NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Clinical evidence review of telotristat for treating carcinoid syndrome in adults

NHS England unique reference number URN1745 / NICE ID009

First published: TBC 2018

Prepared by: NICE on behalf of NHS England Specialised Commissioning

About this clinical evidence review

Clinical evidence reviews are a summary of the best available evidence for a single technology within a licensed indication, for commissioning by NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

This evidence review considers telotristat for treating carcinoid syndrome (CS) diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy.

A literature search identified six published studies appropriate for inclusion in the review with additional evidence taken from a post-hoc analysis of the TELESTAR study. The primary effectiveness evidence comes from one phase III multicentre, double blind placebo controlled randomised controlled trial (RCT; TELESTAR; Kulke et al. 2017; n=135; telotristat 250mg n=45) which included people with CS diarrhoea despite receiving stable dose standard somatostatin analogue (SSA) therapy. An additional phase III RCT (TELECAST, Pavel et al. 2018; n=76; telotristat 250mg n=25) provided effectiveness evidence in people with CS who were either treated with SSA therapy, or were SSA therapy—naïve, but were experiencing less-severe gastrointestinal symptoms than people who had participated in the TELESTAR trial. Additional supportive evidence came from 2 phase II trials involving dose escalation (an RCT, Kulke et al. 2014; n=23; telotristat 250mg n=3, and a single arm study, Pavel et al. 2015; n= 15), and two qualitative studies based upon exit interviews from the TELESTAR trial (Anthony et al. 2017) and the phase II multiple dose escalation RCT (Gelhorn et al. 2016).

Effectiveness

The primary outcome reported in the TELESTAR phase III RCT (Kulke et al. 2017) was change in bowel movement (BM) frequency. In 45 people assigned to receive a 250mg dose of telotristat and 45 people receiving placebo experiencing at least 4 BMs per day and receiving SSA therapy, there was a statistically significant reduction in change from baseline in BM frequency for people receiving the treatment compared with placebo. This finding was replicated in the three quantitative supportive studies including the companion phase III RCT (TELECAST) which included this outcome as a secondary measure. These studies also reported a statistically significant reduction from baseline in BM frequency in people receiving a 250mg dose of telotristat compared with placebo. The two further studies; a phase II RCT of multiple doses of telotristat compared with placebo (Kulke et al. 2014) and an

open label ascending dose single arm study (Pavel et al. 2015) both reported statistically significant reductions from baseline in people receiving telotristat.

A secondary outcome of the TELESTAR trial and a primary outcome of the TELECAST trial was to assess biochemical efficacy and levels of serotonin, based on urinary 5- hydroxyindoleacetic acid (u5-HIAA) levels. Both studies reported statistically significant reductions compared with baseline in u5-HIAA in people receiving telotristat compared with placebo. The phase II RCT (Kulke et al. 2014) reported a higher proportion of proportion of people receiving a durable biochemical response for the treatment group compared with placebo and the single arm study (Pavel et al. 2015) also reported statistically significant reductions compared with baseline.

Further secondary outcomes included urgency to defecate, stool form, abdominal pain, change in frequency of rescue short acting SSA therapy and change in flushing episodes. These outcomes reported no statistically significant differences between groups receiving telotristat treatment, compared with comparators.

Patient reported symptom change and quality of life outcomes were also assessed. The results suggest that patients do report improvements in their CS symptoms as a result of taking telotristat.

Safety and tolerability

Key safety outcomes were also reported. All studies reported some experience of treatment emergent adverse events in people receiving telotristat, although withdrawal rates were low and few serious adverse events were noted across all studies. The highest reported adverse events were gastro-intestinal and there were comparable reports of depression related symptoms in treatment and placebo groups.

Evidence gaps and limitations

Studies either had a short follow up (Kulke et al. 2014) or included no comparator arm (Pavel et al. 2015). Where studies did report a comparator treatment (in the RCTs), these were compared with placebo; as such, there is no evidence to compare the *addition* of telotristat to SSAs with the *addition* of an active comparator

to SSAs .Studies included treatment groups receiving a telotristat dose ranging from 150mg to 500mg, however the licensed dose is 250mg (Pavel et al. 2015; Kulke et al. 2014, Anthony et al. 2017; Gelhorn et al. 2015). Indirect evidence related to people who may have been SSA-naïve (Pavel et al. 2018; Pavel et al. 2015) and therefore not a direct population which would benefit from the indicated treatment, as an addition to SSA therapy.

The studies included doses ranging from 150mg to 500mg. However the licensed dose for telotristat is 250mg three times a day, therefore only the results for the 250mg will be reported. All studies provided evidence relating to the effectiveness of telotristat 250mg for people with CS.

The available evidence does not include a comparison of the addition of telotristat to SSAs with the addition of an active comparator to SSAs (that is, comparative studies included the active treatment SSAs in both arms, but compared the addition of telotristat with the addition of placebo). People were also on varying doses of SSAs in placebo and telotristat arms of studies, which may disguise the true treatment effect of telotristat. No long-term follow-up data for the licensed dose of telotristat (250mg) are available, because all patients switched to 500mg dose after the 12 week primary outcome period (500mg is not a licensed therefore is not reported here) Finally, the small populations (n=10 to 135) should be taken into account when interpreting results, with the phase II studies not being powered to demonstrate efficacy (however, given the rare nature of the disease, it is not possible to have large trials in this disease area, and TELESTAR is one of the largest studies conducted to date in this area).

Table of contents

Abbreviations

Term	Definition
BM	Bowel movement
LAR	Long-acting release
RCT	Randomised controlled trial
EMA	European Medicines agency
EPAR	European Public Assessment report
MDT	Multidisciplinary team

Medical definitions

Term	Definition
CS	Carcinoid syndrome
SSA	Somatostatin analogue
NET	Neuroendocrine tumour
SIRT	selective internal radiation therapy
PRRT	peptide receptor radionuclide therapy
Urinary 5-HIAA	Urinary 5-hydroxyindoleacetic acid

1 Introduction

Disease background

1.1 Well-differentiated neuroendocrine tumours (NETs) are a relatively rare type of tumour that arise from the cells of the neuroendocrine system (the body system that produces hormones). People with NETs may develop carcinoid syndrome (CS), a condition associated with an excessive release of hormones such as serotonin into the bloodstream. This causes a number of symptoms including diarrhoea, flushing, bronchial constriction, and development of mesenteric fibrosis. CS occurs most frequently from NETs that originate in the small intestine, but may also develop in NETs in the lung or pancreas (Caplin et al 2015; Dmitriadis et al 2016). CS occurs in approximately 35% to 40% of people with well-differentiated small intestinal NETs and typically in people with liver metastases (Lamarca et al 2016; Niederle et al 2016; Rorstad 2005; Rinke et al 2009).

NETs may be slow-growing in nature and people can live for many years with the condition. The number of people living for at least 5 years after diagnosis ranges from approximately 60 percent with NETs originating in the small intestine to 95 percent for NETs originating in the lung (Cancer Research, UK).

Focus of review

1.2 In line with the marketing authorisation, the focus of this review is on telotristat for the treatment of CS diarrhoea in combination with SSA therapy in adults inadequately controlled by SSA therapy.

Epidemiology and needs assessment

1.3 The incidence and prevalence of NETs in the UK has been estimated as 19,282. This is based on calculations using data from the PHE National Cancer Registration and Analysis Service (NCRAS) database. NHS England estimates that around 185 people would be eligible for treatment with telotristat. This is based on:

- For lower gastrointestinal NETs (approximately 35% of NETs, 6,643 patients):
  - 75% of gastrointestinal NETs are well differentiated lower GI NETs (G1/G2) (4,982 patients)
  - 58% of well differentiated lower GI NETs are small intestinal NETs (2,890 patients)
  - 40% of people with small intestinal NETs have CS (1,156 patients)
  - 80% of people with CS have CS diarrhoea (925 patients)
  - 17.5% of people with CS diarrhoea require further symptom control after maximum dose SSAs (162 patients).
- For lung NETs (approximately 22% of NETs, 4,155 patients):
  - 36% are well-differentiated lung NETs (G1/G2) (1,142 patients)
  - 5% of patients with well-differentiated lung NETs have CS (75 patients)
  - 30.5% of people with CS require further symptom control after maximum dose SSAs (23 patients)
- Total patients with CS requiring further symptom control 185 (162 patients from lower GI NETs and 23 patients from lung NETs).

In clinical practice it is expected this figure (185 patients) may be lower. Some patients may start treatment with telotristat but would stop because it is not effective for them after 12 weeks (estimated to be the case in around 56% of patients). Discontinuation because of death (estimated to be around 16%) will also reduce this estimate.

Product overview

Mode of action

1.4 Telotristat is a tryptophan hydroxylase (TPH) inhibitor which targets the overproduction of serotonin. Serotonin plays a critical role in regulating several major physiological processes, including secretion, motility, inflammation, and sensation of the gastrointestinal tract, and is overproduced in people with CS. TPH mediates the rate limiting step in serotonin biosynthesis. In the blood telotristat etiprate appears as

telotristat ethyl and its active metabolite telotristat (LX1033 or LP-778902). By inhibiting TPH, the production of serotonin is reduced and symptoms of CS are relieved.

Regulatory status

1.5 Telotristat was granted a UK marketing authorisation on 18th September 2017.

Dosing information

1.6 Telotristat is available in 250mg film-coated tablets.

Telotristat should be taken orally with food. The recommended dose is 250mg three times daily (TID). Please see the summary of product characteristics (SPC) for further details.

Treatment pathway and current practice

1.7 Current treatment of CS diarrhoea involves treatment both of the underlying tumours, as well as the symptoms of the disease. Most patients start with licensed doses of SSAs, but after this the treatment pathway is complex, and for each patient it will be individualised depending on several factors including: the size, site and grade of the tumour; location of any other tumours, and; general health of the patient. A specialist NET MDT will be involved in helping the patient decide on the best approach to treatment, which may include retreatment if required and it can be tolerated. SSAs tend to be maintained throughout treatment.

1.8 The European Neuroendocrine Tumor Society (ENETS) consensus guidelines (Pavel et al. 2016) recommend that standard first line treatment for symptom control in people with CS is long acting somatostatin analogues (SSAs) such as lanreotide and octreotide at licensed doses of 60 to 120 mg/4 weeks and 10 to 30 mg/4 weeks, respectively, after which alternative treatment may be considered, such as surgery to reduce the volume of the tumour accountable for hormone production (debulking).

For people who require further symptom control, (for example, people who have refractory symptoms and/or a progressive disease), the standard treatment currently involves up-titration of SSAs to above licensed doses, either by shortening the time between injections (to 3 weeks or 2 weeks) or increasing the dose (Pavel et al 2016).

After up titration of SSAs to above licensed doses, alternative treatments may be considered. The aim of alternative treatment is to reduce the volume of the tumour responsible for hormone production.

2 Evidence

Literature search

2.1 A literature search was carried out (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons), and 6 studies were included in the clinical evidence review.

Overview of included studies

2.2 Two phase III randomised controlled trials (RCTs) were included in this review (Kulke et al. 2017 and Pavel et al. 2018). The main trial (TELESTAR, Kulke et al. 2017) was an international multicentre RCT of the efficacy and safety of telotristat in people experiencing carcinoid syndrome (CS) diarrhoea despite receiving stable dose standard somatostatin analogue (SSA) therapy. Additional evidence of the effects of telotristat came from a further phase III RCT (TELECAST, Pavel et al. 2018) in people with CS who were both treated with SSA therapy and SSA therapy--naïve but were experiencing less-severe gastrointestinal symptoms than people who had participated in the TELESTAR trial. This evidence was supported by one phase II multiple dose RCT in people with CS experiencing at least 4 BMs per day despite octreotide therapy (Kulke et al. 2014); one phase II single arm, open label dose escalation study in people with CS experiencing at least 4 BMs per day with or without concurrent SSA therapy (Pavel et al. 2015). Additional evidence was taken from two qualitative studies based upon exit interviews from the

TELESTAR trial (Anthony et al. 2017) and the phase II dose escalation RCT (Gelhorn et al. 2016). A summary of the characteristics of each study is shown in Table 2.

Table 2 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Kulke et al (2017) Phase III RCT	Adults with well-differentiated NET and history of CS experiencing at least 4 BMs per day despite stable-dose SSA therapy (n=135)	Telotristat 250mg or telotristat 500mg three times daily versus placebo three times daily	Change from baseline in daily BM frequency averaged over 12 weeks
Pavel et al (2018) Phase III RCT	Adults with well differentiated NETs and symptomatic CS experiencing either less than 4 BMs per day with concomitant SSA therapy or who were not receiving concomitant SSA therapy.	Telotristat 250mg or telotristat 500mg three times daily versus placebo three times daily	Change from baseline in 24-hour u5-HIAA levels at Week 12
Kulke et al (2014) Phase II RCT	Adults with biopsy-proven metastatic NET with CS experiencing at least 4 BMs per day despite octreotide therapy (n=23)	Telotristat 150mg, 250mg, 350mg or 500mg three times daily versus placebo three times daily	Change in BM frequency
Pavel et al (2015) Phase II open label dose escalation study	Adults with biopsy-proven, metastatic NET with CS and a baseline average of at least 4 BMs per day with or without concurrent SSAs therapy (n=15)	Telotristat 150mg, escalating every 2 weeks to 250mg, 350mg or 500mg three times daily over an 8 week period and continuing at highest tolerated dose until week 12 No comparator	Safety outcomes
Anthony et al (2017) Qualitative	Adults with well-differentiated	Telotristat 250mg or telotristat 500mg three	Patent-reported symptom experiences

interview follow up of phase III RCT (Kulke 2017)	NET and history of CS experiencing at least 4 BMs per day despite stable-dose SSA therapy (n=35)	times daily versus placebo three times daily	
Gelhorn et al (2016) Qualitative interview follow up of phase II RCT (Kulke 2014)	Adults with biopsy-proven metastatic NET with CS experiencing at least 4 BMs per day despite octreotide therapy(n=11)	Telotristat 150mg, 250mg, 350mg or 500mg three times daily versus placebo three times daily	Patient-reported symptom experiences
Abbreviations: BM Bowel movement; CS Carcinoid syndrome; NET Neuroendocrine tumour; SSA Somatostatin analogue; urinary 5-HIAA Urinary 5-hydroxyindoleacetic acid			

Key outcomes

2.3 The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 3 provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study are in appendices 3 and 4.

