II, European phase II, TELESTAR, and TELECAST studies. The majority of patients in the TELEPATH study were enrolled in the TELESTAR (n = 61) and TELECAST (n = 24) studies.

Abbreviations: BM, bowel movement; OLE, open-label extension; SSA, somatostatin analog; TELECAST, Telotristat Etiprate for Carcinoid Syndrome Therapy; TELEPATH, Telotristat Etiprate – Expanded Treatment for Patients With Carcinoid Syndrome Symptoms; TELESTAR, Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome; TPH, tryptophan hydroxylase.

of carcinoid syndrome, negatively impacts the emotional well-being and social and physical functioning of patients [5]. Somatostatin analogs, developed in the mid-1980s for the treatment of carcinoid syndrome, are considered a standard treatment option for patients with this condition [1, 6, 7].

Prognostic variables at the time of diagnosis of NETs include age, sex, histological type, location of primary tumor, tumor stage, and the presence/absence of elevated urinary 5-hydroxyindoleacetic acid levels [6, 8, 9]. The median overall survival in patients with localized NETs is >30 years, whereas in patients with regional NETs, it is 10.2 years, and for patients with distant stage G1/G2 NETs of the small intestine, it is 8.6 years with a 3-year survival rate of 80% [1]. Liver failure due to hepatic replacement by tumor is the most frequent cause of death in patients with NETs [6].

An estimated 75% of patients with carcinoid syndrome experience diarrhea, which, along with urgency to defecate, has perhaps the most direct impact on patient lives [5, 10–13]. Uncontrolled diarrhea may contribute to deterioration in overall health, affect how a patient's cancer is treated, and lead to weight loss, malnutrition, vitamin deficiencies, dehydration, and electrolyte imbalance. If the diarrhea is severe, malabsorption may occur and may even cause death [5, 6, 10, 11, 14–21]. A recent population-based analysis found that carcinoid syndrome was significantly associated with tumor grade, tumor stage, and primary tumor site and led to shorter survival compared with patients without carcinoid syndrome [22]. Therefore, effective treatments for carcinoid syndrome are important in order to help patients stay as healthy as possible for as long as possible [5, 22].

Telotristat ethyl is a novel, oral, small-molecule tryptophan hydroxylase inhibitor that is approved in the U.S. and Europe for the treatment of carcinoid syndrome diarrhea (CSD) inadequately controlled by somatostatin analog therapy [23–25]. Telotristat ethyl is also a category 2A recommendation in the National Comprehensive Cancer Network clinical practice guidelines and recommended by the European Neuroendocrine Tumor Society 2016 guidelines for its approved indication [7, 26]. Compared with earlier tryptophan hydroxylase inhibitors, telotristat ethyl has a higher molecular weight, which likely prevents it from crossing the blood-brain barrier at therapeutic dosages [27, 28]. Two randomized, placebo-controlled phase III studies in patients with carcinoid syndrome found that treatment with telotristat ethyl was generally well tolerated and was associated with a significant decrease in bowel movement frequency in patients receiving treatment with somatostatin analogs [29, 30].

The objective of this analysis was to examine pooled adverse events (AEs) data for patients with carcinoid syndrome who received telotristat ethyl in phase II and III clinical trials, in order to describe long-term safety, morbidity, and mortality in this cohort.

SUBJECTS, MATERIALS, AND METHODS

Study Selection

All clinical studies of telotristat ethyl in patients with carcinoid syndrome were included in this analysis (Table 1). These studies include one randomized, placebo-controlled,

