Title
Evaluation of meaningful change in bowel movement frequency for patients with carcinoid syndrome.

Permalink
https://escholarship.org/uc/item/5xf0231g

Journal
Journal of patient-reported outcomes, 3(1)

ISSN
2509-8020

Authors
Hudgens, Stacie
Ramage, John
Kulke, Matthew
et al.

Publication Date
2019-10-26

DOI
10.1186/s41687-019-0153-y

Peer reviewed
Evaluation of meaningful change in bowel movement frequency for patients with carcinoid syndrome

Stacie Hudgens 1*, John Ramage 2, Matthew Kulke 3, Emily Bergsland 4, Lowell Anthony 5, Martyn Caplin 6, Kjell Öberg 7, Marianne Pavel 8, Jonathon Gable 1, Phillip Banks 9, Qi Melissa Yang 9 and Pablo Lapuerta 9

Abstract

Background: Carcinoid syndrome is associated with a reduced quality of life that can be attributed to symptoms such as diarrhea and fatigue as well as social and financial issues. This study was conducted to psychometrically assess meaningful change in bowel movement frequency among carcinoid syndrome patients using data from the TELESTAR clinical study.

Methods: An anchor-based approach for deriving meaningful change thresholds consisted of mapping change from baseline bowel movement frequency to other patient-reported assessments of change. These included the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core Questionnaire (QLQ-C30) Diarrhea Symptom responders, the EORTC Gastrointestinal NET questionnaire (GLNET21) GI Symptom responders, and reported adequate relief at Week 12 (≥ 10-point score decrease from Day 1 to Week 12). Parameters included within-group mean change from baseline to Week 12, t-tests of the change (Wilcoxon rank sum for adequate relief), and effect size.

Results: There were 135 carcinoid syndrome patients with a mean baseline frequency of 5.7 bowel movements a day. A distribution-based method yielded meaningful change estimates of 0.62 bowel movements a day for overall frequency and 0.83 bowel movements a day at Week 12. Anchor-based analysis indicated a large effect size among patients who reported adequate relief at Week 12 (~1.58; n = 18; P = 0.014), the QLQ-C30 Diarrhea domain responders (~1.24; n = 40; P < 0.001), and the GLNET21 GI Symptoms Domain responders (~1.49; n = 25; P = 0.005). Exit interview data for meaningful change yielded effect size estimates of ~1.57 for overall change during the Double-blind Treatment Period and ~1.97 for change between Baseline and Week 12.

Conclusions: Meaningful change derivation is critical to interpret patient outcomes for evaluating treatment efficacy. In this study, carcinoid syndrome patients experienced clinically meaningful reductions in bowel movement frequency of ≥30% over 12 weeks with telotristat ethyl treatment.

Trial registration: NCT01677910.

Keywords: Carcinoid syndrome, Bowel movement frequency, Meaningful change
Introduction
Carcinoid tumors are well-differentiated neuroendocrine tumors (NETs) that originate in neuroendocrine cells [1]. Advanced disease is associated with a reduced health-related quality of life (HRQoL) related to diarrhea, fatigue, and flushing symptoms, besides family, social, and financial issues [2–5]. These NETs usually occur in the small intestine and represent about 0.5% of all newly diagnosed malignancies with an annual incidence of approximately 2 per 100,000 persons [6, 7]. The overall 5-year survival rate is 67.2% [6]. Carcinoid tumor (CS) is caused by bioactive compounds released into the circulation, occurring in almost 20% of NETs patients [8]. Large amounts of serotonin (5-hydroxytryptamine [5-HT]) release is believed to cause diarrhea, endocardial and mesenteric fibrosis [9–11].

The TELESTAR study was conducted to psychometrically assess meaningful change in bowel movement (BM) frequency and evaluate the efficacy and safety of telotristat ethyl in CS patients with diarrhea not adequately controlled by somatostatin analogs (SSA) (TELESTAR study; NCT01677910). The primary objective of TELESTAR was to confirm that at least 1 or more doses of telotristat ethyl in CS patients with diarrhea not adequately controlled by SSA was effective in reducing the number of daily BMs from baseline averaged over the 12-week double-blind period (Treatment Period) [12].

