Special Report

CLINICAL INVESTIGATION

Telotristat etiprate, a novel inhibitor of serotonin synthesis for the treatment of carcinoid syndrome

Excessive serotonin secretion is the hallmark of carcinoid syndrome. It leads to diarrhea, cramping, abdominal pain, wheezing and flushing. It is also associated with serious cardiac valve disease and lower life expectancy. Efforts to control serotonin production in carcinoid syndrome are currently limited to the use of somatostatin analogues and antitumor therapies such as surgery, radiation, or embolization. A significant proportion of patients still suffer from excess serotonin production and its debilitating symptoms. This review addresses the development of telotristat etiprate, a novel serotonin synthesis inhibitor currently being investigated in carcinoid syndrome. Early clinical studies support the conduct of TELESTAR, a Phase III pivotal trial that may determine whether telotristat etiprate will become the first approved serotonin synthesis inhibitor.

Keywords: carcinoid syndrome • serotonin synthesis inhibition • telotristat etiprate

Pablo Lapuerta*[,1], Brian Zambrowicz[1], Doug Fleming[1], Darren Wheeler[1] & Arthur Sands[1]

[1]Lexicon Pharmaceuticals, The Woodlands, TX, USA

*Author for correspondence: plapuerta@lexpharma.com

For several decades it has been known that there is a strong link between excessive serotonin production and carcinoid syndrome [1]. That link led to the concept that a serotonin synthesis inhibitor could help patients with carcinoid syndrome control their symptoms. In 1967, a serotonin synthesis inhibitor, parachlorophenylalanine, was examined in a clinical trial [2]. Results of this small pilot study were published in the *New England Journal of Medicine* showing marked improvements in symptoms of diarrhea and GI discomfort. However, several central nervous system abnormalities were observed and it was suggested that they may be related to depletion of serotonin synthesis in the brain. The use of parachlorophenylalanine was described in a few other case reports [3–5], but it was not developed further.

The concept of developing a more appropriate serotonin synthesis inhibitor recently emerged from the discovery programs at Lexicon Pharmaceuticals. In an extensive drug target research effort based on genetic technology, Lexicon produced 4780 genetic knock-out mice, each lacking a single gene [4]. The mice were put through extensive tests to examine their overall health and investigate their susceptibility and resistance to several models of disease [5].

These knockout mice were used to model drug action. Focus was placed on identifying targets whose genetic inhibition improved physiology or provided resistance to disease models. The resulting hypothesis was that pharmacological inhibition could produce comparable effects.

Lexicon's knockout program developed mice lacking TPH1, the rate-limiting enzyme of serotonin synthesis in the gastrointestinal tract, providing insight into the role of serotonin in animal physiology. The mice deficient in TPH1 were healthy, despite a dramatic reduction in intestinal and blood serotonin [6]. Their serotonin deficiency was well tolerated in terms of gastrointestinal function. The mice also had normal brain serotonin levels and normal behavior.

These observations led to the concept that a safe and effective TPH inhibitor could be developed for several potential indications, among them the treatment of carcinoid syn-

FUTURE SCIENCE part of fsg

drome. Lexicon embarked on a drug discovery program around TPH inhibition with potential drug candidates that lowered peripheral serotonin in animals while not crossing the blood–brain barrier. This effort led to the discovery of telotristat etiprate.

Telotristat etiprate mechanism of action

Telotristat etiprate is an ethyl ester prodrug which is hydrolyzed to its active moiety LP-778902 both *in vivo* and *in vitro* (Figure 1). Systemic exposure of telotristat etiprate is relatively low, as the hydrolysis to the active moiety is rapid. LP-778902 is a potent inhibitor of TPH with an *in vivo* IC50 of 0.028 µM.

In normal mice, telotristat etiprate (administered once daily for 4 days at doses of 15–300 mg/kg/day) was found to reduce serotonin levels throughout the gastrointestinal tract [7]. These reductions occurred in a dose-dependent fashion with maximal effects observed with doses of telotristat etiprate ≥150 mg/kg. No significant change in brain serotonin or 5-hydroxyindoleacetic acid (5-HIAA, a serotonin metabolite) was observed. Similar findings were seen in Sprague-Dawley rats.

Gastrointestinal motility studies were conducted in rats using the charcoal meal test [7]. There was a significant dose-related delay in both gastrointestinal transit and gastric emptying, associated with a reduction in blood serotonin levels and proximal colon serotonin.

A quantitative whole-body autoradiography study was conducted to assess the absorption, distribution and excretion of radioactivity in rats following a single oral dose of telotristat etiprate labeled with carbon 14 [7]. Rats were administered either 30 mg/kg or 100 mg/kg of the compound. The distribution of radioactivity was limited to tissues of the hepatic and renal system and the contents of the GI tract. There was no measurable radioactivity in the brain at any dose tested.

Telotristat etiprate and its active moiety LP-778902 were tested for their inhibition of two related enzymes, phenylalanine and tyrosine hydroxylase, as well as several cytochrome P450 isoenzymes [7]. This demonstrated that telotristat etiprate is a highly specific inhibitor of TPH. Given the low systemic exposure of telotristat etiprate and the high plasma protein binding of LP-778902, results suggested a low potential for drug–drug interactions due to cytochrome P450 inhibition.