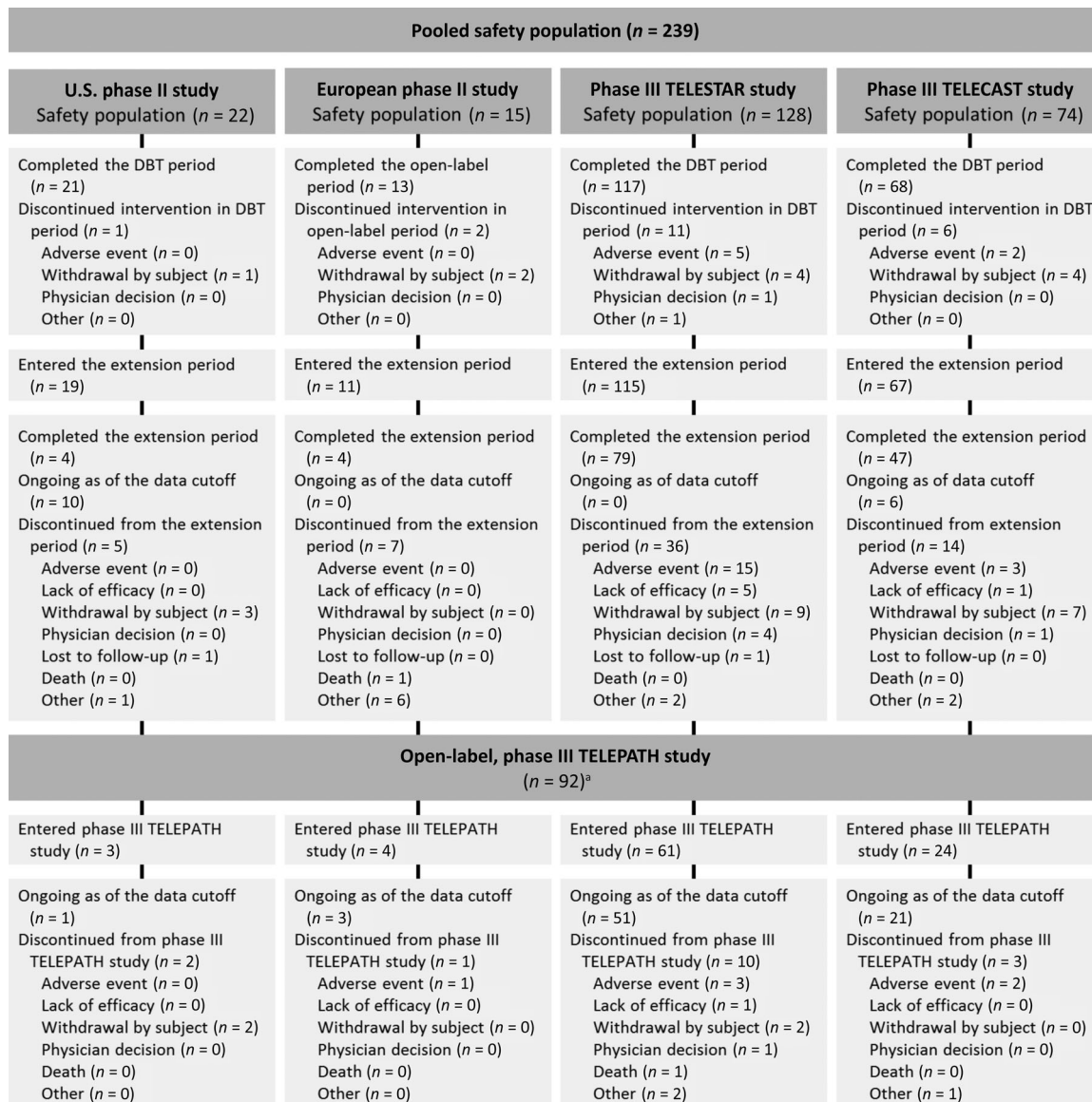


Figure 1. Pooled studies CONSORT flow diagram. ^aConsists only of patients who participated in the phase II and phase III trials described herein. Abbreviation: DBT, double-blind treatment.

double-blind, ascending-multidose phase II study with dosing arms of 150 mg, 250 mg, 350 mg, and 500 mg telotristat ethyl t.i.d. (U.S. Study [NCT00853047]); one open-label, serial ascending-dose phase II dose-finding study with dosing of 150 mg, 250 mg, 350 mg, or 500 mg telotristat ethyl t.i.d. (European Study [NCT01104415]); two randomized, placebo-controlled, double-blind phase III studies assessing telotristat ethyl 250 mg t.i.d. and telotristat ethyl 500 mg t.i.d. (TELESTAR [NCT01677910] and TELECAST [NCT02063659]) [29, 30]; and one open-label, long-term extension study in which patients received telotristat ethyl 250 mg t.i.d. or telotristat ethyl 500 mg t.i.d. (TELEPATH [NCT02026063]); [29–32]. The open-label extension TELEPATH study enrolled patients who had completed the other four studies and is the only study still currently ongoing. Additionally, patients could receive concomitant antitumor therapy during the open-label extension periods of TELESTAR and TELECAST, and the entire study period of

TELEPATH. The study protocols and amendments were approved by the institutional review board or ethics committee at each center, and the studies were conducted in agreement with Good Clinical Practice guidelines and the Declaration of Helsinki [33]. All patients provided written informed consent.

