Telotristat etiprate, a novel serotonin synthesis inhibitor, in patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide

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Abstract

Serotonin produced by neuroendocrine tumors is believed to be a principal cause of the diarrhea in carcinoid syndrome. We assessed the safety and efficacy of telotristat etiprate, an oral serotonin synthesis inhibitor, in patients with diarrhea associated with carcinoid syndrome. In this prospective, randomized study, patients with evidence of carcinoid tumor and ≥ 4 bowel movements (BMs)/day despite stable-dose octreotide LAR depot therapy were enrolled in sequential, escalating, cohorts of four patients per cohort. In each cohort, one patient was randomly assigned to placebo and three patients to telotristat etiprate, at 150, 250, 350, or 500 mg three times a day (tid). In a subsequent cohort, one patient was assigned to placebo and six patients to telotristat etiprate 500 mg tid. Patients were assessed for safety, BM frequency (daily diary), 24 h urinary 5-hydroxyindoleacetic acid (u5-HIAA), and adequate relief of carcinoid gastrointestinal symptoms (using a weekly questionnaire). Twenty-three patients were treated: 18 received telotristat etiprate and five received placebo. Adverse events were generally mild. Among evaluable telotristat etiprate-treated patients, 5/18 (28%) experienced a ≥ 30% reduction in BM frequency for ≥ 2 weeks, 9/16 (56%) experienced biochemical response (≥ 50% reduction or normalization in 24-h u5-HIAA) at week 2 or 4, and 10/18 (56%) reported adequate relief during at least 1 of the first 4 weeks of treatment. Similar activity was not observed in placebo-treated patients.

Key Words

► adult
► carcinoid syndrome
► diarrhea
► neuroendocrine tumor
► serotonin
► tryptophan hydroxylase
Telotristat etiprate was well tolerated. Our observations suggest that telotristat etiprate has activity in controlling diarrhea associated with carcinoid syndrome. Further studies confirming these findings are warranted.

Introduction

Carcinoid syndrome is characterized by watery diarrhea, episodic flushing, bronchoconstriction, and eventually, the development of right-sided valvular heart disease. The symptoms of carcinoid syndrome have been attributed, in part, to elevated levels of 5-HT (serotonin) secreted by the tumor (Druce et al. 2009, Kvols et al. 2012). Serotonin appears to play a particularly important role in the development of carcinoid-related diarrhea. In an early study, treatment with the serotonin receptor antagonist methysergide was reported to reduce the frequency of diarrhea in patients with carcinoid syndrome (Melmon et al. 1965). In a second study published in 1967, inhibition of serotonin synthesis with the drug parachlorophenylalanine (pCPA) resulted in substantial improvement of diarrhea in patients with carcinoid syndrome. The further use of either drug, however, was precluded by the development of psychiatric side effects (Engelman et al. 1967). The development of carcinoid heart disease is likely mediated by serotonin (Creutzfeldt 1996, Möller et al. 2003, Gustafsson et al. 2005, Dobson et al. 2013). Evidence supporting the role of serotonin was previously demonstrated (CDC 1997, Connolly et al. 1997); individuals treated with the serotonin agonist fenfluramine developed cardiac lesions identical to those observed in patients with longstanding carcinoid syndrome.

In current practice, patients with carcinoid syndrome are generally treated with somatostatin analogs (SSAs) given by injection. The effects of SSAs are mediated by somatostatin receptors (predominately receptor subtype 2) that have an inhibitory effect on tumor secretion of serotonin and other neuropeptides into the systemic circulation. In an initial study, s.c. administration of the SSA octreotide at a dosage of 150 μg three times a day (tid) improved the symptoms of carcinoid syndrome in 88% of patients (Kvols et al. 1986). A long-acting depot form of octreotide, which can be administered on a monthly basis, is now commonly used in patients with carcinoid syndrome, together with the use of short-acting octreotide as needed for breakthrough symptoms. Lanreotide, another SSA, appears to be similar to octreotide in its clinical efficacy. Over time, however, patients may develop tachyphylaxis to the effects of SSAs, or may respond to a lesser extent due to increased tumor burden (Kvols et al. 2012). There are few treatment options presently available for these patients, and new therapies are needed.

