

Oncology

Patient-reported outcomes with lanreotide Autogel/Depot for carcinoid syndrome: An international observational study



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ABSTRACT

Background: Lanreotide Autogel/Depot effectively controls symptoms in patients with carcinoid syndrome associated with neuroendocrine tumours. Data on patient-reported outcomes are sparse.

Aim: To evaluate the effect of lanreotide on patient-reported outcomes (PROs) with carcinoid syndrome. **Methods:** This was an international, open-label, observational study of adults with neuroendocrine tumours and history of diarrhoea, receiving lanreotide for >3 months for relief of carcinoid syndrome symptoms. The primary PRO measure was satisfaction with diarrhoea control. Secondary PRO measures included severity, change in symptoms and impact on daily life of diarrhoea; and patient satisfaction with flushing control.

Results: Of 273 patients enrolled, 76% were 'completely' or 'rather' satisfied with diarrhoea control; 79% reported improvement in diarrhoea with lanreotide. The proportion of patients with 'mild', 'minimal', or 'no diarrhoea' increased from 33% before treatment to 75% during treatment; 75% were unconcerned about the impact of diarrhoea on daily life. Satisfaction with flushing control amongst patients with significant flushing at treatment initiation was 73%.

Conclusions: Lanreotide treatment was associated with improvements in symptoms as well as a range of PROs in patients with neuroendocrine tumours and carcinoid syndrome (ClinicalTrials.gov: NCT01234168).

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1. Introduction

Neuroendocrine tumours (NETs) represent a heterogeneous group of neoplasms, arising from neuroendocrine cells of the endocrine system [1]. They can develop in almost any organ, but occur most frequently in the lung, pancreas and gastrointestinal tract [2]. NETs can be silent (non-functioning) or clinically symptomatic (functioning). The latter are characterized by the secretion of peptides and neurotransmitters; this, in turn, leads to the

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development of typical clinical syndromes [3,4]. For example, some NETs release peptides and amines (e.g. serotonin), which produce a characteristic set of symptoms called carcinoid syndrome (CS) [3,4]. CS occurs in approximately 10% of patients with metastatic NETs [4] and is most prevalent in those with NETs of the small intestine (~20%) [3]. The predominant symptoms of CS are flushing (90%), diarrhoea (70%), and abdominal pain (40%) [3]. These can be very distressing for patients and have a negative impact on health-related quality of life (QoL) [5].

Surgery remains the only curative treatment for NETs presenting with early disease or metastatic disease amenable to curative resection [6]; if this is not possible, locoregional treatment of hepatic metastases for selected patients has been advocated [7]. Currently approved systemic treatments to control tumor growth in patients with midgut NETs are limited to somatostatin analogues (SSAs) [6–8].

Depot formulations of SSAs are currently considered the 'standard of care' for symptom control in CS [9]; these include lanreotide (Somatuline®) Autogel (Depot in the US), which is administered by deep subcutaneous injection, and octreotide (Sandostatin®) LAR®, which is administered intramuscularly. SSAs such as lanreotide are available in Europe and several other countries for the treatment of CS, supported by clinical experience and clinical studies [9–13]. Most recently, a large international Phase III study, ELECT, which was conducted in Europe and the US, demonstrated statistically significant symptom relief with lanreotide based on reduced use of a short-acting SSA [14].

In addition, there is evidence for SSAs as antitumour treatment. In particular, a large, international, Phase III study, CLARINET has demonstrated anti-tumour effects with lanreotide for metastatic G1 and G2 NET including midgut tumours [15]. A phase III study, PROMID, also showed anti-tumour effects with octreotide in a smaller population of metastatic G1 midgut NET patients [16]. Peptide receptor radio-targeted therapy with radiolabelled SSAs, which is used more commonly in Europe, may also have therapeutic potential in NETs. Recently, a phase III study, NETTER-1, showed that ¹⁷⁷-Lu-Dotatate combined with a standard dose of SSA versus a high dose SSA alone was associated with a significant improvement in progression-free survival in patients with progressive midgut NETs [17].

To date, only a small number of NET clinical studies have examined both patient-reported outcomes (PROs) and QoL measures with current NET treatments [18]. These have mainly been studies of SSAs and peptide receptor radio-targeted therapies, which have shown treatment was associated with stable or improved QoL outcomes in patients [11,13–15,19]. Most recently, the phase III TELESTAR study of telotristat etiporate, a serotonin synthesis inhibitor under development, showed significant reductions in bowel movements in patients with CS inadequately controlled with SSA, which was associated with treatment satisfaction and perceived symptom relief reported by a subset of patients interviewed after treatment [20]. However, no large prospective clinical studies have focused specifically on the impact of NET treatment on patient-reported satisfaction with symptom control in a large CS patient population.

