

Symptom Diaries of Patients with Midgut Neuroendocrine Tumors Treated with ¹⁷⁷Lu-DOTATATE

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ABSTRACT

We report the impact of ^{177}Lu -DOTATATE treatment on abdominal pain, diarrhea, and flushing, symptoms that patients with advanced midgut neuroendocrine tumors (NETs) often find burdensome.

Methods: All patients enrolled in the international randomized phase 3 Neuroendocrine Tumors Therapy (NETTER-1) trial (^{177}Lu -DOTATATE plus standard-dose octreotide long-acting repeatable [LAR], $n = 117$; high-dose octreotide LAR, $n = 114$) were asked to record the occurrence of predefined symptoms in a daily diary. Change from baseline in symptom scores (mean number of days with a symptom) was analyzed using a mixed model for repeated measures. **Results:** Patients (intent-to-treat) who received ^{177}Lu -DOTATATE experienced a significantly greater decline from baseline in symptom scores than patients who received high-dose octreotide LAR. For ^{177}Lu -DOTATATE, the mean decline in days with abdominal pain, diarrhea, and flushing was 4.10, 4.55, and 4.52 days per 4 weeks, respectively, compared with 0.99, 1.44, and 2.54 days for high-dose octreotide LAR. The mean differences were 3.11 days (95% confidence interval, 1.35–4.88; $P = 0.0007$) for abdominal pain, 3.11 days (1.18–5.04; $P = 0.0017$) for diarrhea, and 1.98 days (0.08–3.88; $P = 0.0413$) for flushing, favoring ^{177}Lu -DOTATATE. A positive repeated measures correlation was found between diary-recorded symptom scores and questionnaire-recorded pain, diarrhea, and flushing. **Conclusions:** In addition to efficacy and quality of life benefits, symptom diaries from NETTER-1 demonstrated that treatment with ^{177}Lu -DOTATATE was associated with statistically significant reductions in abdominal pain, diarrhea, and flushing, constituting the core symptoms of patients with progressive midgut NETs, compared with high-dose octreotide LAR, supporting a beneficial effect of ^{177}Lu DOTATATE on HRQoL.

Key Words: lutetium-177; neuroendocrine; symptom diary; NETTER-1

Neuroendocrine tumors (NETs) of the midgut are the most common type of gastrointestinal NET, affecting approximately 0.63 to 1.65 patients per 100,000 standard population per year, and are associated with 5-year survival rates of <50% in patients with metastatic disease (1,2,3). Patients with advanced midgut NETs frequently develop symptoms due to tumor growth and/or hormone secretion (4). Carcinoid syndrome, the hormonal disorder most closely associated with midgut NETs, consists primarily of diarrhea and flushing (5). Carcinoid syndrome has been found to be present in 32%–72% of patients with midgut NETs (6,7).

Carcinoid syndrome is caused by the secretion of serotonin and other vasoactive substances (5,8). Patients with chronic elevations of blood serotonin may also develop carcinoid heart disease, which ultimately leads to right ventricular dysfunction and to substantial morbidity and mortality (9,10,11). Abdominal pain is another symptom frequently associated with midgut NETs and is most commonly related to tumor volume and tumor-associated desmoplasia, but can also develop as a result of hormone secretion (12,13).

Patient-reported outcomes (PROs) such as experience of symptoms, self-assessments of health or treatment, or formal health-related quality of life (HRQoL) questionnaires are important instruments to inform clinicians about the effects of treatment on the patient's health status as a composite of beneficial treatment effect and side effects (13). PROs in a randomized controlled trial setting are particularly useful to evaluate the impact of a study drug on the patient's health status and are becoming more important from a regulatory point of view as they capture the patient perspective regarding the disease, burden of the disease and impact of treatments. To date, few clinical studies in NETs have reported a HRQoL benefit (14,15,16), highlighting the general difficulty in demonstrating a positive PRO measures outcome in cancer trials (17). Disease progression in patients with NETs is associated with a deterioration in HRQoL, both due to tumor growth and to progressive carcinoid syndrome (18).

Somatostatin analogs (SSAs) are typically used as first-line systemic therapy for NETs, and the clinical benefit of symptomatic relief they provide has also been supported by improved HRQoL (19). Telotristat ethyl has been shown to improve symptoms of diarrhea associated with carcinoid syndrome, although the effects on tumor growth are unknown (20). In the RADIANT 4 study, treatment with everolimus prolonged progression-free survival (PFS) versus placebo (both with supportive care) in patients with advanced nonfunctional gastrointestinal and lung NETs (3).