Data Extraction

Safety data in this analysis are based on AEs from completed phase II studies, completed placebo-controlled phase III studies, and data extracted from the ongoing long-term phase III study at the end of 2016. All patients who received telotristat ethyl in these five studies were included in this analysis. It should be noted that patients in TELEPATH previously participated in the phase II or phase III trials; enrollment in TELEPATH allowed for the collection of longer-term safety data with longer treatment. AEs reported for the patients who received telotristat ethyl were pooled across

Table 2. Summary of patient demographics and selected carcinoid syndrome-related medical history

Patient characteristics	N = 239
Mean age, years (SD)	63.0 (9.9)
Median age, years (range)	64 (35–88)
Male, n (%)	126 (52.7)
Medical history, n (%) ^a	
Carcinoid heart disease ^b	65 (27)
Anemia	36 (15)
Fatigue	70 (29)
Weight decreased	27 (11)
Ascites	8 (3)
Cachexia	5 (2)
Dehydration	4 (2)
Malnutrition	3 (1)
Total ^c	126 (53)

^aTerms as reported by investigators.

^bIncludes the preferred terms tricuspid valve incompetence, mitral valve incompetence, carcinoid heart disease, tricuspid valve replacement, carcinoid syndrome, aortic valve incompetence, pulmonary valve incompetence, pulmonary valve replacement, heart valve incompetence, heart valve replacement, tricuspid valve disease, cardiac valve disease, aortic valve disease, aortic valve stenosis, tricuspid valve stenosis, and mitral valve repair.

^cSome patients had >1 of the conditions listed.

studies. Similar events coded to different Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PT) were counted as separate events. Patients experiencing events coded to the same MedDRA PT more than once were counted once in the calculation of incidence.

Patient deaths were identified based on fatal AEs from patient listings. All serious AEs (SAEs), including the fatal AEs, in the studies were collected as part of routine safety surveillance according to Good Clinical Practice guidelines. All patients with a fatal outcome were summarized in a table that includes patient demographics, fatal events coded to System Organ Class and Preferred Term using the MedDRA, and causes of death categorized into disease progression, complication, or other, based on review of each patient narrative.

All SAEs were reviewed for potential causal relationship with telotristat ethyl, taking into account the clinical course of the event, patient's medical history and concomitant medications, and dechallenge and rechallenge information when available.

Patients with disease progression were identified based on AE listings by statistical programming using a list of MedDRA Preferred Terms that are suggestive of disease progression in this population (supplemental online Table 2). Patients identified were manually reviewed to exclude elective procedures (one patient was excluded based on the review). When a patient experienced more than one AE on the list, the AE with the earliest onset date was used for the analysis.

Statistical Analysis

A single descriptive Kaplan-Meier curve was generated using patient death as the endpoint of interest to estimate survival.

RESULTS

Patient Disposition and Characteristics

Two phase II studies and the two placebo-controlled phase III studies were completed by the end of 2016. A total of 92 of the 239 patients treated with telotristat ethyl elected to enter the open-label, long-term extension study (TELEPATH), which is ongoing. Patient flow from the phase II and phase III studies is illustrated in Figure 1.

No patients discontinued the studies because of non-compliance with study drug (data on file). The rate of premature discontinuation due to treatment-emergent adverse events (TEAEs) was generally comparable across telotristat ethyl and placebo treatment groups during the double-blind treatment period of TELESTAR and TELECAST [29, 30].