Here, we present the results of SymNET, a large multinational observational study of the real-world patient experience of CS symptom management at a single routine clinic visit at a number of specialist centres. The main focus of the study was to evaluate a number of PRO measures – including the primary endpoint, patient satisfaction with diarrhoea control – in NET patients who had received lanreotide Autogel/Depot. The study also evaluated medical records of physician-recorded CS symptoms and other patient characteristics at lanreotide initiation and at the clinic visit in order to explore their relationship with patient satisfaction.

2. Methods

2.1. Patients

Adult patients (≥18 years) diagnosed with an NET were eligible if they had been receiving lanreotide Autogel/Depot for >3 months for relief of symptoms associated with CS, as indicated in their medical records. In particular, all patients were required to have a history of diarrhoea related to CS. Investigators were required to recruit all consecutive eligible and consenting patients in order to avoid recruitment bias.

Patients had to provide written informed consent to allow their medical data to be collected, analyzed, and shared with regulatory authorities.

2.2. Trial design and interventions

SymNET was a multinational, observational, non-interventional study conducted between October 2010 (first patient enrolled) and December 2012 (last patient visit) at 45 secondary or tertiary care centres in eight countries (Czech Republic, France, Hungary, Israel, Italy, Poland, Spain, and UK) (ClinicalTrials.gov: NCT01234168). Patient recruitment and PRO assessment were conducted prospectively during a single study visit; in addition, patient data were collected from medical records.

The study did not impact on usual clinical management. Patients' clinic attendance and the exact prescription of lanreotide or any other concomitant medications was unrestricted and in accordance with routine clinical practice. The decision to prescribe lanreotide was made prior to, and independently from, the decision to enrol patients in the present study.

The conduct of the study was in accordance with Good Pharmacoepidemiological Practice Guidelines from the International Society for Pharmacoepidemiology, and local regulatory requirements for non-interventional studies. The study was approved by independent ethics committees/institutional review boards.

2.3. Assessments and endpoints

2.3.1. Patient-reported outcomes

During a routine clinic visit (assessment visit), patients were asked by the physician to complete questionnaires. The primary endpoint was (i) patient-reported satisfaction with diarrhoea control (PSD) on the day of the visit. Secondary endpoints also collected on day of visit included; (ii) diarrhoea severity and associated impact on daily activities (assessed using a scale derived from the clinical global impression of severity [CGI-S] scale); (iii) overall change in diarrhoea symptoms at the time of the visit compared with before treatment initiation (assessed using the patient global impression of change [PGIC] scale); (iv) patient-reported feelings and consequences of diarrhoea on daily life; (v) patient-reported satisfaction with flushing control (PSF); and (vi) QoL evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-G.I.NET 21 questionnaires. See full details of questionnaires in Supplementary Table S1.

Patient satisfaction with control of CS symptoms other than diarrhoea and flushing was not measured as the primary focus was diarrhoea control, and only limited numbers of patients enrolled with other lesser symptoms.

2.3.2. Medical record review

During the assessment visit, as part of the routine consultation, physicians reviewed patients' medical records for information on demographics, disease characteristics, treatment characteristics, and diarrhoea and other CS symptoms at lanreotide initiation. Physicians also collected information on patients' diarrhoea and

Table 1
Patient and disease characteristics.