Effectiveness

2.4 The studies included doses ranging from 150mg to 500mg. However the licensed dose for telotristat is 250mg three times a day (tid), therefore only the results for the 250mg will be reported unless otherwise stated or referring to exit interview studies (which included, and reported on, all doses collectively). All studies provided evidence relating to the effectiveness of telotristat 250mg for people with CS.

Change in the number of bowel movements per day

2.5 Four studies reported on BM frequency (TELESTAR; Pavel et al. 2018; Kulke et al. 2014 and Pavel et al. 2015), and addressed the most common symptom of CS. The primary outcome reported in TELESTAR was the mean number of BMs averaged over the 12-week study period for people

with CS experiencing at least 4 BMs per day at baseline despite stable use of SSA therapy. A statistically significant reduction was observed for mean change from baseline in BMs per day (-1.43) for telotristat 250mg compared with (-0.62) for placebo [Hodges-Lehman estimated treatment difference median = -0.81 BMs per day; [97.5% confidence interval (CI -1.26, -0.29), p<0.001].

Supplemental analysis of BM frequency included in TELESTAR reported on the number of participants achieving a durable treatment response (the proportion of responders with at least 30% reduction in the number of BMs per day for at least 50% of the time). In total, 20 (44%) of participants receiving telotristat 250mg achieved a durable response, compared with 9 (20%) of participants receiving placebo [odds ratio = 3.49, (95%CI = 1.33, 9.16), p= 0.01]. The change in number of bowel movements per day was a secondary outcome reported in three supportive studies. TELECAST reported a statistically significant mean reduction from baseline in BMs per day (-0.45) for telotristat compared with an increase in BMs per day (0.05) for placebo [Hodges-Lehman estimated treatment difference median = -0.45 BMs per day; (95%CI = -0.72, -0.17), p = 0.004]. Kulke et al. 2014 reported a mean change of -2.2 BMs per day at end-point (12 weeks), for telotristat. Pavel et al. 2015 reported a statistically significant reduction in BMs per day by -2.57 per day (43.5% difference; p<0.001).

Change in urinary 5-hydroxyindoleacetic Acid (u5-HIAA) levels

2.6 This biomarker is used to assess levels of serotonin in the body. Four papers reported this outcome (TELESTAR, TELECAST, Kulke et al. 2014 and Pavel et al. 2015). This was a primary outcome of TELECAST which reported the change from baseline in u5-HIAA levels for participants receiving telotristat (-33.16 %) compared with placebo (97.72 %) was statistically significant [Hodges-Lehman estimated treatment median = -53.95 % (95%CI = -85.0, -25.1) p <0.001]. TELESTAR also reported a statistically significant change for telotristat (-40.1 mg/ 24 hours) compared with placebo (11.46 mg/ 24 hours) [Hodges- Lehman estimated treatment median -30.1 (97.5% CL = -56.00,-8.10) p <0.001], as did Pavel

et al. 2015 of 74.2% from baseline to endpoint ($p<0.05$). Although Kulke et al. 2014 did not report change scores, it was noted that 9 of 16 people receiving telotristat compared with 0 of 5 people receiving placebo achieved a biochemical response in u5-HIAA (defined as a greater than 50% decrease in 24-hour u5-HIAA levels from baseline, or normalisation of u5-HIAA in patients who had elevated baseline levels).

Change in the number of flushing episodes per day

2.7 The mean values for change in number of flushing episodes was a secondary outcome reported in 4 papers (Kulke et al. 2017, Pavel et al. 2018, Kulke et al. 2014 and Pavel et al. 2015). Although the results from TELESTAR and TELECAST found the change in number of flushing episodes was not statistically significant, the open label trial (Pavel et al. 2015) reported a statistically significant change from a baseline of flushing episodes per day by 27% ($p= 0.04$). Please note, because Pavel et al. 2015 did not compare treatment with telotristat to another therapy or placebo treatment, there may be some uncertainty interpreting results. For example, potential sources of bias were not controlled for, therefore there may have been factors other than treatment effectiveness influencing the results (that is, there may have been confounders). Also, as there were no comparators, this trial cannot show that treatment with telotristat is any better or worse than any other treatment or placebo.

Urgency to defecate

2.8 Four studies reported on the sense of urgency to defecate (TELESTAR, TELECAST, Kulke et al. 2014 and Pavel et al. 2015). Values were obtained by daily self-report. Results from TELESTAR did not find a statistically significant difference in the mean proportion of days with a sense of urgency to defecate. Similar findings were reported by the other studies.

Stool form and consistency

2.9 Four papers reported on change from baseline in stool form or consistency (TELESTAR. TELECAST, Kulke et al. 2014 and Pavel et al.

2015) using self-report measures assessed daily using the Bristol Stool form Scale. A mean value was averaged over the 12 week double-blind period. Results from both TELESTAR and TELECAST found the change from baseline in stool consistency was not significantly different [p = 0.57 and p = 0.09 respectively]. Pavel et al. 2015 found a statistically significant improvement in the stool consistency over the study period. From baseline to 12 weeks, mean stool form changed by 19.5% (p<0.001) from a mean grade of 4.09 (approximately loose) 3.30 (soft). Although Kulke et al. 2014) did not report values, the paper reports there were no clear differences between people treated with telotristat compared with placebo.

Abdominal pain and discomfort

2.10 Four papers reported on change in abdominal pain and discomfort TELESTAR, TELECAST; Kulke et al. 2014 and Pavel et al. 2015) obtained from daily self-report assessment. TELESTAR found the mean change from baseline for telotristat (-0.49) compared with placebo (-0.23) was not statistically significant (p=0.28). All other studies also found that changes could not be differentiated between groups.

Change in frequency of rescue short-acting SSA therapy to treat bowel-related symptoms associated with CS

2.11 Change in use of rescue short-acting SSA therapy was a secondary outcome reported in two papers; TELESTAR (Kulke et al. 2017) and TELECAST (Pavel et al. 2018). Although in TELESTAR these showed a small effect in favour of telotristat compared to placebo, the results were not statistically significant different in either study.

Patient-reported change in CS related symptoms

2.12 Patient-reported symptom change was a secondary outcome in Kulke et al. 2014. It was also reported as a primary outcome in the 2 exit interviews (Anthony et al. 2017 and Gelhorn et al. 2016).

In the exit interview of TELESTAR (Anthony et al. 2017) patients stated they felt the 3 most important symptoms to treat were diarrhoea (n=17), BM frequency (n=9), and urgency to defecate (n=5), and 29 out of the 35

people (83%) completing the interview reported BM frequency as more important to treat than stool form. The most frequently reported negative effects of CS symptoms were in social and physical activities with 28 (80%) of the 35 people interviewed reporting negative effects in these areas. This was followed by emotional symptoms (reported by 24 people (69%) and decreased energy (reported by 21 participants (60%). However, during the interview, 7 out of 10 receiving telotristat 250mg compared with 4 out of the 9 receiving placebo reported improvements in their CS symptoms. Most reported symptom improvement was in BM frequency (7 telotristat, 4 placebo).

Kulke et al (2014) reported that 10 out of 18 (56%) receiving telotristat compared with none for placebo reported adequate relief of symptoms. The associated exit interview (Gelhorn et al. 2016) stated that 82% reported an improvement in diarrhoea. Participants also reported improvement during the study period of abdominal pain (45%), abdominal cramping (36%) and flushing (36%).

Quality of life outcomes

2.13 Quality of life outcomes were reported in TELESTAR and Gelhorn et al (2015). Both studies used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and Gelhorn et al. (2015) additionally reported results using GI.NET-21. The EORTC QLQ-C30 is a 30-item questionnaire which assesses quality of life of people with cancer. It uses a seven point rating scale to measure global (overall) health status and quality of life and a four point rating scale to measure functional status (focusing on physical, role, cognitive, emotional, and social outcomes); and symptom outcomes (focusing on fatigue, pain, and nausea and vomiting). Changes from baseline were assessed in these studies, whereby a higher global health scores represented better overall quality of life and higher scores on the functional scale represented higher levels of functioning; whereas conversely higher scores on the symptom scales represent more symptoms. The GI.NET-21 is a supplemental module of the EORTC-QLQ-

C30, which has been specifically devised for people with gastro intestinal-related NETs, at varying stages of disease or treatment options. It contains 21 questions which assess disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality.

2.14 TELESTAR reported the mean change from baseline on the EORTC-QLQ-C30 in points (on a 0 to 100 point scale averaged over the 12 week treatment period, with higher points representing a better quality of life score). Although the study reported a small improvement in the global health status subscale score (1.7 points) at 12 weeks end-point for people receiving telotristat, compared with a worsened global health status subscale score (-2.0 points) from the original average baseline rating for people receiving placebo, this was not statistically significant. A statistically significant improvement in the diarrhoea subscale score of the EORTC-QLQ-C30 was observed, with a mean improvement of 19.2 points for telotristat compared with a mean improvement of 8.5 points for placebo (p=0.039). However, there was no difference in the reduction on the nausea and vomiting subscale score (both groups reported an improvement of 2.4 points). The study authors noted that these similarities across treatment arms suggest there was no detriment to overall quality of life as a result of treatment. However, they noted that minimal changes in global health scores were observed in previous studies of patients with NETs who received SSAs, which suggests the tool may not be sensitive for this domain. It is important to note that the assessment of quality of life outcomes in TELESTAR were based on a subset of the people who were originally randomised.

2.15 Gelhorn et al. (2015), which used both the EORTC-QLQ-C30 and the GI.NET-21, described the impact of diarrhoea on patients. It affects social functioning (e.g. difficulty with travel) and sleep (e.g. waking up at night to have a bowel movement), and it can be related to fatigue or tiredness. It stated that high bowel movement frequency is a central issue for patients, and it directly affects the ability of patients to enjoy life and participate in

social and physical activities. Gelhorn et al (2015) stated that results suggest telotristat may improve key aspects of CS that are important to patients (participants self-reported feeling improvements in diarrhoea (82%), abdominal pain (45%), abdominal cramping (36%) and flushing (36%) over the telotristat trial they were involved in). It also reported results for GI.NET-21, where higher scores represented worse symptoms, where, in general, participants reported scores below a mean value of 50 across all subscale scores (out of a maximum of 100). However, it stated there were limitations in both the EORTC QLQ-C30 and GI.NET21 in assessing people with CS. In EORTC QLQ-C30, BM frequency, which it stated is the highest priority for patients, is captured in only 1 domain (out of 30, all of which have equal weight) and some of the domains are not necessarily related to treatment (e.g. financial worries). It stated this may impact the ability of the tool to show statistically significant differences. There were further limitations to this study, including the small patient numbers (n=11) and because only 2 of the 7 centres that enrolled patients onto the phase II trial (Kulke et al. 2014) that this exit interview was based on participated in the questionnaire..

Safety and tolerability

Number of discontinuations due to treatment-emergent adverse events

2.16 All 4 quantitative papers reported on discontinuations. In TELESTAR, 37 people (82.2%) receiving telotristat reported a treatment emergent adverse event (TEAE) during the double blind study period compared with 39 people (86.7%) receiving placebo. Of these, 6.7% and 13.3% discontinued treatment because of TEAEs for telotristat and placebo respectively. In TELECAST all receiving telotristat and 21 (80.8%) receiving placebo reported a TEAE. Of these, 8.0% (for upper abdominal pain) and 3.8% (malignant neoplasm progression) discontinued treatment for telotristat and placebo respectively.

Kulke et al. 2014 reported that all 3 participants receiving 250mg dose of telotristat and 4 out of 5 participants (80%) receiving placebo reported at least one TEAE. One participant receiving telotristat discontinued

treatment. Pavel et al. 2015 reported that all participants had at least one TEAE during the study. 2 participants discontinued treatment.

Serious adverse events

2.17 Two papers reported on serious adverse events (TELECAST; Kulke et al. 2014). In TELECAST 1 out of 25 participants (4.0%) receiving 250mg telotristat and 5 out of 26 participants (19.2%) receiving placebo reported a serious adverse event over the 12 week period. In Kulke et al. 2014, 2 out of 18 participants (11.1%) receiving any dose of telotristat reported a serious adverse event, for which one person discontinued treatment.

Adverse events relating to Gastro-intestinal symptoms

2.18 Three papers reported on this outcome (TELESTAR; TELECAST and Pavel et al. 2015). In TELESTAR the most commonly reported GI symptom related adverse event was abdominal pain which was reported in 5 (11%) of participants receiving telotristat 250mg and 8 (17.8%) of participants receiving placebo. Nausea was also commonly reported in 6 (13.3%) of people receiving telotristat 250mg and 5 (11.1%) of people receiving placebo. Similar findings were reported in TELECAST and the phase II RCT (Kulke et al. 2014).