Methods
Study design
The design and results of TELESTAR have been previously described [13]. Briefly, patients entered a Screening/Run-in Period of 3- or 4-weeks to establish Baseline symptoms. They were then randomly assigned (1:1:1) on Day 1 to receive one of two dose levels of telotristat ethyl (250 or 500 mg) or placebo thrice daily for 12 weeks. All patients remained on their baseline dose of SSA therapy during the Treatment Period. Subsequently, they participated in a 36-week Open-label Extension Period when everyone received 500 mg of the active study drug thrice daily. This study received Institutional Review Board approval.

The focus is on the primary endpoint, change from baseline in BM frequency during the Double-blind Treatment Period. The intent-to-treat (ITT) analysis population included all randomized patients. All analyses populations were derived from the ITT dataset. All patients participating in the patient interview substudy after the Double-blind Treatment Period were included in the patient interview subpopulation (ISP).

Study instruments
Evaluation of meaningful change in BM frequency required the inclusion of other supportive clinical outcomes assessments: a Yes/No question about CS gastrointestinal symptom relief; European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core Questionnaire (QLQ-C30) and EORTC Gastrointestinal NET questionnaire (GI.NET21) scales; and patient exit interview responses.

Number of daily BMs
Patients electronically recorded the number of daily BMs. The average BM number was mapped to individual analyses using the following criteria: difference between average Baseline BM frequency and the overall average BM frequency; and the difference between average Baseline BM frequency and average BM frequency at Week 12.

EORTC QLQ-C30 and GI.NET21
The QLQ-C30 contained 30 questions incorporated into 5 functional domains (Physical, Role, Cognitive, Emotional, and Social), 9 symptom scales (Fatigue, Pain, Nausea and Vomiting, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties), and a single global HRQoL/Global Health Status scale [14].

The GI.NET21 module contained 21 questions: 4 single-item assessments about muscle and/or bone pain, body image, information, and sexual functioning, plus 17 items organized into 5 scales: Endocrine Symptoms (3 items), GI Symptoms (5 items), Treatment-related Symptoms (3 items), Social Functioning (3 items) and Disease-related Worries (3 items) [15].

Exit interviews
English- and German-speaking patients were invited to participate in the exit interview study as prespecified in the TELESTAR protocol [16]. All participants consented to the interview procedure to be conducted within 2 weeks after they completed the 12-week Double-blind Treatment Period or early termination. Patients were categorized based on reported satisfaction with improvement over the course of treatment (“very satisfied”; “somewhat satisfied”; “neither satisfied nor dissatisfied”; “somewhat dissatisfied”; or “very dissatisfied”). Patients were also categorized according to perception of BM frequency reduction (“a great deal better”; “much better”; “a little better”; “the same”; “a little worse”; “much worse”; or “a great deal worse”).

Analytic methods
Analyses focused on the derivation and evaluation of thresholds to interpret meaningful change and responsiveness in BM frequency. All patients were included irrespective of receiving treatment (n = 90) or placebo (n = 45). Analyses was conducted using SAS Version 9.3 or higher (SAS Institute, Cary, NC, USA) [17].

Meaningful change on a patient-centered endpoint referred to the smallest difference in scores in the domain
of interest (e.g., symptom or functional score), which patients perceived as beneficial. This could then be used further to discriminate between treatment groups and develop a thorough understanding of the HRQOL impact of BM frequency reduction [18, 19].

Change in BM frequency from Baseline was used to develop two individual distribution-based estimates: (1) overall change from Baseline, defined as the difference between average BM frequency during the Run-In Period and average BM frequency during the Double-Blind Treatment Period; and (2) change from Baseline at Week 12, defined as the difference between average BM frequency during the Run-In Period and 7-day average BM frequency at Week 12. Distribution-based thresholds were derived for both estimates independently using the 1/2 standard deviation (SD) rule [18], which is 1/2 the SD of both estimates.