The Neuroendocrine Tumors Therapy (NETTER-1) trial was an international phase 3 study that randomized patients with progressive midgut NETs to receive either peptide receptor radionuclide therapy (PRRT) with the radiolabeled SSA ¹⁷⁷Lutetium(Lu)-DOTATATE plus best supportive care with standard-dose (30 mg) octreotide long-acting repeatable (LAR; investigational arm) or high-dose (60 mg) octreotide LAR alone (control arm) (21). The trial met its primary endpoint of an improvement in PFS compared with high-dose octreotide LAR. The study included two separate PRO assessments: HRQoL questionnaires and patient symptom diaries. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) as well as the EORTC Gastrointestinal NET Quality of Life Questionnaire (QLQ-GI.NET-21), specifically developed for patients with gastrointestinal NETs. Patients in the ¹⁷⁷Lu-DOTATATE treatment group experienced a statistically significant delay in time to deterioration (TTD) in several HRQoL domains: global health status (hazard ratio [HR], 0.406; *P* < 0.001), physical functioning (HR, 0.518; *P* = 0.015), role functioning (HR, 0.580; *P* = 0.030), diarrhea (HR, 0.473; *P* = 0.011), fatigue (HR, 0.621; *P* = 0.030), and pain (HR, 0.566; *P* = 0.025) compared with patients in the high-dose octreotide LAR group (15).

Patients taking part in the NETTER-1 trial also completed daily symptom diaries. Symptom diaries are an important and distinct method for assessing the impact of treatment on symptomatology and patient outcomes. By reporting the presence or absence of a symptom from a given list of 18 symptoms, the patient diary used in the NETTER-1 study provides a means to capture symptoms on a daily basis, helping to map symptomatology experienced by the patient to HRQoL recorded on a less frequent basis.

The results of these diaries are reported here, focusing on the impact of ^{177}Lu -DOTATATE on diary-based assessments of abdominal pain, flushing, and diarrhea, which are the three symptoms regarded as most clinically relevant for patients with midgut NETs.

MATERIALS AND METHODS

NETTER-1 Trial Design and Patients

The design of the NETTER-1 trial is summarized in Fig.1. The international, multicenter, phase 3 NETTER-1 trial (ClinicalTrials.gov identifier: NCT01578239) was a prospective, randomized controlled trial to evaluate the efficacy and safety of ^{177}Lu -DOTATATE in patients with locally advanced or metastatic somatostatin receptor-positive midgut NETs with disease progression during treatment with octreotide LAR. In total, 231 adult (≥ 18 years) patients were randomly assigned in a 1:1 ratio to receive either ^{177}Lu -DOTATATE (consisting of four intravenous infusions at a dose of 7.4 GBq [200 mCi] every 8 weeks plus best supportive care, consisting of intramuscular octreotide LAR 30 mg every 4 weeks for symptom control; 117 patients) or high-dose intramuscular octreotide LAR (60 mg every 4 weeks) alone (114 patients) (21).

The trial was carried out in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation Of Good Clinical Practice guidelines, and all applicable regulatory requirements. The trial protocol was reviewed and approved by a review board or ethics committee at each participating center, and all participants were required to give their written informed consent before study enrollment (21).

Treatment continued until central confirmation of disease progression, intolerable adverse events, or withdrawal of consent. The primary endpoint was PFS, defined as the time from randomization to documented disease progression (based on independent radiologists' review) or death from any cause.

The patient-reported impact of treatment on HRQoL was a key secondary study endpoint and was assessed using EORTC QLQ-C30 and EORTC QLQ-GI.NET-21 every 12 ± 1 weeks. The disease-specific QLQ-GI.NET-21 was devised and validated to supplement the generic QLQ-C30 and to include HRQoL issues tailored specifically to patients with gastrointestinal NETs (14). Per protocol, patients were required to complete the questionnaires until progression or until a maximum of 72 weeks from random assignment had elapsed (21).

Symptom Diary Assessment

Per protocol, all patients enrolled in the NETTER-1 trial were asked to record the presence or absence (in the preceding 24 hours) of 18 predefined symptoms by ticking boxes in a paper-based daily diary (Fig. 2). The predefined symptoms in the patient diary were subdivided into three categories: general symptoms (anxiety, sleeping disorders, palpitations, fatigue, headache, anorexia, impaired sense of taste and smell, swelling, flushing), respiratory symptoms: (breathlessness, wheezing, chest pain), And gastrointestinal symptoms (nausea, vomiting, gastritis, diarrhea, bloating, abdominal pain). Patients also had the option to include other symptoms. The current analysis focuses on the three symptoms most clinically relevant to patients with midgut NETs, namely abdominal pain, diarrhea, and flushing (12,13,18).

At each clinic visit, patients returned their diaries corresponding to the period of time since their previous visit. Per protocol, patients had to complete the diary up to week 72. For each symptom, the number of days on which patients reported the symptom as being present was determined as follows: at baseline, the number of days with symptoms was determined using diary data from the screening period in the 6 weeks before randomization; during the randomized treatment phase (and for up to 48 weeks), the number of days with symptoms was determined using diary data from each of the intervals between consecutive clinic visits.

Statistics

A 'symptom score' was defined as the number of days with each symptom within the 4-week periods between clinic visits during treatment. To make the patients comparable, data from visits that were delayed by more than 1 week were excluded and considered 'missing' (i.e., a filter was applied that omitted observations if the time since last visit [or consent] was more than 1 week longer than planned). Analysis was done using a mixed model for repeated measures (MMRM) approach, which implicitly imputes missing data under a 'missing at random' assumption.

