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CADTH COMMON DRUG REVIEW

Clinical Review Report

TELOTRISTAT (XERMELO)

(Ipsen Biopharmaceuticals Canada Inc.)

Indication: For the treatment of refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients inadequately controlled by SSA therapy alone

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
BSFS	Bristol Stool Form Scale
CDR	CADTH Common Drug Review
CI	confidence interval
DB	double blind
DBT	double-blind treatment
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HRQoL	health-related quality of life
ITT	Intention to treat
MCID	minimal clinically important difference
NET	neuroendocrine tumour
QLQ-GINET21	21-item gastrointestinal neuroendocrine tumour–specific quality-of-life questionnaire
QoL	quality of life
RCT	randomized controlled trial
SSA	somatostatin analogue
ULN	upper limit of normal

Drug	Telotristat ethyl (Xermelo)
Indication	Indicated for the treatment of refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients inadequately controlled by SSA therapy alone.
Reimbursement Request	As per indication
Dosage Form(s)	Tablets
NOC Date	October 12, 2018
Manufacturer	Ipsen Biopharmaceuticals Canada Inc.

Executive Summary

Introduction

Carcinoid syndrome occurs due to the release of various factors from a neuroendocrine tumour, including serotonin, histamine, bradykinin, prostaglandins, and tachykinins. The symptoms associated with carcinoid syndrome, many a direct result of the release of these preceding factors, include diarrhea, abdominal pain, flushing, wheezing, and cardiac valve disease.[1] In addition to serotonin, all of the preceding factors may contribute to the carcinoid syndrome diarrhea; however, other symptoms like flushing are more associated with histamine and bradykinin. Serotonin and the other mediator cause a secretory form of diarrhea, binding to serotonin receptors and stimulating chloride channels to release potassium chloride and sodium chloride. According to the Canadian Cancer Society, specific cancer statistics are not reported for neuroendocrine tumours, as these numbers are most often included with the statistics for the tissue where the tumour originates (i.e., gastrointestinal neuroendocrine tumours are included with gastrointestinal cancers).[2] The Carcinoid Neuroendocrine Tumour Society (CNETS) Canada website suggests that approximately 12,000 to 15,000 Canadians have neuroendocrine tumours, the most common varieties being lung, pancreatic, and gastrointestinal.[3] The guidelines for neuroendocrine tumours suggest that the incidence has more than doubled in the past 15 years.[4] Most of these neuroendocrine tumours present as benign or become metastatic and, in these patients, the mean survival is approximately three years.[4]

Carcinoid syndrome diarrhea has traditionally been managed with somatostatin analogues, most commonly octreotide. These drugs inhibit the release of gastrointestinal hormones from carcinoid tumours and inhibit their growth. Resistance to somatostatin analogues can occur within three months of initiating therapy. The most common approach for those patients with resistant disease is to remove the tumour mass from the liver through surgery. Other options for managing these patients are hepatic artery occlusion and chemotherapy and surgical measures to reduce the size of the tumour. Antidiarrheals like loperamide may also be used to manage diarrhea; however, evidence for their efficacy is lacking.

Telotristat is a tryptophan hydroxylase inhibitor. Tryptophan hydroxylase is the rate-limiting enzyme involved in serotonin synthesis; thus, telotristat reduces serotonin levels. It is administered orally, 250 mg three times daily, and is officially indicated for the treatment of refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients whose condition is inadequately controlled by SSA therapy alone.[5]

The objective of this report is to perform a systematic review of the beneficial and harmful effects of telotristat ethyl for the treatment of refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients whose disease inadequately controlled by SSA therapy alone.

Results and Interpretation

Included Studies

One manufacturer-sponsored multi-centre double-blind randomized controlled trial (RCT) met the inclusion criteria for this systematic review. TELESTAR compared two doses of telotristat (250 mg or 500 mg three times daily) with placebo in 135 patients with diarrhea associated with carcinoid syndrome who were on a stable dose of somatostatin analogues. The initial double-blind treatment period was 12 weeks and patients were randomized 1:1:1 between groups. The primary outcome was the mean change from baseline in number of daily bowel movements, compiled over the 12-week double-blind treatment period. Secondary outcomes, which were adjusted for multiple comparisons, included the change from baseline in urinary 5-hydroxyindoleacetic acid (5-HIAA) levels, as well as change in symptoms of flushing and symptoms of abdominal pain, tested in that order. Only data for the approved telotristat 250 mg dose are reported in this review. An open-label and long-term study extension of 36 weeks was also available to patients enrolled in TELESTAR, and the data from these studies are included in Appendix 7.

Patients in TELESTAR were 63 years old, on average, and the majority were Caucasian with an equal percentage of males and of females. Most were taking octreotide as their somatostatin analogue, and 58% had a urinary 5-HIAA above the upper limit of normal.

Key critical appraisal issues included a difference in baseline bowel movements between comparison groups of 0.8 per day, possibly suggesting a difference in baseline severity of their condition and an imbalance at randomization. Although multiplicity was adjusted for by using a hierarchical testing procedure, no health-related quality-of-life outcomes were included in the hierarchy and, thus, were not adjusted for multiple comparisons. There were more withdrawals in the placebo group than with telotristat, and these were largely attributed to withdrawals due to adverse events. For the change from baseline in urinary 5-HIAA outcome, or the health-related quality-of-life outcomes, an intention-to-treat (ITT) analysis was not performed. Diaries were used to collect data for most of the key outcomes in TELESTAR; however, there appeared to be an assumption that missing data were missing at random, and this may not be an appropriate assumption to make. Given that telotristat employs a novel mechanism of action and modulates a critical neurotransmitter, serotonin, for many processes within and outside the central nervous system, TELESTAR was a relatively small and short-term study for evaluating the potential harms associated with this new drug.

Efficacy

In TELESTAR, the reduction in the number of daily bowel movements from baseline compiled over the 12-week treatment period with telotristat versus placebo was 0.812 (97.5% confidence interval [CI], −1.256 to −0.280; $P < 0.001$). A sensitivity analysis performed on the per-protocol populations yielded results that were consistent with the primary analysis. Nevertheless, this was a relatively modest treatment effect, particularly given that patients began the study averaging 5 to 6 bowel movements daily, according to the clinical expert consulted by the CADTH Common Drug Review (CDR) for this review.

The manufacturer also reported a responder analysis, an exploratory outcome, which examined the percentage of patients who had at least a 30% reduction from baseline in bowel movements for at least 50% of the 12-week double-blind treatment period. There was a higher percentage of responders in the telotristat group versus placebo (44% versus 20%); however, once again, this was an exploratory outcome and not adjusted for multiple comparisons, thus increasing risk of type I error.

There were no statistically significant differences between telotristat and placebo for daily flushing episodes or episodes of abdominal pain over the 12-week double-blind treatment period. These were both secondary outcomes in this study; thus, statistical analysis was adjusted for multiple comparisons. The Hodges–Lehmann estimate of treatment difference between groups was 0.036 counts per day (97.5% confidence limit, −0.230 to 0.330; $P = 0.39$) for flushing episodes and −0.168 (97.5% confidence limit, −0.541 to 0.224) for abdominal pain scores. Quality of bowel movements was assessed by stool consistency using the Bristol Stool Form Scale. Across the 12-week double-blind treatment period in TELESTAR, stool consistency scores decreased in the telotristat group (mean [standard deviation] [SD] change from baseline of −0.265 [0.4712]) and in the placebo group (−0.216 [0.4791] for a Hodges–Lehmann estimate of the difference between groups of −0.087 [95% CI, −0.268 to 0.110; $P = 0.57$]). This was an exploratory analysis and no minimal clinically important difference (MCID) could be found, so the clinical significance is unclear.

Health-related quality of life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30) and the EORTC QLQ-GINET21, a 21-item gastrointestinal neuroendocrine tumour–specific quality-of-life questionnaire, as exploratory outcomes; both were averaged over weeks 6 and 12 and reported at week 6 and week 12 separately. There were no statistically significant differences between telotristat and placebo for a majority of subscales. None of the HRQoL scores were adjusted for multiple comparisons; thus, no conclusions should be drawn regarding subscales that were reported as statistically significant. This represents an important gap in knowledge about this drug, given the major HRQoL issues faced by patients who suffer from this condition.

There was a statistically significant reduction in urinary 5-hydroxyindoleacetic acid (5-HIAA) in the telotristat group compared with placebo at week 12 (Hodges–Lehmann estimate of treatment difference of −30.100 [97.5% CI, −55.800 to −9.200; $P < 0.001$]). This was the first secondary outcome in the statistical hierarchy; therefore, it was adjusted for multiple comparisons. This reduction from baseline was considered to be clinically significant by the clinical expert consulted on this review.

Data from a long-term safety extension (TELEPATH) were also available and are summarized in Appendix 7. There were very few (N = 10) patients in the extension on the approved 250 mg dose, and there was no longer a placebo comparator; therefore, this study provides little additional information regarding the long-term efficacy of telotristat.

Harms

There was one death in the telotristat group versus three deaths in the placebo group. Serious adverse events occurred in 16% of patients in each group.

Adverse events occurred in 82% of telotristat patients versus 87% of placebo patients after 12 weeks. The most common adverse events were nausea (13% for telotristat versus 11% for placebo), and abdominal pain (11% versus 18%).

Withdrawals due to adverse events occurred in 4% of telotristat versus 16% of placebo patients.

Notable harms included depression, which occurred in 4% of patients in the telotristat group and 7% of patients in the placebo group, and constipation (zero in the telotristat group and 4% with placebo). Depression is noted in the warnings in the product monograph, as there is evidence of an increased risk of depression at the higher telotristat 500 mg dose (not reported in this review); however, the lower approved dose does not appear to be linked with depression in this 12-week study. Elevated liver enzymes occurred only in telotristat patients (alanine aminotransferase [ALT] increased 2% versus zero, and gamma-glutamyltransferase [GGT] increased 9% versus zero), and no patients had increased alkaline phosphatase (ALP).

Potential Place in Therapy[1]

Based on currently available therapies and standards of care for patients with metastatic neuroendocrine tumours with refractory diarrhea in the setting of carcinoid syndrome related to serotonin excess, there is an unmet need for diarrhea control.

Standard first-line therapy with SSAs, including lanreotide at 120 mg per dose monthly, and octreotide long-acting release (LAR) formulation at 30 mg or 60 mg monthly, is the first-line treatment option for disease control and diarrhea control. Patients started on octreotide LAR 30 mg with progression or refractory diarrhea should be titrated to 60 mg monthly, as there is evidence that this dose provides benefits in terms of both progression and symptom control. Also, in patients with poor control of diarrhea, there is a need for additional drugs to be given concurrently with SSAs.

Other drugs that have been used with no clear evidence for their use in this population without randomized trials to assess benefit include loperamide and diphenoxylate/atropine (Lomotil). The use of telotristat in this refractory-disease population does decrease the frequency of diarrhea when provided in conjunction with SSAs and could be considered for this setting.

Patients on SSA at the standard dose with lanreotide or higher-dose octreotide LAR without control of diarrheal symptoms with six or more bowel movement per day or reported poor quality of life due to diarrheal symptoms could be offered telotristat for improvement in control. Testing with 24-hour urinary 5-HIAA to demonstrate excess is advised (with appropriate dietary modifications prior to testing and avoidance of proton pump–inhibitor therapy). This test is part of the testing done during the initial assessment of patients with neuroendocrine tumours; thus, it does not generally increase the cost of care provided or pose a barrier to identifying patients.

Conclusions

One manufacturer-sponsored multinational double-blind RCT was included in this review. TELESTAR compared two different doses of telotristat (250 mg and 500 mg three times daily) with placebo over the 12-week double-blind treatment period in a population of patients with at least four bowel movements daily while on a stable dose of SSAs. Results for the approved 250 mg dose are reported in this review. Telotristat was superior to placebo for the primary outcome: reduction in mean daily bowel movements. The reduction

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

versus placebo was less than one bowel movement per day, and the clinical meaningfulness of this to a patient with carcinoid syndrome–associated diarrhea is unknown. Although telotristat reduced urinary 5-HIAA versus placebo, it did not improve symptoms associated with carcinoid syndrome, namely, abdominal pain and flushing. Telotristat also failed to improve the symptoms of importance to patients that are associated with diarrhea, such as urgency, and did not improve a variety of HRQoL subscales associated with this condition (fatigue, body image, pain, impact on finances, and social/cognitive functioning). With respect to harms, there were no clear differences between telotristat and placebo with respect to notable adverse events such as depression or constipation. There was an indication of an increase in hepatic enzymes with telotristat versus placebo.

Table 1: Summary of Results

	TELESTAR	
	TST 250 N = 45	Placebo N = 45
Frequency of BM		
Average number of daily BMs at baseline mean (SD)	6.085 (2.0703)	5.200 (1.3500)
Mean (SD) change from baseline in number of BMs averaged over the DBT period	−1.433 (1.3652) N = 45	−0.623 (0.8275) N = 45
HLE of treatment difference, TST minus placebo (97.5% CI) [a]	−0.812 (−1.256, −0.280) *P* < 0.001	
Adjusted rate, counts/day (95% CI)	4.098 (3.795 to 4.424)	4.656 (4.307 to 5.033)
[redacted]	[redacted]	
Quality of BM		
Mean (SD) baseline stool consistency	5.934 (0.5031)	5.917 (0.6993)
Mean (SD) Change from baseline in stool consistency averaged across all time points	−0.265 (0.4712) N = 45	−0.216 (0.4791) N = 45
HLE of treatment difference, TST minus placebo (95% CI) [a]	−0.087 (−0.268 to 0.110) *P* = 0.57	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
Symptoms		
FLUSHING		
Mean (SD) weekly cutaneous flushing episodes (counts/day) at baseline	2.788 (3.7362)	1.791 (1.9344)
Mean (SD) change from baseline in number of daily cutaneous flushing episodes averaged across all time points during DBT period	−0.296 (1.3097) N = 45	−0.164 (1.1572) N = 45
[redacted]	[redacted]	[redacted]
HLE of treatment difference, TST minus placebo (97.5% CL) [a]	0.036 (−0.230 to 0.330) *P* = 0.39	
ABDOMINAL PAIN		
Mean (SD) weekly abdominal pain (11-point numeric rating scale) at baseline	2.615 (2.2657)	2.473 (2.3201)
Mean (SD) change from baseline in abdominal pain	−0.490 (1.4423)	−0.226 (1.1601)

	TELESTAR	
	TST 250 N = 45	Placebo N = 45
averaged across all time points during DBT period	N = 45	N = 45
[redacted]	[redacted]	[redacted]
HLE of treatment difference, TST minus placebo (97.5% CL)[a]	−0.168 (−0.541 to 0.224) *P* = 0.26	
Durability of Response		
Patients with durable response, n (%)	20 (44.4)	9 (20.0)
Primary analysis odds ratio, TST/placebo (95% CI)[d]	3.49 (1.33 to 9.16) *P* = 0.011	
Urgency		
Mean (SD) proportion of days where urgency/immediate need to defecate	0.664 (0.3431) N = 45	0.753 (0.2932) N = 45
HLE of treatment difference, TST minus placebo (95% CI)[a]	−0.024 (−0.158 to 0.021) *P* = 0.35	
Biomarkers		
Baseline urinary 5-HIAA levels, mg/24 hours, mean (SD)	92.645 (114.8958) N = 42	80.968 (161.0143) N = 44
Change from baseline in urinary 5-HIAA levels, mg/24 hours at week 12, mean (SD)	−40.134 (84.7663) N = 32	11.350 (35.0346) N = 30
Median change from baseline to week 12 (min, max)	−21.650 (−458.60 to 77.20)	1.550 (−35.80 to 155.00)
HLE of treatment difference, TST minus placebo (97.5% CI)[a]	−30.100 (−55.800 to −9.200) *P* < 0.001	
Harms		
Patients with an adverse event, n (%)	37 (82.2)	39 (86.7)
Patients with a serious adverse event, n (%)	7 (15.6)	7 (15.6)

5-HIAA = 5-hydroxyindoleacetic acid; BM = bowel movement; CI = confidence interval; CL = confidence limit; DBT = double-blind treatment; [redacted] GI = gastrointestinal; HLE = Hodges–Lehmann estimate; [redacted] LS = least squares; MD = mean difference; [redacted]; SD = standard deviation; TST = telotristat; ULN = upper limit of normal.

