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Patient-reported Symptom Experiences in Patients With Carcinoid Syndrome After Participation in a Study of Telotristat Etiprate: A Qualitative Interview Approach

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Abstract

Purpose: Telotristat etiprate, a tryptophan hydroxylase inhibitor, was previously evaluated in a Phase II randomized, placebo-controlled clinical trial in patients with carcinoid syndrome (CS) and diarrhea not adequately controlled by octreotide. The objective of the current study was to characterize the symptom experiences of patients participating in that trial.

Methods: Consenting patients participated in one-on-one, qualitative interviews focused on eliciting symptoms they had experienced in association with their CS diagnosis and recollection of symptom changes they experienced while participating in the Phase II trial.

Findings: Among the 23 patients who participated in the previous 4-week dose-escalation study, 16 were eligible for interviews and 11 participated in the present study. The median time from study completion to the interview was 31 months; 4 of 11 patients were receiving telotristat etiprate in a follow-up, open-label trial at the time of interview. All of the patients (100%) described diarrhea as a symptom of CS, with effects on the emotional, social, and physical aspects of their lives. Improvement in diarrhea during the study was described by 82% of participants, and was very impactful in several patients. Results led to the design and implementation of a larger

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CONFLICTS OF INTEREST

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interview program in Phase III and helped to establish a definition of *clinically meaningful change* for the clinical development program.

Implications: The diarrhea associated with CS can have a large impact on daily lives, and patient interviews can characterize and capture clinically meaningful improvements with treatment.

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Keywords

carcinoid syndrome; patient-reported; qualitative; telotristat etiprate

INTRODUCTION

Neuroendocrine tumors (NETs) are thought to arise from neuroendocrine cells and are often found in the gastrointestinal tract; these tumors occur in ~2 per 100,000 persons.¹ Approximately 3 in 10 people with NETs will develop symptoms known as *carcinoid syndrome* (CS).² Patients with CS generally have advanced, metastatic disease and a survival rate lower than that in patients without CS.³ Common symptoms of CS include diarrhea; flushing of the upper chest, neck, and face; abdominal pain; difficulty breathing; and heart valve dysfunction.⁴

Because CS is relatively rare, there is little experience in formally characterizing the condition with standardized patient-reported outcomes questionnaires. Furthermore, clinical trials in CS have small sample sizes, making it difficult to capture statistically significant and clinically meaningful changes with standardized instruments. In this situation, careful review of individual responses becomes especially important, and an interview approach in which the patient can provide a first-hand description of their clinical trial experience is particularly valuable.

Telotristat etiprate is a tryptophan hydroxylase inhibitor developed to treat CS by reducing the production of serotonin within the metastatic neuroendocrine tumor cell. Initial evidence of efficacy was obtained in a 4-week placebo-controlled Phase II clinical study of telotristat etiprate.⁵ In that study, patients were treated in escalating-dose cohorts, and were randomly assigned in a 3:1 ratio to receive either telotristat etiprate or placebo. Clinical response (defined as at least a 50% reduction in bowel movement frequency for at least 2 weeks) was observed in 5 of 18 patients (28%) treated with telotristat etiprate compared with 0 of 5 patients on placebo. There was only 1 overall evaluation of the patient experience, a weekly question (with a “yes” or “no” answer) about the presence of adequate relief of gastrointestinal symptoms of CS. Adequate relief was reported in 10 of 18 telotristat etiprate-treated patients (56%) during at least 1 of the first 4 weeks of treatment, compared with zero patients on placebo.

While these observations clearly suggested that telotristat etiprate has biological activity, key questions remained as to the clinical relevance of these findings. Furthermore, the optimal strategy to assess patient-reported outcomes in Phase III clinical development was unclear. To help address these issues, retrospective interviews of Phase II clinical trial participants were performed.

The objectives of the interviews were to characterize the participants' CS experiences and to identify the important changes they experienced in their symptoms during the clinical trial of telotristat etiprate, during the 4-week, blinded, dose-escalation phase and/or the open-label extension phase.