Clinical development of telotristat etiprate

Phase I

Three Phase I studies of telotristat etiprate have been conducted to date [8–12]. They consist of a single ascending dose study, a multiple ascending dose study, and a cross-over study of two oral formulations (tablet or capsule). These studies showed that telotristat etiprate was present in very low levels after oral administration. These low levels were due to rapid hydrolysis into the active moiety LP-778902. The half-life ranged from approximately 4–12 h. There was no accumulation of LP-778902 with multiple dose administration over 2 weeks. Exposure to LP-778902 was approximately dose proportional.

Telotristat etiprate produced significant reductions in whole blood serotonin levels and urinary 5-HIAA, with reductions of approximately 25 and 45% achieved after 2 weeks of dosing, respectively. These were dose-related, with the most rapid reduction being observed at the highest dose of telotristat etiprate studied, 500 [1]mg administered orally three times daily.

No serious adverse events were reported in these studies. Adverse events were minimal and generally mild to moderate in intensity. There was no increase in central nervous system adverse events. The majority of adverse events were related to the gastrointestinal tract, the most frequent being nausea (Table 1). Mild increases (generally equal to or less than twice the upper limit of normal) were observed in ALT and AST. This led to careful, frequent observation of liver function tests in two Phase II studies. No signal for elevation of liver function tests emerged from those studies.

Phase II

Two Phase II studies examined the safety and efficacy of telotristat etiprate in patients with carcinoid syndrome not adequately controlled by somatostatin analogues. Inadequate control was defined as an average

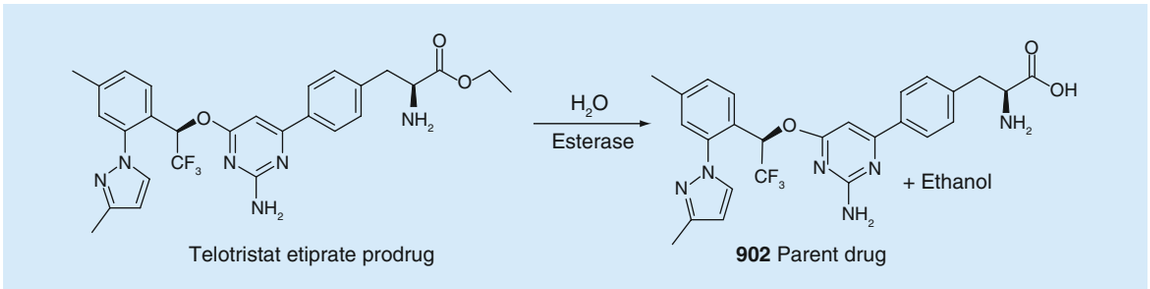

Figure 1. Telotristat etiprate conversion.

Table 1. Frequency of Phase I adverse events occurring in telotristat etiprate treated subjects compared to placebo†.

Preferred term	Telotristat etiprate (N = 88) (%)	Pooled placebo (N = 21) (%)
Nausea	11 (12.5)	2 (9.5)
Diarrhea	9 (10.2)	3 (14.3)
Headache	7 (8.0)	2 (9.5)
Abdominal pain	6 (6.8)	0 (0.0)
Constipation	2 (2.3)	2 (9.5)
Vomiting	3 (3.4)	0 (0.0)
Abdominal distention	2 (2.3)	0 (0.0)
Dyspepsia	1 (1.1)	1 (4.8)
Feeling cold	2 (2.3)	0 (0.0)
Infusion site pain	2 (2.3)	0 (0.0)
Pyuria	2 (23)	0 (0.0)
Upper respiratory tract infection	2 (2.3)	0 (0.0)

†Includes all adverse events with an incidence of at least 2%.
Data from [7].

bowel movement frequency of at least four episodes per day during a baseline assessment period.

One study was conducted in the USA, was placebo-controlled, and included several different doses: 150 mg, 250 mg, 350 mg and 500 mg, each administered orally three times daily [9]. The other study was conducted in Europe, was open-label and progressively titrated patients through each dose level (150 mg, 250 mg, 350 mg and 500 mg, each administered orally three times daily) [10].

The two studies complemented each other. The US study had the advantage of a placebo-control arm, but was of short duration (4 weeks). The European study had the advantage of longer-term dosing (12 weeks). It provided an opportunity to evaluate dose escalation and determine whether symptom improvement could be sustained over longer periods of dosing.

The US study had 18 patients on different doses of telotristat etiprate and five patients on placebo. As a small study, the emphasis of the analysis was to identify potential responders. Prespecified definitions of response were established at thresholds that were expected to be too large to be achievable by patients on placebo. A biochemical response was defined as a reduction of at least 50% in urinary 5-HIAA.

A clinical response was defined as an improvement in bowel movement frequency met for at least 2 of the 4 weeks of double-blind treatment. The improvement had to be either a reduction from baseline of at least 30% in the daily mean number of bowel movements or normalization in the daily mean number of bowel movements per week (defined as achievement of a daily mean ≤3 bowel movements for the week). In addition, a clinical response must have been achieved in the absence of treatment-emergent octreotide rescue treatment during the weekly intervals that clinical response criteria were met. Treatment-emergent rescue was defined as an increase in use of short-acting octreotide treatment above the baseline level of use. Patients not meeting these criteria were classified as nonresponders, including cases with missing data.