Source: Clinical Study Report.[6]

[a] The primary analysis used a blocked two-sample Wilcoxon rank sum statistic (i.e., van Elteren test) stratified by the urinary 5-HIAA levels at randomization.

[b] The supplemental analysis used a generalized linear model based on the negative binomial distribution. The model included the number of BMs per day as the dependent variable and included treatment group and urinary 5-HIAA stratification at randomization as fixed effects, and the baseline number of BMs as a fixed covariate. The natural log value of the number of days with non-missing diary data were used as an offset term to adjust for variable number of days.

[c] The supplemental analysis used a mixed model with repeated measurements. The model uses the change from baseline in each scale score as the dependent variable and includes treatment group, urinary 5-HIAA stratification at randomization, time and treatment-by-time interaction as fixed effects, baseline score as a covariate and patient as a random effect. An unstructured (general) covariance matrix is used to model the within-subject errors. The Kenward–Roger approximation is used to estimate the denominator degrees of freedom.

[d] The primary analysis used a logistic regression model with responder as the dependent variable, treatment group and urinary 5-HIAA stratification at randomization as fixed effects, and baseline mean number of BMs (counts per day) as a covariate. The *P* value was calculated based on a continuity-adjusted chi-square test. “Durable response” was defined as a ≥ 30% reduction in the number of BMs per day for ≥ 50% of time over the DBT period.

Introduction

Disease Prevalence and Incidence

Carcinoid syndrome occurs due to the release of various factors from the tumour, including serotonin, histamine, bradykinin, prostaglandins, and tachykinins. Although many of the tumours originate somewhere in the gut, a large percentage metastasize to the liver at some point. The symptoms associated with carcinoid syndrome, many a direct result of the release of these factors, include diarrhea, abdominal pain, flushing, wheezing and cardiac valve disease.[4] In addition to serotonin, all of the preceding factors may contribute to the carcinoid syndrome diarrhea; however, other symptoms like flushing are more associated with histamine and bradykinin. Serotonin and the other mediator cause a secretory form of diarrhea, binding to serotonin receptors and stimulating chloride channels to release potassium chloride and sodium chloride. According to the Canadian Cancer Society, specific cancer statistics are not reported for neuroendocrine tumours, as these numbers are most often included with the statistics for the tissue where the tumour originates (i.e., gastrointestinal neuroendocrine tumours are included with gastrointestinal cancers).[2] The Carcinoid Neuroendocrine Tumour Society (CNETS) Canada website suggests that approximately 12,000 to 15,000 Canadians have neuroendocrine tumours, the most common varieties being lung, pancreatic, and gastrointestinal.[3] Of these, there are varying estimates as to how many will exhibit carcinoid syndrome. These estimates range from 7% to 35% of patients with neuroendocrine tumours.[7] The guidelines for neuroendocrine tumours suggest that incidence has more than doubled in the past 15 years. Most of these neuroendocrine tumours present as tumours or become metastatic and, in these patients, the mean survival is approximately three years.[4]

Standards of Therapy

Carcinoid syndrome diarrhea has traditionally been managed with somatostatin analogues (SSAs), most commonly, octreotide. These drugs inhibit the release of gastrointestinal hormones from carcinoid tumours and inhibit their growth.[8,9] Resistance to SSAs can occur, and a common approach for those patients with resistant disease is to remove the tumour mass from the liver through surgery. Other options for managing these patients are hepatic artery occlusion, and chemotherapy and surgical measures to reduce the size of the tumour.[4]

Drug

Telotristat is a tryptophan hydroxylase inhibitor. Tryptophan hydroxylase is the rate-limiting enzyme involved in serotonin synthesis; thus, telotristat reduces serotonin levels. It is administered orally, 250 mg three times daily, and is officially indicated for the treatment of refractory carcinoid syndrome diarrhea, in combination with SSA therapy, in patients whose condition is inadequately controlled by SSA therapy alone.[5]

Table 2: Key Characteristics of Telotristat and Somatostatin Analogues

	Telotristat	Octreotide	Lanreotide
Mechanism of Action	Inhibits tryptophan hydroxylase, an enzyme that produces serotonin. Thus, telotristat reduces serotonin.	An analogue of somatostatin; inhibits release of peptides and serotonin produced within the gastroenteropancreatic endocrine system.	An analogue of somatostatin; inhibits release of peptides and serotonin produced within the gastroenteropancreatic endocrine system.
Indication[a]	For treatment of refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients inadequately controlled by SSA therapy alone.	Indicated for the symptomatic treatment of metastatic carcinoid tumours where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.	Treatment of adult patients with carcinoid syndrome. Treatment of enteropancreatic neuroendocrine tumours in adults with grade 1 or a subset of grade 2 unresectable, locally advanced or metastatic disease, to delay progression.
Route of Administration	Oral	Subcutaneous or intramuscular injection	Subcutaneous injection
Recommended Dose	250 mg three times daily	Immediate release: • 100 mcg to 600 mcg daily, divided into two to four doses daily Long-acting: • Maintain: 20 mg every 4 weeks • Symptoms not controlled: 30 mg every 4 weeks	Four-week cycles: 120 mg weekly
Serious Side Effects / Safety Issues		• Hypo- or hyperglycemia • Hypothyroidism • Cardiac conduction abnormalities • Impaired gall bladder function • Fat malabsorption	• Hypo- or hyperglycemia • Hypothyroidism • Cardiac conduction abnormalities • Impaired gall bladder function • Fat malabsorption

[a] Health Canada–approved indication.

Sources: Product monographs for telotristat[5], octreotide, lanreotide.[8,9]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of telotristat ethyl for the treatment of refractory carcinoid syndrome diarrhea, in combination with SSA therapy, in patients whose condition is inadequately controlled by SSA therapy alone.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Patients (18 years of age or older) with refractory carcinoid syndrome diarrhea that is inadequately controlled by somatostatin analogue therapy alone. Subgroups: • Frequency of bowel movements at baseline • Age (adults versus elderly) • SSA dose at baseline
Intervention	Telotristat ethyl 250 mg orally three times daily, as an adjunct to SSA therapy

Comparators	• SSAs
	• In combination SSA therapy:
	  ○ interferon-alpha
	  ○ loperamide
	  ○ diphenoxylate
	  ○ placebo

Outcomes	**Efficacy outcomes:** • frequency of bowel movements[a] • quality of bowel movements • health-related quality of life[a] • symptoms (e.g., abdominal pain, fatigue, flushing, urgency, episodes of fecal incontinence)[a] • response rate • durability of response • productivity • health care resource utilization • biomarkers (e.g., serotonin levels) **Harms outcomes:** • mortality, AEs, SAEs, WDAEs, AEs of special interest (e.g., constipation, elevation in liver enzymes, depression)
Study Design	Published and unpublished phase III and IV RCTs

AE = adverse event; RCT = randomized controlled trial; SAE = serious adverse event; SSA = somatostatin analogue; WDAE = withdrawal due to adverse events.

[a] Outcomes identified as important to patients in input provided to CDR.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid; Embase (1974–) through Ovid; and PubMed. The

search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Xermelo (telotristat).

No methodological filters were applied to limit retrieval to study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on October 24, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on February 20, 2019. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies**,** health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings**,** drug class reviews and databases. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4, excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Table 10.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

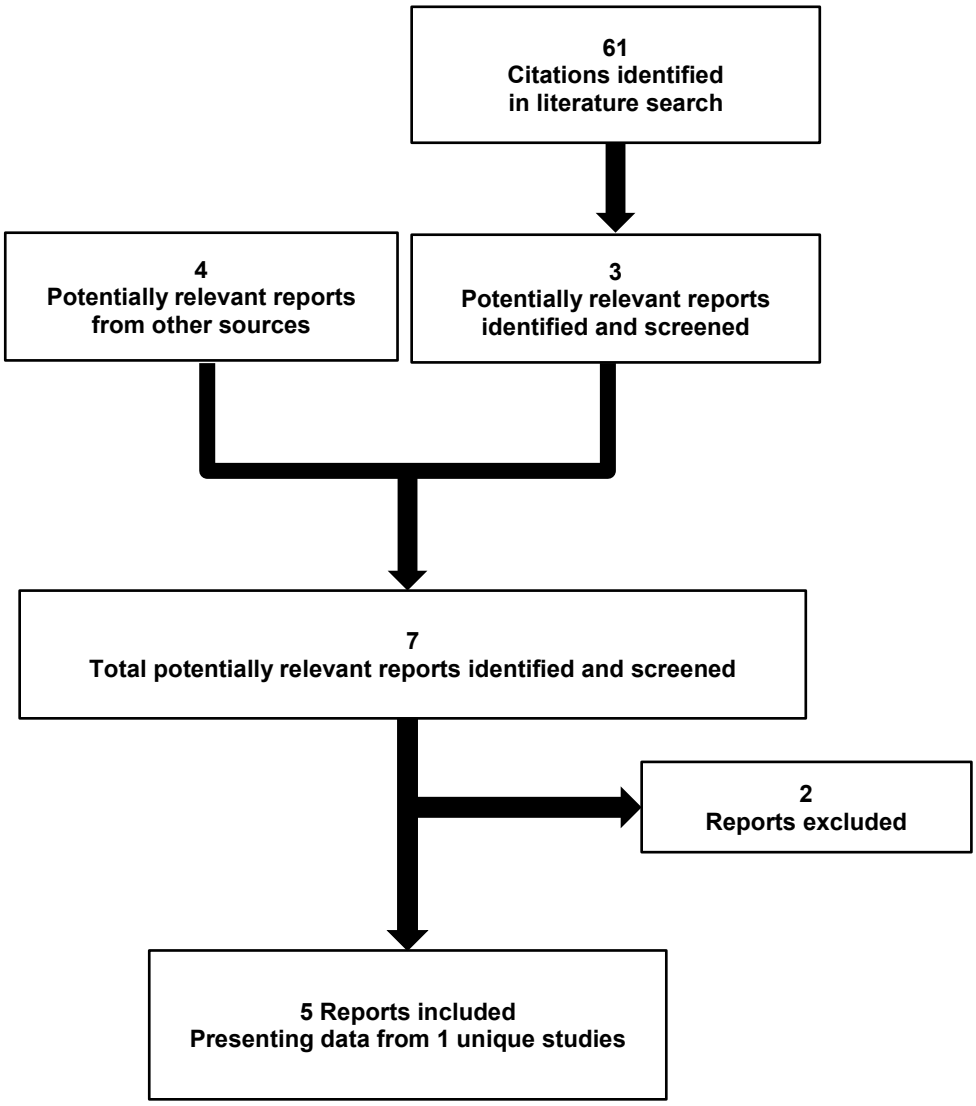


Table 4: Details of Included Studies

		TELESTAR
Designs and Populations	**Study Design**	DB RCT
	Locations	48 sites: Canada, US, EU, Israel, Australia
	Randomized (N)	136
	Inclusion Criteria	• Patients ≥ 18 years of age. • Histopathologically confirmed, well differentiated, metastatic NET with extent documented by CT, MRI, or radionuclide imaging. • Documented history of CS, mean ≥ 4 BMs/day during run-in. • Currently on stable-dose SSA therapy, defined as LAR or depot SSA therapy or a continuous subcutaneous infusion via a pump at the same dose level and frequency for at least 3 months before entering run-in. • Minimum dose of LAR or depot SSA therapy (higher dose[s] or more frequent intervals fulfilled the minimum dose requirement). SSA therapy must have been approved for use in CS in the patient's country of residence or prescriber's country of practice: • octreotide LAR at 30 mg every 4 weeks, or • lanreotide depot at 120 mg every 4 weeks, or • patients who could not tolerate SSA therapy at a level indicated in the preceding bullets were allowed to enter at their highest tolerated dose.
	Exclusion Criteria	• Diarrhea attributed to any condition(s) other than CS (including, but not limited to, fat malabsorption or bile acid malabsorption) • Presence of more than 12 watery BMs/day associated with volume contraction, dehydration, or hypotension compatible with a "pancreatic cholera"-type clinical syndrome, as judged by the investigator • Positive stool examination for enteric pathogens, pathogenic ova or parasites, or *Clostridium difficile* at screening • Karnofsky performance status ≤ 60% • Abnormal clinical laboratory values for hematology, kidney, or liver function • Treatment with any tumour-directed therapy < 4 weeks before screening or hepatic embolization, radiotherapy, radio-labelled SSA, and/or tumour debulking < 12 weeks before screening • Major surgery within 8 weeks before screening visit • History of short bowel syndrome • Pregnant or nursing (lactating) women • Life expectancy < 12 months from the screening visit • Presence of any clinically significant findings at screening medical history, or physical examination (relative to patient population) that would have compromised patient safety or the outcome
Drugs	**Intervention**	• Telotristat 250 mg orally three times daily • Telotristat 500 mg orally three times daily
	Comparator(s)	Matching placebo
Duration	**Phase**	
	Run-in	3 to 4 weeks
	Double-blind	12 weeks
	Follow-up	2 weeks (plus 36 week open-label extension for all patients)
Outcomes	**Primary End Point**	Change in number of daily BMs compiled over the 12-week DBT period of the study
	Other End Points	Secondary: • change from baseline in u5-HIAA at week 12 • number of daily flushing episodes • abdominal pain severity (on a numeric rating scale of 0 to 10) averaged over 12 weeks

		TELESTAR
		Other: • responders — patients experiencing a ≥ 30% reduction in daily BM frequency (relative to baseline) for ≥ 50% of the double-blind treatment period • change from baseline in overall and domain scores of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and QLQ-GINET21 questionnaire • rescue short-acting SSA use • stool consistency • proportion of days with urgency to defecate Harms: • serious adverse events • adverse events • depression-related adverse events
NOTES	**Publications**	Kulke 2017.[10]

5-HIAA = 5-hydroxyindoleacetic acid; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BM = bowel movement; CS = carcinoid syndrome; DB = double blind; DBT = double-blind treatment; LAR = long-acting release; mTOR = mammalian target of rapamycin; NET = neuroendocrine tumour; QLQ-GINET21 = 21-item gastrointestinal neuroendocrine tumour–specific quality-of-life questionnaire; RCT = randomized controlled trial; SSA = somatostatin analogue; TST = telotristat; u5-HIAA = urinary 5-hydroxyindoleacetic acid; ULN = upper limit of normal.