The change from baseline in the mean number of days with symptoms was assessed using an MMRM, adjusting for baseline symptom status, time from randomization, treatment, and interaction between time from randomization and treatment. From the model, least-squares means with 95% confidence intervals (CIs), change from baseline, and corresponding *P* values were calculated. Analysis was performed for patients both with and without imputations.

Pearson and repeated measures correlation (RMC) analyses were carried out to assess the association between the time courses of symptom scores (number of days with symptoms) and the corresponding domains in the EORTC QLQ-C30 or QLQ-GI.NET-21 (measured on a 0-to-100-point scale). A positive score (>0 to 1) indicated a positive correlation and a negative score (-1 to <0) indicated a negative Pearson correlation.

RESULTS

Study Population

The analysis cut-off date was June 30, 2016. In total, 231 patients were randomly assigned to treatment in the study, of whom 117 to the ¹⁷⁷Lu-DOTATATE arm and 114 to the high-dose octreotide LAR arm. The analysis was carried out on all randomly assigned patients according to intent-to-treat principles.

Symptom Diary Results

The change from baseline in the mean number of days with symptoms for both treatment groups during each 4-week period of the 48 weeks post-randomization is illustrated in Fig.3.

Patients in the ¹⁷⁷Lu-DOTATATE study arm experienced a significantly greater reduction compared to baseline in the mean number of days with symptoms (symptom score) than patients in the high-dose octreotide LAR arm, after adjustment for baseline status in the performed MMRM analysis.

The estimated mean reduction compared to baseline in the number of days with symptoms at each time point during the randomized treatment phase is depicted in Fig.4.

For the ¹⁷⁷Lu-DOTATATE group, the mean decline in number of days with abdominal pain (over a 48-week treatment period) was 4.10 days per 4 weeks, whereas, in the high-dose octreotide LAR group, the mean decline was 0.99 days. The difference between the group means was 3.11 days per 4 weeks (95% CI, 1.34–4.88) favoring ¹⁷⁷Lu-DOTATATE. This difference was statistically significant ($P = 0.0007$).

The mean decline in number of days with diarrhea in patients receiving ¹⁷⁷Lu-DOTATATE and high-dose octreotide LAR was 4.55 and 1.44 days, respectively. The difference between the group means was 3.11 days per 4 weeks (95% CI, 1.18–5.04; $P = 0.0017$) favoring ¹⁷⁷Lu-DOTATATE.

The mean decline in number of days with flushing in patients receiving ¹⁷⁷Lu-DOTATATE and high-dose octreotide LAR was 4.52 and 2.54 days, respectively. The difference between the group means was 1.98 days per 4 weeks (95% CI, 0.08–3.88; $P = 0.041$) favoring ¹⁷⁷Lu-DOTATATE.

The treatment arms were well balanced at baseline in terms of symptom days categories (i.e. symptoms present for < 4 days, 4–10 days, > 10 days) (Table 1). Although variable, the greatest improvements in symptoms over 48 weeks were generally seen in patients whose symptoms were present for more than 10 days at baseline. This was particularly the case for patients in the ¹⁷⁷Lu-DOTATATE arm, with

improvements compared with patients in the high dose octreotide LAR arm observed for abdominal pain (-14.2 vs -4.0) and diarrhea (-12.5 vs -4.6), with flushing similar between arms (-16.4 vs -18.0) (Fig. 5).

Correlation Analysis

To validate the symptom score further, a Pearson correlation analysis between diary symptom scores and HRQoL questionnaire scores was carried out for the corresponding symptoms measured by the EORTC QLQ-C30 or the QLQ-GI.NET-21.

As illustrated in Fig.6, the number of patients with a positive correlation (>0 to 1) far exceeded the number of patients with a negative correlation (-1 to <0), demonstrating a strong degree of correlation between diary-recorded symptom scores (abdominal pain, diarrhea, and flushing) and questionnaire-recorded pain and diarrhea (from the EORTC QLQ-C30) and hot flushes (from the EORTC QLQ-GI.NET-21). This finding therefore suggests face validity of the patient diary concept.

The RMC results were 0.39, 0.21, and 0.43 for diarrhea, pain, and flushing, respectively. All *P* values were below 0.001, signifying statistical significance and a positive Pearson correlation (with no imputations).

DISCUSSION

Daily diaries from the phase 3 NETTER-1 trial provided information on the presence or absence of individual symptoms such as abdominal pain, diarrhea, and flushing, the three symptoms most commonly associated with and relevant to patients with midgut NETs.

Analysis of these patient-reported daily symptom diaries from NETTER-1 demonstrated that treatment with ¹⁷⁷Lu-DOTATATE was associated with statistically significant reductions from baseline in the mean

number of days with all three symptoms (abdominal pain, diarrhea, flushing) compared with high-dose octreotide LAR treatment.