At the end of 2016, a total of 239 patients from 12 countries received at least one dose of telotristat ethyl. Patient demographics and characteristics are summarized in Table 2 and supplemental online Table 1. All patients had carcinoid syndrome at enrollment. More than half of the patients (126 [52.7%]) also had conditions at baseline that were potentially complications of carcinoid syndrome, such as carcinoid heart disease, anemia, or weight loss. In addition to symptoms associated with carcinoid syndrome, general, nutritional, and cardiac disorders were common among patients, including asthenia, fatigue, dehydration, cachexia, malnutrition, and carcinoid heart disease. Over half of the patients had urinary 5-hydroxyindoleacetic acid levels above the upper limit of normal at the time of randomization [29–32]. In the phase III TELESTAR and TELECAST studies, 100% and 90% of patients enrolled, respectively, had histories of gastrointestinal disorders, most commonly diarrhea. At baseline, patients in randomized, placebo-controlled phase III clinical trials of telotristat ethyl had already survived an average of 6–8 years with metastatic NETs since their initial diagnoses. A majority of the patients received telotristat ethyl 500 mg t.i.d. Duration of exposure to telotristat ethyl ranged from 1 week to over 5 years, with a mean duration of 1.3 years, a median duration of 1.1 years, and a maximum duration of 5.7 years, with a cumulative total exposure of 309 patient years (Table 3). A total of 131 (55%) patients had been treated with telotristat ethyl for at least 48 weeks by the end of 2016.

Serious Treatment-Emergent Adverse Events

Of the 239 patients analyzed, 233 (97.5%) experienced at least one TEAE; 94 (39.3%) experienced at least one serious TEAE. Depression-related TEAEs were all mild or moderate in intensity and generally did not limit treatment with telotristat ethyl.

Serious TEAEs were defined as any event leading to death, a life-threatening adverse event, inpatient hospitalization or prolonging an existing hospitalization (excludes hospitalization for preplanned elective surgery or routine clinical procedures), persistent or significant disability or incapacitation, a congenital anomaly or birth defect, or events requiring medical or surgical intervention necessary to prevent one of the previously mentioned outcomes. The leading causes of serious TEAEs for patients on telotristat ethyl, by system organ class, were gastrointestinal

Table 3. Duration of exposure by study

Duration	U.S. study (n = 22)	European study (n = 15)	TELESTAR (n = 128)	TELECAST (n = 74)	Overall (N = 239)
Mean (SD), weeks ^a	54.3 (89.8)	89.7 (105.1)	70.3 (48.8)	60.9 (37.7)	67.2 (56.0)
Median (minimum, maximum), weeks	12.1 (2.1, 296.0)	31.6 (5.0, 275.7)	70.3 (1.0, 169.6)	72.0 (1.4, 132.0)	59.9 (1.0, 296.0)

^aIncludes time during double-blind treatment period, extension period, and/or time in the TELEPATH study.

disorders (43 patients) and neoplasms benign, malignant, and unspecified (22 patients; Table 4). The latter events were mostly attributable to the underlying tumor and related treatment. These additional treatments, allowed during only the open-label extension periods of the TELECAST and TELESTAR studies and during the entire study period of TELEPATH, included 10 patients receiving concurrent antitumor therapy, including chemotherapy, radiotherapy, chemoembolization, or undergoing tumor resection, separately or in combination. The most common gastrointestinal disorders leading to hospitalization were abdominal pain (12 patients), diarrhea (6 patients), and small intestinal obstruction (6 patients).

Eight patients experienced TEAEs suggestive of carcinoid heart disease; however, only one patient was hospitalized for the event, and there were no deaths attributed to carcinoid heart disease.

Of note, within the 12-week double-blind treatment period of the two placebo-controlled phase III studies, the number of patients with serious AEs (e.g., AEs leading to hospitalization and/or death) tended to be lower in the telotristat ethyl 250 mg group, with 8 (11.4%) patients, compared with 12 (16.9%) on placebo and 11 (15.7%) on telotristat ethyl 500 mg.

Among patients who experienced tumor progression on study, as determined by the analysis of pooled AEs, and for patients who had data available that were collected as part of routine safety monitoring of concomitant medications, procedures, and adverse events, the most common concomitant antitumor therapies were embolization (10 patients) and radiotherapy (9 patients; Table 5).

Patient Survival

This data set captured 23 patient deaths. One-, 2-, and 3-year survival estimates were 93%, 88%, and 77%, respectively. There was one death in year 4 of patient follow-up in this data set (Fig. 2). The median follow-up was approximately 1 year, and the median survival with telotristat ethyl has not yet been reached because a large proportion of patients have not been evaluable at later time points (Fig. 2).

Among the 23 patients who died during the studies as of the data extraction, 12 died of disease progression, 9 due to complications of the underlying NET or carcinoid syndrome and 2 due to other reasons (supplemental online Table 3). Based on information available for these patients, some of these patients were on telotristat ethyl at the time of death, but by sponsor assessment, none of the deaths were attributable to treatment with telotristat ethyl. These deaths were also reviewed by the U.S. Food and Drug

Administration; the clinical reviewer concluded that the deaths were not treatment related [34].