The anchor-based approach to derive meaningful change thresholds consisted of mapping change from Baseline in BM frequency to other patient reported assessments of change. The relationship between BM frequency and each continuous patient-reported outcome (PRO) anchor was evaluated prior to inclusion in the anchor based analysis using correlational analyses. The criterion threshold value for determining if the anchor was correlated with the outcome is a correlation coefficient > 0.30 at Baseline, Week 12, or change from Baseline [18]. Anchor-based thresholds were developed by calculating mean change and the associated effect size (ES) statistic for each anchor-based. The ES was calculated from the difference between average score in BM frequency over 12 weeks and average Baseline BM frequency, this difference being divided by the SD of average Baseline BM frequency. A negative ES represented BM frequency reduction compared to Baseline [19, 20].

An additional analysis was conducted, where ES was calculated as the mean score in average BM frequency at Week 12 minus the average Baseline BM frequency divided by the SD of the group average Baseline BM frequency. For both analyses, a single value (or range of values for interpreting change in BM frequency) was derived by calculating mean change and the associated effect size (ES) statistic for each anchor-based. The ES was calculated from the difference between average score in BM frequency at Week 12 minus the average Baseline BM frequency divided by the SD of the group average Baseline BM frequency. A negative ES represented BM frequency reduction compared to Baseline [19, 20].

Relationship between potential PRO anchors and BM frequency
Only the QLQ-C30 Diarrhea symptom score yielded a correlation coefficient with average BM frequency exceeding the acceptability threshold of > 0.30 at Week 12 (Pearson = 0.42; Spearman = 0.45). Correlation was at least equal to the acceptability threshold for two items: (1) between change from baseline in the QLQ-C30 Diarrhea symptom score at Week 12 and in overall BM frequency (Pearson = 0.38; Spearman = 0.31); (2) and a correlation between change from baseline in GLN.NET21 GI Symptoms domain score at Week 12 and change from baseline in overall BM frequency (Pearson = 0.30; Spearman = 0.30).

Anchor-based analysis of meaningful overall change from baseline in BM frequency
An anchor-based analysis of thresholds for meaningful overall change in BM frequency produced a large ES (defined as > 0.80) among ITT patients reporting adequate relief at Week 12 (~1.20), EORTC QLQ-C30 Diarrhea Symptom scale (~0.83) and EORTC GLN.NET21
GI Symptoms scale (−1.25) responders. Wilcoxon Rank Sum test analysis indicated a significant difference in adequate relief groups (P-value = 0.011), EORTC QLQ-C30 Diarrhea Symptoms domain (P-value = 0.019), and EORTC GI.NET21 GI Symptoms domain responders and non-responders (P-value < 0.001) (Table 1). Large ES estimates were observed among ISP patients whose perception of change was “a great deal better” (−1.57) and “much better” (−1.52), patients who reported being “very satisfied” (−1.30) and “somewhat dissatisfied” (−1.24) with symptom relief, the collapsed improvement category for carcinoid symptom relief (−0.93), and those that considered their perception of change in BM frequency to be clinically meaningful (−0.99). Kruskal-Wallis Exact test indicated a significant difference between the perceptions of change in BMs response groups (P-value = 0.005) (Fig. 1).

**Analysis of meaningful change in BM frequency at week 12**
Anchor-based analysis indicated a large ES among ITT patients who reported adequate relief at Week 12 (−1.58), responders on the EORTC QLQ-C30 Diarrhea domain (−1.24), and the EORTC GI.NET21 GI Symptoms Domain (−1.49) (Table 1). Wilcoxon Rank Sum test analysis indicated a significant difference in adequate relief groups (P-value = 0.014), EORTC QLQ-C30 Diarrhea Symptoms domain (P-value < 0.001), and EORTC GI.NET21 GI Symptoms domain responders and non-responders (P-value = 0.005).

A large ES was observed among ISP patients who reported change of “A great deal better” and “Much better” in BMs (−1.97, −1.83, respectively), patients who improved in the collapsed perception categories (−0.99), patients who reported being “very satisfied” with the relief (−1.53), improved in the collapsed satisfaction categories (−1.23), and patients who reported their perception of change in BM frequency clinically meaningful (−1.27) (Fig. 2). Kruskal-Wallis Exact test indicated a significant difference between the perceptions of change in BM response groups (P-value = 0.029).

**Distribution-based thresholds**
Overall, the thresholds for meaningful change in overall average BM frequency at baseline and the change in average BM frequency from baseline at Week 12 were 0.62 and 0.86 BM/day, respectively (Table 1).