These findings add important new HRQoL results, namely significant improvements in symptoms, to the previously reported results from NETTER-1 of a statistically significant delay in the decline of HRQoL (including global health status, physical functioning, role functioning, diarrhea, fatigue, and pain domains) for patients in the ¹⁷⁷Lu-DOTATATE treatment arm compared with those in the high-dose octreotide LAR arm. It is noteworthy that there was statistically significantly longer TTD from baseline in HRQoL in the ¹⁷⁷Lu-DOTATATE arm than in the control arm for the domains of diarrhea (HR, 0.47; *P* = 0.011) and abdominal pain (HR, 0.57; *P* = 0.025) (15).

One difference between this study and the previously reported HRQoL analysis is that, while the symptom diary analysis demonstrated a statistically significant symptom improvement in flushing with ¹⁷⁷Lu-DOTATATE compared with high-dose octreotide LAR, no difference in symptom improvement rates occurred between treatment arms in the HRQoL analysis (15). However, HRQoL instruments involve a recall period where patients 'average' their experience in terms of health status for that time. The diary captures symptomatology on a daily basis, which ultimately reflects into the patient's HRQoL. It is useful to note that the endocrine scale mixes different aspects (i.e., flushing and sweats), whereas the diary symptom score only addresses flushing.

Overall, in the present study, diary-recorded symptoms and HRQoL questionnaire symptom scores demonstrated a high degree of correlation at the individual patient level. The analysis of symptom diaries from the NETTER-1 trial therefore provides corroboration that treatment with ¹⁷⁷Lu-DOTATATE among patients with progressive midgut NETs is not only efficacious (improving PFS and overall response rate), but can also palliate clinically relevant symptoms compared with high-dose octreotide LAR. This information is particularly relevant when considering alternative systemic treatments in midgut NET patients, such as everolimus, which may exacerbate symptoms such as diarrhea.

PROs such as those recorded in the daily diaries used in NETTER-1 provide important information on the potential impact of a treatment on a patient's self-assessed experience of symptoms, symptom burden, or quality of life measures, and therefore represent a key patient-centered clinical trial endpoint. Although patient diaries have been used occasionally in other therapeutic areas, few studies have used them to report outcome data for patients with NETs (22,23). The present study is one of the first to have shown positive outcomes of treatment on key symptoms in patients with NETs. The improvement and maintenance of an acceptable level of symptoms is important for patients with advanced NET who typically have long treatment durations and whose disease may have had an indolent course.

A limitation of analysis of data from the NETTER-1 trial, and particularly of the PROs, is that patients (and study staff) were unable to be blinded to treatment owing to the differences in treatment location and administration methods between ^{177}Lu -DOTATATE, which is given intravenously, and octreotide LAR, which is given intramuscularly. It is unclear whether assignment to the investigational ^{177}Lu -DOTATATE arm resulted in a biased response which could have affected patient symptom perception, along with other potential perceptions of worsening of the disease and fear of radiotherapy, among others. Another limitation concerns variations in the intervals between clinic visit cycles, which may affect the method of symptom analysis. The impact of these variations was minimized by excluding visits that were delayed by more than 1 week and using an MMRM analysis which imputes missing data under a 'missing at random' approach.

CONCLUSION

This analysis of patient symptom diaries from the phase 3 NETTER-1 trial demonstrates that, in addition to improving PFS and to prolonging TTD in terms of HRQoL, ^{177}Lu -DOTATATE treatment is also associated with a statistically significant symptom relief that may benefit the patient compared with high-dose octreotide LAR. A significant decline was seen in the number of days that patients experienced

abdominal pain, diarrhea, and flushing. Alleviation of these typical symptoms is particularly relevant to patients with progressive midgut NETs and reflects the overall benefit conferred by ¹⁷⁷Lu-DOTATATE to this patient population.

DISCLOSURE

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AAA/Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

KEY POINTS

QUESTION: What is the impact of ^{177}Lu -DOTATATE treatment on the burdensome symptoms of abdominal pain, diarrhea, and flushing for patients with advanced midgut NETs?

PERTINENT FINDINGS: Patients enrolled in the international randomized phase 3 NETTER-1 trial recorded the occurrence of predefined symptoms in a daily diary. Patients treated with ^{177}Lu -DOTATATE plus standard-dose octreotide LAR experienced a significantly greater decline from baseline in symptom scores than patients who received high-dose octreotide LAR.

IMPLICATIONS FOR PATIENT CARE: Compared with high-dose octreotide LAR, treatment with ^{177}Lu -DOTATATE can provide clinically and statistically significant reductions in abdominal pain, diarrhea, and flushing, which are the core symptoms of patients with progressive midgut NETs.