Note: Four additional reports were included: FDA clinical and statistical review,[11,12] manufacturer's submission,[13] Clinical Study Report.[6]

Source: Clinical Study Report for TELESTAR.[6]

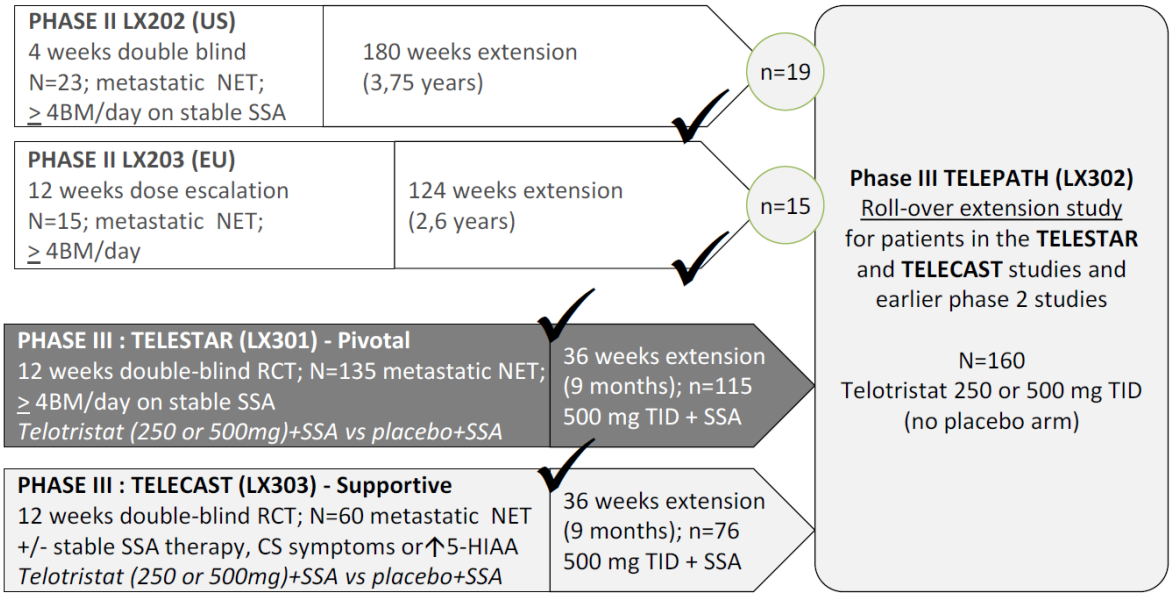
Included Studies

Description of Studies

TELESTAR was the pivotal trial for the Health Canada review of telotristat, and TELECAST was a companion study that did not meet the inclusion criteria for the systematic review due to the fact that not all patients were on a concomitant SSA. TELECAST is summarized in Appendix 6. Further, both the TELESTAR and TELECAST studies included a 36-week open-label extension; these results have been summarized in Appendix 7. A schematic of the key trials for telotristat has been provided in Figure 2. TELESTAR was a manufacturer-sponsored multi-centre double-blind (DB) randomized controlled trial (RCT) comparing two doses of telotristat (250 mg or 500 mg three times daily) with placebo in patients with diarrhea associated with carcinoid syndrome who were on a stable dose of SSAs over an initial double-blind treatment period of 12 weeks. There was a three- to four-week screening/run-in in which baseline symptoms were established and where patients had to demonstrate at least 75% compliance with completing diary entry. Patients who were excluded due to out-of-range laboratory values could have those readings repeated once at the discretion of the medical monitor. During this run-in, patients continued on a stable dose of SSAs. The primary outcome was the mean change from baseline in number of bowel movements per day, a daily average that was compiled over the 12-week double-blind treatment period. Secondary outcomes, which were adjusted for multiple comparisons, included the change from baseline in urinary 5-hydroxyindoleacetic acid (5-HIAA) levels, as well as change in symptoms of flushing and abdominal pain, tested in that order.

Randomization was stratified by baseline urinary 5-HIAA (above or below the upper limit of normal [ULN]) and was conducted using an interactive Web response system.

Figure 2: Overview of Key Clinical Trials for Telotristat



BM = bowel movement; CS = carcinoid syndrome; EU = European Union; NET = neuroendocrine tumour; SSA = somatostatin analogue; RCT = randomized controlled trial; TID = three times per day.

Note: Checkmarks indicate completed studies.

Source: Clinical Summary.[13]

Populations

Inclusion and Exclusion Criteria

Patients in TELESTAR had to have metastatic neuroendocrine tumour confirmed through histology and the extent analyzed by imaging, as well as a documented history of carcinoid syndrome with at least four bowel movements daily during the run-in. They had to have been taking the approved SSA therapy in their country of origin and at the same dose for at least three months prior to study entry. Specific doses of octreotide long-acting release (LAR) 30 mg every four weeks or lanreotide depot 120 mg every four weeks were outlined; however, patients were also allowed to enter at their highest tolerated dose if they were unable to tolerate those pre-defined doses.

Patients were excluded if they had received any therapy that was directed at the tumour itself (e.g., drugs less than four weeks prior to screening, or radiotherapy or surgery less than 12 weeks prior to screening), or if they had a Karnofsky performance status of 60 or lower or a life expectancy of less than 12 months. Patients with diarrhea attributable to other conditions (infection or malabsorption syndrome) or with frequent (12 bowel movements a day) watery diarrhea were also excluded. Patients with low neutrophils, platelets, or hemoglobin were also excluded, as were patients with elevated liver enzymes or elevated bilirubin or serum creatinine.

Baseline Characteristics

Patients in TELESTAR were 63 years old, on average, and there were an equal number of males and females. The majority of patients were Caucasian. The majority of patients were on octreotide as their SSA, [redacted] A total of 58% of patients had baseline urinary 5-HIAA above the ULN. Diarrhea was the most common carcinoid syndrome–associated symptom, followed by flushing and abdominal pain.

At study entry, 89% of telotristat-treated versus 67% of placebo-treated patients were on octreotide, and 11% versus 33% were on lanreotide, respectively. The proportion of patients with abdominal pain was 42% in the telotristat group compared with 33% of the placebo group. Approximately 49% of the telotristat group experienced flushing at baseline compared with 69% in the placebo group.

Table 5: Summary of Baseline Characteristics

	TELESTAR	
Characteristics	**TST 250 N = 45**	**PLA N = 45**
Age (years), mean (SD)	62.4 (9.12)	63.3 (8.67)
< 65 years	26 (57.8)	25 (55.6)
≥ 65 years	19 (42.2)	20 (44.4)
Male sex, n (%)	21 (46.7)	24 (53.3)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
SSA Therapy Name at Study Entry, n (%)		
Octreotide	40 (88.9)	30 (66.7)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Lanreotide	5 (11.1)	15 (33.3)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Unknown		
Urinary 5-HIAA at Randomization, n (%)		
≤ ULN	12 (26.7)	12 (26.7)
> ULN	26 (57.8)	26 (57.8)

Characteristics	TELESTAR	
	TST 250 N = 45	PLA N = 45
Unknown	7 (15.6)	7 (15.6)
Average number of daily BMs at baseline mean (SD)	6.085 (2.0703)	5.200 (1.3500)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

5-HIAA = 5-hydroxyindoleacetic acid; BM = bowel movement; PLA = placebo; SD = standard deviation; [redacted]SSA = somatostatin analogue TST = telotristat; ULN = upper limit of normal.

Source: Clinical Study Report.[6]

Interventions

There were two telotristat groups. One received the Health Canada–approved dose of 250 mg three times daily, while the other received a higher dose of 500 mg three times daily. Only the 250 mg dose is reported in this review, as it is the dose approved by Health Canada. Both groups were compared with a matching placebo. The double-blind treatment period was 12 weeks; there was also an open-label extension available with another 36 weeks of treatment with either telotristat dose.

Patients were allowed concomitant use of antidiarrheals, bile acid sequestrants, or pancreatic enzymes during the study; however, their use had to be associated with a "documented history of disease." Examples provided included fat or bile acid malabsorption, or steatorrhea. The dosing of these drugs was to remain stable during the run-in and double-blind period, unless there was a clear indication to change it.

Patients were to remain on a stable dose of their SSA throughout the duration of the study; changes to their dose or regimen were not permitted. Use of rescue short-acting SSAs (octreotide) was allowed, when deemed clinically necessary. The actual dose of rescue octreotide used was not reported. Patients were to record the dose of their regular SSA and use of rescue therapy and dose, if they needed rescue therapy. Use of SSAs was an

exploratory outcome in this study and there was no statistically significant difference in use of rescue between telotristat and placebo.

Table 6: Concomitant Medications During TELESTAR Study

	TST 250 N = 45	PLA N = 45
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

PLA = placebo; TST = telotristat.

Source: Clinical Study Report.[6]

Outcomes

The primary outcome was the change from baseline in daily bowel movement frequency, compiled over the 12-week double-blind treatment period. Daily diaries were used to assess bowel movement frequency and quality (form, consistency) as well as symptoms such as urgency, nausea, abdominal pain, and flushing; the latter two were assessed as secondary outcomes which were controlled for multiplicity. These diaries were filled out electronically (e-diary), and patients were prompted at the end of each day to respond to the relevant diary questions for that day. Patients had to demonstrate at least 75% compliance with completing entries into the diary in order to be enrolled in the study. Abdominal pain was assessed using an 11-point scale, ranging from zero ("no pain") to 10 ("worst pain ever experienced"). Changes from baseline were arrived at by taking the average of all post-baseline non-missing data and subtracting from the baseline value. Stool quality was assessed using the Bristol Stool Form Scale. It is based on an ordinal scale from type 1 (hardest) to type 7 (softest), with types 1 and 2 considered abnormally hard and indicative of constipation, and types 6 and 7 being abnormally loose/liquid stools indicative of diarrhea (Table 15). The Bristol Stool Form Scale is reviewed in Appendix 5, and no minimal clinically important difference (MCID) was found for this scale.

The manufacturer also developed a responder analysis for bowel movement frequency as an exploratory outcome. A responder was defined as a patient who experienced at least a 30% reduction from baseline in daily bowel movements during at least 50% of the double-blind 12-week treatment period. It was developed as a means for identifying a clinically relevant improvement in bowel movements, in agreement with regulatory bodies.[6]

Health-related quality of life was assessed at weeks 6 and 12 using the European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30) and the EORTC QLQ-GINET21, a 21-item gastrointestinal neuroendocrine tumour–specific quality-of-life questionnaire. The QLQ-C30 is a 30-question, patient-reported questionnaire comprising single-item measures and multi-item

scales. This includes five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status (quality of life [QoL]) scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). All but five of these items rely on a one-week recall, as the questions ask patients about their experience with their condition "during the past week." The two items related to global health status (QoL) are rated on a Likert-type scale from 1 ("very poor") to 7 ("excellent"); therefore, higher scores for this scale correspond to higher QoL for the patient. The remainder of the scales and single items are rated on a scale from 1 to 4, where 1 = "not at all," two = "a little," three = "quite a bit," and 4 = "very much." Higher scores for questions related to the functional scale correspond to a higher or healthy level of functioning, whereas a higher score for symptom scale and items correspond to a higher (worse) level of symptomology or problems. In addition, a linear transformation is used to convert each raw scale/item score to a standardized score that ranges from 0 to 100.[14] Moreover, the raw scores for scales are derived from the mean of the component items. No disease-specific MCID was found for the QLQ-C30; however, the general MCID is 10.[15] See Appendix 5 for more a detailed review.

The EORTC QLQ-GINET21 is a 21-item module developed for patients with gastrointestinal (GI) neuroendocrine tumours and is available in at least nine languages.[16] The 21 items included in the module correspond to three multi-item symptom scales regarding endocrine symptoms ("ED;" three items), GI symptoms ("GI;" five items), and treatment-related side effects ("TR;" three items), as well as two single-item symptoms for muscle and/or bone pain and concern about weight loss. It also includes two psychosocial scales regarding social function ("SF21;" three questions), disease-related worries (DRW; three questions) and two additional single items concerning sexual functioning and communication.[17] Similar to the core questionnaire, 19 of the 21 questions of the QLQ-GINET21 asks patients about their experience in the past week or a one-week recall period.[17] The remaining two questions are about communication and sexuality and are based on a four-week recall period. Items are scored on four-point Likert-type scales from 1 to 4 ("not at all," "a little," "quite a bit," and "very much") and, like the core questionnaire, scores are linearly transformed to a scale from zero to 100. Higher scores correspond to a higher level of symptomology or more severe symptoms.[16] No MCID was found for the GINET instrument. See Appendix 5 for more detailed review.

The key biomarker used in the study was urinary 5-HIAA, an indicator of serotonin levels, and the mean change from baseline in 24-hour urinary 5-HIAA was assessed as a secondary outcome. The manufacturer asserted that urinary 5-HIAA is the standard measure for assessing neuroendocrine tumours and, since it is a 24-hour measure, it is considered to be more reliable than plasma levels. Urine was collected over a 24-hour period and sent to a central laboratory for analysis.

Statistical Analysis

The primary outcome and many of the secondary outcomes were analyzed using the van Elteren test, with a Hodges–Lehmann estimate of treatment difference, and was stratified by urinary 5-HIAA levels (less than or equal to the upper limit of normal [ULN], above the ULN, or unknown). The primary analysis was performed on the intention-to-treat [ITT] population, and a sensitivity analysis was performed on the per-protocol population, using the same testing procedure. The alpha for each of the doses for each outcome was 0.025. For the primary outcome, secondary analyses were also carried out using a generalized

linear model that was based on the negative binomial distribution, with the dependent variable being the number of daily bowel movements and fixed effects, including treatment group and urinary 5-HIAA stratification at randomization, and baseline bowel movements as the fixed covariate. In order to adjust for a variable number of missing days, the natural log of the number of days with non-missing diary data was used. The manufacturer noted that this supplemental analysis was performed because the primary analysis lacks flexibility in accounting for the potential impact of other baseline variables on the analysis of treatment effect.

Several other sensitivity analyses were planned for the primary outcome. One analyzed ITT patients according to the treatment they received, rather than the one to which they were assigned. There were no such patients in the study; therefore, this sensitivity analysis was not necessary. In another, any missing post-baseline values were assigned a change from baseline score of zero, while another included only patients who completed the double-blind treatment period, while again applying a change score of zero for missing values. An analysis was also performed that censored any patients who received rescue SSA therapy, with two methods to handle censored data. In one approach, all censored observations were assigned the mean baseline score (presumably the number of daily bowel movements, though this was not explicitly stated), while in the other, censored observations were assigned the highest value recorded for the patient during the double-blind treatment period. Finally, methods using repeated measures and pattern-mixture techniques were employed, if deemed necessary, based on the extent and reasons for missing observations.

A supplemental analysis using a mixed model with repeated measure was performed for the first secondary outcome: the change from baseline in urinary 5-HIAA. The dependent variable was the change from baseline to week 6 or 12 in urinary 5-HIAA and patient as random effect, and fixed effects of treatment group, baseline urinary 5-HIAA (above or below ULN, or unknown) time (week 6 or 12), and treatment-by-time interaction. The Kenward–Roger approximation was used to adjust the denominator degrees of freedom. Supplemental analyses for the other secondary outcomes were performed in a manner similar to the supplemental analysis for the primary outcome.

The responder analysis (“durable response”) was analyzed using an odds ratio, telotristat versus placebo, and the supplemental analysis used a difference in proportions.

Power

[redacted]

Multiplicity

A Bonferroni correction was employed to account for multiple statistical comparisons involving the primary (change from baseline in bowel movements) and three secondary end points (change in urinary 5-HIAA, flushing, abdominal pain) in TELESTAR. The threshold for statistical significance was an alpha of 0.025 for each of the telotristat doses being tested, and each of the outcomes were tested applying this threshold; if statistical significance was not met for a given comparison within a given outcome in the hierarchy, testing was halted for that specific comparison, but could continue at an alpha of 0.025 for

the other comparison for subsequent outcomes. Therefore, when the comparisons were run, the *P* values were $P < 0.001$ for each of the telotristat doses for each of the primary and first secondary outcomes and, thus, were statistically significant for both. However, for the second secondary outcome (flushing), neither the telotristat 250 mg dose ($P = 0.39$) nor the telotristat 500 mg dose ($P = 0.84$) met statistical significance. At this point, testing should have been halted; however, subsequent analyses were reported for the third and final secondary outcome for both doses. Because the testing should have halted according to the pre-specified testing strategy, the *P* values for abdominal pain would be considered unadjusted for multiplicity, but were statistically non-significant, nonetheless.