**Responsiveness**
Responsiveness analysis suggested that change from baseline in overall average BM frequency was moderately responsive to patient reported changes (Table 2). There were large reductions in average weekly BMs among patients indicating a change from “No” at baseline to “Yes” in adequate relief at Week 12 (SES = −0.99), patients that indicated a great deal of improvement in BMs (SES = −1.44), and among patients who were “Very satisfied” (SES = −1.18) with their relief. The number of ISP patients stratified into the perception of change and satisfaction with study medication response was suboptimal.

Responsiveness analysis indicated slightly greater reductions in BM frequency from baseline at Week 12 when compared to change during the Double-blind Treatment Period. Large negative SES values were observed across several item response categories, including patients who changed their response on the adequate relief item to “Yes” at Week 12 as well as those that continued to report “No” (SES = −1.40 and −0.81, respectively), patients whose self-reported perception of change was “A great deal better” (SES = −1.80), and among patients who reported being “Very satisfied” with their relief of CS symptoms (SES = −1.38).

Cumulative distribution function curves in Figs. 3 and 4 show a clear separation of treatment and placebo at identified thresholds of meaningful change.

---

**Table 1** Summary of Meaningful Change Thresholds

| Parameter | Threshold for Acceptability | Analysis Population | Average Number of Daily BMs | Overall Change from Baseline | Change from Baseline at Week 12 |
|-----------|-----------------------------|---------------------|-----------------------------|-----------------------------|--------------------------------|
|           |                             |                     | N  | ES  | Mean | N  | ES  | Mean |
| Anchor-based Meaningful Change Thresholds |                             |                     |    |     |      |    |     |      |
| Adequate relief (changed to Yes at Week 12) | Effect Size: | ITT | 19 | −1.20 | −1.90 | 18 | −1.58 | −2.52 |
| EORTC QLQ-C30 Diarrhea (Responder) | Small (≥ 0.2) | ITT | 45 | −0.83 | −1.71 | 40 | −1.24 | −2.56 |
| EORTC GI.NET21 GI Symptoms (Responder) | Moderate (≥ 0.5) | ITT | 30 | −1.25 | −1.88 | 25 | −1.49 | −2.27 |
| EORTC GI.NET21 GI Symptoms (Responder) | Large (≥ 0.8) | ITT | 135 | N/A | 0.62 | 108 | N/A | 0.86 |

BM Bowel movement, EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire, ES Effect size, ITT Intent-to-treat, N/A Not applicable, SD Standard deviation
**Discussion**

Diarrhea is a prominent feature of CS, which may require a different impact measurement approach than other forms of diarrhea to understand clinically meaningful change. A distribution-based method yielded meaningful change estimates of 0.62 BM/day for overall BM frequency and 0.83 BM/day at Week 12, indicating that patients whose average BM frequency increased or decreased by more than that level were reporting a meaningful change. An anchor-based approach was developed using exit interview data and change in scores. The QLQ-C30 Diarrhea Symptom and GI.NET21 GI Symptoms scale were found to have an association > 0.3, and were thus used to derive estimates of meaningful change. Specifically, change from baseline in the QLQ-C30 Diarrhea symptom score at Week 12 correlated with Change from baseline in Overall BM frequency at 0.38. When applying exit interview data as the basis for meaningful change, patients’ perception of change in BMs since beginning the study yielded ES estimates of −1.57 for overall change during the Double-blind Treatment Period and −1.97 for change between baseline and Week 12.

When analyzing the responsiveness of BM frequency to various levels of patient reported change, ES estimates for the perception of change item for both overall change and change from Week 12 were significantly different despite the low subject numbers interviewed after the Double-blind Treatment Period. The ES estimates (and the accompanying threshold of −1.97 BMs) could be valuable when approximating meaningful change in BM frequency. When applying these thresholds to the clinical change results in the CDF curves, the trend towards greater reductions in BM frequency among the treatment patients indicate a higher percentage would exceed the anchor and distribution-based thresholds, although this would need to be confirmed as part of an efficacy analysis.