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TABLES

TABLE 1. Baseline symptom score (safety analysis set)

Symptom	¹⁷⁷ Lu-DOTATATE (n = 112) n (%)			High-dose octreotide LAR (n = 111) n (%)		
	< 4 days	4–10 days	> 10 days	< 4 days	4–10 days	> 10 days
Baseline number of days with symptoms						
Abdominal pain	50 (44.6)	12 (10.7)	25 (22.3)	45 (40.5)	13 (11.7)	26 (23.4)
Diarrhea	31 (27.7)	14 (12.5)	42 (37.5)	35 (31.5)	21 (18.9)	28 (25.2)
Flushing	43 (38.4)	17 (15.2)	27 (24.1)	45 (40.5)	13 (11.7)	26 (23.4)

FIGURES

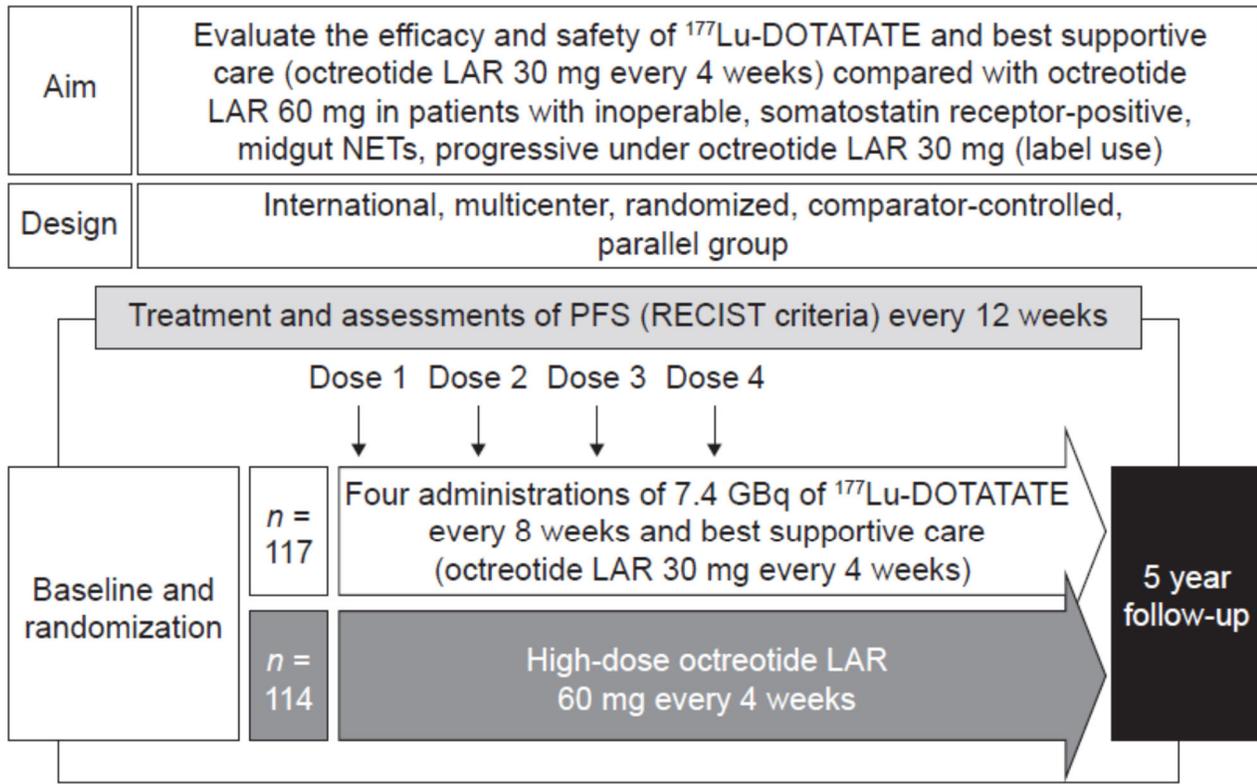


FIGURE 1. NETTER-1 trial design.

LAR = long-acting repeatable; NET = neuroendocrine tumor; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

Patient's diary – Screening period up to week 0, page 1

To be completed by site personnel

Center No. : Patient No. : Start day:

CANCER-RELATED SYMPTOMS	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun
<i>Please tick the corresponding checkbox</i>														
<i>Tick the checkbox in this row in case of no symptoms</i>	<input type="checkbox"/>													
General symptoms														
Anxiety	<input type="checkbox"/>													
Sleeping disorders	<input type="checkbox"/>													
Palpitations	<input type="checkbox"/>													
Fatigue	<input type="checkbox"/>													
Headache	<input type="checkbox"/>													
Anorexia	<input type="checkbox"/>													
Impaired sense of taste and smell	<input type="checkbox"/>													
Swelling	<input type="checkbox"/>													
Flushing	<input type="checkbox"/>													
Respiratory symptoms														
Breathlessness	<input type="checkbox"/>													
Wheezing	<input type="checkbox"/>													
Chest pain	<input type="checkbox"/>													
Gastrointestinal symptoms														
Nausea	<input type="checkbox"/>													
Vomiting	<input type="checkbox"/>													
Gastritis	<input type="checkbox"/>													
Diarrhea	<input type="checkbox"/>													
Bloating	<input type="checkbox"/>													
Abdominal pain	<input type="checkbox"/>													
Other symptoms, please specify:														
1. _____	<input type="checkbox"/>													
2. _____	<input type="checkbox"/>													
3. _____	<input type="checkbox"/>													
4. _____	<input type="checkbox"/>													
5. _____	<input type="checkbox"/>													
USE OF short-acting octreotide														
Please record total dose taken in the day	<input type="text"/>													
Other medication taken														
Please record total dose taken in the day														
1. _____	<input type="text"/>													
2. _____	<input type="text"/>													
3. _____	<input type="text"/>													
4. _____	<input type="text"/>													
5. _____	<input type="text"/>													

FIGURE 2. Patient diary for cancer-related symptoms.