Patient reported outcomes were also assessed with a simple yes/no question of adequate relief. The wording was 'In the past 7 days, have you had adequate relief of your CS bowel complaints such as diarrhea, urgent need to have a bowel movement, abdominal pain or discomfort?'

The result of the US trial was that biochemical response, clinical response and patient reported adequate relief of symptoms were reported only on telotristat etiprate treatment and not on placebo. There were nine biochemical responses on telotristat etiprate (vs zero on placebo). There were five clinical responses on telotristat etiprate (vs zero on placebo). At Week 4, there were six reports of adequate relief on telotristat etiprate (vs zero on placebo; Table 2).

There was a general association between biochemical response, clinical response and patient reported outcomes. Reductions in bowel movement frequency at Week 4 were 31% in those who achieved a biochemical response at Week 4, while patients without a biochemical response at Week 4 experienced a mean increase of 1% in bowel movement frequency (p = 0.028 between the two groups of patients). Similarly, reductions in

Table 2. Efficacy in a Phase II placebo-controlled study of patients with carcinoid syndrome not adequately controlled on somatostatin analog therapy.

	Placebo			Telotristat etiprate		
	N	R	R/N (%)	N	R	R/N (%)
Clinical response (at least 30% reduction in BMs for at least 2 weeks)	5	0	**0**	18	5	**28**
Biochemical response (at least 50% reduction or normalization in u5-HIAA)	5	0	**0**	16	9	**56**
Adequate relief at Week 4	4	0	**0**	13	6	**46**

N: Number of patients available for analysis; R: Number of patients achieving a response.
Data from [9].

bowel movement frequency at Week 4 were 33% in those who reported adequate relief at Week 4, but they were only 3% in patients who reported no adequate relief at Week 4 ($p = 0.019$ between the two groups of patients).

The US study established proof of concept for telotristat etiprate. The results indicated that telotristat etiprate inhibited serotonin synthesis, that it reduced bowel movement frequency, and that this reduction was associated with patient reports of adequate relief of their symptoms [9].

However, a limitation of the study was the small sample size, only 23 patients overall. Furthermore, the treatment duration was short at only 4 weeks. The number of patients per group was too small for conclusions to be made about dose-response. It was therefore important to examine individual cases. A review of the time course of treatment response was informative.

One patient with a strong response provided an interesting perspective on the potential for clinically meaningful change in symptoms with telotristat etiprate (Figure 2). She reported an average of 8.2 bowel movements per day over the 4-week baseline period, prior to beginning study drug. This was despite receiving 60 mg of long-acting octreotide (intramuscular injections) every 3 weeks, a dose that is twice the highest approved level at an interval that is shorter than the recommended 4-week interval. In addition, she was administering herself up to 4 subcutaneous injections of short-acting octreotide every day as rescue therapy.

She reported a reduction in bowel movement frequency soon after initiating double-blind treatment with 500 mg of telotristat etiprate three times daily. Her bowel movement frequency was approximately 3–4 movements per day during that first week. She reported adequate relief of symptoms for that first week, and she stopped using short-acting octreotide injections as rescue therapy. Her baseline urinary 5HIAA was reduced from 126 mg at baseline to 57 mg (in 24 h urine collections) at Week 2.

She then experienced an adverse event, reported as a skin rash. The investigator was concerned that it could be related to study drug, so double-blind treatment was temporarily interrupted. During this period of time her stool frequency increased, and she experienced 4 days in a row with at least 10 bowel movements per day. She began using short-acting octreotide injections again and reported no adequate relief of symptoms during this time.

The patient eventually suggested the rash may have reflected an allergic reaction to a new set of linens that she purchased and had not yet washed. The investigator chose to start therapy again. Upon reinitiation of telotristat etiprate her bowel movements were quickly reduced to approximately 4 bowel movements per day. She stopped using short-acting octreotide again and reported adequate relief of symptoms for Week 4. The time course of response is shown in Figure 2. The rash did not return.

The patient described her clinical trial experience in an open-ended interview conducted by a third party. It took place over a year after she completed the study, but she was able to describe her experience in detail. She recalled wondering whether or not her response soon after initiation of therapy could have been a placebo effect: she felt it was simply too strong. She also recalled the experience with the drug rash, expressed her fears that her investigator might stop study drug, and related her thoughts about the linens as a potential cause for the adverse event. She expressed relief about being able to restart treatment.

The experience of another patient who experienced an interruption of therapy is shown in Figure 3. Bowel movement frequency was reduced from a mean of 10 episodes per day to 7 soon after initiation of therapy with 150 mg of telotristat etiprate three times daily. 5-HIAA levels were reduced from 33 mg to 26 mg per 24 h, and flushing episodes (previously 1 or 2 per day) disappeared. The patient reported adequate relief. A long-term extension was not yet in place at the end of the study, so study drug was stopped. The patient