| | Patients (n = 273) |
|--|-----------------------------|
| Age at assessment visit, n (%) | |
| 31–40 years | 7 (3) |
| 41–50 years | 40 (15) |
| 51–60 years | 69 (25) |
| 61–70 years | 86 (32) |
| >70 years | 71 (26) |
| Men, n (%) | 152 (56) |
| BMI at assessment visit, kg/m ² | |
| Mean (SD) | 25.0 (±4.7) |
| Median (range) | 24.6 (14.2–47.8) |
| Time from diagnosis to assessment visit, years | |
| Mean (SD) | 4.4 (±4.5) |
| Median (range) | 2.7 (0.3–22.4) |
| Tumour primary location, n (%) | (n = 267) |
| Small bowel | 176 (66) |
| Appendix | 4 (1) |
| Right colon | 10 (4) |
| Lung | 11 (4) |
| Unknown | 66 (25) |
| Tumour classification ^a , n (%) | (n = 252) |
| Well differentiated | 203 (81) |
| Moderately differentiated | 18 (7) |
| Unknown | 31 (13) |
| Site of metastases, n (%) | (n = 271) |
| Any | 251 (92) |
| Liver | 217 (80) |
| Lymph nodes ^b | 113 (42) |
| Peritoneum | 43 (16) |
| Bone | 16 (6) |
| Lung | 14 (5) |
| Ovaries, uterus and uterine tubes | 8 (3) |
| Other ^c | 6 (2) |
| CS symptoms at assessment visit | (n = 261–269 ^d) |
| Diarrhoea | 133 (49) |
| Flushes | 90 (34) |
| Wheezing | 5 (2) |
| Carcinoid heart disease | 21 (8) |
| Previous NET surgery, n (%) | (n = 271), 179 (66) |
| Primary tumour | 152 (85) |
| Liver metastases | 37 (21) |
| Primary tumour and liver metastases | 31 (17) |
| Other | 21 (12) |
| Concomitant NET treatments in previous 3 months, n (%) | (n = 269), 61 (23) |
| Intravenous chemotherapy | 19 (31) |
| Embolization or chemoembolization | 16 (26) |
| Peptide receptor radionuclide therapy | 15 (25) |
| Targeted therapy | 15 (25) |
| Interferon alpha | 4 (7) |

SSA, somatostatin analogue; CS, carcinoid syndrome; SD, standard deviation.

^a Tumour classification according to WHO 2000 classification as WHO 2012 grading not available at time of study;

^b Two patients had metastases in the lymph nodes and spleen;

^c Other metastatic sites: thyroid gland, duodenum, colon, pancreas, orbital, and goitre;

^d Diarrhoea N = 269, flushes N = 269, wheezing N = 264, carcinoid heart disease N = 261 (also see Supplementary Table 2).

other CS symptoms at study visit (this was used to determine physician recorded changes in diarrhoea and other CS symptoms between lanreotide initiation and study visit). Adverse drug reactions were required to be reported to the manufacturer in accordance with standard procedures for clinical practice. No safety cases were reported as arising.

2.4. Statistical analyses

Estimated sample size, based on an anticipated PSD of 60% and precision of 5.5%, was 305 patients, assuming a two-sided 95% confidence interval (CI). For PSD-associated factors, assuming alpha = 5% and power = 80%, estimated sample size was 323 patients to detect an odds ratio (OR) ≥ 2 and a probability of exposure to

any given level of a prognostic factor of ≥ 0.5 . In order to ensure 323 evaluable subjects, 340 were to be included in the study. However, because of slow recruitment, the protocol was amended to reduce patient numbers and enrolment ended in December 2012, at which point >80% of the target number (i.e., >250 patients) had been enrolled (see Supplementary Information for protocol amendments).

The primary analysis population was all patients who were enrolled, provided consent and had data available for the relevant endpoints. The primary endpoint (PSD) was also analyzed for the per-protocol (PP) population (all those enrolled with no major protocol deviations). Descriptive methods were used for all other endpoints on PRO measures or physician-recorded changes in CS symptoms. PSD-associated factors were explored first using univariate and then multivariate logistic regression analyses. Post hoc analyses were conducted to evaluate physician-recorded changes in diarrhoea characteristics according to PSD, and patient-reported QoL according to PSD. Missing data were not replaced, and all endpoints were calculated based on patients with available data.

3. Results

3.1. Patient disposition and characteristics

Overall, 273 patients receiving lanreotide Autogel/Depot attended the study visit and were enrolled in this study (ITT population); of these, 92% (252) were included in the PP population (which excluded 19 patients whose lanreotide treatment was not >3 months as per inclusion criteria). More than half of patients were male (56% [152/273]) and >60 years of age (58% [157/273]). The majority of ITT patients had midgut NETs (70% [190/273]), metastasis (92% [251/271]), or had undergone surgery (66% [179/271]). In total, 23% (61/269) received recent concomitant treatment as well as lanreotide (Table 1).

The time between first diagnosis and lanreotide initiation was highly variable (median [range], 0.63 [0,21.9] years). At study visit, the mean (SD) lanreotide treatment duration was 21.7 (28.6) months (median [range] was 10.9 [3–215] months). Almost all patients were receiving lanreotide at standard doses of 60–120 mg (60 mg, 28% [75/270]; 90 mg and 120 mg, each 35% [93/270]) and at 4-weekly dosing intervals (93% [250/269]). Most patients (64% [170/267]) had the same dose at study visit and treatment start.