The diary contains two pages for each period of 4 weeks, except three pages for the up to 6 weeks screening period. At each study day the patient was asked to mark the tick boxes corresponding to the symptoms presented during that day and return the diary at the next study visit.

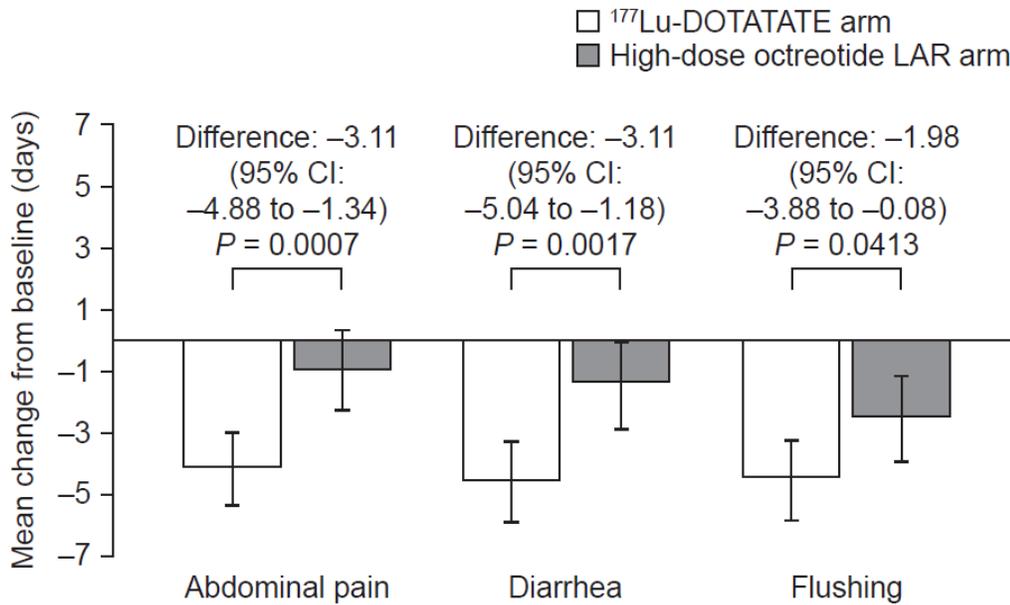


FIGURE 3. Change in mean number of days with symptoms.

A negative score signifies an improvement. Shown are the mean change from baseline in number of days with symptoms in the ¹⁷⁷Lu-DOTATATE and high-dose octreotide LAR arms, adjusted for baseline symptom status. Error bars show 95% CIs.

$N = 87$ (¹⁷⁷Lu-DOTATATE) and $n = 84$ (high-dose octreotide LAR) patients at baseline. The number of patients with diary data decreased throughout the study. Analyses were carried out on the ITT population.

CI = confidence interval; ITT = intent-to-treat; LAR = long-acting repeatable.