Telotristat etiprate is an oral, systemically available, small molecule inhibitor of peripheral serotonin synthesis. Telotristat etiprate acts by inhibiting tryptophan hydroxylase, the rate-limiting enzyme in the conversion of tryptophan to serotonin. In multiple-dose PK studies, the median $T_{\text{max}}$ after telotristat etiprate (at dose levels ranging from 100 to 500 mg) ranged from 2 to 4 h on both days 1 and 14. The $T_{1/2}$ of LP-778902 after multiple doses of telotristat etiprate ranged from 3.65 to 11.7 h consistent with dosing tid.

The molecule was designed not to cross the blood–brain barrier at the intended dose, and preclinical studies suggested that telotristat etiprate acts primarily peripherally, with little, if any, activity observed in the CNS (Lexicon 2007, unpublished observations). Phase I studies in healthy volunteers demonstrated that telotristat etiprate, administered orally at doses up to 500 mg tid, reduced serotonin production, as measured by urinary 5-hydroxyindoleacetic acid (u5-HIAA), a serotonin metabolite (Lexicon 2012, unpublished observations). No obvious neurologic or psychiatric side effects were observed in these studies, and other adverse events (AEs) were infrequent.

In light of the association between excess serotonin production and carcinoid syndrome, we explored the safety and efficacy of telotristat etiprate in patients with carcinoid syndrome and diarrhea inadequately controlled by octreotide in a prospective, randomized study.

Patients and methods

Study design

The primary objective of this prospective, randomized study was to assess the safety of telotristat etiprate in patients with carcinoid syndrome and diarrhea...
inadequately controlled by octreotide. Because of the small sample size, efficacy analyses were considered exploratory. Per protocol, in the dose-escalation phase of the trial, four patients were randomized (one to placebo and three to active drug) in each ascending dose cohort of 150, 250, 350, and 500 mg tid, and evaluated for toxicity (Fig. 1). Dose escalation to the next cohort was permitted only if less than or equal to two patients in the cohort experienced a dose-limiting toxicity and after additional review of all additional toxicities experienced by patients in the previous cohort. Then, in the expansion phase of the trial, an additional cohort of seven patients (six telotristat etiprate, one placebo) was studied at either the maximum tolerated dose or at the maximum defined dose in the study (500 mg tid). The goal of the expansion phase was to gain additional clinical experience at the maximum defined dose of telotristat etiprate. The dose-escalation phase and the expansion phase were conducted under the same conditions, with the same assessments of safety and efficacy. Randomization of all patients was central, via an Interactive Voice Response System (IVRS).

Following completion of the initial 4-week blinded treatment period, all eligible patients were offered enrollment into an open-label extension phase (entry at assigned dose level with opportunity to progress to higher dose levels). The results of the blinded treatment period are described herein.

This study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the respective Institutional Review Board with jurisdiction over each site. All patients gave written informed consent after receiving a full explanation of the purpose and nature of the study as well as all study-related procedures, and before being enrolled into the study.

**Safety review to determine dose escalation after each cohort completes treatment**

**Figure 1**
Five cohorts of patients with carcinoid syndrome were sequentially enrolled in the study. The first four cohorts ranged in telotristat etiprate dose from 150 to 500 mg tid, with four patients in each cohort (three patients randomized to active drug, one on placebo). The fifth cohort enrolled an additional seven patients (six patients randomized to the 500 mg tid dose, one to placebo).
Patient selection

Eligible patients were required to have biopsy-proven metastatic neuroendocrine (carcinoid) tumor and diarrhea inadequately controlled by octreotide therapy. Inadequately controlled diarrhea was defined as an average of ≥4 bowel movements (BMs)/day while on stable-dose octreotide LAR depot therapy for at least 3 months; in addition, patients were allowed to use supplemental short-acting octreotide therapy during the run-in and treatment period. Serum creatinine <1.5 × the upper limit of normal (ULN), hepatic transaminases <2 × ULN, alkaline phosphatase <1.5 × ULN, and total bilirubin within normal limits were required to enter the study.