Depression related adverse events

2.19 Four papers reported on cases of depression (TELESTAR; TELECAST; Kulke et al. 2014 and Pavel et al. 2015). TELESTAR reported that depressive symptoms were experienced in 3 (6.7%) of people receiving telotristat and 3 (6.7%) of people receiving placebo during the study. In TELECAST 1 participant (4.0%) receiving telotristat and 2 (7.7%) receiving placebo reported a mild depressed mood. There were no reports of depression in participants receiving any dose of telotristat or receiving placebo in the phase II multiple dose RCT (Kulke et al. 2014) and there were no reports of depression in the phase II open label dose escalation study (Pavel et al. 2015).

Deaths as a result of an adverse event.

2.20 Two papers reported on this outcome (Kulke et al. 2017 and Pavel et al (2018). In the TELESTAR trial (Kulke et al. 2017) 1 death was reported in a patient with advanced disease receiving telotristat 250mg and 3 deaths of advance disease were reported in the placebo group. In the TELECAST trial (Pavel et al. 2018) there were no treatment emergent adverse events resulting in death.

Evidence gaps

2.21 Studies either had a short follow up (Kulke et al. 2014) or included no comparator arm (Pavel et al. 2015). Where studies did report a comparator treatment (in the RCTs), these were compared with placebo; as such, there is no evidence to compare the addition of an active comparator to the addition of telotristat therapy. Although the primary trial included the population of interest, receiving standard SSA therapy, the companion paper (Pavel et al. 2018) included some people who were receiving SSA therapy and some people who were not (Pavel et al. 2018; Pavel et al. 2015) and therefore not a direct population which would benefit from the indicated treatment, as an addition to SSA therapy.

2.22 Studies included treatment groups receiving a telotristat dose ranging from 150mg to 500mg, however the licensed dose is 250mg (Pavel et al. 2015; Kulke et al. 2014, Anthony et al. 2017; Gelhorn et al. 2015). Indirect evidence related to people who may have been SSA-naïve.

Limitations

2.23 It is important to note that the phase II open label study (Pavel et al. 2015) was a single arm dose escalation study, whereby all participants received an increasing dose of between 150mg at baseline to 500mg dose telotristat TID at endpoint. The study did not use a randomised process to allocate participants to the treatment or compare the treatment with any other standard treatment. Furthermore, participants received escalating doses of telotristat throughout the study ranging from 150mg at baseline

to 500mg at end-point. It is therefore difficult to interpret whether other factors may be influencing the results.

People were on varying doses of SSAs in placebo and telotristat arms of studies, which may disguise the true treatment effect of telotristat. No long-term follow-up data for the licensed dose of telotristat (250mg) are available, because all patients switched to 500mg dose after the 12 week primary outcome period (500mg is not a licensed therefore is not reported here). Finally, the small populations (n=10 to 135 for all doses, and 3 to 45 for 250mg dose) should be taken into account when interpreting results, with the phase II studies not being powered to demonstrate efficacy. However, given the rare nature of the disease, it is not possible to have large trials in this disease area, and TELESTAR is one of the largest studies conducted to date in this area).

Table 3 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Change in number of bowel movements (BMs) per day (treatment response)	Kulke et al (2017)	8/10		A	Based on daily participant self-report. Clinical durable response was defined as ≥ 30% reduction from baseline in BM frequency for ≥ 50% of double blind phase or achieving ≤ 3 BMs per day. The main study (TELESTAR) reported the overall mean reduction from baseline in BMs per day was -1.43 for telotristat compared with -0.62 for placebo ($p<0.001$) at 12 weeks. It also reported that a clinically durable BM response rate was observed in 44% for telotristat compared with 20% for placebo. This finding was supported by the results of several other studies (TELECAST, Pavel et al. 2015 and Kulke et al. 2014). These findings suggest that BM frequency can be significantly reduced at 12 weeks in people with CS receiving telotristat. The odds someone would have a durable response is 3.49 times higher for people receiving telotristat compared with placebo, with a 95% probability that the true value is within the range of 1.33 times to 9.16 times higher. Results should be interpreted with caution because there are possible confounders which may disguise the true treatment effect of telotristat (as suggested by the unexpected placebo response). The use of short-acting SSA rescue therapy was more common in the placebo arm (suggesting worse control in placebo group), there may be variability in the absorption of long-acting SSAs, differences in use of other antidiarrheal medications, and dietary changes, which may have affected this outcome. In addition, there is no long term data for the 250mg dose because patients switched to 500mg after 12 weeks. There is also a small sample size in the studies, although the sample size was reasonable given the rarity of disease this.
	Pavel et al (2018)	8/10	Indirectly applicable		
	Kulke et al (2014)	7/10	Indirectly applicable		
	Pavel et al (2015)	8/10	Directly applicable		
Change in urinary 5-hydroxyindoleacetic Acid (u5-HIAA) levels	Pavel et al (2018)	8/10	Indirectly applicable	A	The change from baseline in 24 hour u5-HIAA levels was used to obtain serotonin levels and was collected at study endpoint (12 weeks). A clinical durable response was defined as ≥ 50% decrease in 24 hour u5-HIAA levels, or normalisation of levels in people who had elevated baseline levels.
	Kulke et al (2017)	8/10	Directly applicable		
	Kulke et al (2014)	7/10	Indirectly applicable		

	Pavel et al (2015)	8/10	Directly applicable		The best evidence is from TELECAST, which reported a statistically significant mean reduction in u5-HIAA levels of 33.16% in telotristat compared with a mean increase of 97.7% for placebo (Hodges- Lehmann Hodges-Lehman estimated treatment median = -53.95 % (95%CI = -85.0, -25.1) p <0.001). Supportive evidence came from TELESTAR and Pavel et al. 2015 which both reported significant reductions in 24 hour u5-HIAA levels. Although Kulke et al (2014) did not report change scores, 9 of 16 people receiving telotristat compared with 0 of 5 people receiving placebo achieved a biochemical response in u5-HIAA. These findings suggest 24 hour u5-HIAA levels (the biomarker for serotonin) can be reduced in people receiving telotristat. This may be by -53.95%, with a 95% probability that the true value is within the range of -85.0% to -25.1% p<0.001). The study authors noted that the clinical significance of this measure has not yet been fully established, although it is a commonly used marker of response in people with CS. TELECAST included a population experiencing less severe symptoms than the TELESTAR trial and included people who may have been SSA-naïve; this is in contrast to the regulated indication for this therapy and this evidence is treated as indirect.
Urgency to defecate	Kulke et al (2017)	8/10	Directly applicable	A	Sense of urgency to defecate values were obtained by daily self-report. The best evidence came from TELESTAR which found the mean proportion of days with a sense of urgency to defecate for people receiving telotristat (0.66) compared with placebo (0.75) was non-significant (p = 0.35). Findings from TELECAST, Kulke et al. 2014 and Pavel et al. 2015 also found there were no clear differences between people treated with telotristat. Results suggest a change in urgency cannot be differentiated between people receiving telotristat compared with those receiving placebo. Results should be interpreted with caution because there are possible confounders which may disguise the true treatment effect of telotristat, including use of SSA rescue therapy, variability in the absorption of long-acting SSAs, differences in use of other antidiarrheal medications, and dietary changes.
	Pavel et al (2018)	8/10	Indirectly applicable		
	Kulke et al (2014)	7/10	Indirectly applicable		
	Pavel et al (2015)	8/10	Directly applicable		
Stool form and consistency	Kulke et al (2017)	8/10	Directly applicable	A	Stool form was reported using daily self-report measures and assessed using the Bristol Stool Form Scale whereby a reduced score demonstrated a decrease in diarrhoea.
	Pavel et al (2018)	8/10	Indirectly applicable		

	Kulke et al (2014)	7/10	Indirectly applicable		Results from TELESTAR (Kulke et al. 2017) found the mean reduction from baseline in stool consistency for people receiving a 250mg dose of telotristat was-0.26 points compared with a placebo reduction of -0.22 points did not differ significantly. Similar findings were reported in TELECAST (Pavel et al. 2018) and the phase II RCT (Kulke et al. 2014) and suggest the change in stool consistency (graded using a stool form scale) cannot be differentiated for people receiving telotristat compared with placebo. Results should be interpreted with caution because there are possible confounders which may disguise the true treatment effect of telotristat, including use of SSA rescue therapy, variability in the absorption of long-acting SSAs, differences in use of other antidiarrheal medications, and dietary changes.
	Pavel et al (2015)	8/10	Directly applicable		
Abdominal pain and discomfort	Kulke et al (2017)	8/10	Directly applicable	A	Abdominal pain and discomfort was obtained from daily self-report assessment. The best evidence came from TELESTAR which reported a mean reduction of -0.49 points for telotristat compared with -0.23 for placebo and was supported by similar findings in TELECAST, Kulke et al. 2014 and Pavel et al. 2015. Findings suggest abdominal pain was not significantly altered in people receiving telotristat compared with placebo treatment. Results should be interpreted with caution because there are possible confounders which may disguise the true treatment effect of telotristat, including use of SSA rescue therapy, variability in the absorption of long-acting SSAs, differences in use of other antidiarrheal medications, and dietary changes.
	Pavel et al (2018)	8/10	Indirectly applicable		
	Kulke et al (2014)	7/10	Indirectly applicable		
	Pavel et al (2015)	8/10	Directly applicable		
Change in number of flushing episodes per day	Kulke et al (2017)	8/10	Directly applicable	A	The change in number of flushing episodes were recorded by self-report data. The results from TELESTAR showed a mean reduction of -0.30 counts per day for people receiving telotristat compared with a mean reduction of -0.16 counts of flushing episodes per day for people receiving placebo was non-significant (p =0.39). Similar findings were reported in TELECAST and Kulke et al. 2014. Pavel et al. 2015 reported a statistically significant change from baseline, with the mean number of flushing episodes decreasing by a mean value of -0.75 counts per day, with a 27% reduction; p= 0.04). However,
	Pavel et al (2018)	8/10	Indirectly applicable		
	Kulke et al (2014)	7/10	Indirectly applicable		
	Pavel et al (2015)	8/10	Directly applicable		

					since this is a single arm non-randomised study, this study cannot provide evidence that telotristat is any better or worse than other treatments. These results suggest although patients report a decrease in the number of flushing episodes per day, results cannot show that treatment with telotristat is any better or worse compared with placebo. Results should be interpreted with caution because there are possible confounders which may disguise the true treatment effect of telotristat, including use of SSA rescue therapy, variability in the absorption of long-acting SSAs, differences in use of other antidiarrheal medications, and dietary changes.
Change in frequency of short acting SSA therapy	Kulke et al (2017)	8/10	Directly applicable	A	The use of rescue short-acting SSA therapy was assessed by reporting an average change in the number of injections per day. TELESTAR found change from baseline in frequency of rescue short acting SSA therapy reduced by -0.11 injections per day for telotristat compared with an increase of 0.18 injections per day for placebo, although this result was not statistically significant. TELECAST also reported a non-significant difference. These results suggest that the change in frequency of SSA rescue therapy cannot be differentiated for people receiving telotristat or placebo. Results should be interpreted with caution because there are possible confounders which may disguise the true treatment effect of telotristat, including use of SSA rescue therapy, variability in the absorption of long-acting SSAs, differences in use of other antidiarrheal medications, and dietary changes.
	Pavel et al (2018)	8/10	Indirectly applicable		
Patient reported change in CS symptoms	Anthony et al (2017)	7/10	Directly applicable	B	Results for this outcome were largely drawn from the two exit interviews; which used a qualitative approach to patient experience. The best evidence came from Anthony et al (2017) which considered patient experience of symptom change following the exit interview of TELESTAR. Patients stated they felt the 3 most important symptoms to treat were diarrhoea (n=17), BM frequency (n=9), and urgency to defecate (n=5), and 29 out of the 35 people (83%) completing the interview reported BM frequency as more important to treat than stool form. The most frequently reported negative effects of CS symptoms were in social and physical activities with 28 (80%) of the 35 people interviewed reporting negative effects in these areas. This was followed by emotional symptoms (reported by 24 people (69%) and decreased energy (reported by 21 participants
	Kulke et al (2014)	7/10	Indirectly applicable		
	Gelhorn et al (2015)	8/10	Indirectly applicable		

					(60%). 21 out of the 25 people completing the interview reported a meaningful improvement. Out of these 21 reports, the most reported improvement was in BMs with 7 participants receiving telotristat compared with 4 participants receiving placebo reporting improvement. Twenty out of 21 participants (95%) reported reduced BM frequency, with 7 for telotristat reporting a meaningful reduction, compared with 3 for placebo. These findings were supported by Kulke et al. 2014 and the exit interview of this trial (Gelhorn et al. 2016) which reported improvements in areas such as abdominal pain and diarrhoea. These results suggest that patients do report improvements in their CS symptoms as a result of taking telotristat. However, results should be treated cautiously, Only 35 people of the original 135 people participating in TELESTAR completed the exit interview with participants who may have been exposed to a different doses of telotristat than the indicated 250 mg dose.
Quality of life outcomes	Kulke et al (2017)	8/10	Directly applicable	A	Quality of life outcomes were assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the GI.NET-21, whereby higher scores on the global health status indicated improved health, higher scores on the symptom subscales indicated worse symptoms. The best evidence came from TELESTAR which found global health status scores improved by 1.7 points on the subscale score of the EORTC-QLQ-C30 for telotristat compared with a worsened global health status subscale score (-2.0 points) from the original average baseline rating for placebo (on a 0 to 100 point scale averaged over the 12 week treatment period, with higher points representing a better quality of life score). This was not statistically significant. When participants were asked to report their experiences of diarrhoea, people receiving telotristat reported a statistically significant mean improvement of 19.2 points in the diarrhoea subscale compared with a mean score of 8.5 points for placebo (p=0.039). However, there was no difference in the reduction on the nausea and vomiting subscale score for treatment at 250mg. (both reported an improvement of -2.4 points). The study authors noted that these similarities across treatment arms suggest there was no detriment to overall quality of life as a result of treatment.
	Gelhorn et al (2016)	8/10	Indirectly applicable		