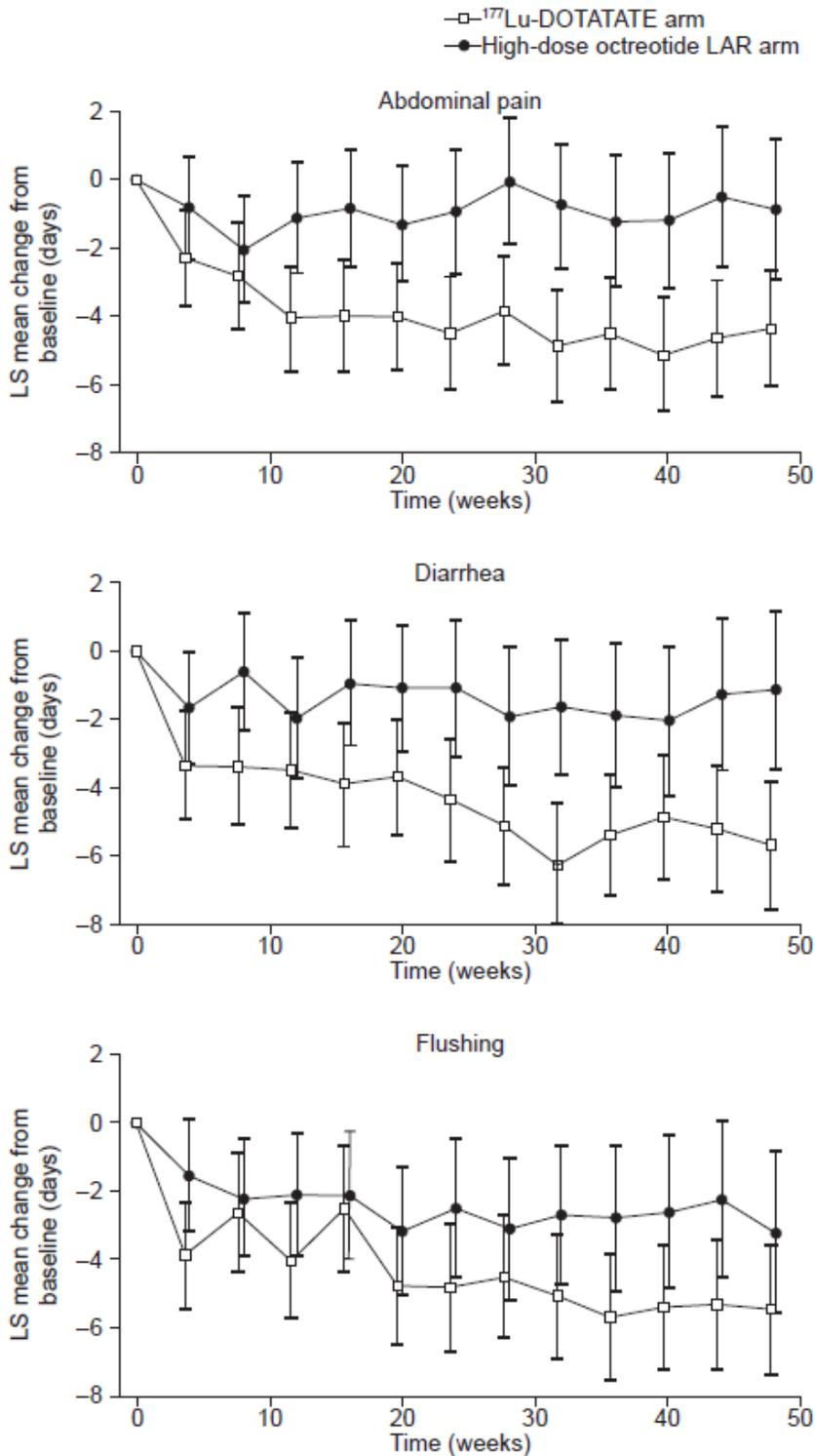


FIGURE 4. Change in mean number of days with symptoms during the first 48 weeks of the randomized treatment phase.

A negative score signifies an improvement. Shown are the estimated mean decline from baseline in the number of days with symptoms at each time point. The estimates are the LS means from an MMRM. Error bars show 95% CIs. Analyses were carried out on the ITT population.

$N = 87$ (^{177}Lu -DOTATATE) and $n = 84$ (high-dose octreotide LAR) patients at baseline. The number of patients with diary data decreased throughout the study.

CI = confidence interval; ITT = intent-to-treat; LAR = long-acting repeatable; LS = least-squares; MMRM = mixed model for repeated measures.

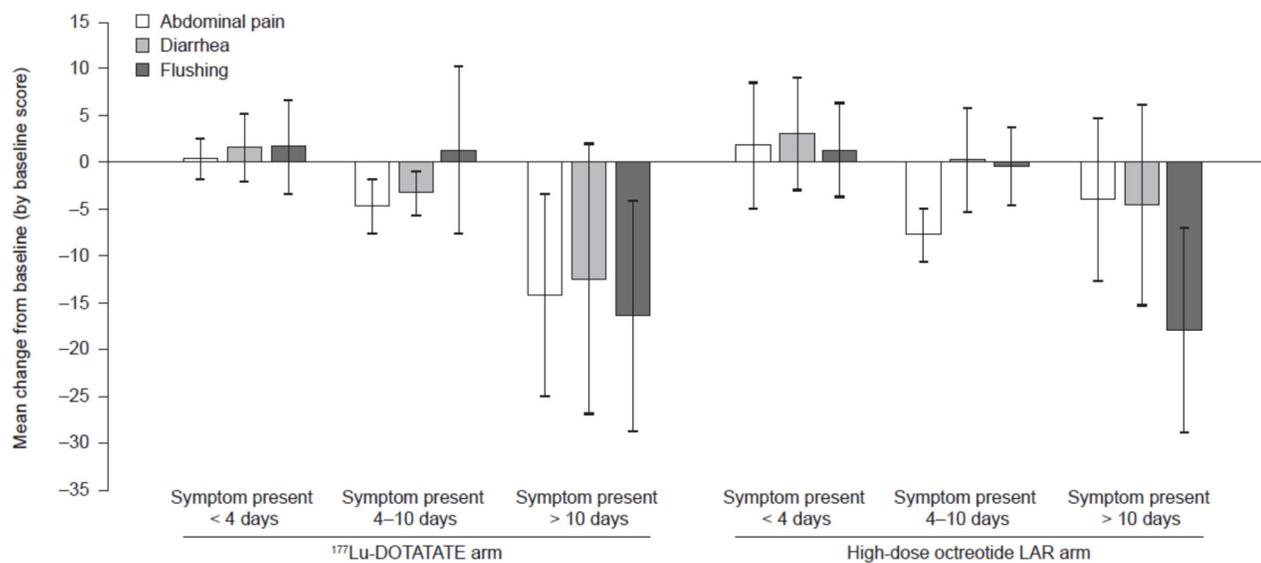


FIGURE 5. Mean change from baseline in diary symptoms over 48 weeks by duration of symptoms at baseline.