The complications leading to death included liver failure due to replacement of liver tissue by tumor; dehydration secondary to severe CSD; compression or obstruction due to tumor tissue leading to gastrointestinal hemorrhage; renal failure; and intestinal obstruction and subsequent perforation, abdominal infection, and sepsis.

Two patients died of events not directly related to progression or complication of the underlying NET or carcinoid syndrome. The first patient was a 60-year-old female who died due to a cardiac arrest likely attributable to difficulty in managing pain medications in the clinical context of progressive NET; the patient's long-acting narcotic analgesics were changed twice in less than 2 weeks. The second patient was a 78-year-old male who was discharged a week after a hospitalization for sepsis following radiation therapy; he suffered a fatal hemorrhagic stroke 17 days after his last dose of telotristat ethyl.

It should be noted that during the 12-week double-blind treatment period of the two placebo-controlled phase III studies, three (4.2%), one (1.4%), and one (1.4%) patients died in the placebo, telotristat ethyl 250 mg, and telotristat ethyl 500 mg groups, respectively.

DISCUSSION

In this analysis, duration of exposure to telotristat ethyl among all patients treated varied greatly. However, because telotristat ethyl was well tolerated, many patients were able to take it without serious AEs over the long term.

According to our review of AEs leading to death, the long-term safety profile, based on the on-study survival rate for patients with carcinoid syndrome treated with telotristat ethyl, is encouraging, given that patients had been diagnosed with metastatic NETs for an average of 6–8 years prior to enrollment in the randomized, placebo-controlled phase III studies.

The deaths observed in the studies were generally attributable to the progression of or complications related to the underlying tumor and associated carcinoid syndrome symptoms. The number and type of deaths observed were consistent with expectations for this population with metastatic NETs. Progression of abdominal metastases can lead to death by causing bowel obstruction, gastrointestinal hemorrhage, perforation, peritonitis, or even renal failure [6, 11, 20, 35–37]. Carcinoid syndrome itself can also lead to death due to fluid and electrolyte imbalance or carcinoid heart disease [11, 20, 38, 39].

According to North American Neuroendocrine Tumor Society guidelines, the most common cause of death in