Missing Data

For outcomes that were based on weekly analyses, if daily diary data were at least 80% complete, then the analysis used the mean response for that week. However, if < 80% of data were available for that week, then the mean response for that week was set to missing. Examples of these outcomes included bowel movement frequency, consistency, urgency, and abdominal pain.

With respect to the primary analysis, if a patient had more than six weeks of missing data (a missing week was defined as missing four or more days of data that week) the change from baseline was imputed as zero. Otherwise, observed data were used, with mean response based on the number of days with valid non-missing data. For the health-related QoL instruments (QLQ-C30 and GI.NET 21) scale scores were computed based on non-missing responses, unless more than half of the responses were missing, in which case the scale score was set to missing.

Subgroups

Subgroup analyses were specified a priori, and no statistical analyses were planned and included the following: age (< 65 years old or ≥ 65 years), sex, baseline urinary 5-HIAA (≤ ULN, > ULN, unknown) and region (North America, Europe, rest of world).

Analysis Populations

The enrolled population were all patients enrolled in the study, while the ITT population included all randomized patients, and patients were to be analyzed according to their assigned treatment. The ITT population was to be used for all efficacy analyses. The safety population was all patients who received a dose of study drug during the study.

Patient Disposition

In TELESTAR there were fewer withdrawals in the telotristat 250 mg group than in the placebo group (7% versus 16% of patients discontinued) (Table 7). The most common reason for withdrawal was due to adverse event, and this accounted for the difference in overall withdrawals between groups (4% versus 13%, respectively).

Table 7: Patient Disposition

Characteristics	TST 250 N = 45	Placebo N = 45
Assessed for eligibility	175	
Did not meet inclusion/met exclusion criteria	32	
Declined/withdrew consent	3	
Death	2	
Other	2	
Randomized	45	45
Completed the DBT period	42 (93.3)	38 (84.4)
Discontinued the DBT period	3 (6.7)	7 (15.6)
Adverse event	2 (4.4)	6 (13.3)
Death	0	0
Lack of efficacy	0	0
Physician decision	0	0
Withdrawal of consent	0	1 (2.2)
Other	1 (2.2)	0
Safety population	45 (100.0)	45 (100.0)
Intention-to-treat population	45 (100.0)	45 (100.0)
Per-protocol population	42 (93.3)	39 (86.7)

DBT = double-blind treatment; TST = telotristat.

Source: Clinical Study Report[6] and Kulke 2017.[10]

Exposure to Study Treatments

[redacted]

Critical Appraisal

Internal Validity

TELESTAR was a randomized and double-blinded study, with randomization stratified by baseline urinary 5-HIAA levels. Although a minimum frequency of bowel movements (at least four per day) was required for enrolment into the study, there was a higher rate of bowel movements in the telotristat group versus placebo at baseline, and this is potentially a source of bias, as a higher baseline value for bowel movements might result in larger reductions in frequency of bowel movements, or may indicate a population that was more difficult to treat; thus, the direct of bias is difficult to ascertain. This difference in bowel movements between groups at baseline is also potentially important because of the relatively modest treatment effect of 0.8 bowel movements per day, averaged over the 12-week double-blind treatment period, which was also the difference between telotristat and placebo at baseline. The effect of baseline bowel movements was not adjusted for in the primary analysis, but was adjusted for in the supplemental analysis, which was statistically significant.

Blinding was facilitated by use of a matching placebo. Other than perhaps constipation, there did not appear to be any other adverse events that are unique enough to telotristat to potentially unblind the trial. Allocation concealment was maintained through use of an interactive Web response system and a centralized randomization schedule carried out by a contract research organization.

Power calculations were performed based on the primary outcome and the manufacturer appeared to meet its minimum target for enrolment (target: 135 patients; enrolled: 146). However, secondary outcomes may have been underpowered, limiting their ability to identify statistically significant differences between groups.

The manufacturer employed a Bonferroni correction and a hierarchical testing procedure to account for multiple statistical comparisons. The Bonferroni correction accounted for the fact that two different doses of telotristat were being compared with placebo for each outcome (i.e., two comparisons per outcome). Although frequency of bowel movements and symptoms (flushing, abdominal pain) were included in the hierarchy, health-related QoL was not, despite the clear impact of this condition on patients' health-related QoL. Thus, all comparisons with placebo that were reported as statistically significant for the EORTC QLQ-C30 and the QLQ-GINET21 scales should be considered exploratory in nature, and this limits any conclusions that can be drawn regarding this important outcome to patients.

The percentage of patients withdrawing in the placebo (16%) group was greater than in the telotristat (7%) group, and this was largely accounted for by withdrawals due to adverse events. ITT analysis was used for most of the outcomes, with the notable exception of the health-related QoL outcomes and urinary 5-HIAA. Between 10% and 15% of data were missing across the various health-related QoL subscales, and about one-third of data were missing from the change from baseline in 5-HIAA at week 12. There was no clear difference in the amount of missing data between groups, despite the higher percentage of withdrawals in the placebo group. Too much missing data increases the risk of losing the original balance between groups achieved at randomization.

Many of the outcomes, including the primary outcome, relied on diary data, often compiled on a daily basis. Observed data were used, unless a patient was missing more than six weeks of diary data, then all of their data were counted as "missing." Non-missing data were used to calculate diary responses. A week of data were "missing" if four or more days were missing from that week. Therefore, it would be possible for a patient to have the majority of their data missing but still be counted in the analysis and, presumably, they would have the same weight in the analysis as a patient who had no missing data at all. This approach likely understates the impact of missing data on the analysis. It also assumes that missing data are missing completely at random and that the missing data would have resembled the non-missing data. This may not be an appropriate assumption, given that patients who are experiencing more symptoms may be less inclined (or more inclined) to complete their daily diary entries. For many outcomes, an average compiled over the course of the 12-week double-blind treatment period was reported, as well as results at week 12; it was not clear what the rationale was for reporting at both of these time points and results were often not consistent between these time points.

The sample size in TELESTAR is relatively small, and this is a limitation when assessing safety for rare serious adverse events. Carcinoid syndrome diarrhea is a relatively uncommon condition and, thus, it would be more challenging to enrol a noticeably larger population than the 135 patients in TELESTAR.

Quality of bowel movements was assessed using the Bristol Stool Form Scale. Bristol is a common scale used clinically, often in patients with constipation, to assess what type of laxative to use based on the quality of their stool. However, responses were assessed simply by using a change from baseline (decrease denoting improvement). it should be noted that the scale covers a range from constipation at the low end of the scale (hard, small, dry stools) to watery diarrhea at the high end of the scale. Thus, where patients begin on the scale is important, as "normal" stools would be somewhere in the middle ranges; therefore, a very large reduction in score might not be desirable, particularly depending on how high a patient begins on the scale.

Patients in TELESTAR were provided rescue short-acting SSA (octreotide) when needed, and their use of rescue medication was to be reported in a diary and was assessed as an exploratory outcome. There was no difference in the use of somatostatin rescue between groups; thus, it is unlikely that the use of rescue therapy would have biased results for either efficacy or harms.

External Validity

The population enrolled into TELESTAR appeared generalizable to the population of patients with diarrhea associated with carcinoid syndrome that would be expected to use telotristat in Canada, according to the clinical expert consulted by CDR on this review. TELESTAR included comparisons of the Health Canada–approved 250 mg three times daily regimen with placebo as well as with a higher dose (500 mg three times daily), and all patients were on stable doses of SSAs. The clinical expert noted that the likely approach to management would be to maximize SSA therapy, as these drugs carry the additional benefit of being able to reduce tumour burden, in addition to their effects on reducing symptoms. All patients were on SSAs at baseline and most were on octreotide and, again, this was considered appropriate and generalizable by the clinical expert. The majority of patients were on a background octreotide dose of 30 mg or less, and this appears to be less than the 60 mg that the clinical expert suggested would be used in patients who were not responding. The comparator was placebo, and this is likely the most appropriate comparator, as SSAs are the only approved therapy for this condition and, per indication, all patients are to use telotristat with an SSA.

The double-blind treatment period in TELESTAR was only 12 weeks, and this is unlikely to be of sufficient duration to assess the harms associated with the use of this drug. Telotristat employs a novel mechanism of action and inhibits production of serotonin, a critical neurotransmitter with a wide variety of receptors throughout the body, including the central nervous system. The product monograph includes a warning about depression, which was seen at the 500 mg dose but not the approved 250 mg dose.[5]

The primary outcome was an assessment of bowel movement frequency and, given the nature of the condition, this appears to be an appropriate choice of primary outcome. It is clearly of critical importance to patients, based on their input to CDR. TELESTAR assessed other key symptoms associated with carcinoid syndrome diarrhea, including abdominal pain and flushing, using a daily electronic diary. There was a general lack of MCIDs specific to this condition for health-related QoL outcomes, and there was no MCID found for the Bristol Stool Form Scale, which measures consistency of stool.

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported below. See Table 8 for detailed efficacy data.

Bowel Movements

In TELESTAR, there was a reduction in the daily number of bowel movements averaged over the 12-week treatment period with telotristat versus placebo, and this difference was statistically significant (the Hodges–Lehmann estimate of treatment difference between groups was −0.812 daily bowel movements [95% CI, −1.256 to −0.280; $P < 0.001$]) (Table 8). A sensitivity analysis performed on the per-protocol population yielded results that were consistent with the primary analysis.

Results for subgroups based on age were reported for the primary outcome, although these were exploratory, and no *P* values were reported (Table 11).

Quality of Bowel Movements

Quality of bowel movements was assessed by stool consistency using the Bristol Stool Form Scale. Across the 12-week double-blind treatment period in TELESTAR, stool consistency scores decreased in the telotristat group (mean [SD] change from baseline of −0.265 [0.4712]) and in the placebo group (−0.216 [0.4791]), for a Hodges–Lehmann estimate of difference between groups of −0.087 [95% CI, −0.268 to 0.110]) (Table 8). This outcome was not adjusted for multiple comparisons.

Health-Related Quality of Life

This outcomes was assessed using the EORTC QLQ-C30 and QLQ-GINET21. In TELESTAR, there was no statistically significant difference in QLQ-C30 between telotristat and placebo for global health status or for many of the domain scores (physical functioning, role functioning, emotional, cognitive, social functioning, fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties); however, there were differences between groups for insomnia and diarrhea (Table 12). Patients treated with telotristat had their insomnia worsen from baseline (mean [SD] of −3.33) while in placebo patients, insomnia improved, for a Hodges–Lehmann estimate of difference between groups of 16.667 (95% confidence limit, 0.000 to 16.667). Conversely, diarrhea improved with telotristat versus placebo (Hodges–Lehmann estimate of difference between groups of −16.667 [95% confidence limit, −16.667 to 0.000]).

In TELESTAR, QLQ-GINET21 domain scores were not statistically different between telotristat and placebo for most subscales (endocrine, GI symptoms, treatment, social function, muscle/bone pain symptoms, sexual function, information/communication function, and body image) while the subscale disease-related worries had a difference between groups, however, the statistical comparison was not adjusted for multiple comparisons (Hodges–Lehmann estimate of treatment difference between groups of 11.111 [95% CI, 0.000 to 16.667]). There were fewer disease-related worries for telotristat versus placebo.

Symptoms

There were no statistically significant differences between telotristat and placebo for daily flushing episodes or episodes of abdominal pain over the 12-week DBT period in

TELESTAR at an alpha of 0.025. The Hodges–Lehmann estimate of treatment difference between groups was 0.036 counts per day (95% CI, −0.230 to 0.330; *P* = 0.39) for flushing episodes and −0.168 (95% CI, −0.541 to 0.224; *P* = 0.26) for abdominal pain scores. These were both secondary outcomes in this study and, thus, the statistical analysis was adjusted for multiple comparisons.

Urgency

There was no statistical difference between telotristat and placebo for urgency/immediate need to defecate after 12 weeks in TELESTAR (Hodges–Lehmann estimate of treatment difference of −0.024 [95% CI, −0.158 to 0.021; *P* = 0.35]).

Response and Durability of Response

In TELESTAR, 44% of telotristat-treated patients and 20% of placebo-treated patients experienced a durable response, defined as a 30% reduction in daily bowel movements for at least 50% of the time during the double-blind treatment period, for an odds ratio of 3.49 (95% CI, 1.33 to 9.16). This outcome was not adjusted for multiple comparisons.

Urinary 5-Hydroxyindoleacetic Acid

There was a statistically significant reduction in urinary 5-HIAA in the telotristat group compared with placebo at week 12 (Hodges–Lehmann estimate of treatment difference of −30.100 [95% CI, −55.800 to −9.200; *P* < 0.001]). This was the first secondary outcome in the statistical hierarchy and, therefore, was adjusted for multiple comparisons.

Table 8: Key Efficacy Outcomes

	TELESTAR	
	TST 250 N = 45	**Placebo N = 45**
Frequency of BM		
Average number of BMs at baseline mean (SD)	6.085 (2.0703)	5.200 (1.3500)
Mean (SD) Change from baseline in number of BMs averaged over the DBT period	−1.433 (1.3652) N = 45	−0.623 (0.8275) N = 45
Differences in arithmetic means, TST minus placebo (95% CI)	−0.810 (−1.283, −0.337)	
HLE of treatment difference, TST minus placebo[a] (97.5% CI)	−0.812 (−1.256, −0.280) *P* < 0.001	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
Quality of BM		
Mean (SD) baseline stool consistency	5.934 (0.5031)	5.917 (0.6993)
Mean (SD) change from baseline in stool consistency averaged across all time points	−0.265 (0.4712) N = 45	−0.216 (0.4791) N = 45
HLE of treatment difference, TST minus placebo [95% CI][a]	−0.087 (−0.268 to 0.110) *P* = 0.57	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

	TELESTAR	
	TST 250 N = 45	Placebo N = 45
Symptoms		
Flushing		
Mean (SD) weekly cutaneous flushing episodes (counts/day) at baseline	2.788 (3.7362)	1.791 (1.9344)
Mean (SD) change from baseline in number of daily cutaneous flushing episodes averaged across all time points during DBT period	−0.296 (1.3097) N = 45	−0.164 (1.1572) N = 45
[redacted]	[redacted]	[redacted]
HLE of treatment difference, TST minus placebo (97.5% CL)[a]	0.036 (−0.230 to 0.330) *P* = 0.39	
Abdominal Pain		
Mean (SD) weekly abdominal pain (11-point numeric rating scale) at baseline	2.615 (2.2657)	2.473 (2.3201)
Mean (SD) change from baseline in abdominal pain averaged across all time points during DBT period	−0.490 (1.4423) N = 45	−0.226 (1.1601) N = 45
[redacted]	[redacted]	[redacted]
HLE of treatment difference, TST minus placebo (97.5% CL)[a]	−0.168 (−0.541 to 0.224) *P* = 0.26	
Overall GI		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
Durability of response		
Patients with durable response, n (%)	20 (44.4)	9 (20.0)
Primary analysis odds ratio, TST divided by placebo (95% CI)[d]	3.49 (1.33 to 9.16) *P* = 0.011	
Urgency		
Mean (SD) proportion of days where urgency/immediate need to defecate	0.664 (0.3431) N = 45	0.753 (0.2932) N = 45
HLE of treatment difference, TST minus placebo (95% CI)[a]	−0.024 (−0.158 to 0.021) *P* = 0.35	
Biomarkers		
Baseline urinary 5-HIAA levels, mg/24 hours, mean (SD)	92.645 (114.8958) N = 42	80.968 (161.0143) N = 44
Change from baseline in urinary 5-HIAA levels, mg/24 hours at week 12, mean (SD)	−40.134 (84.7663) N = 32	11.350 (35.0346) N = 30
Median change from baseline to week 12 (minimum, maximum)	−21.650 (−458.60 to 77.20)	1.550 (−35.80 to 155.00)
HLE of treatment difference, TST minus placebo (97.5% CI)[a]	−30.100 (−55.800,−9.200) *P* < 0.001	

5-HIAA = 5-hydroxyindoleacetic acid; BM = bowel movement; CI = confidence interval; CL = confidence limit; DBT = double-blind treatment; [redacted]; GI = gastrointestinal; HLE = Hodges–Lehmann estimate; [redacted]; [redacted]

SD = standard deviation; TST = telotristat.