Patients were excluded if they had a history of short bowel syndrome, more than 12 high-volume, watery BMs/day or a Karnofsky Performance Status ≤70%. Patients were excluded if they had concomitant use of antidiarrheal agents, anticholinergic antidepressants, opioid analgesic drugs, or drugs specifically affecting bowel motility during the run-in period and for the duration of the study unless, in the opinion of the investigator, discontinuation of such medications would place the subject at unnecessary health risk, and the use of these concomitant medications had been stable for at least 3 months before the run-in period. Specific data on frequency of antidiarrheal use after study entry was not obtained.

Assessment of AEs and dose limiting toxicities

In advance of beginning the study, toxicities were predefined as mild (not sufficient to interfere with usual activity), moderate (severe enough to interfere with usual activity), or severe (preventing subjects from performing their usual activities). AEs were recorded based on standard reporting criteria. Dose-limiting toxicity was defined as ALT ≥4 × ULN (if normal at baseline) or ≥2 × baseline (if above normal at baseline), total bilirubin ≥2 × ULN, alkaline phosphatase ≥3 × ULN (if normal at baseline) or ≥2 × ULN (if above normal at baseline), or constipation, defined as more than 3 consecutive days without a BM.

Assessment of efficacy

Efficacy was explored using a responder analysis across several endpoints, including BM frequency, change in 24-h u5-HIAA, and patient-reported adequate relief of symptoms. Patients initially completed a run-in period in which baseline values including BM frequency, flushing frequency, and use of short-acting subcutaneous octreotide as needed for acute symptoms (also known as ‘rescue’ octreotide) were recorded (Table 1).

BM frequency was assessed using a daily patient report via IVRS system. A clinical response in BM frequency was defined either as a ≥30% reduction from baseline in the daily mean number of BMs/week for ≥2 weeks or as achievement of ≤3 BMs/day averaged across the daily values for the week, in the absence of rescue octreotide use.

Baseline 24-h u5-HIAA was obtained on the day before treatment; subsequently, 24 h urine collections for u5-HIAA were obtained at weeks 2 and 4 of treatment. Biochemical response was defined either as a ≥50% decrease in 24-h u5-HIAA levels from baseline, or as normalization of u5-HIAA (in patients who had elevated baseline levels) at either week 2 or 4. In addition, there must have been absence of octreotide rescue treatment in the week preceding the postdose value when response was achieved.

Patient-reported adequate relief of symptoms was assessed weekly via IVRS, using responses to the question, ‘In the past 7 days, have you had adequate relief of your carcinoid syndrome bowel complaints such as diarrhea, urgent need to have a BM, abdominal pain, or discomfort?’ Other efficacy endpoints included changes in stool consistency, urgency to defecate, abdominal pain, frequency of flushing, and use of short-acting rescue octreotide.

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Number and percentage (%) of patients</th>
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<tr>
<td>Number of eligible patients</td>
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<tr>
<td>Age</td>
</tr>
<tr>
<td>Mean (years)</td>
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<tr>
<td>Minimum, maximum</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>BM frequency</td>
</tr>
<tr>
<td>Mean (n/day)</td>
</tr>
<tr>
<td>Minimum, maximum</td>
</tr>
<tr>
<td>Octreotide dose</td>
</tr>
<tr>
<td>30 mg every 4 weeks</td>
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<tr>
<td>30 mg every 3 weeks</td>
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<tr>
<td>40 mg every 2–4 weeks</td>
</tr>
<tr>
<td>60 mg every 3 weeks</td>
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<tr>
<td>Octreotide infusion pump</td>
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<tr>
<td>Urinary 5-HIAA, mg/24 h (range)</td>
</tr>
<tr>
<td>Mean (mg/24 h)</td>
</tr>
<tr>
<td>Minimum, maximum</td>
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<tr>
<td>Primary tumor site</td>
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<tr>
<td>Midgut</td>
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<tr>
<td>Hindgut</td>
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</table>
Statistical analyses

Descriptive methods were used to summarize the study data. These statistics included sample size (n), mean, S.D., median, minimum, and maximum values for continuous variables and counts with related percentages for categorical variables. Statistical tests were conducted in an exploratory manner to help guide inferences for a limited number of efficacy variables. Maximum likelihood methods were used to derive all point estimates of treatment effect. For continuous variables, this was the difference between treatment group least squares means derived from analysis of covariance statistics and the difference between treatment group proportions for binomial variables. All analyses were based on the observed data; imputation for missing data points was not performed.