Current clinical outcome assessment research has demonstrated that it is possible to establish defensible
**Table 2** Summary of Responsiveness Results

| Parameter                                      | Threshold for Acceptability | Analysis Population | Average Daily BMs                                      |
|------------------------------------------------|-----------------------------|---------------------|-------------------------------------------------------|
|                                                 |                             | N                  | SES        | Change from Baseline at Week 12 |                                 |
| Responsiveness (SES)                           |                             | ITT                 | 19         | -0.99 | 18 | -1.40 |
| Adequate relief (changed to Yes at Week 12)*   | Standard Effect Size:       |                     |            |            |                                 |
|                                                 | Small (≥ 0.2)               |                     |            |            |                                 |
|                                                 | Moderate (≥ 0.5)             |                     |            |            |                                 |
|                                                 | Large (≥ 0.8)               |                     |            |            |                                 |
| Perception of change in BMs^b                  |                             | ISP                 | 9          | -1.44 | 8  | -1.80 |
| A great deal better                            |                             | ISP                 | 4          | -0.50 | 4  | -0.60 |
| Much better                                    |                             | ISP                 | 7          | -0.15 | 6  | -0.38 |
| Satisfaction with study medication—Relief of CS^c |                             | ISP                 | 12         | -1.18 | 12 | -1.38 |
| Very satisfied                                 |                             | ISP                 |            |            |                                 |
| Somewhat satisfied                             |                             | ISP                 |            |            |                                 |

*Bowel movement, CS Carcinoid syndrome, ISP Interview subpopulation, ITT Intent-to-treat, SES Standardized effect size*

*There were *n* = 75 "not changed to yes at Week 12"*

*There were *n* = 10 "a little better"; *n* = 10 "the same"; and *n* = 1 "a little worse"*

*There were *n* = 8 "neither satisfied nor dissatisfied"; *n* = 3 "somewhat dissatisfied"; and *n* = 3 "very satisfied"*
responder thresholds, which support informed treatment decisions [22]. Some physicians interpret clinically meaningful change based on means; however, it is important to examine the distribution of response as in the CDF. The relevance of the CDF is reflected by its inclusion in product labeling [23]. Figure 4 shows that some responders achieved reductions in the range of 3 to 9 BMs/day on treatment, but not on placebo. These are results averaged over 12-weeks, corresponding to BM reductions during this time frame.

A limitation is that a minimum change is difficult to identify. The mean BM frequency change in a responder group is not necessarily a minimum; it would be of interest to examine empiric density distributions to see which levels of BM frequency change distinguish between responders and non-responders.

**Conclusions**

Meaningful change derivation is critical for the interpretation of patient outcomes in the evaluation of treatment efficacy. Analyses identified a meaningful change
in BM frequency which would coincide with improvement across each of the patient reported anchors (retropective and prospective). More specifically, CS patients treated with telotristat ethyl experienced clinically meaningful reductions in BM frequency of ≥30% over 12 weeks.

Abbreviations

ANOVA: Analysis Of Covariance; BM: Bowel movement; CDF: Cumulative distribution function; CS: Carcinoid syndrome; EORTC: European Organization for Research and Treatment of Cancer; ES: Effect size; GLNET21: EORTC Gastrointestinal NET; HRQoL: Health-related quality of life; ISP: Interview subpopulation; ITT: Intent-to-treat; NET: Neuroendocrine tumors; PRO: Patient-reported outcome; QLQ-C30: Quality of Life Questionnaire - Core Questionnaire; SD: Standard deviation; SES: Standardized effect size; SSA: Somatostatin analogs

Acknowledgments

The authors thank the patients who shared their experiences from the TELESTAR clinical trial with the interviewers.

Authors’ contributions

SH: study concepts; study design; data acquisition; quality control of data and algorithms; data analysis and interpretation; statistical analysis; manuscript preparation; manuscript editing; manuscript review. JR: data analysis and interpretation; manuscript preparation; manuscript editing; manuscript review. MK: data analysis and interpretation; manuscript preparation; manuscript editing; manuscript review. EB: data analysis and interpretation; manuscript preparation; manuscript editing; manuscript review. LA: data analysis and interpretation; manuscript preparation; manuscript editing; manuscript review. MC: data analysis and interpretation; manuscript preparation; manuscript editing; manuscript review. KD: data analysis and interpretation; manuscript preparation; manuscript editing; manuscript review. PB: study concepts; study design; data acquisition; data analysis and interpretation; manuscript preparation; manuscript editing; manuscript review. QMY: study concepts; study design; data acquisition; data analysis and interpretation; manuscript preparation; manuscript editing; manuscript review. PL: study concepts; study design; data acquisition; data analysis and interpretation; manuscript preparation; manuscript editing; manuscript review. All authors read and approved the final manuscript.