[a] The primary analysis used a blocked two-sample Wilcoxon rank sum statistic (i.e., van Elteren test) stratified by the urinary 5-HIAA levels at randomization.

[b] The supplemental analysis used a generalized linear model based on the negative binomial distribution. The model included the number of BMs per day as the dependent variable and included treatment group and u5-HIAA stratification at randomization as fixed effects, and the baseline number of BMs as a fixed covariate. The natural log value of the number of days with non-missing diary data were used as an offset term to adjust for variable number of days.

[c] The supplemental analysis used a mixed model with repeated measurements. The model uses the change from baseline in each scale score as the dependent variable and includes treatment group, urinary 5-HIAA stratification at randomization, time and treatment-by-time interaction as fixed effects, baseline score as a covariate and patient as a random effect. An unstructured (general) covariance matrix was used to model the within-subject errors. The Kenward–Roger approximation was used to estimate the denominator degrees of freedom.

[d] The primary analysis used a logistic regression model with responder as the dependent variable, treatment group and u5-HIAA stratification at randomization as fixed effects, and baseline mean number of BMs (counts per day) as a covariate. “Durable response” was defined as a ≥ 30% reduction in number of BMs per day for ≥ 50% of time over the DBT period.

Source: Clinical Study Report.

Harms

Only those harms identified in the review protocol are reported subsequently (see 2.2.1, Protocol).

Adverse Events

Adverse events occurred in 82% of telotristat patients versus 87% with placebo after 12 weeks. The most common adverse events were nausea (13% of telotristat versus 11% placebo), and abdominal pain (11% versus 18%).

Serious Adverse Events

Serious adverse events occurred in 16% of patients in each group.

Withdrawals Due to Adverse Events

Withdrawals due to adverse event occurred in 4% of telotristat versus 16% of placebo patients.

Mortality

There was one death in the telotristat group versus three deaths with placebo.

Notable Harms

Notable harms included depression, which occurred in 4% of patients in the telotristat group and 7% of patients in the placebo group, and constipation (zero in the telotristat group and 4% with placebo). Patients with elevated liver enzymes occurred only in the telotristat group (alanine aminotransferase [ALT] increased: 2% versus zero, and gamma-glutamyltransferase [GGT] increased: 9% versus zero), and no patients had increased alkaline phosphatase (ALP).

Table 9: Harms

	TELESTAR	
	TST 250 N = 45	Placebo N = 45
Adverse Events		
Patients with an AE, n (%)	37 (82.2)	39 (86.7)
Most common (10% of patients in any group)		
Nausea	6 (13.3)	5 (11.1)
Abdominal pain	5 (11.1)	8 (17.8)
Headache	5 (11.1)	2 (4.4)
Serious Adverse Events		
Patients with an SAE, n (%)	7 (15.6)	7 (15.6)
WDAE		
Patients with WDAE, n (%)	2 (4.4)	7 (15.6)
Gastrointestinal-related	0	2 (4.4)
Mortality		
Deaths, n (%)	1 (2.2)	3 (6.7)

	TELESTAR	
	TST 250 N = 45	Placebo N = 45
	Cholestasis / Pancreatic NEC / DIC	Carcinoid Tumour Sepsis Carcinoid Heart Disease
Notable Harms		
Depression, n (%)	[redacted]	3 (6.7)
[redacted]	[redacted]	[redacted]
ALT increased, n (%)	1 (2.2)	0
ALP increased, n (%)	0	0
GGT increased , n (%)	4 (8.9)	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; AST= aspartate transaminase; DIC = disseminated intravascular coagulation; GGT = gamma-glutamyltransferase; NEC = neuroendocrine carcinoma; SD = standard deviation; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Clinical Study Report.

Discussion

Summary of Available Evidence

One manufacturer-sponsored multi-centre double-blind RCT met the inclusion criteria for this systematic review. TELESTAR compared two doses of telotristat (250 mg or 500 mg three times daily) with placebo in 135 patients with diarrhea associated with carcinoid syndrome and on a stable dose of SSAs. The initial double-blind treatment period was 12 weeks and patients were randomized 1:1:1 between groups. The primary outcome was the mean change from baseline in number of bowel movements per day, a daily average that was compiled over the 12-week double-blind treatment period. Secondary outcomes, which were adjusted for multiple comparisons, included the change from baseline in urinary 5-HIAA levels, as well as change in symptoms of flushing and change in symptoms of abdominal pain, tested in that order.

Key critical appraisal issues included the difference in baseline bowel movements between comparison groups of 0.8 per day, an important confounder when trying to assess the clinical significance of the relatively small treatment effect. Although multiplicity was adjusted for by use of a hierarchical testing procedure, none of the health-related QoL outcomes were included in the hierarchy and, thus, were not adjusted for multiple comparisons, an issue for subscales where statistical significance was reported. The pivotal study, TELESTAR, the only study included in this review, was of limited size and duration to assess efficacy and harms associated with telotristat. TELECAST was a non-pivotal companion study to TELESTAR, which did not meet the inclusion criteria for this review because patients were not required to be on an SSA at the time of study enrolment. This study is summarized in Appendix 6.

Interpretation of Results

Efficacy

All patients in TELESTAR were required to be on a stable dose of an SSA and this reflects the anticipated indication for telotristat, which is to be used in patients already taking somatostatin as an adjunct. Somatostatin has an advantage of having some antitumour effects of its own; however, patients may develop a resistance to it.[18] Given that patients with carcinoid syndrome typically survive many years with symptoms of the disease, a drug like telotristat that could be added to existing regimens, particularly without a noteworthy increase in side effects, would be beneficial to patients, according to the clinical expert consulted by CDR for this review. Other options for carcinoid syndrome–associated diarrhea fall into one of two categories: those that are disease modifying (i.e., reduce tumour burden, such as the mammalian target of rapamycin [mTOR] inhibitors or interferon) or those that act as antidiarrheals employing mechanisms outside of the pathophysiology of this disease (i.e., standard antidiarrheals like loperamide).[4]

The treatment effect for telotristat versus placebo amounts to less than one bowel movement per day, according to results from the primary outcome of TELESTAR, and this is of questionable clinical significance, according to the clinical expert consulted on this review. The clinical expert did note, however, that it is difficult to know what improvement in bowel movements would be clinically meaningful to a patient with this condition. Given that, it might be informative to look at the overall impact telotristat is having on symptoms and health-related QoL. There was no evidence that telotristat reduced symptoms of abdominal

pain or flushing, both key symptoms associated with carcinoid syndrome diarrhea. Importantly, telotristat also did not improve the urgency to defecate, and this is clearly a key symptom for patients according to their input to CDR. Given the limited impact on symptoms then, it should not be surprising that telotristat failed to improve health-related QoL on all but one of the subscales of the EORTC QLQ-C30 and the QLQ-GINET21 instruments. Patients identified diarrhea, but also fatigue/weakness, flushing/rash, and abdominal pain as symptoms that most impact their QoL, and they also noted significant impact on finances, ability to work, and energy levels. All of these were captured in some way by the subscales in one or both of the health-related QoL instruments used in TELESTAR. Looking at the MCID, the only subscale that demonstrated a clinically significant improvement for telotristat versus placebo was diarrhea and, although this is consistent with the beneficial effects seen on frequency of bowel movements with the primary outcome, no conclusions can be drawn about the statistical significance of this data, as it was not adjusted for multiple comparisons, and that is a significant gap in understanding the potential benefit of this drug. The reduction in 5-HIAA achieved by telotristat was deemed to be clinically significant by the clinical expert consulted for this review, albeit with a considerable amount of missing data; thus, it is not clear why there was such a limited impact of telotristat on symptoms and health-related QoL, and such a modest treatment effect on bowel movement frequency.

In order to perhaps better characterize the response to telotristat, the manufacturer created a “durable response” outcome, where they looked at patients with at least a 30% reduction from baseline in bowel movements during more than 50% of the double-blind treatment period. In this analysis, they found 44% of patients in TELESTAR responded to telotristat, although it is noteworthy that 20% of patients responded to placebo.

TELECAST was a smaller companion study to TELESTAR that did not meet the inclusion criteria for this review because patients were not required to be on SSAs at baseline. TELECAST may have provided additional insight as to the efficacy of telotristat on carcinoid syndrome–associated diarrhea; however, the primary outcome in the study was the biomarker, urinary 5-HIAA, and no adjustments were made for multiple comparisons of any of the secondary outcomes, including frequency of bowel movements; therefore, this study (summarized in Appendix 6) adds little to our knowledge of the efficacy of telotristat. The difference in frequency of bowel movements between telotristat and placebo was 0.5 in TELECAST, which is less than that seen in TELESTAR. TELEPATH was a long-term safety extension that included patients from both TELESTAR and TELECAST; however, only a small number of patients (N = 10) were on the Health Canada–approved 250 mg dose in this study, and there was no longer a placebo comparator; thus, this study adds little to knowledge of the long-term efficacy of telotristat (see Appendix 7 for detailed review).

Harms

In TELESTAR, a numerically higher proportion of patients treated with telotristat 500 mg dose experienced depression, and this was one of the factors that resulted in this dose not being approved for use. There was no indication of an increased risk of depression at the approved telotristat 250 mg dose; however, there is a clear mechanistic rationale for a negative impact of telotristat on mood, and the potential for causing depression remains in the product monograph, despite the lack of evidence for depression at the approved dose.[5] The follow-up in TELESTAR was only 12 weeks in the double-blind phase, and this may not be of sufficient duration to assess the risk of depression. There was a long-term safety extension that included patients enrolled in both TELESTAR and TELECAST; however,

only 10 patients in this study were on the approved telotristat 250 mg dose (see Appendix 7 for detailed review). There were no reports of depression as an adverse event at the 250 mg dose; however, once again there were reports of depression at the 500 mg dose. The small sample size at the approved dose is a limiting factor when trying to assess long-term risk of depression.

Telotristat was associated with elevated hepatic enzymes, and this is noted in the product monograph. The mechanism behind the elevation in liver enzymes has not been established. There were few reports of adverse events related to elevated liver enzymes, although all of the reports were in patients treated with telotristat. Once again, there were relatively few patients in the long-term safety extension who were on the approved dose, thus limiting any conclusions that can be drawn about the impact of telotristat on liver enzymes in the long-term. Constipation is another notable harm associated with the use of telotristat, although this is a common harm associated with antidiarrheals in general.

Potential Place in Therapy[2]

Based on currently available therapies and standards of care for patients with metastatic neuroendocrine tumours with refractory diarrhea in the setting of carcinoid syndrome related to serotonin excess, there is an unmet need for diarrhea control.

Standard first-line therapy with SSAs, including lanreotide at 120 mg per dose monthly, and octreotide LAR formulation 30 mg or 60 mg monthly is the first-line treatment option for disease control and diarrhea control. Patients started on octreotide LAR 30 mg with progression or refractory diarrhea should be titrated to 60 mg monthly, as there is evidence that this dose provides benefits in terms of both progression and symptom control. Also, in patients with poor control of diarrhea, there is a need for additional drugs to be given concurrently with SSAs.

Other drugs that have been used with no clear evidence for their use in this population without randomized trials to assess benefit include loperamide and diphenoxylate/atropine (Lomotil). The use of telotristat in this refractory-disease population does decrease frequency of diarrhea when provided in conjunction with SSAs and could be considered for this setting.

Patients on SSAs at a standard dose with lanreotide or higher-dose octreotide LAR without control of diarrheal symptoms with six or more bowel movement per day or reported poor QoL due to diarrheal symptoms could be offered telotristat for improvement in control. Testing with 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) demonstrating excess is advised (with appropriate dietary modifications prior to testing and avoidance of proton pump–inhibitor therapy). This test is part of the testing done during the initial assessment of patients with neuroendocrine tumours; thus, it does not generally increase the cost of care provided or result in a barrier to identifying patients.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

One manufacturer-sponsored multinational DB RCT was included in this review. TELESTAR compared two different doses of telotristat (250 mg and 500 mg three times daily) with placebo over the 12-week double-blind treatment period in a population of patients with at least four bowel movements daily while on a stable dose of SSAs. Results for the approved 250 mg dose are reported in this review. Telotristat was superior to placebo for the primary outcome: reduction in mean daily bowel movements. The reduction versus placebo was less than one bowel movement per day, and the clinical meaningfulness of this to a patient with carcinoid syndrome–associated diarrhea is unknown. Although telotristat reduced urinary 5-HIAA versus placebo, it did not improve symptoms associated with carcinoid syndrome, namely, abdominal pain and flushing. Telotristat also failed to improve symptoms of importance to patients that are associated with diarrhea, such as urgency, and did not improve a variety of health-related QoL subscales associated with this condition (fatigue, body image, pain, impact on finances, and social/cognitive functioning). With respect to harms, there were no clear differences between telotristat and placebo with respect to notable adverse events such as depression or constipation. There was an indication of an increase in hepatic enzymes with telotristat versus placebo.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input

The Carcinoid Neuroendocrine Tumour Society (CNETS) Canada was the only group that submitted a patient input response for the review of telotristat for treatment of refractory carcinoid syndrome as an adjunct to somatostatin analogue (SSA) therapy. The submission described CNETS as a organization that is widely recognized across Canada, both by patients and the medical community, that aims to improve the quality of life (QoL) and survival of patients with neuroendocrine tumour (NET). This patient group collaborates with medical and scientific experts, stakeholders, and partner associations, and provides patients, caregivers, health care professionals, and others with NET-related information regarding research, treatment, and support. It also offers support and guidance for patients regarding their options for care. In addition, the organization advocates on behalf of individual patients with NET and for the support of patients through policy. CNETS did not receive external help with the completion of this submission or data within, but has received funding from various companies in the last two years, including Novartis, Ipsen, Sanofi Genzyme, Pfizer, BTG, and AAA.

Both quantitative and qualitative information was collected for this submission through an online survey, which was open during September 2018 and promoted on the CNETS Canada website, public Facebook page and its Facebook closed support group. Ten patients with NET and one caregiver responded to the survey. All respondents were adults (aged 30 to 39 [n = 3], 50 to 59 [1], 60 to 69 [2], and 70 to 79 [4] years), 70% were male, and all had experience being treated with telotristat. Four patients were from Ontario, two were from Alberta, and there was one each from Manitoba, Quebec, New Brunswick, and outside of Canada.

2. Condition Related Information

CNETS describes carcinoid syndrome as the release of excess amounts of hormones, such as serotonin, by NETs into the bloodstream, which typically causes symptoms like diarrhea and flushing. It was also noted that the diarrhea can be extremely debilitating and has a significant effect on a patient's QoL, "affecting patients physically, emotionally, and socially in their day-to-day life."