Based on medical records, most common CS symptoms at study visit were diarrhoea (49% [133/270]) and flushing (33% [90/269]) (Table 1). Diarrhoea and flushing symptoms were also estimated to have occurred in 91% (244/269) and 165/269 (61%), respectively, at lanreotide initiation (Supplementary Table S2). Note that the whole study population was selected based on a history of diarrhoea at some point prior to the study. Of those patients for whom a reason for diarrhoea was provided (n = 262), 30% (79) had another potential cause of diarrhoea in addition to CS. The most common were small bowel resection (44% [35/79]), pancreatic insufficiency (32% [25/79]), and ileocecal valve/colonic resection (24% [19/79]).

3.2. Patient-reported outcomes for carcinoid syndrome symptom control

According to the primary PRO measure PSD, 76% of patients (203/268) were 'completely' or 'rather satisfied' with diarrhoea control at study visit (Fig. 1). Similar results were obtained in the PP population (76%). PSD was lower for the patients with (66% [51/77]) versus those without (80% [152/194]) other contributing factors to diarrhoea.

The secondary PRO measures also showed favourable patient experience. Overall, 79% of patients (213/269) reported improved

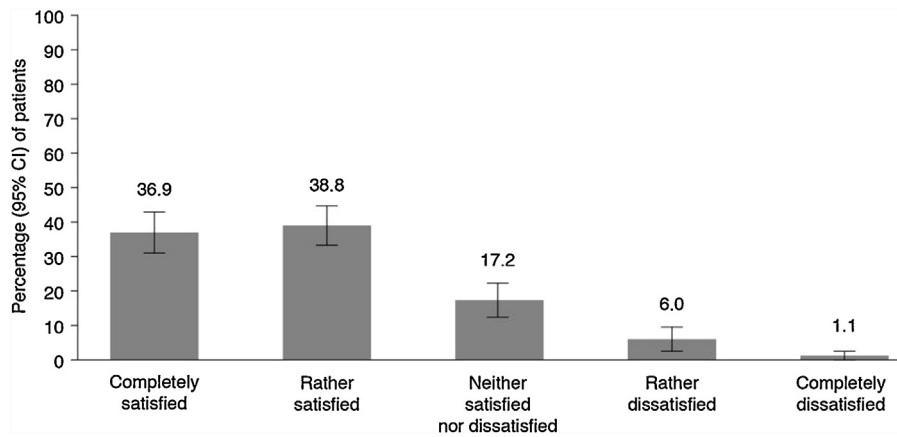


Fig. 1. Patient satisfaction with diarrhoea control associated with lanreotide treatment (primary endpoint).

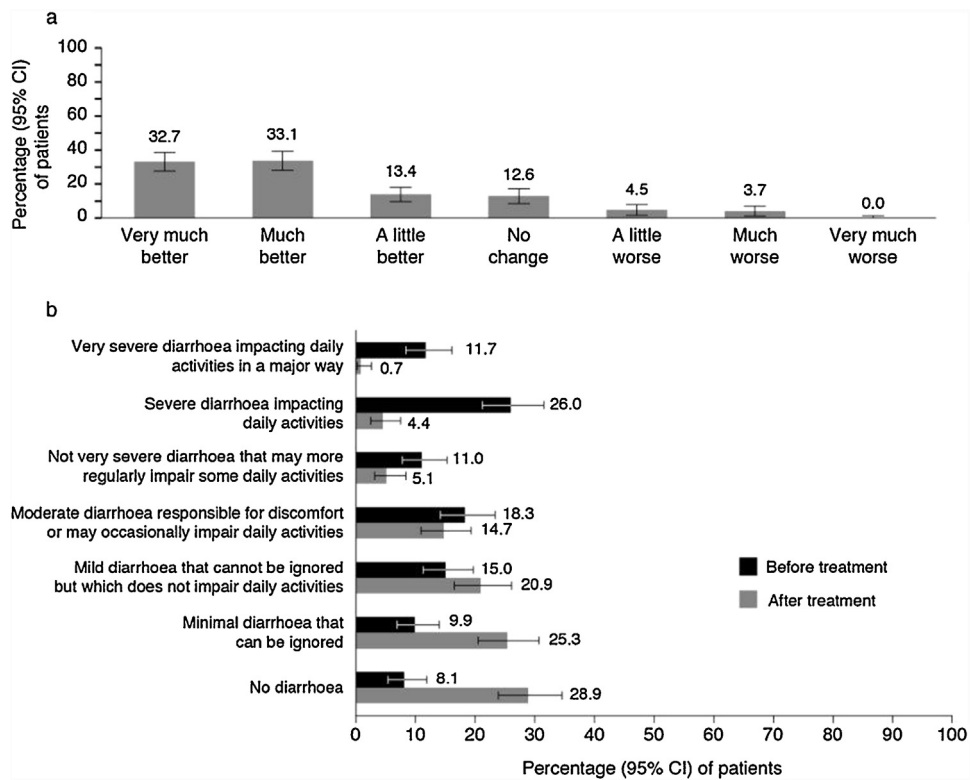


Fig. 2. Patient satisfaction with diarrhoea control associated with lanreotide treatment. (a) Patient global impression of change. (b) Clinical global impression of severity.