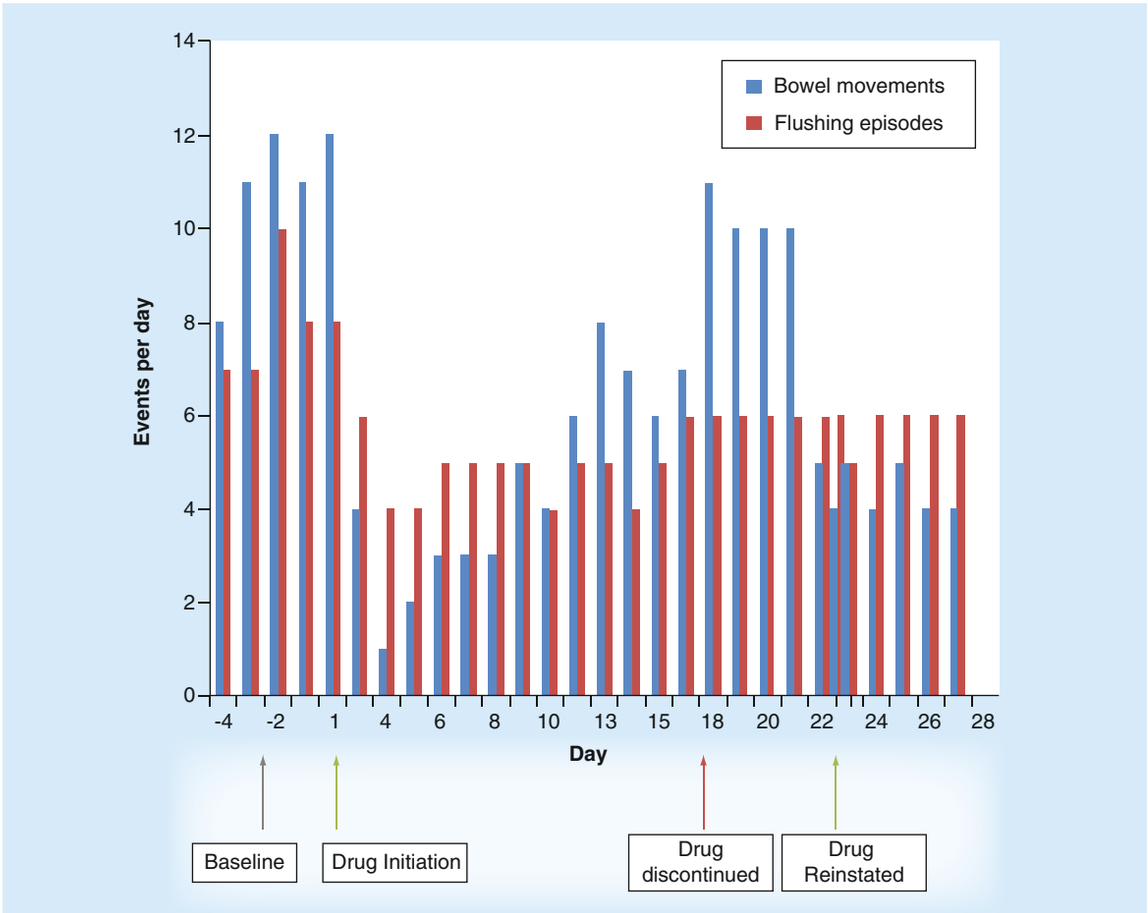

Figure 2. Individual patient response in a Phase II study of telotristat etiprate.

recorded symptoms on several days over the next 2 weeks, documenting a return of bowel movement frequency and flushing episodes to baseline levels.

This type of time course data suggested how clinical response can be associated with onset of treatment and reduction in urinary 5HIAA. The experiences are similar to those of case cross-over studies. They indicated that a clinical response is lost if therapy is interrupted. It also seemed that clinical response could be regained again. Given the limited sample size of the US Phase II study, these experiences provide some useful insight and support the overall rationale for an evaluation of longer-term therapy in a larger trial of telotristat etiprate.

Results of the European study [10] were also consistent with the US experience. There were 15 patients treated in Europe. As in the USA, they all had an average of at least four bowel movements per day at baseline. They progressed through several increasing dose steps, and most received the maximum dose of 500 mg three times daily for the last 6 weeks of the study.

Since there was no placebo group, the European study was analyzed in terms of change from baseline in bowel movement frequency, other gastrointestinal symptoms, urinary 5HIAA, and patient reports of adequate relief of symptoms (using the same question as in the US study). There was a significant reduction in bowel movement frequency, from a baseline of 5.9 to a mean of 3.3 BMs/day at Week 11–12 ($p < 0.001$). Stool consistency improved significantly ($p < 0.05$). Biochemical responses were observed in most patients (87%; 13 out of 15). The majority of patients (75%; 9 out of 12) reported adequate relief of symptoms at Week 12. There was also a 27% reduction in the number of flushing episodes during the study, from a baseline of 2.78 episodes per day ($p = 0.04$). Telotristat etiprate appeared to be treating carcinoid syndrome more broadly rather than just reducing bowel movement frequency.