PATIENTS AND METHODS

Participants

All recruiting sites from the Phase II clinical trial (LX1606.202)⁵ were invited to join the present qualitative interview study, and 2 of the 8 sites chose to participate. A member of each site's study staff contacted potential participants to explain the purpose, procedures, benefits, and risks of the present interview-based study using a standardized recruitment script. If the patient was interested in participating, the site's staff member documented eligibility and obtained written informed consent and the participant was scheduled for an interview. All study procedures were approved by an institutional review board.

Participants meeting the following inclusion criteria were eligible for the study: participation in the previous telotristat etiprate Phase II clinical trial⁵; 18 years of age or older; able to participate in a one-on-one telephone interview; able to read, speak, and understand English and complete all study assessments; and willing and able to provide written informed consent before the interview. Participants with a cognitive or other impairment (eg, vision or hearing) that would have interfered with completing the interview were not eligible for the study.

Interview Procedures

Before each participant's telephone interview, he or she received a packet that contained an introductory letter, the European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal NET questionnaire (GI.NET-21),^{6,7} the EORTC Quality of Life (QOL) Questionnaire (QLQ-C30; EORTC 2012),⁸ and a Sociodemographic and Clinical Characteristics form. The questionnaires were in a sealed envelope and participants were directed not to open these materials until instructed to do so by the interviewer. Participants were asked to return the materials at the conclusion of the interview.

Trained and experienced interviewers, blinded to treatment arm, conducted the one-on-one interviews over the telephone using a prescribed interview discussion guide to assess the participants' symptom experiences. The interview began with confirmation of the patient having previously provided written informed consent, followed by an overall explanation of the study; the interview then moved into a prescribed discussion of the patient's experiences with symptoms of CS. The interviews were audio-recorded and then subsequently transcribed.

Questionnaires and Forms

The EORTC GI.NET-21⁷ is a 21-item self-reported questionnaire module supplemental to the EORTC QLQ-C30,⁸ a 30-item questionnaire assessing the QOL of patients with cancer. The GI.NET-21 comprises questions assessing disease symptoms, adverse events

with treatment, body image, disease-related worries, social functioning, communication, and sexuality. These measures were scored according to the developer's guidelines.

The Sociodemographic and Clinical Characteristics form was used for documenting the participants' self-reported information on age, race, employment status, education, and current CS symptoms; this information was used for assisting with interpretation of the results of individual interviews.

Staff members from the clinical sites were asked to complete a clinical form for each participant who provided informed consent and who completed an interview. The clinical form documented information such as tumor site, concurrent medications, and time since diagnosis. The information from the EORTC measures and the clinical forms was used for describing the sample and assisting with interpretation of the results of the interviews.

Data Analysis

Data from the qualitative interviews were analyzed with a content analysis approach using qualitative data analysis software (ATLAS.ti version 5.2).⁹ A coding dictionary, based on the themes and concepts that emerged during the interviews, was developed to group words and phrases provided by the interview participants into key themes, attributes, concepts, and relationships.^{10,11}

The principal investigator (H.L.G.) conducted an internal training with the team member(s) who were coding the transcripts to ensure that the meaning and purpose of each code were understood, in turn to ensure consistency in coding of the transcripts. The interview transcripts were independently coded by 2 team members (J.K. and P.A.), which was followed by comparison and reconciliation whenever differences occurred. Coded text was associated with qualitative output tables that identified and categorized participants' responses.

The key themes and concepts that were identified were entered into a saturation grid, with each case serving as a column and each concept serving as a row. Concepts identified in each interview were analyzed, with the goal of comparing and tallying the amount of novel information that was observed in each subsequent interview. Descriptive statistics (mean, SD, frequency) were used for characterizing the sample in terms of sociodemographic and clinical characteristics.

RESULTS

Sample Description

A total of 11 participants were interviewed for the study between December 20, 2012, and February 15, 2013, and 10 of the interview participants returned all of the postinterview study materials. Reported sociodemographic characteristics (Table I) and clinical disease characteristics (Table II) are based on these 10 participants. The calculated mean time between end of participation in the telotristat etiprate core study and this study interview was 29.5 months.