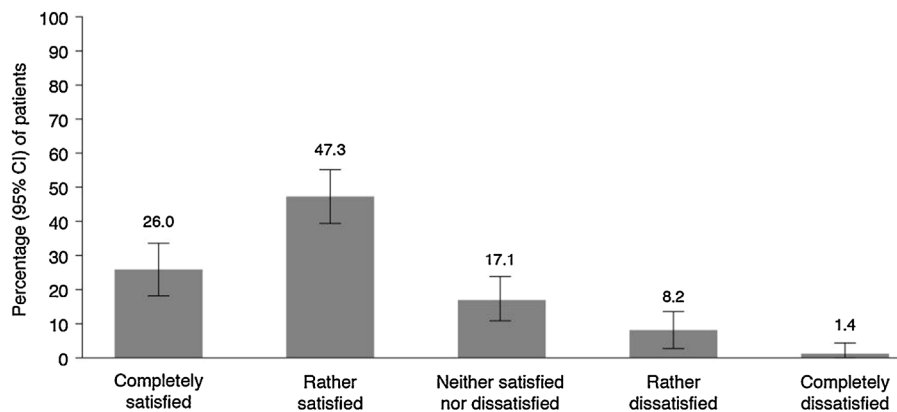


Fig. 3. Patient satisfaction with flushing control associated with lanreotide treatment.

Table 2
Factors associated with better patient satisfaction with diarrhoea control.

| Variables ^a included in multivariate logistic regression analysis | Odds ratio [95% CI]; p value (n = 212) ^b |
|--|---|
| Stool leakage at treatment initiation | |
| No versus yes | 0.31 [0.11, 0.89]; p = 0.029 |
| Localization of primary tumour in small bowel | |
| No versus yes | 2.02 [0.93, 4.36]; p = 0.074 |
| Body mass index (kg/m ²) | p = 0.143 |
| <18.5 versus ≥18.5–25 | 0.80 [0.27, 2.43] |
| ≥25 versus ≥18.5–25 | 1.71 [0.79, 3.69] |
| ≥30 versus ≥18.5–25 | 3.85 [0.95, 15.60] |
| Treatment with prior long-acting SSAs ^c | |
| No versus yes | 1.69 [0.80, 3.57]; p = 0.165 |
| 4-week dose of lanreotide at treatment initiation in mg | p = 0.173 |
| [60,90] versus ≤60 | 0.59 [0.25, 1.44] |
| [90,120] versus ≤60 | 0.80 [0.34, 1.90] |
| >120 versus ≤60 | 0.06 [0.00, 0.87] |

CI, confidence interval; PSD, patient satisfaction with diarrhoea control; SSA, somatostatin analogue.

^a Variables shown above are those that were associated with patients' satisfaction at a 20% level in univariate analyses, unless two variables were correlated, in which case those at a lower significance level were excluded from the multivariate analysis.

^b Associations were tested using the Chi-square test or Fisher's exact test (if expected counts < 5).

^c Long acting SSA include lanreotide microparticles and octreotide LAR.

diarrhoea after treatment (PGIC scale) (Fig. 2a). Proportion of patients reporting 'mild', 'minimal', or 'no diarrhoea' also increased after treatment, from 33% (90/273) to 75% (205/273) on CGI-S (Fig. 2b). Less than one-third of patients answered with concern to various questions about their diarrhoea or its consequences on daily life (Supplementary Table S3). For PSF, 73% [107/147] of those patients who reported experiencing significant flushing episodes at treatment initiation were 'completely' or 'rather satisfied' with the control of flushing at study visit (Fig. 3).

3.3. Physician-recorded changes in carcinoid syndrome symptoms

According to their medical records, patients had significantly lower daily stool frequency at study visit than at lanreotide initiation (mean [SD] stools/day: 4.7 [3.0] versus 2.6 [2.5]; mean [95% CI] reduction: 2.1 [1.7, 2.5]). In addition, there were fewer patients with stool urgency, leakage and pain at study visit than before (Supplementary Table S2). At the study visit, 29% of patients (75/263) were receiving other treatments for diarrhoea, compared with 35% (93/269) at the time of lanreotide initiation. There were fewer patients experiencing flushing episodes at lanreotide initiation than at study visit (Supplementary Table S2).