Time course data in the European study were similar to those observed in the USA. Some patients experienced an interruption in therapy because a long-term extension was not available early on during the conduct of the study. Patients lost their response with interruption of therapy and regained it once the long-term extension was in place. Patients appeared to sustain the

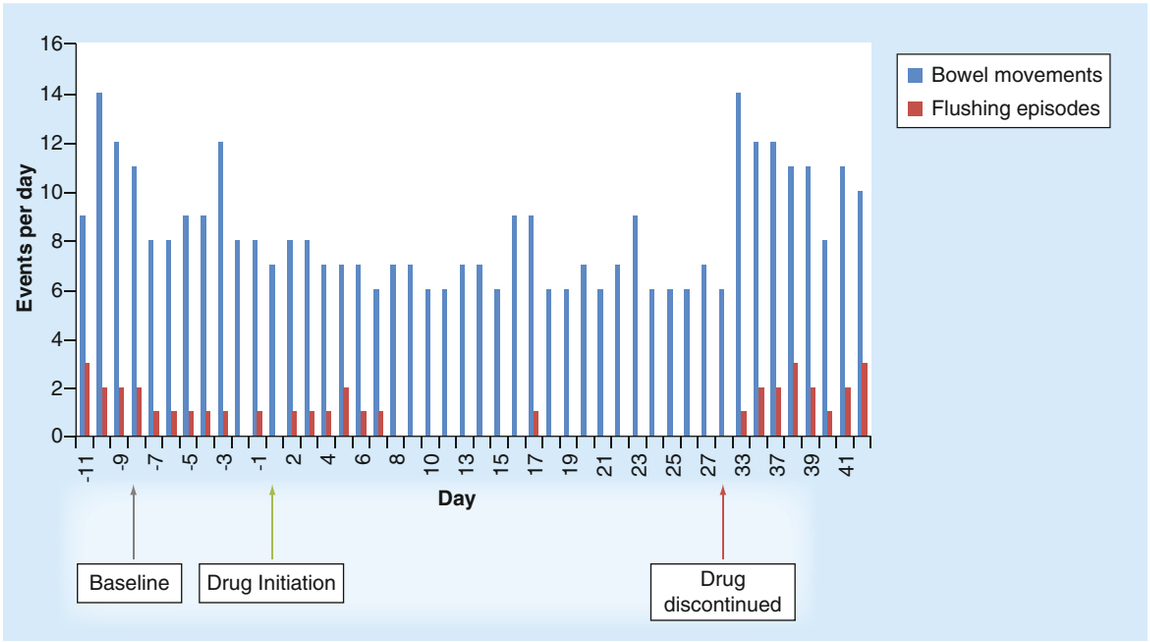

Figure 3. Individual patient response of drug interruption.

reductions in urinary 5HIAA and reductions in bowel movement frequency throughout the extension period.

One difference between the European and US study is that the overall reduction in bowel movement frequency was somewhat greater in Europe. The exact reason is unclear, but one potential explanation is that the European study had a full 12 weeks of treatment. The observed bowel movement frequencies in the two studies were similar for the first 4 weeks, but in the European study continued improvement was seen in the last several weeks of therapy. This suggests that in clinical practice efficacy may improve over time.

Results of both the Phase II studies showed reductions in bowel movement frequency that may be expected to improve quality of life. In a large cross-sectional study of patients with neuroendocrine tumors, stool frequency greater than four bowel movements per day was associated with reduced quality of life overall and in subscales such as sleep, depression and physical functioning. Further, in multivariate models controlling for a variety of potential confounders, stool frequency independently predicted quality of life overall and in subscales [11].

The overall safety profile of the Phase II studies appeared acceptable. Most adverse events were mild to moderate, and they resolved while the patient continued study drug. As in Phase I, there was no pattern of central nervous system adverse events. The most common system organ class affected was gastrointestinal and consistent with the underlying nature of carcinoid syndrome. There was no signal of elevation in liver function tests.

In the US study there was some nausea associated with the 500 mg dose administered three times daily. This was not observed in Europe, potentially because of the titration design of the trial. For this reason an initial titration step has been included for patients who receive 500 mg three times daily in the Phase III program.

Safety exposure from Phase II has continued in extension periods for relatively long periods of time. Of the 37 patients exposed to the 500 mg TID dose in the two studies, 14 have been exposed for 6 months or greater, and 10 have been exposed for 12 months or greater. The maximum exposure for a single patient is greater than 4 years. Overall, telostristat etiprate has been safe and well-tolerated in both Phase II studies, as in all studies to date. Furthermore, reductions in urinary 5-HIAA and bowel movement frequency have been sustained in the long-term extensions.

Phase III

The use of telotristat etiprate for the treatment of carcinoid syndrome not adequately controlled by somatostatin analogues has received Orphan Drug designation from both the Food and Drug Administration and European Medicines Agency. The Phase III program includes a single pivotal trial, TELESTAR.

TELESTAR begins with a run-in period of 3–4 weeks (depending on the patient's usual interval of somatostatin analogue dosing). During this time the baseline bowel movement frequency is determined. It must be at least four bowel movements per day for patients to be randomized.

Randomization is done in a blinded fashion with a ratio of 1:1:1 for assigning patients to either placebo, telotristat 250 mg given orally three times daily, or telotristat 500 mg given orally three times daily. As in Phase II, background somatostatin analogue therapy is continued throughout the study. Standard antidiarrheals are allowed, as is short-acting octreotide rescue therapy. The randomized, double-blind portion of the study lasts 12 weeks. This is followed by an open-label extension phase that will provide additional safety information. The study schematic is shown in Figure 4.

The primary objective of TELESTAR is to establish that at least one of two doses of telotristat is effective in reducing the daily number of bowel movements from baseline averaged over the 12-week double-blind portion of the study. Secondary endpoints include levels of urinary 5-HIAA, the incidence of facial flushing, and the degree of abdominal pain experienced by patients.