					It is important to note that the assessment of quality of life outcomes in TELESTAR were based on a subset of the people who were originally randomised. Furthermore, the study authors noted that minimal changes in global health scores had also been found in previous studies of patients with NETs who received SSAs, and suggested the EORTC QLQ-C30 tool may not be sensitive for this domain.
Adverse events	Kulke et al (2017)	8/10	Directly applicable	A	Adverse events were noted by the investigators and graded as mild, moderate or severe. In TELESTAR 82% of telotristat reported experiencing a treatment emergent adverse event (TEAE) compared with 86.7% placebo. 6.7% telotristat discontinued treatment due to a TEAE compared with 13.3% placebo. One death was reported in the TELESTAR trial in a patient with advanced disease receiving telotristat and 3 deaths were reported in the placebo group. Similar findings were reported in TELECAST, Kulke et al. 2014 and Pavel et al. 2015. In TELESTAR the most commonly reported GI symptom related adverse event was abdominal pain (11% telotristat, 17.8% placebo), which was supported by findings from TELECAST and Pavel et al. 2015. Depressive symptoms were also reported. In TELESTAR 6.7% telotristat and 6.7% placebo reported a depressed mood during the study. Similar findings were reported in TELECAST. These results suggest telotristat was generally well-tolerated for people receiving a 250mg dose, gastro intestinal disorders were commonly reported in people receiving telotristat and depressive outcomes were generally low, and difficult to differentiate between people receiving telotristat compared with placebo. Results should be interpreted with caution because there are possible confounders which may disguise the true treatment effect of telotristat, including use of SSA rescue therapy, variability in the absorption of long-acting SSAs, differences in use of other antidiarrheal medications, and dietary changes
	Pavel et al (2018)	8/10	Indirectly applicable		
	Kulke et al (2014)	7/10	Indirectly applicable		
	Pavel et al (2015)	8/10	Directly applicable		

3 Related NICE guidance and NHS England clinical policies

Related NICE work

Published

Endocrine, nutritional and metabolic conditions overview (2017) NICE pathway

Metastatic malignant disease of unknown primary origin overview (2015) NICE pathway

Metastatic malignant disease of unknown primary origin in adults: diagnosis and management (2010) NICE guideline CG104

Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease (2017) NICE technology appraisal guidance TA449

In development

Gastroenteropancreatic neuroendocrine tumours (somatostatin, non-progressive) - lutetium-177 DOTATATE. NICE technology appraisal guidance, publication date TBC.

Neuroendocrine tumours (metastatic, unresectable, progressive) - 177 Lu-dotatate. NICE technology appraisal guidance, publication date TBC

Neuroendocrine tumours (metastatic, unresectable, progressive) - everolimus and sunitinib NICE technology appraisal guidance, publication expected June 2017

NHS England clinical policies

NHS England has not issued any guidelines or policies on managing carcinoid syndrome diarrhoea with telotristat.

4 References

Anthony L, Ervin C, Lapuerta P, Kulke M H, Kunz P, Bergsland E, Horsch D, Metz D C, Pasieka J, Pavlakis N, Pavel M, Caplin M, Oberg K, Ramage J, Evans E, Yang Q M, Jackson S, Arnold K, Law L, and DiBenedetti D B (2017) Understanding the Patient Experience with Carcinoid Syndrome: Exit Interviews from a Randomized, Placebo-controlled Study of Telotristat Ethyl. Clinical Therapeutics 39(11), 2158-2168

Caplin ME, Baudin E, Ferolla P, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol 2015; 26(8):1604 20

Dmitriadis GK, Weickert MO, Randeva HS, et al. Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer 2016; 23(9):R423 36

Gelhorn H L, Kulke M H, O'Dorisio T, Yang Q M, Jackson J, Jackson S, Boehm K A, Law L, Kostelec J, Auguste P, and Lapuerta P (2016) Patient-reported Symptom Experiences in Patients With Carcinoid Syndrome After Participation in a Study of Telotristat Etiprate: A Qualitative Interview Approach. Clinical Therapeutics 38(4), 759-68

Kulke M H, O'Dorisio T, Phan A, Bergsland E, Law L, Banks P, Freiman J, Frazier K, Jackson J, Yao J C, Kvols L, Lapuerta P, Zambrowicz B, Fleming D, and Sands A (2014) Telotristat etiprate, a novel serotonin synthesis inhibitor, in patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide. Endocrine-Related Cancer 21(5), 705-14

Kulke M H, Horsch D, Caplin M E, Anthony L B, Bergsland E, Oberg K, Welin S, Warner R, Lombard-Bohas C, Kunz P L, Grande E, Valle J W, Fleming D, Lapuerta P, Banks P, Jackson S, Zambrowicz B, Sands A T, and Pavel M (2017) Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. Journal of Clinical Oncology 35(1), 14-23

Lamarca A, Barriuso J, McNamara MG, et al. Telotristat ethyl: a new option for the management of carcinoid syndrome. Expert Opin Pharmacother 2016; 17(18):2487 98

Niederle B, Pape UF, Costa F, et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. Neuroendocrinology 2016; 103(2):125 38

Pavel M, Horsch D, Caplin M, Ramage J, Seufferlein T, Valle J, Banks P, Lapuerta P, Sands A, Zambrowicz B, Fleming D, and Wiedenmann B (2015) Telotristat etiprate for carcinoid syndrome: a single-arm, multicenter trial. Journal of Clinical Endocrinology & Metabolism 100(4), 1511-9

Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, Krenning E, Knigge U, Salazar R, Pape U F, and Oberg K (2016) ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 103(2), 172-185

Pavel M, Gross D; Benavent M, et al. Efficacy and safety results of telotristat ethyl in patients with carcinoid syndrome during the double blind treatment period of the TELECAST Phase 3 Clinical Trial. Endocrine Related Cancer (Epub ahead of print)

Public Health England. Incidence and survival in neuroendocrine tumours and neuroendocrine carcinomas (NETs/NECs) in England, 2013 2014. October 2016. Available from: https://www.netpatientfoundation.org/wp content/uploads/Incidence and survival in neuroendocrine tumours and neuro endocrine carcinomas.pdf

Ramage JK, Ahmed A, Ardill A, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012; 61(1):6 32

Rinke A, Müller HH, Schade Brittinger C, et al. Placebo controlled, double blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009; 27(28):4656 63

Rorstad O. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. J Surg Oncol 2005; 89(3):151 60

This clinical evidence review has been written by NICE, following the process set out in the standard operating procedure.

Appendix 1 Search strategy

Databases

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Platform: Ovid
Search date: 15 Dec 17
Number of results retrieved: 20
Search Strategy:

---

1 telotristat.mp. (19)
2 Xermelo.mp. (0)
3 ("LP-778914" or "LX-1032" or "LX-1606").mp. (0)
4 (LP778914 or LX1032 or LX1606).mp. (5)
5 ("LP 778914" or "LX 1032" or "LX 1606").mp. (0)
6 ("lp 778902" or "lp778902").mp. (0)
7 1 or 2 or 3 or 4 or 5 or 6 (20)

Database: Embase
Platform: Ovid
Version: 1974 to 2017 December 13
Search date: 15 Dec 17
Number of results retrieved: 129
Search strategy:

---

1 telotristat.mp. (118)
2 Xermelo.mp. (6)
3 ("LP-778914" or "LX-1032" or "LX-1606").mp. (13)
4 (LP778914 or LX1032 or LX1606).mp. (24)
5 ("LP 778914" or "LX 1032" or "LX 1606").mp. (13)
6 ("lp 778902" or "lp778902").mp. (1)
7 1 or 2 or 3 or 4 or 5 or 6 (129)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR – 12 of 12, December 2017
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – 11 of 12, November 2017
HTA – 4 of 4, October 2016
NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 15 Dec 17
Number of results retrieved: CDSR 0; DARE 0; CENTRAL 21; HTA 0; NHS EED 0.
Search strategy:

#1 telotristat 21
#2 Xermelo 0
#3 "LP-778914" or "LX-1032" or "LX-1606" 0
#4 LP778914 or LX1032 or LX1606 1

#5 "LP 778914" or "LX 1032" or "LX 1606" 0
#6 "lp 778902" or "lp778902" 0
#7 #1 or #2 or #3 or #4 or #5 or #6 21

Trials registries

Clinicaltrials.gov

Search date: 19/12/17
Number of results retrieved: Telotristat: 9
Xermelo: 15

Results given on p.2. Only results for drug also relating to carcinoid syndrome are given, see below for excluded results.

Clinicaltrialsregister.eu

Search date: 19/12/17
Number of results retrieved: Telotristat: 5
Xermelo: 0

Results given on p.2. Only results for drug also relating to carcinoid syndrome are given.

Excluded results from trials registry searches

Study title	Reason discarded
An Open-Label Food Effect Study of Telotristat Etiprate	Healthy population
A Open-Label Drug-Drug Interaction Study of Telotristat Etiprate and Midazolam in Healthy Subjects	Drug interactions, healthy population
An Open-Label Drug-Drug Interaction Study of Telotristat Etiprate and Fexofenadine in Healthy Subjects	Drug interactions, healthy population
Phase 1, Open-label, Drug-drug Interaction Study With Octreotide Acetate Injection and Telotristat Etiprate in Healthy Subjects	Drug interactions, healthy population

Study to Evaluate a Dose of Telotristat Etiprate in Male and Female With Mild, Moderate and Severe Hepatic Insufficiency and Matched Healthy Subjects	Hepatic impairment
A Phase 1 Study to Evaluate the Effects of Omeprazole and Famotidine on the Absorption of Telotristat Ethyl in Healthy Subjects	Drug interactions, healthy population
A Thorough QT Study of Telotristat Etiprate	QT intervals
A Study to Evaluate Safety and Efficacy of LX1606 in Subjects With Acute, Mild to Moderate Ulcerative Colitis	Ulcerative colitis
Phase 2 Assessment of the Relationship between Serotonin and Efficacy in Ulcerative Colitis: A Multi-Center Randomized, Double Blind, Placebo-Controlled, Pilot Study to Evaluate Safety and Preliminary Efficacy of Orally Administered LX1606 in Subjects with Acute, Mild to Moderate Ulcerative Colitis	Ulcerative colitis

Appendix 2 Study selection

The search strategy presented in appendix 1 yielded 115 studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

Sifting criteria	**Inclusion**	**Exclusion**
Population	Adults with carcinoid syndrome diarrhoea that is inadequately controlled by SSA therapy.	Non-humans, healthy volunteers
Intervention	Telotristat (Xermelo) (Note: has a marketing authorisation for the treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy.)	
Comparator	• Octreotide (at above licensed doses) • Lanreotide (at above licensed doses • Cyproheptadine hydrochloride • Interferon • Best supportive care	
Outcomes	• Change in the number of bowel movements per day • Urgency to defecate • Stool form and consistency • Abdominal pain and discomfort • Change in urinary 5-hydroxyindoleacetic	

	Acid (5-HIAA) levels • Change in the number of flushing episodes per day • Change in frequency of rescue short-acting SSA therapy to treat bowel-related symptoms associated with CS • Patient-reported change in CS related symptoms • Number of discontinuations due to treatment-emergent adverse events	
Other		Editorials or letters to the editor; conference or poster abstracts