Data were summarized by treatment group. The placebo group consisted of patients pooled from the dose-escalation phase and the expansion phase of the study. In a likely manner, patients treated with the dose of telotristat etiprate selected from the dose-escalation phase were pooled with patients receiving that same dose in the expansion phase, making a single-dose group at 500 mg tid. All other telotristat etiprate treatment groups were summarized as planned from the dose-escalation phase of the study. The subjects were included in the treatment group as assigned by the randomization plan.

A waterfall plot (Fig. 2) was used to visually display the percentage change from baseline in the number of BMs measured over the course of the study for both telotristat etiprate and placebo groups. Subset analyses, Wilcoxon two-sample tests, were performed to explore the percentage changes from baseline in BM frequency at week 4 (Fig. 3). Subsets included those patients who reported adequate relief and those who did not as well as those who achieved biochemical response and those who did not. All analyses were performed, and summaries were prepared, using SAS (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 23 patients were randomly assigned (18 to telotristat etiprate and five to placebo) and treated at 11 clinical sites. Study design and patient disposition are
shown in Fig. 1; baseline demographics are described in Table 1. All but one patient had midgut NET. At baseline, 65% of patients were on standard antidiarrheal medications (e.g. lomotil, loperimide, tincture of opium, and cholestyramine); 87% of those patients on antidiarrheals at baseline either continued or resumed concomitant antidiarrheals during the reported study period. Four patients were receiving octreotide at the maximum approved dose (30 mg i.m. q 4 weeks); all other patients were receiving octreotide at higher doses.

Safety

Telotristat etiprate was well tolerated at all dose levels. Of the 23 patients who received either telotristat etiprate or placebo, 4/5 (80%) of the placebo patients and 18/18 (100%) of the patients receiving telotristat etiprate reported at least one treatment-emergent AE (Table 2). There were no serious AEs (SAEs) in the placebo patients and 2/18 patients receiving telotristat etiprate experienced SAEs. One of these patients was hospitalized for nausea and vomiting; this patient had a pre-existing history of similar symptoms and subsequently elected to withdraw from the study. The second patient had a recurrence of squamous cell carcinoma on the hand, deemed unlikely related to treatment. In interpreting the incidence of AEs, it is useful to recall that patients on telotristat etiprate (18) outnumbered placebo patients (5) by a ratio of > 3.

Most reported AEs were mild and gastrointestinal in nature. These included mild nausea, vomiting, or abdominal discomfort. A majority of AEs were transient and resolved during the course of the treatment period or open-label extension. Reported psychiatric events were rare; a single patient reported depression while receiving telotristat etiprate. This patient had a preexisting diagnosis of anxiety disorder and the AE resolved while the patient continued to receive study therapy. The levels of transaminases were elevated over baseline during the 4 weeks of the study in both treatment groups and included 3/18 (17%) on telotristat etiprate and 2/5 (40%) on placebo. All elevations were \(< 2\times\) the patient’s baseline; the majority of elevations were transient. No patient experienced elevations in total bilirubin above the reported normal range during the treatment period. No clear correlation between dose level and the frequency of AEs was observed.

Clinical response/decrease in BM frequency

Five (28%) of 18 patients treated with telotristat etiprate and zero of five patients treated with placebo achieved a clinical response, defined either as a \(\geq 30\%\) reduction from baseline in the daily mean number of BMs/week for 2 or more of the 4 weeks on trial. Of note, these clinical responses included only reductions in BM frequency in the absence of elective, rescue octreotide use.

Most (12/16) telotristat etiprate patients had at least some reduction in BM frequency for 2 or more weeks of the 4-week treatment period, as compared with one of five placebo patients (Fig. 2). At week 4, mean decreases in BM frequency were observed in all dose cohorts for patients receiving telotristat etiprate; no mean decrease in BM frequency was observed in patients receiving placebo (Table 3).
Based on the analysis of a related measure of activity of complete response, (i.e. <4 BMs/day averaged over the week, a ≥50% from decrease from baseline in daily BMs averaged over the week, or a positive global assessment for the last 2 weeks of treatment), telotristat etiprate-treated patients again showed a favorable outcome compared to those on placebo; six of eight patients treated with telotristat etiprate achieved a complete response at week 4 compared to a rate of 0% in placebo-treated patients (zero of five) at week 4.