The patient group submission primarily described the disease experience in terms of impact on QoL, based on responses to questions that were rated on a scale of 1 (no impact) to 7 (extremely large impact) on day-to-day life. Diarrhea as a symptom of NET had the largest impact on patients' QoL with a rating of 5.8, followed by fatigue/weakness (4.8), flushing/rash (4.3), abdominal pain (3.5), sweating/headaches (3.2), anxiety (2.6), and breathlessness (1.7). Living with NET had the greatest impact on finances (5.0) according to the patient response, but also the ability to work (4.6), energy levels (4.5), and travel (4.4). It also had an emotional impact on patients (3.9) as well as an effect on their social life (3.9), relationships (3.7), and participation in leisure activities (3.6).

Finally, the majority of patients (90%) expressed that gaining control of their diarrhea was a priority in terms of managing their disease. Control of disease progression and flushing was rated the second most important aspect of NET for 70% of patients, and half of patients reported fatigue as an important symptom to control.

3. Current Therapy Related Information

Patients that completed the online survey had experience with the following treatments and therapies for the management of NET cancer: telotristat (100%), SSA (100%), surgery (90%), liver embolization (30%), ablative techniques (10%), and alternative therapies (30%).

Patients reported that the current treatments for NET cancer did not cure or halt the progression of the disease. While some treatments were able to help control symptoms according to patients, they were also associated with long recovery times, debilitating side effects, and complications. One patient reported experience with multiple treatments, including two mid-gut surgeries, sando[statin] and lanreotide, and more recently, liver ablation and embolization. These treatments take a toll on the patient. Another quote from patients was provided, which describes the liver embolization as “the hardest to endure but provides the most relief.” Further, that patient required somatostatin every two weeks, but “over time, the injection sites have suffered” causing regular pain. Another patient reported that lanreotide works for symptoms; however, receiving an injection every three weeks was inconvenient. They also noted that telotristat also worked for symptoms and, despite it being an oral medication, needing “to take six 250 mg pills per day is also very inconvenient.”

4. Expectations About the Drug Being Reviewed

As previously mentioned, all 10 of the patient respondents had experience with telotristat, with 90% gaining access through a clinical trial. Further, all patients agreed that “the most important outcome for treatment with telotristat was symptom (diarrhea) control,” noting that this would also improve QoL in terms of the ability to function socially, having increased energy, and improved self-esteem. The majority (90%) reported control of severe diarrhea with treatment with telotristat; however, one (10%) patient experienced a rash/hives and had to discontinue use of telotristat, while another reported pill burden associated with carrying around multiple pills. When asked about the overall impact of treatment with telotristat, the response provided was positive, with patients reporting improved an improvement in QoL and well-being:

“Not afraid to go out anymore because of an ‘accident’”

“Huge; I wasn't able to go out for long periods, and was getting very depressed”

“Improved ability to function socially”

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 24, 2018
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.nm	Name of substance word
.pt	Publication type
.rn	Registry number
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(Xermelo* or telotristat* or LX1032 or LX1606 or LX 1032 or LX 1606 or LP-778902 or LP778902 or 8G388563M7 or 381V4FCV2Z or 4NUK2IW1VH or 3T25U84H4U).ti,ab,ot,kf,hw,rn,nm.
2	1 use medal
3	*telotristat/ or *telotristat ethyl/ or *telotristat etiprate/
4	(Xermelo* or telotristat* or LX1032 or LX1606 or LX 1032 or LX 1606 or LP-778902 or LP778902).ti,ab,kw,dq.
5	or/3-4

MULTI-DATABASE STRATEGY	
6	5 use oemezd
7	6 not (conference review or conference abstract).pt.
8	2 or 7
9	remove duplicates from 8

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (ClinicalTrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	October 2018
Keywords:	Xermelo (telotristat), carcinoid syndrome diarrhea
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Table 10: Excluded Studies

Reference	Reason for Exclusion
Pavel M. Endocrine-Related Cancer 2018	Population not on somatostatin analogues
Anthony L. Clinical Therapeutics 2017	Wrong outcome

Appendix 4: Detailed Outcome Data

Table 11: Subgroup Analysis of the Primary Outcome (TELESTAR)

	TST 250 N = 45	PLA N = 45
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

Table 12: Detailed Health-Related Quality of Life From TELESTAR

[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
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Source: Clinical Study Report.

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Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)
- QLQ-GI.NET21 (a neuroendocrine tumour [NET]–specific quality-of-life questionnaire module)
- Bristol Stool Form Scale (BSFS)

Findings

Health-related quality of life (QoL), measured using the EORTC QLQ-C30 and QLQ-GI.NET21, was an exploratory outcome in the TELESTAR trial and a secondary outcome in the TELECAST trial. Stool consistency was also an exploratory outcome in Study 301 and a secondary outcome in Study 303, measured using the BSFS. A summary of these outcomes and their measurement properties has been summarized in Table 13, followed by further detail subsequently.

Table 13: Summary of Outcome Measures and Their Measurement Properties

Instrument	Type	Evidence of Validity	MCID	References
EORTC QLQ-C30	30-item self-reported questionnaire that measures HRQoL of adult cancer patients based on a one-week recall and 4- and 7-point Likert-type scales.	Yes	General = 10 points Condition-specific not identified	*The EORTC QLQ-C30 Scoring Manual*[14] Osoba et al. 1998[15]
QLQ-GI.NET21	Supplementary module to the EORTC QLQ-C30, specific to patients with GI NETs. Self-reported based on one- or four-week recall and 4-point Likert-type scales.	Yes	Not identified	Yadegarfar et al. 2013[16] Johnson et al. 2011[19] Davies et al. 2006[17]
Bristol Stool Form Scale	The BSFS is a standardized method for classification of stool form that uses an ordinal scale from type 1 (hardest) to type 7 (softest), with types 1 and 2 considered abnormally hard/indicative of constipation, and types 6 and 7 being abnormally loose/liquid stools indicative of diarrhea.	Yes	Not identified	Blake et al., 2016 [20]

BSFS = Bristol Stool Form Scale; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GI = gastrointestinal; HRQoL = health-related quality of life; MCID = minimal clinically important difference; NET = neuroendocrine tumour; QLQ-GINET21 = 21-item gastrointestinal neuroendocrine tumour–specific QoL questionnaire.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0

The EORTC QLQ-C30 was created for use in clinical trials to assess the health-related quality of life of adult cancer patients. The original version, developed in 1987, was designed to be cancer-specific, multidimensional, easy for patients to complete, and applicable across various cultures.[14] Further, it is available in 90 different languages. Version 3.0, which is an updated version and the current standard for use in clinical trials,[14] was used in the clinical trials for telotristat.

The QLQ-C30 is a 30-question, patient-reported questionnaire comprising single-item measures and multi-item scales. This includes five functional scales, three symptom scales, a global health status (QoL) scale, and six single items. All but five of the items rely on a one-week recall, as the questions ask patients about their experience with their condition "during the past week." [14]A list of the scales and corresponding number of items has been provided in Table 14.

Table 14: Summary of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (Version 3.0), Items and Scales

Measures	Scales/Items	Item Range[a]	Number of Items
Global health status/QoL	Global health status / QoL (revised)	6	2
Functional scales	Physical functioning (revised)	3	5
	Role functioning (revised)	3	2
	Emotional functioning	3	4
	Cognitive functioning	3	2
	Social functioning	3	2
Symptom scales	Fatigue	3	3
	Nausea and vomiting	3	2
	Pain	3	2
Symptom items	Dyspnea	3	1
	Insomnia	3	1
	Appetite loss	3	1
	Constipation	3	1
	Diarrhea	3	1
	Financial difficulties	3	1

QoL = quality of life.

[a] Item range refers to the difference between the maximum and minimum response to individual items.

The two items related to global health status (QoL) are rated on a Likert-type scale from 1 ("very poor") to 7 ("excellent"); therefore, higher scores for this scale correspond to higher QoL for the patient. The remainder of the scales and single items are rated on a scale from 1 to 4, where 1 = "not at all," 2 = "a little," 3 = "quite a bit," and 4 = "very much." Higher scores for questions related to the functional scale correspond to a higher or healthy level of functioning, whereas a higher score for symptom scale and items correspond to a higher (worse) level of symptomology or problems. In addition, a linear transformation is used to convert each raw scale/item score to a standardized score that ranges from 0 to 100.[14] Moreover, the raw score for scales are derived from the mean of the component items.

Although well validated in cancer patients, evidence of validity for patients with NETs and/or carcinoid syndrome was not identified.

Bjordal et al. (2000) evaluated the reliability and validity of version 3.0 of the EORTC QLQ-C30 in a study involving 622 head and neck cancer patients from 12 countries. More specifically, the internal consistency reliability, construct validity, and responsiveness were assessed.[21] The EORTC QLQ-C30 was completed by patients before starting treatment or at a regular follow-up visit. The questionnaire was completed again within seven days or up to six weeks later, with a total of 591 (95%) patients having completed both of the questionnaires. Cronbach's alpha coefficient was used to assess the internal consistency of the scales of the questionnaire, which was greater than 0.70 for all of the scales. The reliability of the physical functioning scale of the QLQ-C30 specifically was assessed, as the response format was changed for the updated version. Cronbach's alpha coefficient for the updated scale had increased from 0.66 (earlier scale) to 0.84, indicating an improvement in internal consistency. The construct validity of the questionnaire was also assessed via a known-groups approach to assess the differences in the scales and single items between patients who had recently been diagnosed, patients with recurrent disease, and disease-free patients. There was a statistically significant difference across groups for the following domains: role functioning, emotional functioning, social functioning, fatigue, pain, appetite loss, insomnia, and general QoL, demonstrating construct validity. In addition, responsiveness was demonstrated by a change in scores of the questionnaire over time, although they were generally representative of a small-to-medium change (score difference of 5 to 10).[21] A difference of 10 points, which has been suggested as clinically meaningful (see next paragraph), was used to determine a change in the evaluation of responsiveness.

Lastly, an estimate for the minimally important difference was provided by Osoba et al.,[15] based on a sample of patients with breast and small-cell lung cancer. An anchor-based approach was taken, using global ratings of change measured by a subjective significance questionnaire, as an anchor. The mean change in scores for patients who indicated a small difference, either positive or negative, was 5 to 10 points.[15] A "moderate" change reported by patients had corresponding changes of about 10 to 20.[15] Similar findings were reported in a study by King, et al.[22] The two studies combined have resulted in a mean difference of 10 points being widely accepted as the minimal clinically important difference (MCID) for the EORTC QLQ-C30.[15,22] Of note, these evaluations are limited, as they may not be appropriate for all cancer patients and are also based on previous versions of the questionnaire. A specific MCID for carcinoid syndrome and NET was not identified from the literature search.

The 21-Item Gastrointestinal Neuroendocrine Tumour–Specific Quality-of-Life Questionnaire

To supplement the EORTC QLQ-C30, a variety of modules have been developed that are specific to the tumour site, treatment modality, or dimension of QoL. The modules have been designed for use in clinical trials, but are appropriate for other research settings as well.[19] The EORTC QLQ-GINET21 is a 21-item module that was developed for patients with gastrointestinal (GI) NET, and is available in at least nine languages.[16] The 21 items included in the module correspond to three multi-item symptom scales regarding endocrine symptoms ("ED;" three items), GI symptoms ("GI," five items), and treatment-related side effects ("TR;" three items), as well as two single-item symptoms for muscle and/or bone pain and concern about weight loss. It also includes two psychosocial scales related to social function ("SF21;" three questions), disease-related worries ("DRW;" three questions)

and two additional single items concerning sexual functioning and communication.[17] Similar to the core questionnaire, 19 of the 21 questions of the QLQ-GI.NET21 asks patients about their experience in the past week, or a one-week recall period.[17] The remaining two questions are about communication and sexuality, and are based on a four-week recall period. Items are scored on a four-point Likert-type scale from 1 to 4 ("not at all," "a little," "quite a bit," and "very much") and also, like the core questionnaire, scores are linearly transformed to a scale from zero to 100. Higher scores correspond to more a higher level of symptomology, or more severe symptoms.[16]

The QLQ-GINET21 module was validated in a study by Yadegarfar et al.[16] that included an international group of 253 adult patients with NET, either confirmed by histological diagnosis or a combination of radiological findings and elevated plasma hormone levels or urine indicative of a NET. Reliability was assessed in terms of internal consistency and test–retest reliability. The internal consistency of the module was assessed using Cronbach's alpha coefficient, which was acceptable in comparison with the generally accepted threshold of 0.70[23] for the ED, GI, and DRW scales (Cronbach's alpha = 0.80 to 0.79, and 0.83, respectively), but fell short for the TR and SF21 scales with a value of 0.54 and 0.57 for Cronbach's alpha, respectively. The intraclass correlation coefficient (ICC) was also used to evaluate the test–retest reliability of the questionnaire on a subset of the patients (n = 48) who were asked to complete the questionnaire a second time, 14 days post-baseline. An ICC of ≥ 0.90 was reported for all of the scales and single items, demonstrating acceptable test–retest reliability, with the exception of weight gain (0.84), muscle and/or bone pain (0.87), and communication (0.87).

Validity was also assessed in this population. The known-groups comparison approach using the Mann–Whitney U-test was used to assess the difference between subgroups of NET patients with differing clinical status based on Karnofsky performance status.[16] Statistically significant differences in scores were observed for each of the scales ($P < 0.001$) and the communication item ($P = 0.0029$), but not for weight gain ($P = 0.869$). Construct validity was also demonstrated, as all items had a strong correlation (> 0.50) with their own scales and < 0.40 with other scales, with the exception of SF21 and DRW, which correlated with four and one items, respectively, that were not included in the corresponding scales. In addition, the responsiveness to clinical change of health status over time was evaluated using three sets of questionnaires for each patient over time. In summary, the difference in mean scores over time, calculated by repeated-measure analysis of variance (ANOVA), was statistically significant for the ED, GI, SF21, and DRW scales, and the single-item question regarding weight loss.

Lastly, an MCID was not identified in the literature for the QLQ-GINET21 module.

Bristol Stool Form Scale

The BSFS was created to provide a standardized method for the classification of stool form, which is a proxy for determining stool consistency.[20] There are a number of stool scales available, with the BSFS being the most widely used both in clinical and research settings.[20] It is based on an ordinal scale from type 1 (hardest) to type 7 (softest), with types 1 and 2 considered abnormally hard and indicative of constipation, and types 6 and 7 being abnormally loose/liquid stools indicative of diarrhea (Table 15).[20] Each of the seven types are described using both written descriptors and pictorial representations.[20]

The validity and reliability of the BSFS was recently published in a study of healthy patients and patients with irritable bowel syndrome with diarrhea.[20] Concurrent validity was

determined through a comparison of the measured water content of real stools to the BSFS classification by 169 lay participants, as well as expert opinion from a GI researcher. The stool type classification was moderately correlated with the amount of water in the stool (Spearman's rho of 0.491) and 36% were correctly categorized by the healthy subjects, according to the expert's assignment indicating fair agreement (κ = 0.25). An assessment of construct validity was also performed through an analysis of stool samples from 169 healthy volunteers compared with 19 patients irritable bowel syndrome with diarrhea (IBS-D). The mean rating of BSFS type for stool from patients IBS-D was significantly greater (softer/looser) than that of healthy volunteers.[20] The accuracy of the BSFS was also evaluated using stool models, which demonstrated substantial overall accuracy (κ = 0.78). Inter-rater reliability was assessed as well, by comparing the healthy volunteers' classification of duplicate stool models, which revealed substantial intra-rater reliability (κ = 0.72). This corresponded to 76% of volunteers with the same stool type classification for duplicate models. No assessment or measure of responsiveness of the BSFS was identified to determine the extent that the score could capture changes over time or with treatment.[20] Lastly, no evidence of responsiveness to change or an MCID was identified.