Table 4 Studies excluded at full text

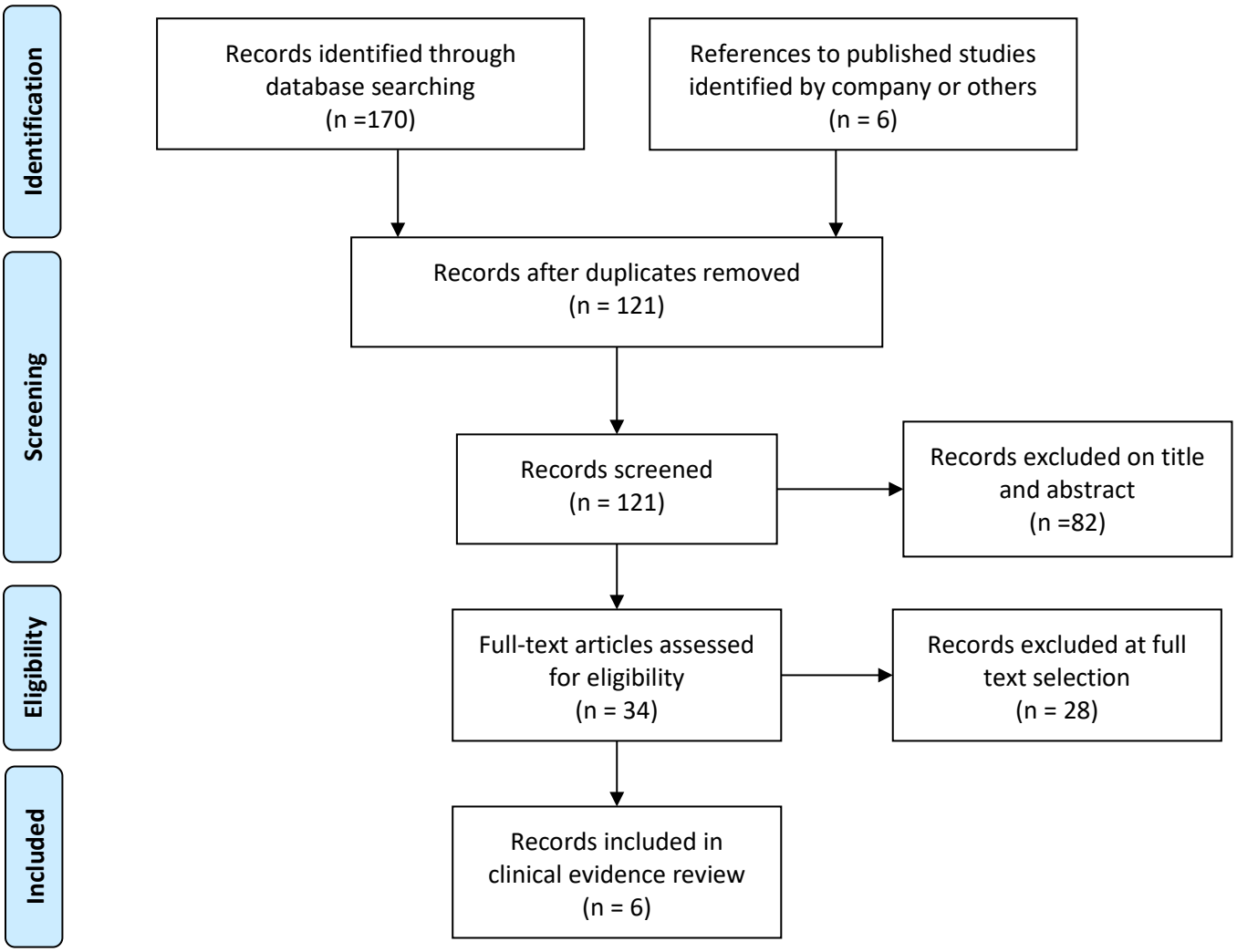
Study reference	Reason for exclusion
Anonymous (2017) Telotristat ethyl (Xermelo) for carcinoid syndrome diarrhea. Medical Letter on Drugs and Therapeutics 59 (1525), 119-120	Abstract only
Anonymous (2016) Efficacy and safety results of telotristat ethyl in patients with carcinoid syndrome during the double-blind treatment period of the TELECAST phase 3 clinical trial. Clinical Advances in Hematology and Oncology 14(12 Supplement 13), 7-9	Article is not a primary or secondary analysis (guideline only)
Anthony L, Horsch D, Ervin C, Kulke MH, Pavel M, Bergsland E, Caplin M, Oberg K, Warner R, Kunz P, Metz Dc, Pasieka J, Pavlakis N, Dibenedetti D, Haydysch E, Yang QM, Jackson S, Arnold K, Law L, and Lapuerta P (2016) Assessing treatment benefit of telotristat etiprate in patients with carcinoid syndrome: patient exit interviews. Pancreas. Conference: 8th annual meeting of the north American Neuroendocrine Tumor society. United states 45(3), 470	Abstract only
Brown P, Pappas C, Frazier K, Turnage A, and Liu Q (2009) LX1032: A novel approach for managing gastrointestinal symptoms in carcinoid syndrome. Neuroendocrinology 90 (1), 100-101	Abstract only

Brown P, Frazier K, Jackson S, Turnage A, and Liu Q (2010) LX1032: A novel agent to reduce serotonin in carcinoid syndrome. Pancreas 39 (2), 272	Abstract only
Cella D, Beaumont J, Marteau F, Feuilly M, Gabriel S, Ramage J, Pavel M, Horsch D, and Kulke M H (2017) Examining the symptoms and quality of life improvements with durable response in patients with carcinoid syndrome from the TELESTAR open-label extension. Quality of Life Research 26 (1 Supplement 1), 129	Abstract only
Fleming D, Ye G L, Jackson J, Jackson S, Murgai D, and Lapuerta P (2013) Cumulative safety experience of telotristat etiprate in clinical trials supports advancement to phase 3. European Journal of Cancer 49, S182	Abstract only
Horsch D, Kulke M, Caplin M, Anthony L, Bergsland E, Oberg K, Welin S, Warner R, Lombard-Bohas C, Kunz P, Valle J, Fleming D, Lapuerta P, Banks P, and Pavel M (2016) Efficacy and safety of telotristat etiprate in patients with carcinoid syndrome not adequately controlled by somatostatin analog therapy: Analysis of the ongoing telestar extension period. Neuroendocrinology 103, 88	Abstract only
Hudgens S, Gable J, Kulke M H, Bergsland E, Anthony L B, Caplin M E, Oberg K E, Pavel M E, Banks P, Yang Q M, and Lapuerta P (2017) Evaluation of meaningful change in bowel move frequency for patients with carcinoid syndrome. Journal of Clinical Oncology. Conference 35(4 Supplement 1),	Abstract only
Kulke M, O'Dorisio T, Phan A, Bergsland E, Freiman J, Law L, Banks P, Frazier K, Jackson J, and Zambrowicz B (2012) Efficacy of telotristat etiprate in refractory carcinoid syndrome: Results of a randomized, placebo controlled, multicenter study. Neuroendocrinology 96, 43	Abstract only
Kulke M H, O'Dorisio T, Phan A, Langdon R, Marek B, Ikhlaque N, Bergsland E, Freiman J, Law L, Banks P, Frazier K, Jackson J, and Zambrowicz B (2012) Efficacy of telotristat etiprate in refractory carcinoid syndrome: Preliminary results of a randomized, placebo-controlled, multicenter study. Pancreas 41 (2), 346	Abstract only
Kulke M H, O'Dorisio T, Yang Q M, Jackson J, Jackson S, Boehm K A, Law L, Lapuerta P, Kostelec J, Auguste P, Sommers R, and Gelhorn H L (2014) Patient-reported symptom experiences following participation in a study of telotristat etiprate for patients with neuroendocrine tumors and diarrhea not adequately controlled on octreotide. Neuroendocrinology 99 (3-4), 278	Abstract only
Kulke M H, Horsch D, Caplin M, Anthony L, Bergsland E, Oberg K, Welin S, Warner R, Lombard-Bohas C, Kunz P, Grande E, Valle J, Fleming D, Lapuerta P, Banks P, Jackson S, Wheeler D, Zambrowicz B, Sands A, and Pavel M (2015) Telotristat etiprate is effective in treating patients with carcinoid syndrome that is inadequately	Abstract only

controlled by somatostatin analog therapy (the phase 3 TELESTAR clinical trial). European Journal of Cancer 51, S728	
Kulke M, Horsch D, Caplin M, Anthony L, Bergsland E, Oberg K, Welin S, Warner R, Lombard Bohas, C , Kunz P L, Grande E, Valle J W, Lapuerta P, Banks P, Jackson S, Jiang W, Biran T, and Pavel M (2016) Integrated placebo-controlled safety analysis from clinical studies of telotristat ethyl for the treatment of carcinoid syndrome. Annals of Oncology. Conference: 41st European Society for Medical Oncology Congress, and ESMO 27(no pagination),	Abstract only
Kulke MH, Horsch D, Caplin M, Anthony L, Bergsland E, Oberg K, Welin S, Warner R, Lombard-Bohas C, Kunz P, Grande E, Valle JW, Fleming D, Lapuerta P, Banks P, Jackson S, Wheeler D, Zambrowicz B, Sands A, and Pavel M (2016) Telotristat etiprate shows benefit in treating Patients with carcinoid syndrome that is inadequately controlled by somatostatin analog therapy in the phase 3 TELESTAR clinical trial. Pancreas. Conference: 8th annual meeting of the north american neuroendocrine tumor society. United states 45(3), 478	Abstract only
Neuenfeldt M (2017) Telotristat ethyl relieves carcinoid syndrome-induced diarrhea: Add-on therapy for patients with neuroendocrine tumors. Deutsche Apotheker Zeitung 157(45),	Article not in English
O'Dorisio T M, Phan A T, Langdon R M, Marek B J, Ikhlaque N, Bergsland E K, Freiman J, Law L, Lee Banks, P , Frazier K, Jackson J, Zambrowicz B, and Kulke M (2012) Relief of bowel-related symptoms with telotristat etiprate in octreotide refractory carcinoid syndrome: Preliminary results of a double-blind, placebo-controlled multicenter study. Journal of Clinical Oncology. Conference 30(15 SUPPL. 1),	Abstract only
Pappas C, Turnage A, Frazier K S, Liu Q, and Brown P (2009) LX1032: A potential new therapy for carcinoid syndrome (CS). Journal of Clinical Oncology 1), e14555	Abstract only
Pappas S C, Brown P, Turnage A, Frazier K, Yang Q M, Shi Z C, and Liu Q (2009) LX1032: A potential new therapy for chronic diarrhea in carcinoid syndrome (CS). Gastroenterology 1), A56	Abstract only
Pavel M, Wiedenmann B, Caplin M, Hoersch D, Freiman J, Law L, Banks P, Frazier K, Jackson J, and Zambrowicz B (2013) Telotristat etiprate produces clinical and biochemical responses in patients with carcinoid syndrome: Update of a phase 2, multicenter, open-label, serial-ascending, European study. Pancreas 42 (2), 379	Abstract only
Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, Krenning E, Knigge U, Salazar R, Pape U F, and Oberg K (2016) ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine	Article is not a primary or secondary analysis (guideline only)

neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 103(2), 172-185	
Pavel M, Horsch D, Anthony L, Ervin C, Kulke M, Bergsland E, Caplin M, Oberg K, Warner R, Kunz P, Metz D, Pasieka J, Pavlakis N, DiBenedetti D, and Lapuerta P (2016) Patient interviews in telestar, a phase 3 study of telotristat etiprate, report meaningful improvement in carcinoid syndrome. Neuroendocrinology 103, 89	Abstract only
Pavel M E, Gable J, Kulke M H, Bergsland E, Anthony L B, Caplin M E, Oberg K E, Banks P, Yang Q M, Lapuerta P, and Hudgens S (2017) Evaluation of meaningful change in bowel move frequency for patients with carcinoid syndrome. Oncology Research and Treatment 40 (Supplement 3), 238	Abstract only
Weickert M O, Kaltsas G, Horsch D, Lapuerta P, Pavel M, Valle J W, Caplin M E, Bergsland E K, Kunz P L, Anthony L B, Grande E, Oberg K E, Warner R. P, Lombard-Bohas C, Welin S, Fleming R, Kittur A, Arnold K, Yang Q M, and Kulke M H (2017) Association of weight change with telotristat ethyl in the treatment of carcinoid syndrome. Journal of Clinical Oncology. Conference 35(15 Supplement 1),	Abstract only
Wheeler D, Kulke M H, O'Dorisio T, Horsch D, Jackson S, Ye G L, Kim H W, Zambrowicz B, Sands A, and Fleming D (2014) Telotristat Etiprate (TE) in a cohort of carcinoid heart disease patients in two phase 2 trials. Neuroendocrinology 99 (3-4), 281	Abstract only
Wheeler D, Horsch D, Valle J, Lapuerta P, Zambrowicz B, Sands A, and Fleming D (2015) Telotristat etiprate in a subset of carcinoid syndrome patients who have high levels of urinary 5-hydroxyindoleacetic acid and frequent flushing. Neuroendocrinology 102 (1-2), 135	Abstract only
Wiedenmann B, Pavel M E, Seufferlein T, Freiman J, Law L, Lee Banks, P , Frazier K, Jackson J, and Zambrowicz B (2012) The effect of telotristat etiprate on clinical and biochemical responses in patients with symptomatic carcinoid syndrome: Preliminary results of an ongoing phase II, multicenter, open-label, serial-ascending dose study. Journal of Clinical Oncology. Conference 30(15 SUPPL. 1),	Abstract only
Zacks J, Lavine R, Ratner L, and Warner R (2016) Telotristat etiprate appears to halt carcinoid heart disease. Neuroendocrinology 103, 90	Abstract only

Figure 2 Flow chart of included studies



Appendix 3 Evidence tables

Table 5 Kulke et al. (2017)

Study reference	Kulke MH, Horsch D, Caplin M, Bergland AE et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. Journal of Clinical Oncology 2017; 35; 14-22
Unique identifier	TELESTAR (LX1606-301) NCT01677910
Study type (and NSF-LTC study code)	International, multicentre, phase III randomised double-blind placebo controlled trial (P1)
Aim of the study	To assess the safety and efficacy of telotristat ethyl in people with carcinoid syndrome not adequately controlled by somatostatin analogue (SSA) therapy
Study dates	31st January 2013 to 4th March 2015
Setting	16 clinical sites across 12 International countries
Number of participants	N= 135 (45= placebo; 45= 250mg telotristat ethyl; 45=500mg telotristat ethyl)
Population	Adults with well-differentiated metastatic neuroendocrine tumours (NETs) and a history of carcinoid syndrome (CS receiving SSA therapy and experiencing at least 4 bowel movements (BMs) per day
Inclusion criteria	People aged ≥18 years with a histopathological confirmed well-differentiated metastatic NET; documented history of CS; receiving stable dose of SSA long acting release depot or infusion pump for at least 3 months before enrolment. People with U5-HIAA levels that were above or below the upper limit of normal (0-15mg/24 hours) and with unknown values were also allowed to participate.
Exclusion criteria	People experiencing 12 or more watery BMs per day associated with volume contraction, dehydration or hypotension, or showing evidence of enteric infection. People with a Karnofsky performance status equal to or less than 60%; a history of short bowel syndrome; clinically important baseline elevation in liver function; previously undergone tumour directed therapy; hepatic alanine transaminase (ALT) values equal to or greater than 5.5 x ULN (for people with a documented history of hepatic metasteses) or hepatic ALT values equal to or greater than 2.5 x ULN; total bilirubin greater than 1.5 x ULN (unless the patient had documented history of Gilbert's syndrome); if total bilirubin was greater than ULN then an alkaline phosphatase equal to or greater than 5 x ULN was also excluded.
Intervention(s)	After a screening period of 3 or 4 weeks depending on SSA schedule, participants received either 250mg telotristat or 500mg telotristat three times a day whilst continuing to receive their baseline SSA therapy for a 12 week period. Following the double blind phase participants were offered open label treatment with 500mg telotristat three times a day for a 36 week period.
Comparator(s)	Placebo three times a day