Biochemical response

Nine of 16 evaluable telotristat etiprate patients and zero of five placebo patients achieved a biochemical response in u5-HIAA (normal, ≤6 mg/24 h), defined either as a ≥50% decrease in 24-h u5-HIAA levels from baseline or as normalization of u5-HIAA (in patients who had elevated baseline levels) at either week 2 or 4 (Table 3).

Adequate relief

As described earlier, patient-reported adequate relief of symptoms was collected weekly using IVRS during the 4-week active treatment period. Data were available for 80/92 weekly patient assessments (Table 3). During this period, no patients receiving placebo reported adequate relief, whereas 10/18 (56%) of the telotristat etiprate-treated patients reported relief at 1 or more weekly time points. At the end of the blinded treatment period (week 4), four patients receiving placebo and 13 patients receiving telotristat etiprate completed the assessment of adequate relief. None of these four patients receiving placebo reported adequate relief, whereas 6/13 (46%) receiving telotristat etiprate reported relief.

Associations between efficacy parameters

We retrospectively explored associations between decreases in BM frequency and patient-reported adequate relief.
relief (Fig. 3A). We focused our analysis on week 4 (end of treatment period) data, for which 15 patients were evaluable. Patients who reported adequate relief at week 4, regardless of treatment, experienced a 33.4% mean reduction in BM frequency during week 4 (\( n = 5 \)), from pretreatment baseline. Patients who did not report adequate relief at week 4 had a 3.0% mean decrease in mean BM frequency (\( n = 10 \)). The difference between these two groups, based on achieving adequate relief, was significant (\( P = 0.019 \)).

Similarly, we explored associations between decreases in BM frequency and biochemical response, defined here as a 50% or greater reduction in u5-HIAA at week 4 (Fig. 3B). Fifteen patients were evaluable in this analysis. Patients with biochemical response at week 4 experienced a mean 30.9% reduction in mean BM frequency during week 4 (\( n = 5 \)), compared with baseline. In contrast, patients who did not have biochemical response at week 4 had a 1.4% mean increase in mean BM frequency (\( n = 10 \)). The difference between these two groups, based on achieving a biochemical response, was significant (\( P = 0.028 \)).

Clinical responses in BM frequency and in adequate relief were found among patients with elevated u5-HIAA at baseline and also among those with normal baseline u5-HIAA. Of the 11 patients who entered the study with elevated baseline u5-HIAA levels, 3 (27%) were clinical responders and 2 (18%) reported adequate relief at week 4. Of the ten patients who entered the study with u5-HIAA values in the normal range, 2 (20%) were clinical responders and 3 (30%) reported adequate relief at week 4.

Other endpoints

No clear differences in use of rescue octreotide between patients treated with telotristat and placebo were observed. No clear differences in stool consistency, urgency to defecate, abdominal pain, or frequency of flushing were observed between patients treated with telotristat etiprate or those receiving placebo.

Discussion

Excess serotonin production has been implicated as a causative factor in carcinoid-associated diarrhea and other manifestations of the carcinoid syndrome (Druce et al. 2009). In carcinoid syndrome, increased frequency of BMs has been associated with a decreased quality of life (Beaumont et al. 2012). Our results provide evidence supporting the safety of telotristat etiprate, a tryptophan hydroxylase inhibitor. Our observations further suggest that telotristat etiprate may have promising clinical activity in patients with carcinoid syndrome and diarrhea inadequately controlled by octreotide.

Overall, at all doses, including the maximum dose tested (500 mg tid), telotristat etiprate was safe and well tolerated, as evidenced by the comparable occurrence of AEs between placebo and telotristat dose groups. In our