Site staff at the telotristat etiprate study sites also provided clinical information on the participants (Table III). All of the participants (100%) had NETs that had metastasized; the most commonly reported metastatic site was the liver (n = 9 [82%]). Four of the 11 participants (36%) were in the open-label phase of the telotristat etiprate clinical trial at the time of their interviews. A majority of the participants (n = 9 [82%]) were on long-acting octreotide treatment and had received, on average, 1 injection in the past month. Two participants (18%) had received embolizations since exiting the telotristat etiprate clinical trial.

EORTC QLQ-30 and GI.NET-21

On the EORTC measures, higher global health scores represent better QOL, and high scores on the functional scale represent a higher level of functioning; however, higher scores on the symptom scales represent more symptoms. Participants in this study had scores reflecting poorer QOL, symptoms, and functioning than the general population, with mean global health status/QOL, physical functioning, role functioning, and emotional functioning scores of 56.7, 71.7, and 80.0, respectively, compared with general population's reference values of 71.2, 89.8, 84.7, and 76.3, respectively.¹² Of the symptom scales assessed, diarrhea, had the highest reported mean (70.0; general population reference, 7.0), followed by fatigue (48.9; general population reference, 24.1), and insomnia (36.7; general population reference, 21.8). Other mean symptom scale scores ranged between 10.0 and 53.3, with constipation and nausea exhibiting the lowest values. Table IV summarizes participants' mean and median scores on the EORTC QLQ-30 during the interview study.

For the GI.NET-21, a higher score was equivalent to worse symptoms or problems. In general, participants scored below a mean of 50 across all subscales. Table V summarizes the participants' responses on the GI.NET-21 during the interview study.

Most Commonly Reported Symptoms Attributed to CS

Table VI summarizes the symptoms attributed to CS. Participants generally described diarrhea as the most severe and frequent symptom. Most participants were actively seeking treatment to decrease their diarrhea and had varying levels of success with multiple medications. Urgency related to diarrhea was described as severe, and participants mentioned difficulty controlling their bowels, which often was associated with bowel-related accidents. The frequency of diarrhea was usually the participants' main concern. Improvement in this symptom was most commonly described as a reduction in the frequency of bowel movements. Several participants described being embarrassed or anxious about dining out in public and/or traveling due to their diarrhea, and needing to be aware of bathroom locations when they did leave the house.

All of the participants (n = 11 [100%]) reported experiencing abdominal pain, while 6 of the participants (55%) also reported having abdominal cramping, a symptom that the participants reported as distinct from abdominal pain. Both pain and cramping were symptoms that participants experienced daily and caused some of the participants to take pain medications due to the severity.

Nine of the participants (82%) reported that they experienced flushing. Their experiences were consistent in some ways; all of them reported redness/flushing in the face and most of them reported that these experiences were not painful or very noticeable. Four of the participants mentioned that they knew that they were experiencing flushing only when someone asked about it during an episode. Nine participants (82%) reported being tired or experiencing fatigue. Participants described having to nap or rest during the day because they felt exhausted and had no energy. One participant mentioned being able to sleep 20 of 24 hours. This symptom was described as severe, and participants felt fatigued even after a full night of rest. Some participants noted that sleep interruptions, often related to diarrhea, would cause them to be tired the next day. Fatigue also affected participants' ability to complete daily activities, such as work and family obligations, and caused irritability and problems with mental acuity.

Impact of CS

Several of the participants discussed specific effects of CS symptoms. The most common concern described was an unwillingness, or inability, to travel or participate in hobbies or usual activities due to concerns about bowel accidents and/or loss of control of bodily functions (eg, diarrhea, gas, belching). A few mentioned an impaired ability to sleep associated with waking up to go to the bathroom, and effects on mood (including irritability) that were particularly noticeable as their long-acting somatostatin analogue wore off near the end of the dosing interval (generally after 3–4 weeks).