Length of follow-up	Double blind phase 12 weeks Open label extension (all participants received 500mg telotristat) 36 weeks
Outcomes	Primary outcome: • Mean reduction from baseline in daily BMs (averaged over 12 weeks)
	Secondary outcomes: • Change from baseline in U5-HIAA • Number of flushing episodes • Abdominal pain severity (0 to 10 point scale) • Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) • Use of rescue short acting SSA • Stool consistency • Proportion of days with urgency to defecate
	Safety outcomes: • Adverse events (graded as mild, moderate or severe) • Depression cases • Number of deaths • Pharmacokinetic sub analysis (based on 40 participants)
Source of funding	Lexicon pharmaceuticals

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Yes, clearly stated aims and reporting of design
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Yes, multicentre, international double blind placebo controlled trial
3. Are the methods clearly described?	1/2	Although there was a full clear reporting of methods used and CONSORT diagram provided reporting the transition of patients through the trial, this was downgraded because limited methods were reported for data assessments – for example there is no clear reporting of how data was obtained; limited reporting of allocation, concealment and blinding.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Although the population included people receiving stable dose SSA therapy, interpretation of the results may have been confounded by the high percentage of people (greater than 40% in each arm) receiving the above label dose of SSA (used for poor control of carcinoid syndrome).
5. Are the results generalisable?	2/2	Yes, although the trial includes a small sample, the results can be incorporated to represent general clinical practice
Total	8/10	
Applicability	Directly applicable	Yes, this includes a direct population of people with carcinoid syndrome inadequately controlled by SSA therapy.

* Note - Direct studies focus on people with the indication and characteristics of interest.

Indirect studies are based on evidence extrapolated from populations with other conditions and characteristics. We'll put this in our methods manual

Table 6 Pavel et al. (2018)

Study reference	Pavel M, et al. 2018
Unique identifier	(LX1606-203) NCT02063659
Study type (and NSF-LTC study code)	International, multicentre, phase III randomised double-blind placebo controlled trial (P1)
Aim of the study	To assess the safety and efficacy of telotristat in people with symptomatic CS who did not qualify for the TELESTAR trial but had other manifestations of CS (including elevated u5-HIAA or flushing)
Study dates	April 2014 to April 2015
Setting	Clinical sites in 11 countries
Number of participants	N=76 (26=placebo; 25=250mg telotristat ethyl; 25= 500mg telotristat ethyl)
Population	Adults with histopathologically confirmed, well‐ differentiated metastatic NETs with a documented history of CS. If receiving SSA therapy this was required to be at a stable dose for at least 3 months prior to study entry.
Inclusion criteria	Eligibility was dependent on having at least 1 of the following signs or symptoms or an average of less than 4 BMs per day. Symptoms included: Daily stool consistency ≥5 on the Bristol Stool Form Scale (indicating that the patient had diarrhoea or stools that were softer than normal); average daily cutaneous flushing frequency of equal to or greater than 2; average daily rating of ≥3 for abdominal pain; nausea present equal to or greater than 20% of days; or u5-HIAA above the upper limit of normal (ULN). For patients not receiving SSA therapy, 137 eligibility depended on having at least 1 of the above signs or symptoms or an average 138 of ≥4 BMs/day.
Exclusion criteria	Exclusion included: Diarrhoea attributable to any condition other than CS; Experiencing 4 or more BMs per day while on concomitant SSA therapy; Showed evidence of enteric infection; A Karnofsky performance status of 60% or more; A history of short bowel syndrome or chronic or idiopathic constipation; Clinically important baseline elevation in liver function tests; or had undergone tumor-directed therapy within 4 weeks prior to screening Hepatic embolization, radiotherapy, radiolabelled SSA therapy, and/or tumour debulking within 12 weeks prior to screening.

Intervention(s)	Participants were randomly assigned to receive telotristat ethyl 250mg, 500mg 3 times a day Participants assigned to 500mg dose underwent a blinded up-titration to 500mg for first 7 days.
Comparator(s)	Placebo three times a day
Length of follow-up	Double blind phase 12 weeks Open label extension (all participants received 500mg telotristat) 36 weeks
Outcomes	Primary outcome • Change from baseline in 24-hour u5-HIAA levels at Week 12
	Secondary outcomes • Change from baseline in daily BM frequency • Change from baseline in stool consistency • Change from baseline in cutaneous flushing episodes • Change from baseline in Abdominal pain • Change from baseline in frequency of rescue short-acting SSA treatment.
	Safety outcomes • Incidence of treatment-emergent adverse events (TEAEs)
Source of funding	Lexicon pharmaceuticals

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Yes, clearly reported aims and design
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Yes, international, multicentre RCT
3. Are the methods clearly described?	1/2	Downgraded because there is limited description of assessment process, blinding and allocation
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Yes, full clear reporting
5. Are the results generalisable?	1/2	Downgraded because it includes a population who were SSA therapy--naïve
Total	8/10	
Applicability	Partially applicable	Due to the lack of stratification for people who were SSA therapy--naïve

Table 7 Kulke et al. (2014)

Study reference	Kulke MH, O' Dorisio T, Phan A, Bergsland E et al. Telotristat etiprate, a novel serotonin synthesis inhibitor, in patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide. Endocrine Related Cancer 2014; 21; 705-14
Unique identifier	(LX1606-202) NCT00853047
Study type (and NSF-LTC study code)	International, multicentre, phase II randomised double blind, placebo controlled dose escalation study (P1)
Aim of the study	To assess the safety and tolerability of telotristat etiprate in people with diarrhoea associated with carcinoid syndrome not adequately controlled by somatostatin analogue (SSA) therapy
Study dates	15 June 2010 to 12 February 2014
Setting	11 clinical sites in Germany and UK

Number of participants	N= 23 Five cohorts of participants sequentially enrolled to one of each drug dose or placebo 150mg n=3; 250mg n=3; 350mg n =3; 500mg n=9; Placebo n=5
Population	Adults with biopsy proven metastatic neuroendocrine (carcinoid) tumours (NETs) and diarrhoea inadequately controlled by octreotide therapy
Inclusion criteria	Adults (aged 18 years or over) with biopsy proven metastatic neuroendocrine (carcinoid) tumours (NETs) and experiencing at least 4 BMs per day and on stable dose octreotide LAR for at least 3 months) People with serum creatine less than1.5 x the upper limit of normal (ULN), hepatic transaminases less than 2 x ULN, alkaline phosphatase less than 1.5xULN and total bilirubin within normal limits
Exclusion criteria	People with a history of short bowel syndrome, more than 12 high-volume, watery BMs/day, or a Karnofsky Performance Status equal to or greater than 70%. People were also 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
Intervention(s)	After a 2 week run in phase, participants received a dose escalation every 14 days of either 150mg, 250mg, 350mg or 500mg telotristat three times a day until a stable tolerated dose was achieved. Participants then continued with their maximum tolerated dose for a further 4 week period.
Comparator(s)	Placebo
Length of follow-up	Double blind phase 8 weeks Stable dose period 4 weeks
Outcomes	Primary outcome: • Mean change in number of daily BMs
	Secondary outcomes: • Stool form/ consistency • Proportion of days with urgency to defecate • Patient reported relief of symptoms • Change in 24 hour reported U 5-HIAA
	Safety outcomes: • Adverse events (graded as mild, moderate or severe)
Source of funding	Lexicon pharmaceuticals

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Yes, clearly stated aims and reporting of design
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Downgraded because the aim of the study is reported as assessing the safety and efficacy, yet later in the paper, it reports that due to sample size efficacy analyses was considered to be exploratory only.
3. Are the methods clearly described?	1/2	Clear reporting of the method including escalation and dose limiting toxicity, and data assessments although limited reporting of blinding and allocation concealment
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Yes, full reporting of results-authors acknowledging exploratory findings due to sample size
5. Are the results generalisable?	1/2	Overall results are appropriate, based on the direct population of people with carcinoid syndrome inadequately controlled by SSA therapy, but small sample size would limit generalisability of efficacy findings.
Total	7/10	
Applicability	Partially applicable	Indirectly applicable due to sample receiving escalating doses of telotristat up to 500mg TID

Table 8 Pavel et al. (2015)

Study reference	Pavel M, Hörsch D, Caplin M, Ramage J, Seufferlein E et al. Telotristat etiprate for carcinoid syndrome: A single-arm, multicenter trial. J Clin Endocrinol Metab,2015 100; 1511-1515
Unique identifier	(LX1606-203) NCT01104415
Study type (and NSF-LTC study code)	International, multicentre, open label ascending dose escalation study (P1)
Aim of the study	To assess the safety and tolerability of telotristat etiprate in people with diarrhoea associated with carcinoid syndrome not adequately controlled by somatostatin analogue (SSA) therapy
Study dates	15 June 2010 to 12 February 2014
Setting	6 clinical sites in Germany and UK
Number of participants	N= 15
Population	Adults with biopsy-proven metastatic, well-differentiated, and carcinoid syndrome experiencing at least four bowel movements (BMs) per day
Inclusion criteria	Adults (aged 18 years or over) with biopsy proven metastatic biopsy-proven, metastatic, well-differentiated NET and carcinoid syndrome and a baseline average of at least four bowel movements per day. Participants may have both been receiving concurrent SSA therapy or not receiving concurrent SSA therapy
Exclusion criteria	People with a Karnofsky Performance Status (9) ≤70; evidence of cardiovascular volume depletion; other diseases causing diarrhoea such as pancreatic insufficiency, enteric infections, or short bowel syndrome; elevations of transaminases ≥5 x the upper limit of normal (ULN), total bilirubin exceeding the ULN, or alkaline phosphatase (ALP) ≥3 x ULN.
Intervention(s)	After a 2 week run in phase, participants received a dose escalation every 14 days of either 150mg, 250mg, 350mg or 500mg telotristat three times a day until a stable tolerated dose was achieved. Participants then continued with their maximum tolerated dose for a further 4 week period.
Comparator(s)	No comparator
Length of follow-up	12 weeks
Outcomes	Primary outcome: • Mean change in number of daily BMs
	Secondary outcomes: • Stool form • Abdominal pain • Flushing • Urgency to defecate • Change in 24-h reported u5-HIAA
	Safety outcomes: • Adverse events (graded as mild, moderate or severe)

Source of funding	Lexicon pharmaceuticals

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Yes, clearly stated aims and reporting of design
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Downgraded because the aim of the study is reported as assessing the safety and efficacy, but it is based on a small sample size which may have had a confounding result
3. Are the methods clearly described?	2/2	Yes, clear reporting of the method including escalation and dose limiting toxicity,
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Although single arm noted, and therefore more open to bias-results are interpreted in line with confounds
5. Are the results generalisable?	1/2	Partially generalizable because some participants may not have been receiving SSA therapy
Total	8/10	
Applicability	Partially applicable	Due to small sample size and mixed sample population

Table 9 Gelhorn et al. (2016)

Study reference	Gelhorn HL, Kulke MH, O'Dorisio T, Yang QM et al. Patient-reported symptom experiences in patients with carcinoid syndrome after participation in a study of telotristat etiprate: a qualitative interview approach. Clinical Therapeutics,2016; 38; 759-68
Unique identifier	LX1606-203

Study type (and NSF-LTC study code)	Retrospective interviews of Phase II participants involved in the phase II clinical trial LX1606-202 (P2)
Aim of the study	To characterize the symptom experiences of patients participating in that trial.
Study dates	20th December 2012 to 15th February 2013
Setting	2 of the original 8 clinical sites involved in the original phase II trial
Number of participants	N= 10 from original 23 participants
Population	All recruiting participants from 2 of the 8 sites involved in the phase II trial (LX1606.202; Kulke et al. 2014)
Inclusion criteria	Participants in the previous phase II trial; aged 18 years or older; able to participate in a one to one telephone interview; able to read, speak, and understand English and complete all study assessments; willing and able to provide written informed consent before the interview.
Exclusion criteria	Participants with a cognitive or other impairment (for example vision or hearing) that would interfere with completing the interview were not eligible for the study.
Intervention(s)	Administration of self-reported EORTC GI.NET-21 questionnaire (an adapted version of EORTC QLQ-C30,a 30-item questionnaire assessing quality of life in patients with cancer. The GI.NET-21 comprises questions assessing disease symptoms, adverse events with treatment, body image, disease-related worries, social functioning, communication, and sexuality. Self-reported information on information on age, race, employment status, education, and current CS symptoms was documented using the Sociodemographic and Clinical Characteristics form. This information was used for assisting with interpretation of the results of individual interviews. Staff members from the sites completed a clinical form documenting information such as tumour site, concurrent medications, and time since diagnosis.
Comparator(s)	No comparator
Length of follow-up	At end of phase II study period
Outcomes	Primary outcome: • Patient reported experience of CS symptoms
	Secondary outcomes: • None reported
	Safety outcomes: • Non reported
Source of funding	Lexicon pharmaceuticals