Improvements in diarrhoea frequency, stool leakage, stool urgency, and associated pain were more common among patients reporting satisfaction with diarrhoea control than in those reporting dissatisfaction or neither satisfaction nor dissatisfaction. In those who were rather/completely satisfied, for stool frequency, 78% showed improvements versus 22% who showed no change/worsening. Similarly, for stool leakage, 18% showed improvement, 75% showed no change (remaining absent), 5% showed no change (remaining present) and 3% showed worsening.

Univariate analysis of the association of patient characteristics with PSD identified nine factors that were potentially associated with better PSD (at the alpha = 0.10 level). In the multivariate analysis, statistical significance (at the alpha = 0.05 level) was only evidenced for the association of stool leakage with better PSD, while primary tumour outside of small bowel showed a trend towards an association with better PSD (Table 2).

3.4. Patient-reported quality of life

According to the EORTC QLQ-C30 questionnaire at study visit, patients had high levels of functioning for all scales and good global QoL. Based on median scores (higher scores, worse symptoms), the most problematic symptoms were fatigue, insomnia, and diarrhoea (median [range] = 33.3 [0–100] for all three symptoms) and, to a lesser extent, pain (16.7 [0–100]); in contrast, the majority of patients had no problems with vomiting, dyspnoea, appetite loss, constipation, and financial difficulties (i.e. the median score was 0). A similar pattern among symptoms was apparent based on mean scores.

Based on the median scores for the EORTC G.I.NET 21 questionnaire at study visit, problematic symptoms were disease-related worries (44.4 [0–100]), social function (33.3 [0–100]), muscle/bone pain (33.3 [0–100]) and, to a lesser extent, gastrointestinal (20.0 [0–100]) and endocrine symptoms (11.1 [0–100]). The majority of patients had no problems with other symptoms, including treatment-related effects, although a high mean value for sexual function (31.3 [SD 37.4]) and, to a lesser extent, body image (19.6 [31.3]) suggests some patients found these aspects particularly problematic.

More patients who were satisfied with diarrhoea control also reported EORTC QLQ-C30 global QoL scores as good/very good/excellent (70%, 140/200) compared with patients who were dissatisfied (39%, 7/18) or neither satisfied nor dissatisfied with diarrhoea control (48%, 22/46).

4. Discussion

Data from this large real-world study demonstrate that lanreotide Autogel/Depot not only improved physician-rated symptoms in patients with CS and diarrhoea, but also a variety of subjective PROs including patient satisfaction with diarrhoea and with flushing. Satisfaction rates for diarrhoea control were slightly lower in those with versus without other contributing factors to diarrhoea. It was also shown that factors associated with even better satisfaction were the presence of stool leakage and primary tumour outside the small bowel. These data were obtained in patients mostly receiving standard doses at standard dosing intervals.

PROs are an important component of monitoring drug efficacy and patient management, particularly for symptomatic conditions such as CS and functional gastrointestinal disorders [21]. The patient's point of view on their health status is highly important, can play a role in disease management decisions and its assessment has the potential to enhance patient-centred care. Indeed, PRO assessment has been advocated by regulatory authorities [22,23]. Recent oncology clinical trials, to support clinical benefits of new treatment options, have utilized endpoints on patient preference [24] and symptom relief [25]. Furthermore, it has been established that there is a relationship between patient preference, adherence and clinical outcomes in patients with cancer [26].

Although some previous studies have evaluated QoL in a limited way for patients with NETs treatment, including some with lanreotide showing QoL benefits [11,13–15,27,28] there is a paucity of detailed studies focusing on PROs following treatment for CS. The current study, therefore, provides new and useful data. The results are consistent with, and may explain, at least in part, observations that have shown once-monthly dosing of lanreotide is associated with good patient adherence [28] and patient perception of lanreotide injection [29]. The results also underscore the utility of PROs and that future studies assessing the efficacy of treatment of CS should endeavour to include appropriate PRO endpoints.

In the current study, patients' QoL using the validated EORTC questionnaires was evaluated only at the study visit. This allows benchmarking of the QoL in the current study against previous studies, in order to support the other new PRO measures in this study, but it does not allow the treatment effect of lanreotide on QoL to be evaluated directly. The QoL scores obtained at the study visit, which were consistent with the primary endpoint PSD, were similar to those reported from previous cross-sectional QoL surveys of the general NET population [30–32].