Reported Changes in CS

In response to queries about changes in symptomatology that the patients experienced specifically during the Phase II clinical trial of telotristat etiprate, there were 21 symptoms reported by between 1 and 9 of the participants. It should be noted that 1 participant on telotristat etiprate 350 mg tid indicated that there was no change in any symptoms during the clinical trial, and another participant on telotristat etiprate 150 mg TID noted that he or she did not recall his or her symptom experience during the trial. Symptoms reported by 3 or more participants are summarized in Table VI. The most commonly reported changes were in diarrhea, abdominal pain, flushing, and abdominal cramping. There were 6 participants who reported a large number (ie, >3) of changes in symptoms, while the remaining 3 participants reported changes in only 1 or 2 symptoms in response to treatment with telotristat etiprate. No worsening of symptoms was described with telotristat etiprate use.

Among the transcripts, one of the most informative was from a patient who had an interruption in therapy. Her experience has been described elsewhere.¹³ She believed that her relief of diarrhea was too great to be explained by a placebo effect: "I don't think anybody that's had as violent diarrhea as I have had for as many years as I have had it could psychologically change with a placebo." Her therapy was stopped for about a week because of a rash that was initially suspected to be related to study drug. Therapy was resumed after the investigator attributed the rash to another cause. The patient recalled this episode spontaneously in great detail, expressing concerns about the potential of not being able to continue receiving a medication that had been so important to her. As indicated in the

electronic diary, in the first week during the study, the bowel movement frequency had an initial reduction from 8.2 to ~3 or 4 per day. This frequency returned to baseline during the interruption of therapy, and came back down to ~4 per day with the resumption of treatment. She was on telotristat etiprate 500 mg TID.

Another relevant transcript was from a patient on telotristat etiprate 250 mg TID whose reduction in bowel movement frequency in the electronic diary developed gradually but also reached a magnitude of at least 30% in weeks 3 and 4. He said, “once I started seeing some improvement I naturally had a sense of well-being, I felt good, I felt like, you know, I wanted to go outside again, I wanted to go uptown to the grocery store with my wife.” He spoke about being less embarrassed about his condition (not having to buy adult diapers), and about seeing a greater effect of concurrent medications; he felt that a slowing of gastrointestinal transit time allowed him to obtain pain relief from his analgesic medication.

Bowel movement frequency data from all 11 patients from the double-blind period and extension were reviewed, and overall a mean reduction in bowel movement frequency of 1.2 per day was associated with more positive descriptions of the clinical trial experience. Given the characteristics of this population, the data support the concept of a 30% reduction being used for a responder analysis in Phase III.

DISCUSSION

The results of the present study provide an understanding of how diarrhea, a primary symptom of CS, affects the lives of patients with CS and show that it affects social functioning (eg, difficulty with travel) and sleep (eg, waking up at night to have a bowel movement), and that diarrhea may be related to fatigue or tiredness in some patients. This improved understanding of the impact of diarrhea supports the clinical importance of reducing bowel movement frequency as a primary end point in CS clinical trials. Use of diarrhea as a symptomatic end point in clinical trials is consistent with regulatory guidance on the use of patient-reported outcomes as clinical end points.¹⁴

The small sample size and the fact that only a subset of patients in the treatment study were interviewed preclude any firm conclusions about the efficacy of telotristat etiprate. However, the patients' descriptions suggest that treatment may help to improve several symptoms, and they provide support for a patient interview approach in assessing the clinical relevance of symptom relief, in combination with other patient-reported outcomes measures, in future studies. Key concepts for consideration as end points in future CS clinical trials should include diarrhea, abdominal pain, abdominal cramping, flushing, and gas. Other symptom concepts that may be worthy of consideration include lack of appetite, dehydration, fatigue/tiredness, and sleep interruptions.

The results of the interviews further support the selection of flushing and abdominal pain as secondary end points in Phase III clinical trial programs, and they suggest a role for the EORTC-QLQ-C30 and EORTC QLQ-GI.NET21. Relevant concepts in the QLQ-GI.NET21 include diarrhea (item 17), abdominal discomfort (item 34), flushing (item 31), gas (item

36), energy/tiredness (item 18), appetite and eating (items 13 and 38), and night sweats (item 33). In addition, the QLQ-GI.NET21 addresses limitations to hobbies or other leisure activities (item 7) and interference with social activities (item 27).

The interviews support the selection of a definition of *clinically meaningful change* for Phase III clinical development: a 30% reduction in bowel movement frequency experienced for at least half of the days during the double-blind treatment period.