Table 15: Bristol Stool Form Scale

Type	Description
Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on the surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges (passed easily)
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces, entirely liquid

Source: Blake 2016.[20]

Conclusion

In summary, the EORTC QLQ-C30 is a widely used patient-reported outcome measure of health-related QoL in cancer patients. It has been validated in terms of reliability, validity, and responsiveness, and the MCID has been estimated to be 10 points (improvement and deterioration) for both individual items and scale scores. A number of modules specific to cancer type have been developed to complement the EORTC QLQ-C30, including the QLQ-GINET21 for GI NETs and carcinoid syndrome. This module has been well validated as well, demonstrating acceptable reliability, validity, and responsiveness although internal consistency was below the accepted threshold for the treatment-related side effects scale and social functioning scale. Also, construct validity was not demonstrated for the item related to weight gain. An MCID was not identified for this module. Finally, the BSFS provides a standardized method for classifying stool form and is another widely used measure in both research and clinical settings. The BSFS has been validated in terms of reliability and validity; however, evidence of responsiveness and an MCID was not identified.

Appendix 6: Summary of Other Studies, TELECAST

TELECAST was a manufacturer-sponsored multinational double-blind randomized controlled trial that compared two different doses of telotristat (250 mg and 500 mg three times daily) with placebo over a 12-week double-blind treatment period. Only the approved 250 mg dose is reported in this review. This study was similar in design to the pivotal TELESTAR study; however, in TELECAST, patients were not required to be on somatostatin analogue (SSA) at baseline. Hence, this study did not meet the inclusion criteria for this systematic review. The patients on SSA were required to have fewer than four bowel movements a day, while those not taking SSA were to have at least four bowel movements daily. Other symptoms and signs of carcinoid syndrome could be similar between groups on SSA and those not on SSA. The primary outcome was the change in urinary 5-hydroxyindoleacetic acid (5-HIAA) from baseline to week 12; the secondary and other outcomes are listed and defined in Table 16.

In TELECAST, power calculations were performed according to the following assumptions: a two-sided blocked Wilcoxon Rank Sum (WRS) test, a mean difference between treatment groups of 40%, and a common standard of 35%, resulting in an effect size (mean / standard deviation [SD]) of 1.143, and this corresponded to a blocked WRS effect size of 0.79. This resulted in an estimated required sample size of 16 per group for 80% power, which was then adjusted again for an assumption of 10% withdrawals across groups, arriving at a final sample of 20 per group for the primary outcome. However, the manufacturer also posited that a sample of between 60 and 90 patients across the three groups would provide a more accurate assessment of safety, as a larger sample would have a higher probability of establishing a “true” incidence of adverse events. A hierarchical design was used to account for multiple tests of doses for the primary outcome, starting with the higher telotristat 500 mg dose, and the 250 mg dose was to be tested only if the prior test was statistically significant at an alpha of 0.05. Otherwise, no further adjustments were made for multiple comparisons beyond the primary outcome.

With respect to missing data, for outcomes with diary data, as long as at least 80% of the data were complete, the analysis used the mean response for that week, using the non-missing data; if less than 80% of the data were available, the mean response was set to “missing” for that week. For outcomes that included a change from baseline averaged daily over the double-blind treatment period, when there was more than six weeks of missing data, the change from baseline was imputed as zero. Otherwise the mean was derived from non-missing data. For the health-related quality-of-life outcomes, non-missing data were to be used, unless the data were missing for more than half of the items in the scale, in which case the score was set to missing.

The population in TELECAST were similar in demographics to TELESTAR: approximately 63 years old, similar percentages of males (53%) and females (47%), and almost all Caucasian (98%). As far as background SSA therapy, 88% were taking either octreotide (68%) or lanreotide (20%) in the telotristat group, while all placebo patients were on an SSA (octreotide: 46%; lanreotide: 54%).

Efficacy

Only the results for the approved telotristat 250 mg dose are reported here. A reduction in bowel movements after 12 weeks for telotristat versus placebo was observed; however,

there was no adjustment for multiple comparisons for this or any subsequent outcomes (Hodges–Lehmann estimate of treatment difference of −0.452 [95% confidence interval [CI], −0.719, −0.173]). As such, the risk of type I error was not controlled. In TELECAST, 40% of patients in the telotristat group and none in the placebo group experienced a durable response, defined as a reduction from baseline in daily bowel movements of ≥ 30% for at least 50% of the double-blind treatment period. The mean (SD) change in stool consistency in the telotristat group was −0.196 (0.712) and 0.006 (0.4127) with placebo, for a Hodges–Lehmann estimate of treatment difference of −0.203 (95% CI, −0.447 to 0.019). There were no differences between telotristat and placebo groups for any subscales of the QLQ-C30 or for daily flushing episodes or episodes of abdominal pain over the 12-week double-blind treatment period. A statistically significant reduction in urinary 5-HIAA of −53.955 mg/24 hours [95% CI, −84.955, −25.119], $P < 0.001$ was observed for telotristat versus placebo at 12 weeks, and this was the primary outcome of this study. This reduction from baseline was considered to be clinically significant by the clinical expert consulted on this review.

Harms

Only results for the approved telotristat 250 mg dose are reported here. There were no deaths in TELECAST. After 12 weeks, all telotristat patients and 81% of placebo experienced an adverse event, 4% of telotristat versus 19% placebo experienced a serious adverse event, and 8% of telotristat versus 4% of placebo patients withdrew due to an adverse event. Of the notable harms, depression occurred in 4% of telotristat patients and 8% of placebo, constipation in 16% of telotristat and 4% placebo, and elevations in alanine aminotransferase and gamma-glutamyltransferase occurred in 4% of telotristat patients, and none in placebo.

Limitations

The major limitation and the reason why this study did not meet the inclusion criteria for the systematic review is that patients were not required to be on SSAs. The findings from TELECAST are thus not generalizable to the indication for telotristat, as it is to be used in patients on SSA therapy. Other key limitations of TELECAST include the fact that the only outcome that was adjusted for multiple statistical comparisons was the surrogate end point of change from baseline in urinary 5-HIAA levels and, thus, the study was not designed to assess the impact of telotristat on bowel movements, the most important outcome for patients. A number of outcomes, including health-related quality of life and urinary 5-HIAA were not based on an ITT analysis and, thus, randomization may have been compromised. There was a significant amount of missing data for the 5-HIAA outcome, in particular, as only 68% of patients in the telotristat group had data reported at week 12.

Conclusions

Given the small sample size and limitations of its design, TELECAST adds little to our understanding of the efficacy of telotristat in managing carcinoid syndrome diarrhea. Aside from the generalizability issues (patients were not required to be on an SSA), the study was not designed to assess key outcomes such a change from baseline in daily bowel movements and, thus, no conclusions can be drawn about this critical outcome. Telotristat does appear to reduce the daily frequency of bowel movements by about 0.5; however, there is no indication that it improves symptoms or health-related quality of life and, in this respect, results were consistent with TELESTAR. The percentage of patients experiencing depressed mood was 4% with telotristat and 8% with placebo, constipation 16% versus 4%, respectively, and elevations in various liver enzymes, 4% versus zero with placebo.

Table 16: Study Design (TELECAST)

		TELECAST
Designs and Populations	**Study Design**	DB RCT
	Locations	31 sites: Canada, US, EU, Israel, Australia
	Randomized (N)	76
	Inclusion Criteria	Patients ≥ 18 years of age at the time of the screening visit Histopathologically confirmed, well differentiated, metastatic NET confirmed by CT, MRI, or radionuclide imaging Documented history of CS and met one of the following two criteria: • If currently receiving LAR/depot/infusion SSA therapy for the treatment of CS, must have been currently receiving a stable dose, averaging < 4 BMs/day, and must have had ≥ 1 of the following signs/symptoms of CS: ○ daily stool form/consistency ≥ 5 on the Bristol Stool Form Scale for ≥ 50% of the days during the run-in period ○ average daily flushing frequency of ≥ 2 ○ average daily rating of ≥ 3 for abdominal pain ○ nausea present ≥ 20% of days, or u5-HIAA > ULN • If not currently receiving SSA therapy, must have had ≥ 1 of the following signs/symptoms of CS: ○ daily stool form/consistency ≥ 5 on the Bristol Stool Form Scale for ≥ 50% of the days during the run-in period ○ average daily flushing frequency of ≥ 2 ○ average daily rating of ≥ 3 for abdominal pain ○ nausea present ≥ 20% of days ○ u5-HIAA >ULN ○ currently averaging ≥ 4 BMs/day
	Exclusion Criteria	• Presence of diarrhea attributed to any condition(s) other than CS, including, but not limited to, fat malabsorption or bile acid malabsorption • Presence of > 12 watery BMs/day associated with volume contraction, dehydration, or hypotension compatible with a “pancreatic cholera”-type clinical syndrome, as judged by the investigator • Positive stool examination for enteric pathogens, pathogenic ova or parasites, or *Clostridium difficile* at screening • Karnofsky performance status ≤ 60% • Clinical laboratory values for hematology (at screening): ○ absolute neutrophil count of ≤ 1,500 cells/mm3, or ○ platelets ≤ 75 000 cells/mm3, or ○ hemoglobin ≤ 9 g/dL for males and ≤ 8 g/dL for females • Hepatic laboratory values (at screening) such that: ○ aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is: ▪ ≥ 5.5 × ULN if patient had documented history of hepatic metastases, or ▪ ≥ 2.5 × ULN if patient did not have documented history of hepatic metastases • total bilirubin of > 1.5 × ULN (unless patient had a documented history of Gilbert’s syndrome), or • alkaline phosphatase (ALP) of ≥ 5 × ULN, if total bilirubin was > ULN (no upper limit on the ALP value if the total bilirubin was ≤ ULN) • Serum creatinine of ≥ 1.5 × ULN • Treatment with any tumour-directed therapy including, but not limited to: interferon, chemotherapy, or mTOR inhibitors < 4 weeks before screening, or hepatic embolization, radiotherapy, radio-labelled SSA, and/or tumour debulking < 12 weeks before screening • Major surgery, defined as procedures requiring general anesthesia or major regional anesthesia within 8 weeks before screening • A history of short bowel syndrome • Current complaints of constipation or history of chronic or idiopathic constipation within 2 years before screening • Life expectancy of < 12 months from the screening visit

		TELECAST
Drugs	**Intervention**	• Telotristat 250 mg orally three times daily • Telotristat 500 mg orally three times daily[a]
	Comparator(s)	Matching placebo
Duration	**Phase**	
	Run-in	3 to 4 weeks
	Double-blind	12 weeks
	Follow-up	2 weeks (plus 36 week open-label extension for all patients)
Outcomes	**Primary End Point**	Per cent change from baseline in 24-hour u5-HIAA levels at week 12 Occurrence of treatment-emergent adverse events
	Other End Points	*Secondary outcomes (all change from baseline):* • number of daily BMs averaged over the 12-week DBT period • stool form/consistency averaged across all time points during the DBT period • number of daily cutaneous flushing episodes averaged across all time points during the DBT period • abdominal pain averaged across all time points during the DBT period • frequency of rescue short-acting SSA used to treat CS symptoms averaged across all time points during the DBT period • number of daily BMs averaged over the 12-week DBT period and at each study week, among patients who were not receiving SSA therapy at baseline [redacted]
Notes	**Publications**	Pavel 2018

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BM = bowel movement; CS = carcinoid syndrome; CT = computerized tomography; DB = double-blind; DBT = double-blind treatment; LAR = long-acting release; [redacted] mTOR = mammalian target of rapamycin; NET = neuroendocrine tumour; [redacted] RCT = randomized controlled trial; SSA = somatostatin analogue; TST = telotristat; u5-HIAA = urinary 5-hydroxyindoleacetic acid; ULN = upper limit of normal.

[a] The telotristat 500 mg dose was not reported in results because only the 250 mg dose is approved in Canada.

Source: Clinical Study Report for TELECAST.[24]

Table 17: Baseline Characteristics (TELECAST)

Characteristics	TST 250 N = 25	PLA N = 26
Age (years), mean (SD)	63.6 (12.62)	62.2 (10.32)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Male sex, n (%)	14 (56.0)	13 (50.0)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
SSA therapy name at study entry		
Octreotide	17 (68.0)	12 (46.2)
Lanreotide	5 (20.0)	14 (53.8)
Unknown	0	0
Urinary 5-HIAA at randomization		
≤ ULN	5 (20.0)	9 (34.6)
> ULN	18 (72.0)	17 (65.4)
Unknown	2 (8.0)	0
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Metastases to liver	16 (64.0)	14 (53.8)
Carcinoid tumour	11 (44.0)	6 (23.1)
Neuroendocrine tumour	10 (40.0)	12 (46.2)
Metastases to lymph nodes	6 (24.0)	5 (19.2)
Metastatic carcinoid tumour	2 (8.0)	6 (23.1)
Metastases to bone	NR	NR
Neuroendocrine carcinoma metastatic	NR	NR
Psychiatric disorders	8 (32.0)	9 (34.6)
Depression	3 (12.0)	8 (30.8)
Insomnia	4 (16.0)	1 (3.8)
Anxiety	0	2 (7.7)
Carcinoid tumour of the small bowel	2 (8.0)	4 (15.4)

5-HIAA = 5-hydroxyindoleacetic acid; BM = bowel movement; PLA = placebo; NR = not reported; SD = standard deviation; SSA = somatostatin analogue; TST = telotristat; ULN = upper limit of normal.

Source: Clinical Study Report for TELECAST.[24]

Table 18: Disposition (TELECAST)

Characteristics	TST 250 N = 25	PLA N = 26
Assessed for eligibility	94	
Excluded	18	
Randomized	25	26
Completed the DBT period	22 (88.0)	24 (92.3)
Discontinued the DBT period	3 (12.0)	2 (7.7)
Adverse event	2 (8.0)	1 (3.8)
Death	0	0
Lack of efficacy	0	0
Physician decision	0	1 (3.8)
Withdrawal of consent	1 (4.0)	0
Other	0	0
Safety population	25 (100)	26 (100)
Intention-to-treat population	25 (100)	26 (100)
Per-protocol population	18 (72.0)	25 (96.2)

DBT = double-blind treatment; PLA = placebo; TST = telotristat.

Source: Clinical Study Report for TELECAST.[24]

Table 19: Efficacy (TELECAST)

	TST 250 N = 25	PLA N = 26
Average number of BMs at baseline mean (SD)	2.529 (1.2497)	2.186 (0.6706)
Mean (SD) change from baseline in the number of BMs averaged over the DBT period (12 weeks)	−0.452 (0.6940) N = 25	0.050 (0.3263) N = 25
Differences in arithmetic means, TST minus placebo (95% CI)	−0.502 (−0.810 to −0.194)	
Hodges–Lehmann estimate of treatment difference, TST minus placebo (95% CI)[a]	−0.452 (−0.719 to −0.173) *P* = 0.004	
Quality of BM		
Mean (SD) baseline stool form/consistency	5.113 (0.8410)	4.965 (0.9052)
Mean (SD) change from baseline in stool consistency averaged across all time points (12 weeks)	−0.196 (0.7012) N = 25	0.006 (0.4127) N = 25
Hodges–Lehmann estimate of treatment difference (TST minus placebo) (95% CI)[a]	−0.203 (−0.447 to 0.019) *P* = 0.09	
Quality of Life (EORTC QLQ-C30)		
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[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]

	TST 250 N = 25	PLA N = 26
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[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]

	TST 250 N = 25	PLA N = 26
[redacted]		
Symptoms		
Mean (SD) change from baseline in number of daily cutaneous flushing episodes averaged across all time points during the DBT period (12 weeks)	−0.061 (0.9754) N = 25	−0.333 (1.2203) N = 25
Hodges–Lehmann estimate of treatment difference, TST minus placebo (95% CI)[a]	0.105 (−0.173 to 0.614)	

	TST 250 N = 25	PLA N = 26
	P = 0.67	
Mean (SD) change from baseline in abdominal pain averaged across all time points during the DBT period (12 weeks)	−0.234 (0.9697) N = 25	−0.063 (0.7823) N = 25
Hodges–Lehmann estimate of treatment difference, TST minus placebo (95% CI)[a]	0.058 (−0.424 to 0.332) *P* = 0.61	
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[redacted]		
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[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
Biomarkers		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Hodges–Lehmann estimate of treatment difference (TST minus placebo) (95% CI)[a]	−53.955 (−84.955 to −25.119) *P* < 0.001	

5-HIAA = 5-hydroxyindoleacetic acid; BM = bowel movement; CI = confidence interval; CS = carcinoid syndrome; [redacted] DBT = double-blind treatment; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; PLA = placebo; SD = standard deviation; SSA = somatostatin analogue; TST = telotristat; ULN = upper limit of normal.