These endpoints are clinically meaningful. The patient population in TELESTAR is expected to have an average of approximately five to six bowel movements per day (the minimum is four). Therefore, it is likely that the number of bowel movements on placebo during the 12-week double-blind portion of the study will be between 400 and 600. If telotristat etiprate is effective then the total number of bowel movements may be reduced by about 100–200 or more during this time period, with many patients seeing at least a 30% reduction in bowel movement frequency from their baseline. Reductions of 30% or more were associated with adequate relief of symptoms in Phase II of clinical development, and they provided patients an opportunity to lead more normal lives with less of a burden from carcinoid syndrome.

Of note, the population in TELESTAR will have patients whose diarrhea is attributed to carcinoid syndrome. There are exclusions for other causes of diarrhea such as infections and short-bowel syndrome. Yet for some subjects it may be difficult to completely exclude at least some contribution of prior surgery or other factors to the diarrhea of carcinoid syndrome. For this reason the focus is on a proportional reduction in bowel movement frequency rather than complete normalization. The aim of TELESTAR is to determine whether symptomatic improvement similar to that observed in Phase II can be established.

Urinary 5HIAA reduction as an objective is also important. Despite the availability of somatostatin analogs and antitumor therapies, these patients will have persistent elevations of urinary 5HIAA that reflect excessive serotonin production. A reduction of urinary 5HIAA supports the mechanism of action, and it also is clinically relevant because of the strong association between 5HIAA elevations and cardiac valve disease [12].

Examination of facial flushing and abdominal pain over the course of the study will be helpful in providing a perspective of how broadly telotristat etiprate may impact carcinoid syndrome beyond changes in bowel movement frequency.

Other endpoints include several patient reported outcomes, among them the EORTC QLQ-C30 and GI.NET21 questionnaires. While these address clinically important domains, their sensitivity to change with therapy is not well known, so it is unclear whether there is adequate power to establish statistically significant differences among treatment groups. The ques-

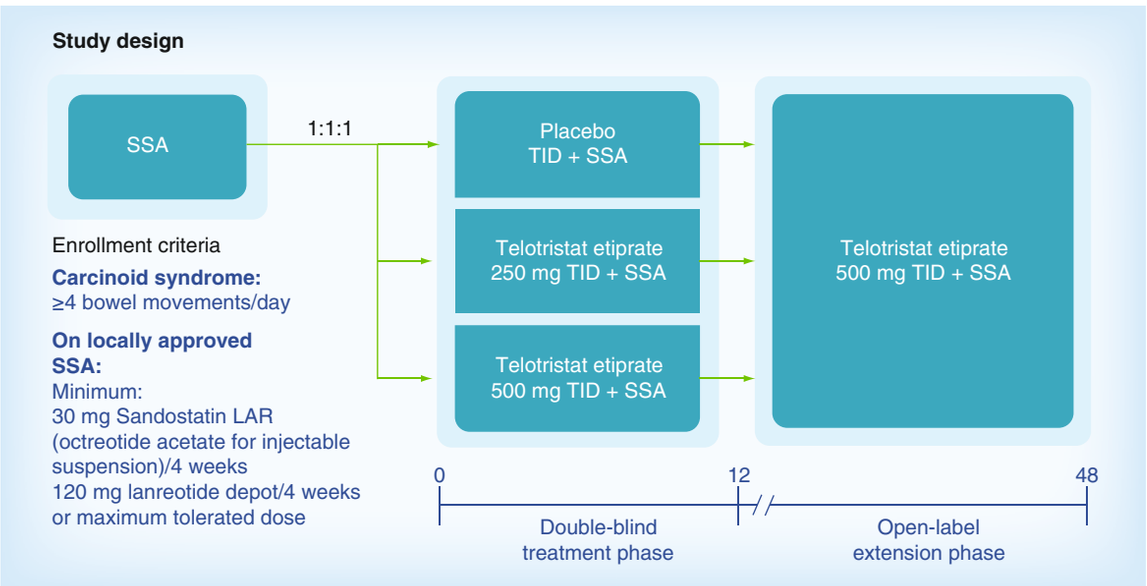

Figure 4. TELESTAR study schematic.
LAR: Long-acting release; SSA: Stable somatostatin analog; TID: Thrice a day.

tion from Phase II about adequate relief is included, and so is a numeric rating scale where patients report their perception of the overall severity of carcinoid syndrome.

Recruitment in TELESTAR is expected to continue until approximately 105 patients are randomized on a background of octreotide. This sample size is not large, but it is adequate to determine whether the Phase II experience can be replicated, and it is larger than the program which led to registration of octreotide for this patient population.

Sequential imaging of tumors is not required in TELESTAR. Carcinoid tumors grow relatively slowly, and while some patients do progress over intervals as short as 12 weeks, given the sample size of TELESTAR, it is unlikely that robust evidence would be available to evaluate the potential for antitumor effects. Serotonin is a known mitogen, so it is possible that telotristat etiprate could reduce tumor growth on a long-term basis. But the patients in TELESTAR have a very large burden of symptoms due to inadequate control of carcinoid syndrome, and the priority must be on the patient and symptom response. Those who receive placebo should have the opportunity to switch over to open-label therapy after 12 weeks, and the extension period of TELESTAR addresses this need.