The results of this study suggest limitations in the EORTC QLQ-C30 and GI.NET21 in assessing patients with CS. The greatest priority of patients was reducing bowel movement frequency, which is captured in only 1 domain. The overall EORTC-QLQ-C30 may not be expected to show statistically significant improvement because it includes 30 items and provides equal weight to all of them. The domains include concepts such as financial worries that are not necessarily related to treatment. A validation study of the EORTC QLQ-C30 and GI.NET21 showed responsiveness on the subscales of diarrhea, appetite loss, disease-related worries, and social functioning when patients initiated antitumor therapy, while several other domains showed little change.¹⁵

Therefore, a strategy of repeating the interviews in Phase III of development of telotristat etiprate was chosen as a means of supplementing the standardized questionnaire. The interviews in Phase III were to be done prospectively at the time of completion of double-blind treatment. Patients were to be interviewed only once (no baseline interview) to minimize their burden. The interviews were to include questions about whether the changes that patients experienced were meaningful, and participant responses would be analyzed in relation to the objective data on bowel movement frequency obtained from electronic diaries.

The results of the present study should be interpreted with consideration of a few limitations. First, the study comprised a fairly small sample of 11 participants, and only those patients who had participated in the earlier clinical trial were eligible for the interview study. Second, only 2 of 7 centers that enrolled patients into the Phase II trial agreed to participate in the patient interview study, thus reducing the number of potentially eligible participants from 23 to 16. At the time of the interviews, only 4 of the participants were in the open-label phase of the clinical trial, while the others had completed their trial participation; thus, recall accuracy and bias may have been issues as, for most patients, there was a long gap between study participation and the interview. This time lag (>2 years for several individuals) was related to the processes of interview protocol development and ethics committee approval, which were initiated after the results from the double-blind portion became available. However, most of the patients appeared to have had very good and detailed recollections of their experiences, as evidenced by the detailed and consistent descriptions of their symptom and treatment experiences that they were able to provide during the interviews. As CS is very rare, a qualitative approach with interviews has been highly informative. Finally, those who agreed to participate in the interviews may have been more willing to participate due to a positive response to therapy, and further, those who were participating in the open-label extension phase of the study were obviously aware of their treatment status.

The results of this study were included in a constructive dialogue with the US Food and Drug Administration (FDA) about clinically meaningful change and the choice of the primary end point for Phase III. The FDA accepted the interview results as a part of an overall dossier that served to define clinically meaningful change. In this respect, the exercise provides useful information and an example of how patient-reported outcomes can support a clinical development program and an overall regulatory strategy, even if they are not intended for a specific role of labeling.

The exercise is also consistent with guidance on patient-reported outcomes issued by the FDA.¹⁴ In particular, the FDA encourages the development of an end point model. The interview approach in this study can form the basis of a model by connecting different signs, symptoms, and patient-reported outcomes: high bowel movement frequency is a central issue for patients, and it directly affects the ability of patients to enjoy life and participate in social and physical activities.

More broadly, the interviews reflect greater patient engagement in the conduct of clinical research. The value of this engagement is increasingly recognized and supported by groups such as the Patient Centered Outcomes Research Institute.¹⁶

The approach used for this study may be helpful for other conditions. Common practice now includes holding focus groups with patients early in clinical development and piloting patient-reported outcomes assessments in Phase II. Yet focus groups are not always conducted early, and the size of the patient population for rare diseases may not support recruitment of individuals for this purpose. Furthermore, it may be difficult to select or reject instruments based on quantitative data from small numbers of patients in Phase II studies. In such cases, a detailed qualitative assessment based on patient interviews that are conducted in parallel with the trial may be the most feasible and informative approach to the identification, selection, and refinement of appropriate end points and their corresponding measures. Even in larger-scale Phase III trials, direct interviews may identify patients' priorities more effectively and provide a better context for interpreting clinically meaningful change than standardized questionnaires, or may perhaps provide a complementary approach.