### Table 3: Extent of exposure and efficacy by treatment group

<table>
<thead>
<tr>
<th>BM frequency (clinical response)</th>
<th>Placebo (( n = 5 ))</th>
<th>150 mg tid (( n = 3 ))</th>
<th>250 mg (( n = 3 ))</th>
<th>350 mg tid (( n = 3 ))</th>
<th>500 mg tid(^*) (( n = 9 ))</th>
<th>Pooled telotristat etiprate (( n = 18 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean BM frequency, n/day (range)</td>
<td>5.3 (4–8)</td>
<td>8.0 (5–10)</td>
<td>6.9 (5–9)</td>
<td>5.8 (5–7)</td>
<td>6.5 (4–9)</td>
<td>6.3 (4–10)</td>
</tr>
<tr>
<td>Clinical responders, n/evaluable (%)</td>
<td>0/5 (0)</td>
<td>1/3 (33)</td>
<td>2/3 (67)</td>
<td>0/3 (0)</td>
<td>2/9 (22)</td>
<td>5/18 (28)</td>
</tr>
<tr>
<td>Mean change daily BM frequency week 4</td>
<td>+0.8</td>
<td>-1.4</td>
<td>-2.2</td>
<td>-1.2</td>
<td>-0.7</td>
<td>-1.2</td>
</tr>
</tbody>
</table>

| Urinary 5-HIAA (u5-HIAA; biochemical response) | Baseline mean u5-HIAA, mg/24 h (range) | 100.04 (0.3–246.0) | 51.53 (4.6–117.0) | 2.4 (1.7–3.6) | 3.33 (2.8–3.9) | 105.2 (8.4–217.0) | 56.8 (2.8–217) |
| Biochemical responders at week 2 or 4 (n/evaluable) | 0/5 (0) | 2/3 (67) | 1/3 (33) | 0/2 (0) | 6/8 (75) | 9/16 (56) |

| Patient-reported adequate relief | Week 1, n/evaluable (%) | 0/4 (0) | 1/3 (33) | 1/3 (33) | 0/3 (0) | 4/9 (44) | 6/18 (33) |
| Week 2, n/evaluable (%) | 0/5 (0) | 2/3 (67) | 1/3 (33) | 0/2 (0) | 2/8 (25) | 5/16 (31) |
| Week 3, n/evaluable (%) | 0/5 (0) | 1/2 (50) | 1/3 (33) | 1/2 (50) | 2/8 (25) | 5/15 (33) |
| Week 4, n/evaluable (%) | 0/4 (0) | 1/2 (50) | 2/3 (67) | 1/2 (50) | 2/6 (33) | 6/13 (46) |

\(^*\)One patient from the 500 mg group was excluded from u5-HIAA baseline and week 4 value calculation and included in the biochemical response calculation based on prespecified definitions of timing of u5-HIAA collection.
endocrine-related cancer syndrome, it is possible that some of the patients with carcinoid syndrome had diarrhea on the basis of normal u5-HIAA levels at baseline. The protocol required a diagnosis of carcinoid syndrome (Engelman et al. 1967). Carcinoid syndrome is an imperfect predictor of serotonin-mediated diarrhea in patients who are already receiving treatment with SSAs.

In conclusion, in this preliminary study, telotristat etiprate exhibited a favorable safety profile and was well tolerated in these patients with carcinoid syndrome. Evidence of clinical benefit was observed in this study across several endpoints, including decreased BM frequency, decreased u5-HIAA levels, and patient-reported adequate relief of symptoms. Further studies of telotristat etiprate in patients with carcinoid-related diarrhea are warranted.

Declaration of interest
M H Kulke, T O’Dorisio, A Phan, E Bergsland, J C Yao, and L Kvols have received payment for their time spent conducting study-related tasks. M H Kulke has received paid honoraria from Lexicon Pharmaceuticals, Inc. P Banks, P Lapuerta, B Zambrowicz, D Fleming, and A Sands are currently employees of Lexicon Pharmaceuticals, Inc., and own stock. J Law, J Freeman, K Frazier, and J Jackson were employees of Lexicon Pharmaceuticals, Inc., at the time the study was conducted and may currently own stock. A Sands is on the Board of Directors for Lexicon Pharmaceuticals, Inc.

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Author contribution statement
The authors have made the following contribution about their contribution: M H Kulke, D Fleming, and A Sands designed the study; M H Kulke, T O’Dorisio, E Bergsland, and P Banks worked on statistical analysis. M H Kulke, P Banks, J Freeman, K Frazier, and J Jackson provided data; M H Kulke, T O’Dorisio, A Phan, and E Bergsland wrote the manuscript; M H Kulke, T O’Dorisio, A Phan, and E Bergsland approved the final manuscript.

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