A negative score signifies an improvement. Shown are the mean changes from baseline in symptom scores in the ¹⁷⁷Lu-DOTATATE and high-dose octreotide LAR arms. Error bars show standard deviation. The number of patients with diary data decreased throughout the study. Analyses were carried out on the safety analysis set.

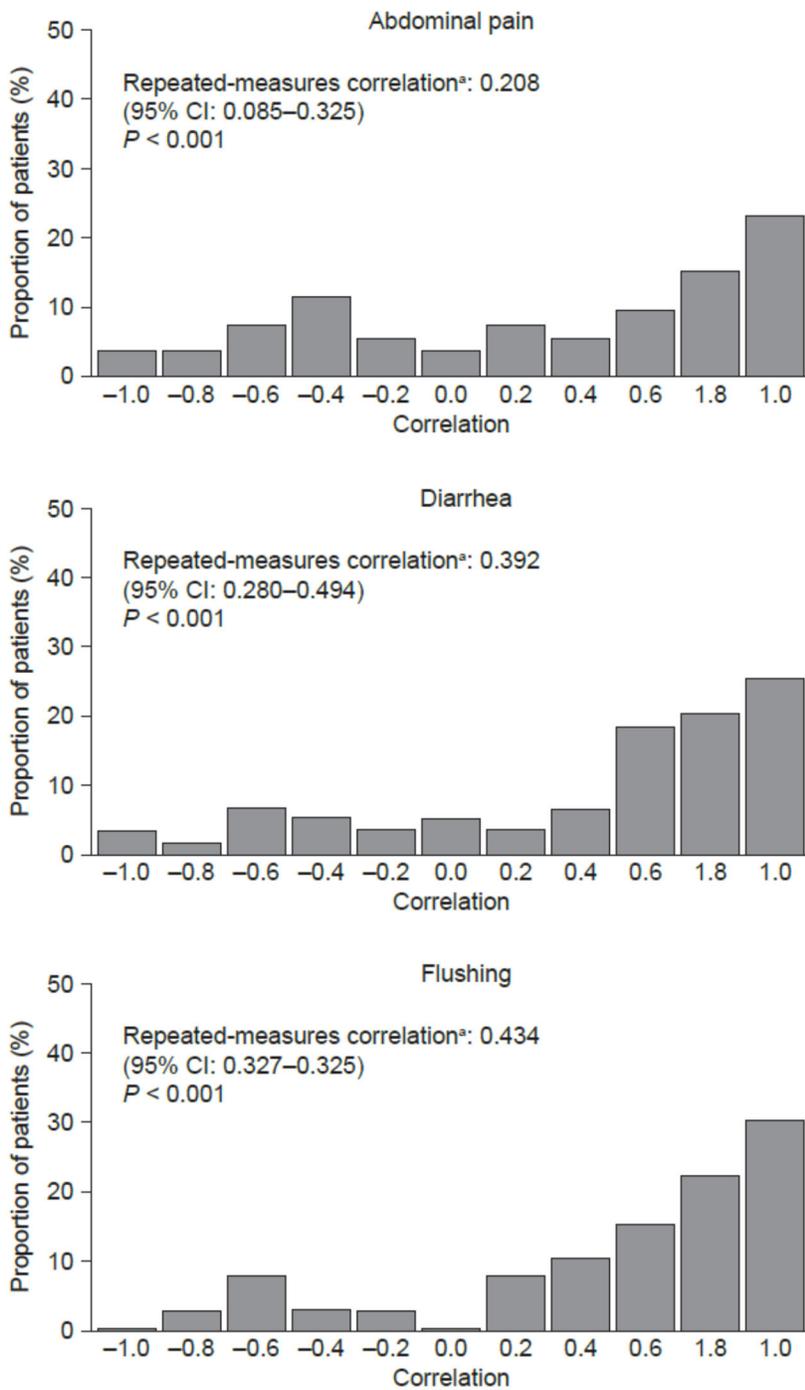


FIGURE 6. Correlation between diary-recorded and EORTC QLQ-C30- or QLQ-GI.NET-21-reported evolution of symptoms.

Correlation coefficients measuring the degree of association between the time course of symptom score (number of days with symptoms) and quality of life score (0–100 on EORTC QLQ-C30 or QLQ-GI.NET-

21 scale) for individual patients. A positive value (>0 to 1) indicates a positive correlation, and a negative value (-1 to <0) indicates a negative correlation.

^aThe repeated measures correlations summarize the correlations across all patients, using the Bland–Altman method (24).

CI = confidence interval; EORTC = European Organisation for Research and Treatment of Cancer; QLQ-C30 = Core Quality of Life Questionnaire; QLQ-GI.NET-21 = Gastrointestinal Neuroendocrine Tumor Quality of Life Questionnaire.