CONCLUSIONS

The findings from this qualitative interview study suggest that bowel movement frequency in patients with CS is a clinically relevant end point with a significant impact on patients' lives. The results also suggest that telotristat etiprate may improve key aspects of CS that are important to patients. These observations have guided the selection of end points, instruments, and an interview substudy in the Phase III clinical program for telotristat etiprate. The approach described for identifying relevant symptoms and their impact on daily life may be relevant to patient-reported outcomes strategies for other oncology studies and studies of other rare conditions.

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All of the authors reviewed and approved the final version of the manuscript.

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Table I.Participant-reported sociodemographic characteristics at the time of questionnaire completion (N = 10^{*}).

Participant Characteristic	Value
Age, y	
Mean (SD)	57.0 (7.1)
Median (range)	57.0 (46–69)
Sex, no. (%)	
Female	5 (50.0)
Male	5 (50.0)
Hispanic or Latino, no. (%)	0
Race, no. (%)	
White	10 (100)
Employment status, [†] no. (%)	
Employed full-time	4 (40.0)
Employed part-time	1 (10.0)
Retired	3 (30.0)
Disabled	3 (30.0)
Highest level of education, no. (%)	
Secondary/high school	2 (20.0)
Some college	1 (10.0)
College degree	3 (30.0)
Postgraduate degree	4 (40.0)

* One participant did not return the postinterview study materials.

[†] One participant indicated both employed part time and disabled.

Table II.Participant-reported clinical characteristics at the time of questionnaire completion (N = 10^{*}).

Clinical Characteristic	Value
General health state in past week, no. (%)	
Very good	1 (10.0)
Good	3 (30.0)
Fair	6 (60.0)
Number of bowel movements in past 24 h	
Mean (SD)	8.3 (5.5)
Median (range)	5.5 (3–20)
Level of abdominal pain experienced today, no. (%)	
None	6 (60.0)
Mild	2 (20.0)
Moderate	1 (10.0)
Severe	1 (10.0)
Number of daily cutaneous flushing episodes in past 24 h	
Mean (SD)	0.5 (0.8)
Median (range)	0.0 (0–2)
Felt or experienced a sense of urgency to pass stool today, no. (%)	
No	1 (10.0)
Yes	9 (90.0)

* One participant did not return the postinterview study materials.

Table III.

Clinician-reported clinical characteristics at the time of questionnaire completion (N = 11).

Clinical Characteristics	Value
Neuroendocrine tumor has metastasized, no. (%)	
Yes	11 (100)
On octreotide treatment, no. (%)	
No	2 (18.2)
Yes	9 (81.8)
Number of octreotide injections in past month	
Mean (SD)	0.8 (0.4)
Median (range)	1.0 (0–1)
Value of most recent urinary 5-HIAA test (mg/24 h) [*]	
Mean (SD)	25.4 (26.7)
Median (range)	19.0 (3–68)
Carcinoid therapies received because exiting trial, no. (%)	
Embolization [‡]	2 (18.2)
None	5 (45.5)
Not applicable; participant on long-term extension of LX1606.202 trial	4 (36.4)

^{*} Three participants had missing values. One participant, whose results were reported in alternative units (5280 ng/mL), was not included in the calculation of the mean.

[‡] The normal range for the urinary 5-HIAA test is 2 to 6 mg/24 h.¹⁷

[‡] Often performed on liver metastases in the setting of progressive disease.

Table IV.EORTC QLQ-C30 (N = 10).^{*}

Questionnaire Variable	Value
Global health status/QOL [†]	
Mean (SD)	56.7 (11.7)
Median (range)	50.0 (42–75)
Functional scale [‡]	
Physical functioning	
Mean (SD)	82.7 (13.8)
Median (range)	80.0 (60–100)
Role functioning	
Mean (SD)	71.7 (20.9)
Median (range)	66.7 (33–100)
Emotional functioning	
Mean (SD)	80.0 (21.6)
Median (range)	83.3 (25–100)
Cognitive functioning	
Mean (SD)	61.7 (31.5)
Median (range)	58.3 (0–100)
Social functioning	
Mean (SD)	53.3 (15.3)
Median (range)	58.3 (33–67)
Symptom scales/items [§]	
Fatigue	
Mean (SD)	48.9 (26.3)
Median (range)	44.4 (0–89)
Nausea and vomiting	
Mean (SD)	10.0 (16.1)
Median (range)	0.0 (0–50)
Pain	
Mean (SD)	25.0 (23.9)
Median (range)	33.3 (0–67)
Dyspnea	
Mean (SD)	26.7 (21.1)
Median (range)	33.3 (0–67)
Insomnia	
Mean (SD)	36.7 (36.7)
Median (range)	33.3 (0–100)
Appetite loss	
Mean (SD)	26.7 (30.6)
Median (range)	33.3 (0–100)