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Yes, clearly stated aims and reporting of design
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Yes, clearly reported with use of validated questionnaire
3. Are the methods clearly described?	1/2	Clear reporting of the methods
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Yes, adequate interpretation
5. Are the results generalisable?	1/2	Although validated tool was used, downgraded because it is based on a small sample size. Also as participants received titrated doses up to 500mg (tid) it's not clear how these results can be generalised to receipt of only the 250mg dose
Total	8/10	
Applicability	Partially applicable	Indirectly applicable due to sample receiving escalating doses of telotristat up to 500mg TID

Table 10 Anthony et al. (2017)

Study reference	Anthony L, Ervin C, Lapuerta, Kulke, MH, Kunz P et al. Understanding the Patient Experience with Carcinoid Syndrome: Exit Interviews from a Randomized, Placebo-controlled Study of Telotristat Ethyl. Clinical Therapeutics,2017; 39; 2158-68
Unique identifier	
Study type (and NSF-LTC study code)	Qualitative sub study of exit interviews from an International, multicentre, double blind placebo controlled RCT (P2)
Aim of the study	To explore the experiences of patients' with carcinoid syndrome and assess the extent to which their experiences were affected by the treatment intervention, by conducting prospective, qualitative exit interviews with volunteers from TELESTAR.
Study dates	TELESTAR ran from 31st January 2013 to 4th March 2015
Setting	11 clinical sites across 5 countries originally conducting TELESTAR trial (Australia, Canada, England, German and United States)
Number of participants	N= 35 from original 135 participants
Population	Adults with well-differentiated metastatic neuroendocrine tumours (NETs) and a history of carcinoid syndrome (CS receiving SSA therapy and experiencing at least 4 bowel movements (BMs) per day
Inclusion criteria	Volunteers from the participants originally included in TELESTAR (see evidence table for Kulke et al. 2017 for complete inclusion criteria)
Exclusion criteria	Not reported (see evidence table for Kulke et al. 2017 for complete exclusion criteria)
Intervention(s)	At the end of treatment (week 12) participants were invited to take part in a semi-structured exit interview. The interview was structured in 2 parts: Part 1 focused on patients experiences of CS symptoms before they took part in the study; Part 2 focused on CS symptom experiences during the trial and reporting any experiential changes
Comparator(s)	No comparator
Length of follow-up	At end of 12 week trial
Outcomes	Primary outcome: • Patient reported experience of CS symptoms
	Secondary outcomes: • None reported
	Safety outcomes: • Non reported
Source of funding	Lexicon pharmaceuticals

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Yes, clearly stated aims and reporting of design
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Clearly reported methods but unclear from write up if semi structured interview questions had been through a validation process
3. Are the methods clearly described?	1/2	Clear reporting of the methods but downgraded because it is not clearly reported in inclusion criteria of how volunteers were selected
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Yes, adequate interpretation
5. Are the results generalisable?	1/2	Downgraded because results based on approx. one quarter of those completing original trial
Total	7/10	
Applicability	Directly applicable	Yes

Appendix 4 Results tables

Table 11 Kulke et al. (2017)

	Telotristat 250mg (n=45)	**Placebo (n=45)**	**Significance (p-value)**
Primary outcome: (Intention to treat analysis) Change from baseline in BM frequency at week 12 Mean (SD)			
Mean change in daily BM frequency (averaged over 12 weeks)	-1.43 (1.36)	-0.62 (0.83)	not reported
Arithmetic mean	-1.7 (SD not reported)	-0.9 (SD not reported)	not reported

reduction in daily BM frequency (to week 12)			
BM frequency: Arithmetic mean treatment difference	Mean difference = -0.81 (SD not reported)		not reported
BM frequency: Hodges Lehmann estimator of treatment difference [a]	Estimated treatment effect = -0.81 (97.5% CL = -1.26,-0.29)		p<0.001
Primary outcome: (Intention to treat analysis) **Number of participants who had meaningful treatment benefit with durable treatment response n (%)** **Responder analysis[b]**			
N=90	**Telotristat 250mg n=45**	**Placebo n=45**	**Significance (p-value)**
Responders	20/45 (44)	9/45 (20)	
Non responders	25/45 (55.6)	36/45 (80)	
Effect estimate	Odds ratio OR= 3.19; (95%CL = 1.33, 9.16)		p = 0.01
Primary outcome: (Responder analysis [b]) **Change from baseline in BM frequency at week 12 Mean (SD)**			
BM responders: Mean proportion of days with ≥30% reduction in BMs/ day	-2.6 (1.6)	-1.9 (0.8)	not reported
BM non responders: Mean proportion of days with ≥30% worsening in BMs/ day	-1.0 (0.5)	-0.5 (1.1)	not reported
Secondary outcome: (Intention to treat analysis) **Change from baseline in u5-HIAA levels at week 12 mean (SD)**			
	Telotristat 250mg (n=45)	**Placebo (n=45)**	**Significance (p-value)**

u5-HIAA levels: Absolute change from baseline at week 12 (mg/24h)	-40.1 (84.8)	11.5 (35.6)	not reported
u5-HIAA levels: Arithmetic mean treatment difference	Mean difference = -51.6 (SD not reported)		not reported
u5-HIAA levels: Hodges Lehmann estimator of treatment difference[a]	Estimated treatment effect = -30.1 (97.5% CL = -56.00,-8.10)		p<0.001
Secondary outcome: (Per protocol analysis) Quality of life: outcomes over 12 week period EORTC QLQ-C30 Change from baseline Mean (SD)			
	Telotristat 250mg (n=45)	**Placebo (n=45)**	
Global health status (Quality of life)	n= 39 1.7 (19.1)	n=39 -2.0 (18.3)	
Diarrhoea sub scale scores	n=39 -19.2 (29.3)	n=39 -8.5 (21.9)	
Nausea and vomiting sub scale scores	n=39 -2.4 (20.3)	n=39 -2.4 (13.5)	
Insomnia sub scale scores	n=40 3.3 (18.9)	n=39 -7.7 (25.9)	
Physical functioning sub scale scores	n=40 -0.2 (11.1)	n=39 -1.2 (13.3)	
Role functioning sub scale scores	n=39 7.7 (2.8)	n=39 -1.3 (16.8)	
Emotional functioning sub scale scores	n=39 0.7 (16.4)	n=39 0.5 (13.7)	

Cognitive functioning sub scale scores	n=39 -2.4 (13.2)	n=39 0.0 (20.8)	
Social functioning sub scale scores	n=39 2.6 (23.4)	n=39 0.4 (15.8)	
Fatigue sub scale scores	n=40 -2.4 (22.2)	n=39 0.4 (18.7)	
Pain sub scale scores	n=40 -5.2 (28.4)	n=39 -1.7 (19.6)	
Dyspnoea sub scale scores	n=40 -1.7 (20.9)	n=39 1.7 (18.7)	
Appetite loss sub scale scores	n=40 1.3 (25.7)	n=38 -7.5 (25.9)	
Constipation sub scale scores	n=39 2.6 (7.2)	n=38 0.9 (3.8)	
Financial difficulties sub scale scores	n=39 -5.1 (15.4)	n=38 -1.3 (19.1)	
Secondary Outcome: (Intention to treat analysis) Change from baseline in daily flushing episodes Mean (SD)			
	Telotristat 250mg (n=45)	**Placebo (n=45)**	**Significance (p-value)**
Daily flushing episodes (counts per day) (averaged over 12 weeks)	-0.30 (1.31)	-0.16 (1.16)	not reported
Daily flushing episodes: Arithmetic mean treatment difference	Mean difference = -0.13 (SD not reported)		not reported
Daily flushing episodes: Hodges Lehmann estimator[a]	Estimated treatment effect = 0.036 (97.5% CL = not reported)		p=0.39
Secondary Outcome: (Intention to treat analysis) Change from baseline in abdominal pain Mean (SD)			
	Telotristat	**Placebo**	**Significance**

	250mg (n=45)	(n=45)	(p-value)
Abdominal pain (averaged over 12 weeks)	-0.49 (1.44)	-0.23 (1.16)	not reported
Abdominal pain: Arithmetic mean treatment difference	Mean difference = -0.26 (SD not reported)		not reported
Abdominal pain: Hodges Lehmann estimator of treatment difference[a]	Estimated treatment effect = -0.17 (97.5% CL = not reported)		p=0.28
Secondary outcome: Change from baseline in Daily rescue short acting SSA use Mean (SD)			
	Telotristat 250mg (n=45)	**Placebo (n=45)**	**Significance (p-value)**
Daily rescue short acting SSA use (injections per day (averaged over 12 weeks)	-0.11 (SD not reported)	0.18 (SD not reported)	not reported
Daily rescue short acting SSA use: Arithmetic mean treatment difference	Mean difference = -0.30 (SD not reported)		not reported
Daily rescue short acting SSA use: Hodges Lehmann estimator of treatment difference[a]	Estimated treatment effect = 0 (97.5% CL = not reported)		p=0.19
Secondary outcome: (Intention to treat analysis) Change from baseline in stool consistency Mean (SD)			
	Telotristat 250mg (n=45)	**Placebo (n=45)**	**Significance (p-value)**

Stool consistency: (points averaged over 12 weeks)	-0.26 (0.47)	-0.22 (0.48)	not reported
Stool consistency: Arithmetic mean treatment difference	Mean difference = -0.05 (SD not reported)		not reported
Stool consistency: Hodges Lehmann estimator[a]	Estimated treatment effect = -0.09 (97.5% CL = not reported)		p=0.57
Secondary outcome:(Intention to treat analysis) Urgency to defecate Mean (SD)			
	Telotristat 250mg (n=45)	**Placebo (n=45)**	**Significance (p-value)**
Urgency to defecate (Proportion of days)	0.67 (0.34)	0.75 (0.29)	not reported
Urgency to defecate: Arithmetic mean treatment difference	Mean difference = -0.09		not reported
Urgency to defecate: Hodges Lehmann estimator[a]	Estimated treatment effect = -0.02 (97.5% CL = not reported)		p=0.35
Safety during 12 week study period			
Discontinuations as a result of TEAE	3 participants (6.7%) of those receiving telotristat 250mg discontinued treatment due to a TEAE compared with 6 participants (13.3%) of those receiving placebo.		
Any TAEA	37 participants (82.2%) of those receiving telotristat 250mg reported any TEAE during the double blind study period compared with 39 participants (86.7%) of those receiving placebo.		
Adverse events relating to GI symptoms	The most commonly reported GI symptom related AE was abdominal pain (reported in 5 (11%) of people receiving telotristat 250mg and 8 (17.8%) of people receiving placebo. Nausea was also highly reported (in 6 (13.3%) of people receiving telotristat 250mg and 5 (11.1%) of people receiving placebo		
Adverse events:	Over the course of the study depressive symptoms were reported in 3 (6.7%) of people receiving telotristat 250mg and 3 (6.7%) of people receiving placebo.		

Depression cases	At study entry 8 out of 10 (80%) people in the telotristat 250mg group and 2 out of 6 (33%) of people receiving placebo reported a history of depression
Adverse events: Deaths	One death in a patient with advanced disease was reported in the telotristat 250mg group and 3 deaths of advance disease were reported in the placebo group.
Data shown as mean (SD), unless otherwise stated. CL Confidence limit BM: Bowel movement. EORTC European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30. GI Gastrointestinal; TEAE Treatment emergent adverse event [a] Hodges Lehmann estimator is a nonparametric measure taken as the median of all possible differences between groups and used to explain magnitude of treatment effect. For all 97.5%CLs reported in the estimated treatment effect, values were taken as reported in the EPAR [b]Responders were defined as participants having ≥ 30% reduction in BM frequency for ≥ 50% of the study period. Quality of life: For all domain scores (Global health status; Physical functioning; Emotional functioning; Cognitive functioning) a higher score indicates higher functional status. For all symptom scores a higher score indicates a less favourable outcome	

Table 12 Pavel et al. (2018)

	Telotristat 250mg (n=25)	Placebo (n=26)	Significance (P-value)
Primary outcome: (Intention to treat analysis) Change from baseline in u5-HIAA levels (%) at week 12 mean (SD)			
	n=17	n=22	
u5-HIAA levels: Percentage change from baseline at week 12 (mg/24h)	-33.16 (58.47)	97.72 (397.01)	
u5-HIAA levels: Arithmetic mean treatment difference	Mean difference = -130.88 (SD not reported)		
u5-HIAA levels: Hodges Lehmann estimator of treatment difference[a]	Estimated treatment effect Median = -53.95 (95%CL-85, -25.1)		p<0.001
Secondary outcome: (Intention to treat analysis) Absolute change from baseline in u5-HIAA levels at week 12 mean (95%CI)			
u5-HIAA levels: Absolute change from baseline at week 12 (mg/24h) Hodges Lehmann estimator of treatment difference[a]	-29.800 (SD not reported)		
Secondary outcome: Change from baseline in BM frequency (/day) mean (SD)			
Mean change in daily BM frequency (averaged over 12 weeks)	-0.45 (0.69)	0.05 (0.32)	
BM frequency: Arithmetic mean treatment difference	Mean difference = -0.50 (95%CL -0.81, -0.19)		
BM frequency: Hodges Lehmann estimator of treatment difference[a]	Estimated treatment effect Median = -0.45 (95%CL -0.72, -0.17)		p= 0.004