Within the constraints of differences in study design and measurement of outcomes, the results obtained for physician-reported control of carcinoid symptoms are broadly consistent with the findings of other studies of SSAs showing that lanreotide achieves favourable rates of symptom control [9,11,12,33]. The recent ELECT study showed that lanreotide achieved significant symptom relief versus placebo based on a one-third reduction in use of rescue therapy over its 16-week double-blind phase [9]. A retrospective study of 9 years' clinical experience with lanreotide at a specialist centre reported that 94% of patients had initial symptomatic control of flushing and stool frequency, and sustained control in 54% after median follow-up of 27 months (range 7–93) [27], which are similar to the results in the current study obtained over a median treatment duration of 10.9 months (range 3–215) [27].

There are some important limitations that should be considered when interpreting the SYMNET study data. Firstly, the PRO measures in this study were completed only at one visit. These data were intended to provide an accurate “snapshot” of current patient experience in routine practice. They do not provide longitudinal information. Secondly, the study intended to capture experience in a general NET population in the real world, which would have variable treatment duration, dose and dosing interval for lanreotide. These results do not reflect those that would likely be observed in a more restricted and homogenous clinical study population. Finally, inter-patient and within-patient variability are inherent to subjective PROs; however, the main PRO data were corroborated by the objective data from medical records on CS symptoms and the validated QoL questionnaires. Nevertheless, the major overall strength of this study is its conduct in a large patient cohort in a real-life clinical setting, as this increases the external validity of the results.

In conclusion, lanreotide Autogel/Depot is an effective and convenient treatment for patients with NETs and associated CS. This is supported by the PRO measures of symptom control used in this study, which were consistent with physician-rated measures during the study. PRO measures were also consistent with previous clinical data.

Conflict of interest

PR has been a consultant/advisory board member for Ipsen, Novartis, Pfizer and Keocyt; has been a speaker for Ipsen and Novartis; and has received research support from Ipsen and Novartis. JWV has been a consultant and a speaker for Ipsen. CLB has been a consultant/advisory board member for Ipsen, Novartis, Keocyt, Sanofi, and Pfizer; and has been speaker for Ipsen and Novartis. DFC has received research support from Ipsen. PN has been a speaker for Ipsen. MEC has been an advisory board member for Ipsen, Novartis and Lexicon. PM and PA are employees of Ipsen. PP, LH, GDF, and DS have nothing to declare. Writing assistance provided by Watermeadow Medical was funded by Ipsen.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.dld.2015.12.013>.