Questionnaire Variable	Value
Constipation	
Mean (SD)	0.0 (0.0)
Median (range)	0.0 (0–0)
Diarrhea	
Mean (SD)	70.0 (29.2)
Median (range)	66.7 (33–100)
Financial difficulties	
Mean (SD)	53.3 (39.1)
Median (range)	50.0 (0–100)

* Scores range from 0 to 100, with a high scale score representing a higher response level. Each subscale is based on the after items: global health status/quality of life (QOL) (items 29 and 30), physical functioning (1–5), role functioning (6 and 7), emotional functioning (21–24), cognitive functioning (20 and 25), social functioning (26 and 27), fatigue (10, 12, and 18), nausea and vomiting (14 and 15), pain (9 and 19), dyspnea (8), insomnia (11), appetite loss (13), constipation (16), diarrhea (17), and financial difficulties (28).

[†] A high score on the global health status/QOL subscale represents a high quality of life.

[‡] A high score on the functional subscale represents a high/healthy level of functioning.

[§] A high score is equivalent to worse or more problems.

Table V.

GI.NET21 (N = 10).

Questionnaire Variable	Value
Subscale [*] †	
Endocrine symptoms scale	
Mean (SD)	17.8 (10.7)
Median (range)	16.7 (0–33)
GI symptoms scale	
Mean (SD)	28.7 (19.9)
Median (range)	23.3 (7–60)
Treatment-related symptoms scale	
Mean (SD)	20.8 (26.8)
Median (range)	11.1 (0–67)
Social function scale	
Mean (SD)	37.8 (24.1)
Median (range)	27.8 (11–78)
Disease related worries	
Mean (SD)	38.9 (24.1)
Median (range)	33.3 (11–100)
Symptoms	
Muscle/bone pain symptom	
Mean (SD)	46.7 (35.8)
Median (range)	33.3 (0–100)
Sexual function	
Mean (SD)	41.7 (29.5)
Median (range)	50.0 (0–67)
Information/communication function	
Mean (SD)	6.7 (14.1)
Median (range)	0.0 (0–33)
Body image	
Mean (SD)	16.7 (36.0)
Median (range)	0.0 (0–100)

* Scores range from 0 to 100, with a high scale score representing a higher response level. Each subscale is based on the after items: endocrine scale (items 31–33); gastrointestinal scale (34–38); treatment scale (39, 40, and 46); social function scale (42, 44, and 49); disease related worries scale (41, 43, and 47); muscle/bone pain (48), sexual function (51), information/communication function (50), and body Image (45).

† A high score is equivalent to worse or more problems.

Table VI.

Most common participant-reported symptoms associated with carcinoid disease in 3 participants, and reported changes during the LX1606.202 study, by recall (N = 11). Data are given as number (%) of patients.

Symptom	Reported Symptoms	Participant Recalls Improvement in Symptom During Participation in LX1606.202 Study
Diarrhea	11 (100)	9 (82)
Abdominal pain	11 (100)	5 (45)
Flushing	9 (82)	4(36)
Fatigue/tiredness	9 (82)	2 (18)
Sleep interruptions	8 (73)	0
Irregular heartbeat	7 (63)	1 (9)
Abdominal cramping	6 (55)	4 (36)
Feeling sick	5 (45)	0
Wheezing	5 (45)	0
Gas	4 (36)	3 (27)
Breathing difficulty	4 (36)	0
Blood in stool	3 (27)	0
Dehydration	3 (27)	2 (18)
Lack of appetite	3 (27)	2 (18)
Hot flashes/night sweats	3 (27)	1 (9) each