TELESTAR will be accompanied by another study, TELECAST. It has the same randomization scheme, doses, and treatment period and extension period as TELESTAR. The key difference is that TELECAST accepts only patients who do not qualify for TELESTAR, either because their bowel movement frequency is not at least four episodes per day or because for some reason they do not tolerate or will not take somatostatin analogues. TELECAST is an opportunity for patients who fail screening for TELESTAR to have access to telotristat etiprate, and it will supplement the safety database in patients with carcinoid syndrome.

Discussion

The development of telotristat etiprate for the treatment of carcinoid syndrome is related to advancement in genomics technology. Lexicon has performed extensive physiologic tests on thousands of genetic knock-out mice. The knowledge gained has given a new perspective on both novel and previously investigated targets. The key observation was the general good health of mice completely lacking the tryptophan hydroxylase enzyme in the gastrointestinal tract. This provided a perspective on safety and suggested a program to develop a serotonin synthesis inhibitor would be viable. The result was telotristat etiprate.

The overall clinical program for telotristat etiprate has been small, consistent with carcinoid syndrome being a rare disease. This has been recognized with Orphan Drug status being granted by regulatory authorities for the development of telotristat etiprate.

In a relatively small clinical program it is important to review individual patient responses in addition to overall clinical trial results. The examples of the patients who started and stopped therapy in the US Phase II study were therefore informative (Figures 2 & 3). Since bowel movement frequency is a daily measure, there was an opportunity to review time course data and observe initial response, loss of response with interruption of therapy, and return of response with reinitiation of treatment. This was seen in other patients in the European study. These changes in bowel movement frequency were also associated with changes in rescue octreotide use, changes in urinary 5-HIAA and changes in patient reports of adequate relief. These observations complement the overall efficacy results in supporting continued development.

They also suggest that telotristat etiprate should be taken daily for the response to be maintained. If there is an interruption of treatment, due to a surgical procedure or other reason, reinitiation of therapy should be considered when appropriate.

Early studies of the serotonin synthesis inhibitor parachlorophenylalanine also examined carefully the time course of response for individual patients. These studies were also small in size, and bowel movement frequency reductions occurred soon after initiation of treatment, disappeared soon after treatment was interrupted and returned again after it was restarted. The overall time relationships were similar to what has been observed with telotristat etiprate.

Early studies of parachlorophenylalanine also examined the time course of potential adverse effects. Engelman *et al.* reported potential neuropsychiatric adverse effects in three out of five subjects with short-term use [2]. These included fatigue, mental confusion, anxiety, ataxia, depression (in a patient with a prior history of depression) and dysarthria. Shani and Sheba described restlessness, insomnia and hallucinations just 4 days after initiation of high-dose parachlorophenylalanine [13]. Several of these symptoms returned after their patient tried parachlorophenylalanine a second time. While Satterlee *et al.* reported no side effects from parachlorophenylalanine in one patient, Bax *et al.* described depression starting 9 days after initiation of therapy and resolving quickly when the drug was stopped [3,14].

The clinical safety experience with telotristat etiprate has been very different. The Phase II experience includes several dozen patients, and long-term treatment has continued for over 4 years. There has been no pattern of neuropsychiatric adverse events. This suggests that

telotristat etiprate has a very different clinical profile. The experience is consistent with the overall telotristat etiprate research and development program, one that was designed to avoid crossing the blood–brain barrier.

The Phase III program with TELESTAR and TELECAST will provide much more information on efficacy and safety. As trials of treatment of carcinoid syndrome, they can be conducted with relatively short-term treatment, which is 12 weeks of double-blinded therapy. The trials are therefore oriented toward the patient rather than the tumor. This is different from many trials in oncology, but it involves a relatively robust dataset where clinical change can be reliably detected in several dozen patients. With daily patient response data to document the primary endpoint, and with support from data on patient reported outcomes and 5HIAA assessments, the program will be positioned to address whether telotristat etiprate provides clinically meaningful improvement in the symptoms of carcinoid syndrome.

Furthermore, the information from TELESTAR and TELECAST will provide more insight on the role of serotonin in the symptoms of carcinoid syndrome. It is known that neuroendocrine tumors secrete vasoactive peptides and amines other than serotonin [15]. These include tachykinins that may have a role in symptoms such as flushing. Initial Phase II experience has indicated that telotristat etiprate may have an impact on flushing [10]. The Phase III results and magnitude of effect will provide further insight.

If the safety profile of telotristat etiprate in TELESTAR and TELECAST is acceptable, then additional clinical investigation for other conditions may be considered. These include ulcerative colitis and pulmonary artery hypertension, conditions where serotonin and the tryptophan hydroxylase enzyme may play an important role [16–20].

Conclusion

Carcinoid syndrome is a serious condition that is linked to excessive serotonin production. It is difficult to control. The symptoms can be debilitating for patients, and the high serotonin levels are associated with a high incidence of cardiac disease and relatively lower overall survival. A serotonin synthesis inhibitor, telotristat etiprate, has the potential to reduce serotonin levels and address the key elements of carcinoid syndrome. A pivotal clinical trial, TELESTAR, will address the efficacy and safety of telotristat etiprate, and TELECAST will provide important additional information on the use of telotristat etiprate.