Secondary outcome: (Intention to treat analysis) **Number of participants who had meaningful treatment benefit with durable treatment response n (%)** **Responder analysis[b]**			
	Telotristat 250mg n=25	**Placebo n=25**	**Significance (p-value)**
Responders	10/25 (40)	0/25 (0)	p=0.001
Secondary outcome: (Responder analysis [b]) **Change from baseline in BM frequency at week 12 Mean (SD)**			
BM responders: (BM reduction) Mean proportion of days with ≥30% reduction in BMs/ day	0.43 (SD not reported)	0.15 (SD not reported)	
BM responders (BM reduction) Hodges Lehmann estimator[a]	Estimated treatment effect = 0.25 (95%CI 0.07, 0.44)		p<0.001
Secondary outcome: (Responder analysis [b]) Change from baseline in BM frequency Hazard Ratio (95%CI)			
BM non responders: (BM worsening ≥30%) time to occurrence	HR= 0.53 (95%CI 0.18, 1.41)		
Secondary outcome: (Intention to treat analysis) **Change from baseline in stool consistency Mean (SD)**			
	n=26	n=25	
Stool consistency: (points averaged over 12 weeks)	-0.19 (0.70)	0.01 (0.41)	
Stool consistency: Arithmetic mean treatment difference	Mean difference = -0.02 (95%CL -0.53, 0.13)		
Stool consistency: Hodges Lehmann estimator[a]	Estimated treatment effect Median = -0.20 (95%CL -0.45, 0.02)		p=0.09
Secondary outcome: (Intention to treat analysis) **Change from baseline in daily flushing episodes Mean (SD)**			
	n=26	n=25	
Cutaneous flushing:	-0.06 (0.98)	-0.33 (1.22)	

Change from baseline in daily cutaneous flushing episodes (averaged over 12 weeks)			
Cutaneous flushing: Arithmetic mean treatment difference	Mean difference = 0.27 (95%CL -0.36, 0.90)		
Cutaneous flushing: Hodges Lehmann estimator[a]	Estimated treatment effect Median = 0.11 (95%CL -0.17, 0.61)		p=0.67
Secondary outcome: Change from baseline in abdominal pain (Intention to treat analysis) Mean (SD)			
	n=26	n=25	
Abdominal pain: Change from baseline in abdominal pain (averaged over 12 weeks)	-0.06 (0.78)	-0.23 (0.97)	
Abdominal pain: Arithmetic mean treatment difference	Mean difference = -0.17 (95%CL -0.67, 0.33)		
Abdominal pain: Hodges Lehmann estimator[a]	Estimated treatment effect Median = 0.06 (95%CL -0.42, 0.33)		p=0.61
Secondary outcome: Change from baseline in rescue short acting SSA use (Intention to treat analysis) Mean (SD)			
	n=26	n=25	
Rescue short acting SSA use: Change from baseline in abdominal	-0.07 (0.35)	-0.01 (0.14)	

pain (averaged over 12 weeks)			
Rescue short acting SSA use: Arithmetic mean treatment difference	Mean difference = -0.05 (95%CL -0.20, 0.10)		
Rescue short acting SSA use: Hodges Lehmann estimator[a]	Estimated treatment effect Median = 0.00 (95%CL 0.00, 0.00)		p=0.45
Primary outcome: Safety and tolerability			
All participants (100%) receiving 250mg telotristat and 21 out of 26 participants (80.8%) reported any TEAE. 1 out of 25 participants (4.0%) receiving 250mg telotristat and 5 out of 26 participants (19.2%) receiving placebo reported a serious adverse event over the 12 week period. 1 participant (4.0%) receiving 250mg telotristat and 2 (7.7%) participants receiving placebo reported a mild depressed mood 2 out of 25 participants (8.0%) receiving 250mg telotristat and 1 participant (3.8%) receiving placebo discontinued treatment due to an adverse event (for upper abdominal pain and diarrhoea, and for malignant neoplasm progression, respectively). 16 out of 25 (64%) of participants receiving telotristat 250mg and 15 out of 25 (57.7%) of those receiving placebo reported a gastro-intestinal TEAE. In participants receiving telotristat 250mg, abdominal pain was the most reported with 8 participants (32%) experiencing compared with 4 (15.4%) receiving placebo. 4 people (16%) receiving telotristat 250mg experienced diarrhoea compared with 5 (19.2%) receiving placebo; 4 people receiving telotristat 250mg reported constipation compared with 1 (3.6%) receiving placebo and 3 participants (12%) receiving telotristat 250mg reported nausea compared with 4 (15.4%) receiving placebo There were no TEAEs resulting in death			
Data shown as mean (SD), unless otherwise stated. CL Confidence limit BM: Bowel movement. HR Hazard ratio TEAE Treatment emergent adverse event [a] Hodges Lehmann estimator is a nonparametric measure taken as the median of all possible differences between groups and used to explain magnitude of treatment effect [b]Responders were defined as participants having ≥ 30% reduction in BM frequency for ≥ 50% of the study period.			

Table 13 Kulke et al. (2014)

Primary outcome: Safety and tolerability				
18 out of 18 participants (100%) receiving any dose of telotristat and 4 out of 5 participants (80%) receiving placebo reported at least one treatment emergent adverse event. All 3 participants (100%) receiving 250mg dose of telotristat reported any treatment emergent adverse event 2 out of 18 participants receiving any dose of telotristat for which one person discontinued treatment and no participants receiving placebo reported at least one serious adverse event No participants receiving 250mg dose reported a serious adverse event No participants receiving any dose of telotristat and no participants receiving placebo reported depression				
Secondary outcome: Mean change in daily BM frequency at week 4				
At baseline, the mean daily BM frequency for participants receiving any dose of telotristat was 6.3 BMs (range 4 to 10) at end point this had reduced in frequency by a mean change of -1.2 BMs per day For people receiving the 250mg dose of telotristat the baseline mean value was 6.9 BMs (range 5 to 9) at end point this had reduced by a mean change of -2.2 BMs per day For people receiving placebo the baseline mean value was 5.3 BMs (range 4 to 8) at endpoint this had increased by a mean change of 0.8 BMs per day				
Secondary outcome: (Responder analysis [b]) **Number of participants who had meaningful treatment benefit with durable BM treatment response n (%)**				
N=23	**Telotristat (250mg) (n=3)**	**Telotristat pooled value**	**Placebo n=5**	
Responders	2/3 (67)	5/18 (28)	0/5 (0)	
Secondary outcome (Responder analysis) **Number of participants who had meaningful treatment benefit with durable biochemical response (u5-HIAA levels) n (%)**				
u5-HIAA levels: (biochemical responders at week 2or week 4)	1/3 (33)	9/16 (56)	0/5 (0)	

Secondary outcome: **Patient reported adequate relief n (%)**				
Number of participants reporting adequate relief at week 4	2/3 (67)	6/13 (46)	0/4 (0)	
Secondary outcome : Stool consistency				
No clear differences reported – exact values not reported				
Secondary outcome : Urgency to defecate				
No clear differences reported – exact values not reported				
Secondary outcome : flushing episodes				
No clear differences reported – exact values not reported				
Secondary outcome : Abdominal pain				
No clear differences reported – exact values not reported				
Data shown as mean ±SD, unless otherwise stated. CL Confidence limit BM: Bowel movement. [a] Hodges Lehmann estimator is a nonparametric measure taken as the median of all possible differences between groups and used to explain magnitude of treatment effect [b]Responders were defined as participants having ≥ 30% reduction in BM frequency for ≥ 50% of the study period. [c]Pooled results are based on participants in the treatment group receiving one dose of telotristat (150mg up to 500mg) three times per day				

Table 14 Pavel et al. (2015)

Primary outcome: Mean change in BM frequency at week 11 to 12 (Least squares mean LSM analysis)
At baseline, the mean daily BM frequency was 5.88 (95%CI = 4.0, 8.5), at endpoint this had decreased by a reported mean value of -2.57 (95%CI -3.20, -1.95) BMs per day (43.5% difference ; p<0.001)
Secondary outcome: Mean change in daily stool form at week 11 to 12 (Least squares mean LSM analysis)
At baseline, mean stool form was graded as 4.09 (approximately loose) with 8 participants (53%) reporting a loose stool form (graded as ≥4), at end point this had decreased by 0.8 points to a mean grade of 3.30 (soft) 19.5% reduction (p<0.001)
Secondary outcome: Mean percentage change from baseline in u5-HIAA levels at week 11 to 12 (Least squares mean LSM analysis)
At baseline mean u5-HIAA values were 121.8mg/ 24 hours (range 4.6 to 500mg/24 hours) at endpoint the mean reduction in u5-HIAA levels was 74.2% (p<0.05)
Secondary outcome: Number of people reporting adequate relief of CS symptoms at week 11 to 12 (Least squares mean LSM analysis)
At baseline the number of participants reporting adequate relief was 2 participants (15%) at week 11-12 this had increased to 9 participants (75%)
Secondary outcome: Mean change in number of flushing episodes per day at week 11 to 12 (Least squares mean LSM analysis)
At baseline the mean number of flushing episodes per day was reported as 2.78 (95%CI 0, 11.4) at endpoint this had decreased by a mean value of -0.75 (95%CI -1.46, -0.03) (27% reduction; p= 0.04)
Secondary outcome: Mean change in patients reported severity of abdominal pain (VAS) at week 11 to 12 (Least squares mean LSM analysis)
At baseline, the mean VAS for abdominal pain severity was 28.31. At week 11 to 12 this had decreased by a mean value of -8.23 VAS (95%CI 16.82, 0.36) points (29% reduction, p=0.06)
Secondary outcome: Mean change in reported sense of urgency at week 11 to 12 (Least squares mean LSM analysis)
At baseline the mean value of reported sense of urgency was 0.94. At week 11 to 12 this value had reduced by a value of -0.03 (95%CI -0.16, 0.11, p=0.71)
Safety and tolerability: Number of reported adverse events during study period
Over the course of the study period 7 participants (46.7%) had AEs considered by study investigators to be related to the study drug. All participants reported at least one treatment emergent adverse event during the study. Gastro intestinal disorders were the most common reported with 10 (66.7%) participants reporting either abdominal pain n=7; 46.7%), diarrhoea (n=3, 20%), flatulence (n=2, 13.3%), vomiting, (n=2, 13.3%), nausea (n=2, 13.3%) during the course of the study. There were no reported episodes of depression and no reports of constipation during the study.
Data shown as mean ±SD, unless otherwise stated. CL Confidence limit BM: Bowel movement. VAS Visual analogue scale [a] Hodges Lehmann estimator is a nonparametric measure taken as the median of all possible differences between groups and used to explain magnitude of treatment effect

[b] Responders were defined as participants having ≥ 30% reduction in BM frequency for ≥ 50% of the study period. [c] Pooled results are based on participants in the treatment group receiving one dose of telotristat (150mg up to 500mg) three times per day

Table 15 Gelhorn et al. (2016)

Primary outcome: Patient reported change in CS symptoms
All participants reported experience of diarrhoea, however 9 participants (82%) reported an improvement during participation in the study. All participants reported abdominal pain with 5 (45%) reporting improvement during study period. Six participants (55%) reported abdominal pain, with 4 participants (36%) reporting improvement. Nine participants (82%) reported flushing with 4 (36%) reporting improvement during study period. Five participants reported experience of wheezing although no one reported experiencing an improvement during the study period.
Secondary outcome: Quality of life outcomes as reported in EORTC-QLQ-C30 and GI.NET-21
Participants reported lower QOL and general functioning compared with the general population (mean global health status 56.7 compared with general population reference value of 71.2; mean physical functioning value 82.7 compared with reference value 89.8; mean role functioning value 71.7 compared with reference value 84.7 ; mean emotional functioning 80.0 compared with reference value 76.3) The highest reported symptom was diarrhoea (mean value 70.0 compared with reference value 7.0); fatigue (mean value 48.9 compared with reference value 24.1); and insomnia (mean value 36.7 compared with reference value 21.8) Scores on all of the subscales of the GI.NET-21 were less than the mean (50%) indicating lower response level (higher scores indicated worse symptoms or problems)
EORTC European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 a 30 item self-report questionnaire assessing quality of life of people with cancer. GI.NET-21is a 21 item self-report questionnaire supplemental to EORTC QLQ: C30.

Table 16 Anthony et al. (2017)

Primary outcome: Patient reported change in CS symptoms
Of the 25 participants completing the interview and reporting CS symptom improvement 7 out of the 10 participants receiving telotristat 250mg compared with 4 out of the 9 participants receiving placebo reported improvements in their CS symptoms. Participants stated the 3 most important symptoms to treat were reported as diarrhoea (n=17), BM frequency (n=9), and urgency to defecate (n=5), and 29 out of the 35 people (83%) completing the interview reported BM frequency as more important to treat than stool form. The most frequently reported negative effects of CS symptoms were in social and physical activities with 28 (80%) of the 35 people interviewed reporting these as negative effects. This was followed by emotional symptoms (reported by 24 people (69%) and decreased energy (reported by 21 participants (60%). 21 out of the 25 participants reported meaningful improvement. Out of these 21 reports, the most reported improvement was in BMs with 7 participants receiving telotristat 250mg compared with 4 participants receiving placebo reporting improvement. The remaining participants reporting improvement received the 500mg dose. 20 out of 21 participants (95%) reported reduced BM frequency, with 7 participants receiving 250mg reporting a meaningful reduction, compared with 3 participants receiving placebo.
BM: Bowel movement. CS: Carcinoid syndrome

Appendix 5 Grading of the evidence base

NHS England has requested that NICE use the following system for grading the evidence.

Each study is assigned one of the following codes:

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	Criteria
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.