[a] The primary analysis used a blocked two-sample Wilcoxon rank sum statistic (i.e., van Elteren test) stratified by the urinary 5-HIAA at randomization.

[redacted]

[c] *P* values were calculated based on a continuity-adjusted chi-squared test.

Source: Clinical Study Report for TELECAST.[24]

Table 20: Harms (TELECAST)

	TST 250 N = 25	PLA N = 26
Adverse Events		
Patients with an AE, n (%)	25 (100)	21 (80.8)
Most common (10% in any group)		
Nausea	3 (12.0)	4 (15.4)
Abdominal pain	8 (32.0)	4 (15.4)
Diarrhea	4 (16.0)	5 (19.2)
Abdominal distension	3 (12.0)	0
Abdominal pain upper	1 (4.0)	3 (11.5)
Fatigue	3 (12.0)	2 (7.7)
Pyrexia	3 (12.0)	0
Urinary tract infection	3 (12.0)	0
Dizziness	0	3 (11.5)
Flushing	3 (12.0)	2 (7.7)
Serious Adverse Events		
Patients with an SAE, n (%)	1 (4.0)	5 (19.2)
WDAE		
Patients with WDAE, n (%)	2 (8.0)	1 (3.8)
Mortality		
Deaths, n	0	0
Notable Harms		
Depressed mood, n (%)	1 (4.0)	2 (7.7)
Depression	0	0
Decreased interest	0	1 (3.8)
Constipation	4 (16.0)	1 (3.8)
ALT increased	1 (4.0)	0
GGT increased	1 (4.0)	0
Liver function test abnormal	0	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; [redacted]GGT = gamma-glutamyltransferase; PLA = placebo; SAE = serious adverse event; SD = standard deviation; TST = telotristat; WDAE = withdrawal due to adverse event.

Source: Clinical Study Report for TELECAST.[24]

Appendix 7: Summary of Other Studies, Open-Label Extensions

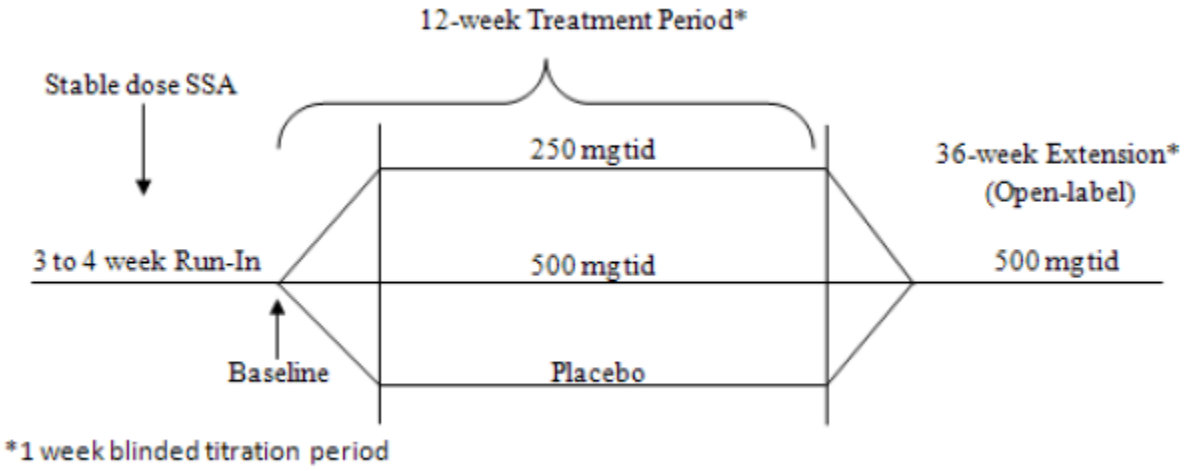
Objective

The objective is to summarize the results of the 36-week open-label extension (OLE) phase of both Study 301 (TELESTAR) and Study 303 (TELECAST). The aim of the OLE was to assess the long-term efficacy and safety of continued treatment with telotristat ethyl (telotristat) at a dose of 500 mg three times daily, in patients experiencing refractory carcinoid syndrome diarrhea that is inadequately controlled by somatostatin analogue (SSA) therapy alone.

Methods

The two parallel-group, multi-centre, double-blind randomized controlled trials of interest to this review, Study 301 (TELESTAR) and Study 303 (TELECAST), involved a three- to four-week screening / run-in period, a 12-week double-blind treatment (DBT) period, and finally a 36-week OLE period beginning at week 13. A summary of the treatment schema is shown in Figure 3. Patients were randomized to one of three treatment groups during the DBT period: 250 mg telotristat, 500 mg telotristat, or placebo, all taken three times a day. Upon completion of the DBT period, all patients who continued to the OLE underwent a one-week blinded titration to 500 mg telotristat, which was the dose used for the remainder of the OLE. Of note, the data has been reported by the original treatment group patients were assigned to during the DBT period), and the titration period was blinded to preserve blinding from the DBT period. Patients who experienced intolerability were able to lower their dose to 250 mg of telotristat three times daily, and those who experienced intolerability at 250 mg three times daily were discontinued from the study.

Figure 3: Treatment Schema (Figure 9.1-1 From Clinical Study Reports)



SSA = somatostatin analogue; tid = three times daily.
Source: Clinical Study Report 301,[6] Clinical Study Report 303.[24]

The key efficacy outcomes included frequency of bowel movements (BM), quality of BM, measurements of health-related quality of life via the EORTC QLQ-C30 and QLQ-GINET21, symptoms of carcinoid syndrome (cutaneous flushing episodes and abdominal pain), urgency (immediate need to defecate), and urinary 5-hydroxyindoleacetic acid (u5-HIAA) biomarker. Safety data of interest included treatment-emergent adverse events (TEAEs) or adverse events (AEs), treatment-emergent serious AEs (SAEs), withdrawal from study due to AE (WDAE), and deaths. Safety outcomes related to depression (depression, depressed mood) and liver enzymes (gamma-glutamyl transferase [GGT], aspartate aminotransferase [AST], and alanine aminotransferase [ALT]) were also included as notable AEs. Efficacy data were reported via descriptive summaries and changes from baseline during the OLE phase, and safety data were descriptive as well. No statistical testing was performed.

Results

Of those who completed the TELESTAR trial, 39 (92.9%), 38 (100%), and 38 (100%) from the 250 mg, 500 mg, and placebo treatment arms, respectively, continued to the OLE phase (Table 21). All of the patients who completed the TELECAST trial continued to the OLE phase, with the exception of one patient from the 500 mg treatment arm. The completion rate for the OLE phase was approximately 69% and 70% for the two trials. The most common reasons why patients discontinued the TELESTAR and TELECAST trials were due to AEs (13.0% and 10.4%), withdrawal of consent (7.8% and 13.4%), and lack of efficacy (4.3% and 1.5%).

Table 21: Patient Disposition From Start of Open-Label Extension Period (Week 13)

	[redacted]			TELECAST (N = 67)		
	[redacted]	[redacted]	[redacted]	TST 250 mg	TST 500 mg	Placebo
Continued to OLE phase, n (%)	[redacted]	[redacted]	[redacted]	22 (88.0)	21 (84.0)	24 (92.3)
Completed OLE phase, n (%)	[redacted]	[redacted]	[redacted]	19 (86.4)	13 (61.9)	15 (62.5)
Discontinued OLE phase, n (%)	[redacted]	[redacted]	[redacted]	3 (13.6)	8 (38.1)	9 (37.5)
AE	[redacted]	[redacted]	[redacted]	2 (9.1)	1 (4.8)	4 (16.7)
Lack of efficacy	[redacted]	[redacted]	[redacted]	0	1 (4.8)	0
LTFU	[redacted]	[redacted]	[redacted]	0	0	0
Physician decision	[redacted]	[redacted]	[redacted]	0	1 (4.8)	0
Withdrawal of consent	[redacted]	[redacted]	[redacted]	1 (4.5)	4 (19.0)	4 (16.7)
Other	[redacted]	[redacted]	[redacted]	0	1 (4.8)	1 (4.2)

AE = adverse event; LTFU = lost to follow-up;OLE = open-label extension; TST = telotristat.

Source: Clinical Study Reports 301[6] and 303.[24]

[redacted]

[redacted]

Table 22: Baseline Characteristics Prior to the Double-Blind Period for Patients Entering the Open-Label Extension

	TELESTAR [redacted]			TELECAST [redacted]		
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[redacted]

Source: Clinical Study Reports 301[6] and 303.[24]

[redacted]

[redacted]

Table 23: Key Efficacy Outcomes, TELESTAR [redacted]

		TELESTAR		
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		TELESTAR		
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[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: Clinical Study Reports 301[6] and 303.[24]

Table 24: Key Efficacy Outcomes, TELECAST Intention-to-Treat Population (N = 67)

		TELECAST		
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Source: Clinical Study Reports 301[6] and 303.[24]

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Table 25: Summary of Adverse Events (Safety Population)

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Source: Clinical Study Reports 301[6] and 303.[24]

Limitations

There are a number of limitations associated with the OLE phases of the TELESTAR and TELECAST trials that should be noted. Firstly, this was an open-label phase of the study that lacked a comparator, which makes the true long-term effect of telotristat ethyl 500 mg three times daily difficult to interpret. This becomes more problematic due to the absence of any statistical testing, as well as a discontinuation rate of ≥ 30%. Moreover, the OLE evaluated the efficacy and safety of a dose of telotristat at 500 mg three times daily, which is greater than what has been approved for use in Canada (250 mg telotristat, three times daily), and thus a major limitation in terms of generalizability in the Canadian context. Also of note, it was reported that 13 patients in the TELESTAR trial and five patients in the TELECAST trial underwent a dose reduction during the OLE; however, the data were not reported by this subgroup, and the duration of dose reduction was also not reported.

Summary

In summary, the changes for the efficacy outcomes between baseline of the DBT period and the end of week 48 were minimal. For the outcomes where an observed change was reported, a wide range and small sample size was also noted, which lessens the confidence in the results. Regarding the safety outcomes, most patients reported having experienced an AE during the OLE phase, with the most commonly reported events being abdominal pain, nausea, vomiting, and diarrhea. Reporting of AEs related to depression and an increase of hepatic enzymes were also noted, which should be carefully considered. Finally, 7.8% of patients in the OLE of the TELESTAR trial were reported as having a TEAE resulting in death.

Appendix 8: Summary of Other Studies, TELEPATH

Objective

To summarize the results of the long-term safety extension (LTSE) of the phase II and phase III studies of telotristat, which evaluated the long-term safety and efficacy of treatment with telotristat in combination with somatostatin analogue (SSA) therapy in patients experiencing refractory carcinoid syndrome diarrhea that is inadequately controlled by SSA therapy alone.

Methods

The characteristics of Study LX1606.1-302-CS (Study 302 or TELEPATH) are outlined in Table 26. TELEPATH was an open-label, LTSE of the phase III telotristat studies, i.e., TELESTAR and TELECAST, as well as the preceding phase II studies, which were conducted in 11 countries including Canada, the US, Australia, and countries in Europe. Those who participated in the phase II and phase III studies (including the open-label extension [OLE] of TELESTAR and TELECAST) were eligible for enrolment in Study 302 if they had no major violations or concerns regarding tolerability of the study drug. Participants were not randomized for the LTSE; they were assigned to the same dose level and regimen that they were taking in the parent study, that is, 250 mg of oral telotristat three times daily or 500 mg of oral telotristat three times daily. Downward dose adjustments were permitted if there was evidence of intolerability; however, those requiring an adjustment below a 250 mg dose were discontinued from study treatment. The LTSE is currently ongoing; therefore, there are participants who have not yet reached week 84 (end of study).

The primary end point for TELEPATH was incidence of treatment-emergent adverse events (TEAEs), and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was included as a secondary end point for the efficacy analysis. Primary end points such as change from baseline in clinical laboratory results, vital sign results, and electrocardiogram findings, and other secondary end points related to quality-of-life (QoL) outcomes were also included; however, only select clinical laboratory results related to hepatic enzymes, i.e., alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) were reported in this review summary.

The safety population (N = 66) was used to evaluate the safety outcomes, and the efficacy outcomes were evaluated using the per-protocol population (N = 66). The efficacy outcomes were assessed at baseline and at week 24, 48, 72, and 84 but, as noted, this study is currently ongoing and therefore only data collected up until October 16, 2015 was available from the interim Clinical Study Report provided. A mixed model with repeated measures analysis was used to account for missing data for the efficacy analysis of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) data.

Table 26: Characteristics of TELEPATH (Study 302)

		TELEPATH (Study 302)
Designs and Populations	**Study Design**	Open-label, LTSE study
	Locations	Canada, USA, Australia, Europe
	Enrolled (N)	71 (66 included)
	Inclusion Criteria	Ongoing participation in a phase II (LX1606.1-202-CS or -203-CS) or phase III (LX1606.1-301-CS/TELESTAR or -303-CS/TELECAST) study
	Exclusion Criteria	Major protocol violations or concerns regarding tolerability of study drug in a phase II or phase III study
Drugs	**Intervention**	250 mg telotristat three times daily, orally 500 mg telotristat, three times daily, orally Same dose level and regimen as identified in the parent study
	Comparator(s)	NA
Duration	**Phase**	
	Extension period	84 weeks
	Follow-up	2 weeks
Outcomes	**Primary End Point**	• Incidence of TEAEs • Change from baseline in clinical laboratory results • Change from baseline in vital sign results • Change from baseline in ECG findings
	Other End Points	• EORTC QLQ-C30 (version 3.0) questionnaire • EORTC QLQ-GINET21 questionnaire • Subjective global assessment of symptoms associated with CS
Notes	**Publications**	None

ALT = alanine aminotransferase; AST = aspartate aminotransferase; EORTC = European Organization for Research and Treatment of Cancer; GGT = gamma-glutamyl transferase; LTSE = long-term safety extension; NA = not applicable; QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-GINET21 = 21-item gastrointestinal neuroendocrine tumour–specific quality-of-life questionnaire; TEAE = treatment-emergent adverse event.

Source: Clinical Study Report 302.[25]

Results

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Table 27: Baseline Characteristics

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Source: Clinical Study Report 302.[25]

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Table 28: Patient Disposition

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Source: Clinical Study Report 302.[25]

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Table 29: Summary of Adverse Events

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Source: Clinical Study Report 302.[25]

Table 30: Summary of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Scores (Per-Protocol Population)

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CI = confidence interval; SD = standard deviation; QoL = quality of life.

[a] As part of the group of symptom subscales, a higher score for diarrhea corresponds to a higher level of symptom or worse state of the patient.

[b] Change from baseline value based on n = 37.

Source: Clinical Study Report 302.[25]

Limitations

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Summary

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