Table 4. Serious^a TEAEs experienced by ≥5% of patients in any study

System organ class preferred term, n (%)	U.S. study (n = 22)	European study (n = 15)	TELESTAR (n = 128)	TELECAST (n = 74)	Overall (N = 239)
At least one serious TEAE	9 (40.9)	8 (53.3)	65 (50.8)	28 (37.8)	110 (46.0)
Gastrointestinal disorders	3 (13.6)	5 (33.3)	23 (18.0)	12 (16.2)	43 (18.0)
Abdominal pain	0	1 (6.7)	10 (7.8)	1 (1.4)	12 (5.0)
Diarrhea	0	2 (13.3)	3 (2.3)	1 (1.4)	6 (2.5)
Small intestinal obstruction	0	1 (6.7)	2 (1.6)	3 (4.1)	6 (2.5)
Intestinal obstruction	0	1 (6.7)	0	1 (1.4)	2 (0.8)
Neoplasms benign, malignant, and unspecified (including cysts and polyps) ^{b,c}	3 (13.6)	1 (6.7)	11 (8.6)	7 (9.5)	22 (9.2)
Neoplasm progression	0	1 (6.7)	0	0	1 (0.4)
General disorders and administration site conditions	1 (4.5)	1 (6.7)	12 (9.4)	6 (8.1)	20 (8.4)
Disease progression ^c	1 (4.5)	0	8 (6.3)	1 (1.4)	10 (4.2)
General physical health deterioration	0	1 (6.7)	4 (3.1)	1 (1.4)	6 (2.5)
Pyrexia	0	0	1 (0.8)	4 (5.4)	5 (2.1)
Surgical and medical procedures ^{d,e}	2 (9.1)	2 (13.3)	8 (6.3)	6 (8.1)	18 (7.5)
Radiotherapy	0	1 (6.7)	3 (2.3)	0	4 (1.7)
Therapeutic embolization	0	2 (13.3)	1 (0.8)	1 (1.4)	4 (1.7)
Cardiac operation	0	1 (6.7)	0	0	1 (0.4)
Inguinal hernia repair	0	1 (6.7)	0	0	1 (0.4)
Infections and infestations	0	2 (13.3)	11 (8.6)	4 (5.4)	17 (7.1)
Bronchitis	0	1 (6.7)	0	0	1 (0.4)
Gastroenteritis	0	1 (6.7)	0	0	1 (0.4)
Rhinitis	0	1 (6.7)	0	0	1 (0.4)
Nervous system disorders	1 (4.5)	2 (13.3)	9 (7.0)	5 (6.8)	17 (7.1)
Epilepsy	0	1 (6.7)	1 (0.8)	0	2 (0.8)
Loss of consciousness	0	1 (6.7)	0	0	1 (0.4)
Investigations ^{e,f}	0	2 (13.3)	10 (7.8)	3 (4.1)	15 (6.3)
Investigation	0	1 (6.7)	7 (5.5)	0	8 (3.3)
Blood creatinine increased	0	1 (6.7)	0	0	1 (0.4)
Cardiac disorders	2 (9.1)	1 (6.7)	6 (4.7)	1 (1.4)	10 (4.2)
Angina pectoris	2 (9.1)	0	0	0	2 (0.8)
Carcinoid heart disease	0	1 (6.7)	0	0	1 (0.4)
Injury, poisoning, and procedural complications	0	1 (6.7)	3 (2.3)	5 (6.8)	9 (3.8)
Upper limb fracture	0	1 (6.7)	0	1 (1.4)	2 (0.8)
Renal and urinary disorders	2 (9.1)	0	5 (3.9)	1 (1.4)	8 (3.3)
Hepatobiliary disorders	1 (4.5)	1 (6.7)	5 (3.9)	0	7 (2.9)
Acute hepatic failure	0	1 (6.7)	0	0	1 (0.4)
Respiratory, thoracic, and mediastinal disorders	0	1 (6.7)	3 (2.3)	2 (2.7)	6 (2.5)
Dyspnea	0	1 (6.7)	1 (0.8)	0	2 (0.8)
Vascular disorders	1 (4.5)	1 (6.7)	3 (2.3)	0	5 (2.1)
Hypertension	0	1 (6.7)	0	0	1 (0.4)
Endocrine disorders	0	1 (6.7)	3 (2.3)	0	4 (1.7)
Carcinoid syndrome	0	1 (6.7)	1 (0.8)	0	2 (0.8)

^aEvents leading to death, a life-threatening adverse event, inpatient hospitalization or prolonging an existing hospitalization (excludes hospitalization for preplanned elective surgery or routine clinical procedures), persistent or significant disability or incapacitation, a congenital anomaly or birth defect, or events requiring medical or surgical intervention necessary to prevent one of the previously mentioned outcomes.

^bIncludes preferred terms related to tumor progression.

^cThese terms relate to worsening of the underlying disease.

^dAlso includes preferred terms related to planned antitumor therapies.

^eThese terms arise from the methodology of TEAE capture; they are not normally considered adverse events.

^fAlso includes the preferred terms blood potassium decreased, cholangiogram, diagnostic procedure, general physical condition abnormal, hepatic enzyme increased, laparoscopy, liver function test abnormal, and transaminases increased.

Abbreviation: TEAE, treatment-emergent adverse event.

Table 5. Concomitant antitumor therapy^a after disease progression for patients with available data

Antitumor therapy	No. of patients (%) (n = 26) ^b
Embolization ^c	10 (38.5)
Radiotherapy	9 (34.6)
Surgery ^d	6 (23.1)
Systemic therapy ^e	5 (19.2)

^aConcomitant antitumor therapy was allowed during the OLE period of the TELECAST and TELESTAR studies, as well as during the entire period of the TELEPATH study.

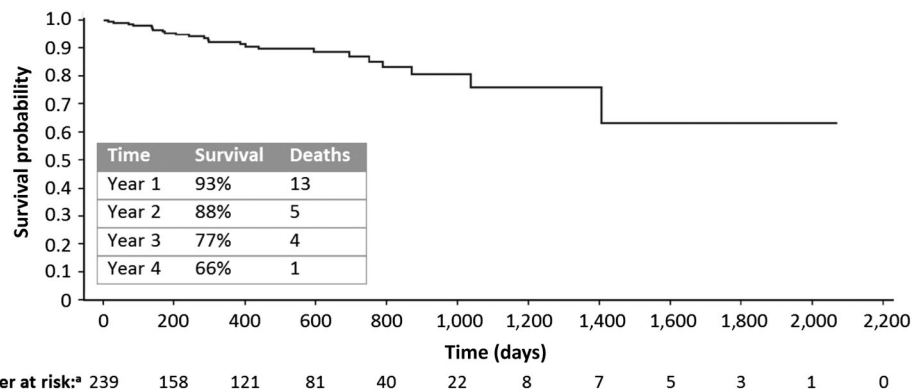
^bSome patients received >1 therapy.