Funding

This work was supported by Lexicon Pharmaceuticals, Inc.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This observational study included no administration of any therapeutic or prophylactic agent. There were no anticipated physical risks or direct benefits to patients participating in the study, although patients may become uncomfortable or emotional discussing their experiences with carcinoid syndrome symptoms. As such, participation was completely voluntary and participants could withdraw at any time and still receive (as applicable) the full exit study incentive. Participation in the exit interview was not a requirement for TELESTAR clinical trial participation (e.g., should a patient decide not to participate in an exit interview, they could still continue in any remaining clinical trial activities [e.g., open-label treatment period]). An incentive for participation in the exit interview substudy was provided, if approved by each participating clinical site’s local ethics review board, to compensate patients for their time. The amount and payment methods was reviewed and approved by each ethics committee to ensure that payments (if allowed) were commensurate with the time needed to participate in the interview and were not coercive.

Consent for publication

Not applicable.

Competing interests

S. Hudgens and J. Gable are employed by Clinical Outcomes Solutions, the organization contracted by Lexicon to analyze the data and develop this manuscript. These authors have no additional financial relationships or otherwise to declare. M. Kulkle has received consulting fees from Lexicon, Novartis, and Ipsen outside the submitted work. E. Bergland is an uncompensated adviser for Lexicon Pharmaceuticals, Inc., and Ipsen. L. Anthony has received grants from Lexicon Pharmaceuticals Inc. M. Caplin has received compensation from Lexicon Pharmaceuticals Inc for participation on an advisory board. K. Öberg has received honoraria and speakers’ bureau fees from Novartis and Ipsen. M. Pavel has received consulting fees from Lexicon Pharmaceuticals Inc, Novartis, and Ipsen. P. Banks, Q.M. Yang, and P. Lapuerta are all currently employees of Lexicon Pharmaceuticals Inc and own stock. The authors have declared that they have no other competing interests regarding the content of this article.

Author details

1CEO & Strategic Lead, Quantitative Science, Clinical Outcomes Solutions, 1790 E. River Rd, Suite 205, Tucson, AZ 85718, USA. 2Hamphshire Hospitals NHS Foundation Trust, Aldermaston Road, Basingstoke, Hampshire RG24 9NA, UK. 3Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215, USA. 4UCSF Helen Diller Family Comprehensive Cancer Center, 1450 3rd St, San Francisco, CA 94158, USA. 5University of Kentucky, 410 Administration Dr, Lexington, KY 40508, USA. 6Royal Free Hospital, Pond St, Hampstead, London NW3 2QG, UK. 7Uppsala University, 752 36 Uppsala, Sweden. 8Friedrich Alexander University Erlangen-Nürnberg, Schloßplatz 4, 91054 Erlangen, Germany. 9Lexicon Pharmaceuticals Inc., 8800 Technology Forest Pl, The Woodlands, TX, USA.