References

- [1] Cives M, Strosberg J. An update on gastroenteropancreatic neuroendocrine tumors. *Oncology (Williston Park)* 2014;28.
- [2] Anlauf M. Neuroendocrine neoplasms of the gastroenteropancreatic system: pathology and classification. *Hormone and Metabolic Research* 2011;43:825–31.
- [3] Massironi S, Sciola V, Peracchi M, et al. Neuroendocrine tumors of the gastro-entero-pancreatic system. *World Journal of Gastroenterology* 2008;14:5377–84.
- [4] Oberg KE. Gastrointestinal neuroendocrine tumors. *Annals of Oncology* 2010;21(Suppl. 7):vii72–80.
- [5] Beaumont JL, Cella D, Phan AT, et al. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. *Pancreas* 2012;41:461–6.
- [6] Kulke MH, Shah MH, Benson III AB, et al. Neuroendocrine tumors. *Journal of the National Comprehensive Cancer Network* 2015;13:78–108.
- [7] Oberg K, Knigge U, Kwekkeboom D, et al. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2012;23(Suppl. 7):vii124–30.
- [8] Pavel M, O'Toole D, Costa F, et al. Consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 2016, <http://dx.doi.org/10.1159/000443167>.
- [9] Toumpanakis C, Caplin ME. Update on the role of somatostatin analogs for the treatment of patients with gastroenteropancreatic neuroendocrine tumors. *Seminars in Oncology* 2013;40:56–68.
- [10] Bajetta E, Procopio G, Catena L, et al. Lanreotide autogel every 6 weeks compared with Lanreotide microparticles every 3 weeks in patients with well differentiated neuroendocrine tumors: a Phase III Study. *Cancer* 2006;107:2474–81.
- [11] O'Toole D, Ducreux M, Bommelaer G, et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer* 2000;88:770–6.
- [12] Ruzsiewicz P, Ish-Shalom S, Wymenga M, et al. Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology* 2004;80:244–51.
- [13] Wymenga AN, Eriksson B, Salmela PI, et al. Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *Journal of Clinical Oncology* 1999;17:1111.
- [14] Vinik A, Wolin EM, Audry H, et al. ELECT: A phase 3 study of efficacy and safety of lanreotide Autogel/Depot treatment for carcinoid syndrome in patients with neuroendocrine tumors. *Journal of Clinical Oncology* 2014;32(Suppl. 3). Abstr 268.
- [15] Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *New England Journal of Medicine* 2014;371:224–33.
- [16] Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *Journal of Clinical Oncology* 2009;27:4656–63.
- [17] Strosberg J, Wolin E, Chasen B, et al. 177-Lu-Dotatate significantly improves progression-free survival in patients with midgut neuroendocrine tumours: results of the phase III NETTER-1 trial. *European Journal of Cancer* 2015;51(Suppl. 3):S709–11. Abstr 6LBA.
- [18] Jiménez-Fonseca P, Carmona-Bayonas A, Martín-Pérez E, et al. Health-related quality of life in well-differentiated metastatic gastroenteropancreatic neuroendocrine tumors. *Cancer and Metastasis Reviews* 2015;34:381–400.
- [19] Khan S, Krenning EP, van EM, et al. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]octreotate. *Journal of Nuclear Medicine* 2011;52:1361–8.
- [20] Anthony L, Horsch D, Ervin C, et al. Assessing treatment benefit of telotristat etiprate in patients with carcinoid syndrome: patient exit interviews. In: NANETS 2015 Neuroendocrine Tumor Symposium Abstracts website: abstract C1. 2015. Available at: https://www.nanets.net/nanets.cd/2015/Browse.NET_Abstracter.html [accessed November 2015].
- [21] Lackner J, Jaccard J, Baum C, et al. Patient-reported outcomes for irritable bowel syndrome are associated with patients' severity ratings of gastrointestinal symptoms and psychological factors. *Clinical Gastroenterology and Hepatology* 2011;9:957–64.

- [22] European Medicines Agency. Oncology Working Party. Reflection Paper on the use of patient reported outcome (PRO) measures in oncology studies 17 June 2014 (EMA/CHMP/292464/2014); 2014.
- [23] U.S. Department of Health and Human Services FDA. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims; 2009.
- [24] Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. *Journal of Clinical Oncology* 2014;32:1412–8.
- [25] Kulke MH, O'Dorisio T, Phan A, et al. Telotristat etiprate, a novel serotonin synthesis inhibitor, in patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide. *Endocrine-Related Cancer* 2014;21:705–14.
- [26] Shingler SL, Bennett BM, Cramer JA, et al. Treatment preference, adherence and outcomes in patients with cancer: literature review and development of a theoretical model. *Current Medical Research and Opinion* 2014;30:2329–41.
- [27] Khan MS, El-Khouly F, Davies P, et al. Long-term results of treatment of malignant carcinoid syndrome with prolonged release Lanreotide (Somatuline Autogel). *Alimentary Pharmacology and Therapy* 2011;34:235–42.
- [28] Ricci S, Antonuzzo A, Galli L, et al. Long-acting depot lanreotide in the treatment of patients with advanced neuroendocrine tumors. *American Journal of Clinical Oncology* 2000;23:412–5.
- [29] Johanson V, Wilson B, Abrahamsson A, et al. Randomized crossover study in patients with neuroendocrine tumors to assess patient preference for lanreotide Autogel® given by either self/partner or a health care professional. *Journal of Patient Preference and Adherence* 2012;6:703–10.
- [30] Frojd C, Larsson G, Lampic C, et al. Health related quality of life and psychosocial function among patients with carcinoid tumours. A longitudinal, prospective, and comparative study. *Health and Quality of Life Outcomes* 2007;5:18.
- [31] Larsson G, Sjoden PO, Oberg K, et al. Health-related quality of life, anxiety and depression in patients with midgut carcinoid tumours. *Acta Oncologica* 2001;40:825–31.
- [32] Larsson G, von Essen L, Sjoden PO. Are importance-satisfaction discrepancies with regard to ratings of specific health-related quality-of-life aspects valid indicators of disease- and treatment-related distress among patients with endocrine gastrointestinal tumours? *European Journal of Cancer Care* 2007;16:493–9.
- [33] Ruzniewski P, Ducreux M, Chayvialle JA, et al. Treatment of the carcinoid syndrome with the longacting somatostatin analogue lanreotide: a prospective study in 39 patients. *Gut* 1996;39:279–83.