Financial & competing interests disclosure

The authors are employees of Lexicon Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Excessive serotonin secretion is the hallmark of carcinoid syndrome.
- Telotristat etiprate is a serotonin synthesis inhibitor currently being investigated in carcinoid syndrome.
- Phase I studies of telotristat etiprate showed reductions in urinary 5-HIAA.
- Phase II studies of telotristat etiprate suggested symptom improvement in patients with carcinoid syndrome.
- The safety profile of telotristat etiprate has supported the conduct of longer-term studies.
- The Phase III study TELESTAR may determine whether telotristat etiprate will become the first approved serotonin synthesis inhibitor.

References

Papers of special note have been highlighted as: • of interest

1 Haverback BJ, Sjoerdsma A, Terry LL. Urinary excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid, in various clinical conditions. *N. Engl. J. Med.* 255(6), 270–272 (1956).

2 Engelman K, Lovenberg W, Sjoerdsma A. Inhibition of serotonin synthesis by para-chlorophenylalanine in patients with the carcinoid syndrome. *N. Engl. J. Med.* 277(21), 1103–1108 (1967).

• **Landmark study describing the first significant experience with serotonin reduction in carcinoid syndrome.**

3 Satterlee WG, Serpick A, Bianchine JR. The carcinoid syndrome: chronic treatment with para-chlorophenylalanine. *Ann. Intern. Med.* 72, 919–921 (1970).

4 Zambrowicz BP, Turner CA, Sands AT. Predicting drug efficacy: knockouts model pipeline drugs of the pharmaceutical industry. *Curr. Opin. Pharmacol.* 3(5), 563–570 (2003).

5 Tang T, Li L, Tang J *et al.* A mouse knockout library for secreted and transmembrane proteins. *Nat. Biotechnol.* 28(7), 749–755 (2010).

6 Liu Q, Yang Q, Sun W *et al.* Discovery and characterization of novel tryptophan hydroxylase inhibitors that selectively inhibit serotonin synthesis in the gastrointestinal tract. *J. Pharmacol. Exp. Ther.* 325(1), 47–55 (2008).

7 Investigator's Brochure for LX1606, Version 8. Lexicon Pharmaceuticals, Inc., The Woodlands, TX (2014).

8 A Phase 1, randomized, double-blind, placebo-controlled, ascending single dose study to determine the safety and

tolerability of orally administered LX1606 in healthy human subjects. Clinical study report 1606.101. Lexicon Pharmaceuticals, Inc., The Woodlands, TX (2008).

9 Kulke MH, O'Dorisio T, Phan A *et al.* Telotristat etiprate, a novel serotonin synthesis inhibitor, in patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide. *Endocr. Relat. Cancer* 21(5), 705–714 (2014).

• **First clinical experience with telotristat etiprate in carcinoid syndrome.**

10 Pavel M, Hörsch D, Caplin M *et al.* Telotristat etiprate for carcinoid syndrome: a single-arm, multicenter trial. J. Clin. Endocrinol. Metab (under review).

• **Telotristat etiprate 12-Week data on reductions in bowel movement frequency and urinary 5-HIAA.**

11 Beaumont JL, Cella D, Phan AT, Choi S, Liu Z, Yao JC. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. *Pancreas* 41, 461–466 (2012).

• **Describes a strong relationship between higher bowel movement frequency and worse patient reported outcomes in a neuroendocrine tumor population.**

12 Bhattacharyya S, Toumpanakis C, Chilkunda D, Caplin ME, Davar J. Risk factors for the development and progression of carcinoid heart disease. *Am. J. Cardiol.* 107(8), 1221–1226 (2011).

13 Shani M, Sheba C. Parachlorophenylalanine treatment in carcinoid syndrome. *Br. Med. J.* 4, 784–785 (1970).

14 Bax NDS, Boulton AJ, Woods HF, Green AR. Clinical and biochemical effects of parachlorophenylalanine in a patient with the carcinoid syndrome. *Postgrad. Med. J.* 58, 493–495 (1982).

• **Case report describing rapid onset of depression with parachlorophenylalanie, with rapid resolution upon discontinuation of therapy.**

15 Öberg KE. Gastrointestinal neuroendocrine tumors. *Ann. Oncol.* 21(Suppl. 7), vii72–80 (2010).

16 Margolis KG1, Stevanovic K, Li Z *et al.* Pharmacological reduction of mucosal but not neuronal serotonin opposes inflammation in mouse intestine. *Gut* 63(6), 928–937 (2014).

17 A Phase 1, randomized, double-blind, placebo-controlled, ascending multiple-dose study to determine the safety and tolerability of orally administered LX1606 in healthy human subjects. clinical study report 1606.102. Lexicon Pharmaceuticals, Inc., The Woodlands, TX (2009).

18 A Phase 1, randomized, open-label, two-way crossover study of two oral formulations of LX1606 in healthy human subjects. clinical study report 1606.103. Lexicon Pharmaceuticals, Inc., The Woodlands, TX (2012) [Amended February 14, 2013].

19 Kim JJ, Khan WI. 5-HT7 receptor signaling: improved therapeutic strategy in gut disorders. *Front. Behav. Neurosci.* 11(8), 396 (2014).

20 Dempsie Y, MacLean MR. Pulmonary hypertension: therapeutic targets within the serotonin system. *Br. J. Pharmacol.* 155(4), 455–462 (2008).