^cIncluded TACE, chemoembolization, and hepatic embolization.

^dIncluded hepatectomy, resection of ovarian metastases, small intestinal resection, and rectal resection.

^eIncluded everolimus, capecitabine, cisplatin, fluorouracil, streptozotocin, and temsirolimus.

Abbreviations: OLE, open-label extension; TACE, transcatheter arterial chemoembolization.

**Figure 2.** Kaplan-Meier survival curve for patients treated with telotristat ethyl in five clinical studies.

^aNumber at risk includes only patients who received treatment with telotristat ethyl, shown according to duration of telotristat ethyl treatment.

patients with metastatic NETs is liver failure due to the progression of liver metastases [6]. In our studies, two patients died of liver failure due to replacement of liver tissue by tumor; a review of the clinical course and laboratory results for the patients showed no evidence of clinically significant drug-induced liver injury in either case.

Given the age of this patient population, a small number of cardiovascular deaths is expected. One patient died of a cardiac arrest attributable to difficulty in managing pain medications in the clinical context of progressive NET, and another died of hemorrhagic stroke 17 days after the last dose of telotristat ethyl.

In the telotristat program all patients were able to receive antitumor therapies such as radiotherapy, systemic therapies, embolization, and surgery. This was allowed so that the real-world medical needs of the patient population could be addressed. These antitumor therapies may have supported the long-term survival of the population. The experience to date suggests that a variety of antitumor therapies can be tolerated with telotristat ethyl.

It is worth noting that between the two placebo-controlled phase III studies of telotristat ethyl, one study (TELESTAR) enrolled patients who had more (≥ 4) bowel movements per day at baseline, and the deaths occurred almost exclusively in patients enrolled in this study, either during the double-blind treatment period or during the open-label extension period [29]. It is possible that the

number of bowel movements either indicates the severity of the underlying disease or has significant impact on the survival of these patients [40].

The strengths of this analysis are the inclusion of three randomized, placebo-controlled studies, the duration of follow-up, and the relatively large sample size for the rare condition of carcinoid syndrome. A key limitation of the analysis is the lack of a placebo group for the long-term follow-up. However, it was not considered ethical for patients to remain on placebo long term. Other limitations are that the median follow-up time is slightly longer than 1 year and the long-term exposure was primarily to telotristat ethyl 500 mg t.i.d. in the open-label extension periods. It should be noted that telotristat ethyl is approved in the U.S. and Europe at a dose of 250 mg t.i.d. [23, 24]. Although down-titration was permitted during the studies for safety reasons, it rarely occurred, attesting to the tolerable side-effect profile of telotristat ethyl. The analysis of survival is limited by the duration of follow-up. Some patients withdrew from the study (or chose not to enter long-term follow-up) for a variety of reasons, and it is not possible to determine their long-term outcomes. In the survival analysis, these patients were censored at the time of last observation. The analysis is also limited by the fact that disease progression was not formally, prospectively evaluated with RECIST criteria in the studies [41] but retrospectively identified based on AEs indicative of disease progression. Nevertheless, the patients received a high standard of care and

were followed frequently for disease progression, the evidence of which was assessed by review of AEs using a comprehensive set of terms. To ensure complete capture of disease progression, concomitant medications and procedures during the studies were also reviewed for chemical/biological therapy and surgeries/procedures known to be used to treat NET; this review did not identify additional patients. Follow-up is still ongoing, and it will be important to examine future data extractions.

CONCLUSION

Long-term treatment with telotristat ethyl (250 mg or 500 mg t.i.d.) was generally well tolerated with few serious AEs and no negative impact on patient survival. This analysis of the pooled safety data suggests that tryptophan hydroxylase inhibition with telotristat ethyl represents a novel treatment approach with a good tolerability profile for patients with carcinoid syndrome.

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DISCLOSURES

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