Received: 18 March 2019 Accepted: 25 September 2019

Published online: 26 October 2019

References

1. Robertson, R., Geiger, W., & Davis, N. (2006). Carcinoid tumors. American Family Physician, 74, 429–434.
2. Beaumont, J., Cella, D., Phan, A., Choi, S., Liu, Z., & Yao, J. (2012). Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. Pancreas, 41, 461–466.
3. Kaupp- Roberts, S., Sirajakasanthan, R., & Ramage, J. (2015). Symptoms and quality of life in gastrointestinal neuroendocrine tumours. EMU Oncology, 3, 34–40.
4. Ramage, J., & Davies, A. (2003). Measurement of quality of life in carcinoid/ neuroendocrine tumours. Endocrine-Related Cancer, 10, 483–486.
5. Vadegarif, G., Friend, L., Jones, L., Plum, L., Ardill, J., Taal, B., Larsson, G., Jeziorski, K., Kwekkeboom, D., & Ramage, J. (2013). Validation of the EORTC QLQ-GINET21 questionnaire for assessing quality of life in patients with gastrointestinal neuroendocrine tumours. British Journal of Cancer, 108, 301–310.
6. Modlin, L., Lyke, E., & Kidd, M. (2003). A 5-decade analysis of 13,715 carcinoid tumors. Cancer, 97, 934–959.
7. Zuetenhorst, J., & Taal, B. (2005). Metastatic carcinoid tumors: A clinical review. Oncologist, 10, 123–131.
8. (2018) National Cancer Institute. Gastrointestinal carcinoid tumors treatment (PDQ) - health professional version. Available at: https://www.cancer.gov/types/gi-carcinoid-tumors/hp/gi-carcinoid-treatment-pdq. Accessed 15 June 2018.
9. Bhattacharyya, S., Toumpaakis, C., Chilkunda, D., Caplin, M., & Davar, J. (2011). Risk factors for the development and progression of carcinoid heart disease. The American Journal of Cardiology, 107, 1221–1226.
10. Moller, J., Connolly, H., Rubin, J., Seward, J., Modesto, K., & Pelliika, P. (2003). Factors associated with progression of carcinoid heart disease. The New England Journal of Medicine, 348, 1005–1015.
11. Duce, M., Rockall, A., & Grossman, A. (2009). Fibrosis and carcinoid syndrome: From causation to future therapy. Nature Reviews. Endocrinology, 5, 276–283.
12. (2017) National Institutes of Health. ClinicalTrials.gov website. Available at: https://clinicaltrials.gov/ct2/show/NCT01677910. Accessed 15 June 2018.
13. Kulke, M., Horsch, D., Caplin, M., Anthony, L., Bergsland, E., Oberg, K., Welin, S., Warner, R., Lombard-Bohas, C., Kunz, P., Grande, E., Valle, J., Fleming, D., Lapuerta, P., Banks, P., Jackson, S., Zambrowicz, B., Sands, A., & Pavel, M. (2017). Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. Journal of Clinical Oncology, 35, 14–23.

14. Aaronson, N., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N., Filiberti, A., Flechtny, H., Fleishman, S., & de Haes, J. (1993). The European Organization for Research and Treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute, 85, 365–376.

15. (2017) EORTC Quality of Life. EORTC QLQ-GI.NET21. Available at: http://groups.eortc.be/qol/sites/default/files/img/slider/specimen_gi.net21_english.pdf. Accessed 15 June 2018.

16. Anthony, L., Ervin, C., Lapuerta, P., Kulke, M., Kunz, P., Bergsland, E., Horsch, D., Metz, D., Pasieka, J., Pavlakis, N., Pavel, M., Caplin, M., Oberg, K., Ramage, J., Evans, E., Yang, Q., Jackson, S., Arnold, K., Law, L., & DiBenedetti, D. (2017). Understanding the patient experience with carcinoid syndrome: Exit interviews from a randomized, placebo-controlled study of telotristat ethyl. Clinical Therapeutics, (17), 30987–30986. https://doi.org/10.1016/j.clinthera.2017.09.013 [Epub ahead of print].

17. (2013). SAS version 9 [computer software]. Cary: SAS Institute Inc.

18. Revicki, D., Hays, R., Cella, D., & Sloan, J. (2008). Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. Journal of Clinical Epidemiology, 61, 102–109.

19. Litwin, M. S. (1995). How to measure survey reliability and validity. Thousand Oaks: Sage Publications.

20. Kazis, L., Anderson, J., & Meenan, R. (1989). Effect sizes for interpreting changes in health status. Medical Care, 27, S178–S189.

21. Cohen J (1977) Statistical power analysis for the behavioral sciences (rev. Lawrence Erlbaum Associates, Inc).

22. Coon, C., & Cook, K. (2017). Moving from significance to real-world meaning: Methods for interpreting change in clinical outcome assessment scores. Quality of Life Research. https://doi.org/10.1007/s11136-017-1616-3 [Epub ahead of print].

23. (2017) Xermelo (telotristat ethyl) prescribing information. United States Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208794s000lbl.pdf. Accessed 10 July 2018.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.