Lanreotide Depot to Treat Gastroenteropancreatic Neuroendocrine Tumors in a US Community Oncology Setting: A Prospective, Observational Study

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ABSTRACT

Introduction: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) can result in symptoms such as diarrhea, flushing, abdominal pain, and fatigue and are often associated with a significant disease burden and poor prognosis. This non-interventional, prospective, observational study evaluated the real-world safety and effectiveness of lanreotide depot, a somatostatin analog (SSA) used to treat GEP-NETs, in a community setting.

Methods: In this prospective, non-interventional study (NCT02730104), adult patients with locally advanced (inoperable), metastatic GEP-NETs treated with lanreotide depot were evaluated by their physician every 6 months from enrollment for 24 months. Clinically defined time to disease progression (TTDP) and overall survival (OS) were estimated for the total population and by primary tumor type (gastrointestinal [GI], pancreatic, unknown origin), and an exploratory analysis determined the rate of progression-free survival (PFS) at 12 and 24 months. Patient satisfaction was evaluated via the Treatment Satisfaction Questionnaire for Medication (TSQM-9), and safety information was recorded.

Results: Of 99 patients, the 24-month PFS rate was 73.7% (95% confidence interval [CI] 63.1–81.7) and 24-month OS rate was 84.2% (95% CI 74.0–90.7). Median TTDP was not reached because few patients experienced disease progression during the study period. The majority of responding patients expressed satisfaction with treatment on each domain of the TSQM-9, and safety information was recorded.

Conclusions: Lanreotide depot is an effective and well-tolerated treatment for GEP-NETs in the real-world community setting.

Trial registration: ClinicalTrials.gov identifier, NCT02730104.
PLAIN LANGUAGE SUMMARY

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare tumors that develop in the gut or pancreas. GEP-NETs may lead to a reduced lifespan, and people with GEP-NETs may have symptoms such as fatigue, muscle weakness, diarrhea, stomach pain/cramping, and skin reactions. One approved treatment for patients whose tumor cannot be removed with surgery is lanreotide depot. Clinical trials have found lanreotide depot to be effective at prolonging survival and managing symptoms in people with GEP-NETs. However, clinical trials take place under very strict conditions and often do not represent all people with a certain disease in the ‘real world’. It is important to determine whether treatments are still effective when used outside of clinical trials. This study was conducted in the real world and followed 99 people with GEP-NETs whose physicians were treating them with lanreotide depot. Each person was monitored for 24 months and assessed during check-ups by their physician every 6 months. After 24 months, 73.7% of people did not have progression (worsening) of disease. The percentage of people who had not died by the end of the study was 84.2%. Most patients (91.6%) said they were satisfied with their treatment. Only 19.2% of patients experienced side effects, none of which were serious.

**Keywords:** GEP-NETs; Lanreotide depot; Neuroendocrine tumors; Oncology; Progression-free survival; Patient satisfaction; Prospective study; Real-world evidence

| Key Summary Points |
|---------------------|
| **Why carry out this study?** |
| Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare malignancies frequently diagnosed as locally advanced or metastatic, which can substantially impact patients’ health and quality of life. |
| Somatostatin analogs such as lanreotide depot are recommended as the first-line medical treatment for GEP-NETs and have demonstrated efficacy in clinical trials; however, real-world evidence studies, which provide a more accurate representation of the overall patient population and their clinical management, are limited. |
| This prospective, observational study aimed to evaluate the effectiveness and tolerability of lanreotide depot to treat patients with GEP-NETs in a real-world, community setting. |

| **What was learned from the study?** |
| Patients with GEP-NETs receiving treatment with lanreotide depot had a high rate of progression-free survival and overall survival and no serious adverse events related to the study drug; the majority of patients expressed satisfaction with treatment. |
| The findings from this real-world study align with data from clinical trials and provide unique insight into the use of lanreotide depot in clinical practice, indicating that lanreotide depot is an effective and well-tolerated treatment for managing GEP-NETs and associated symptoms in patients receiving care in a community setting. |
INTRODUCTION

Neuroendocrine tumors (NETs) are a group of rare malignancies arising from cells throughout the endocrine system, with an annual age-adjusted incidence of 6.98 per 100,000 people as of 2012 [1, 2]. Of all NETs, approximately 60% originate either in the gastrointestinal system (stomach, small and large intestine, colon, rectum, appendix) or the pancreas, and are known collectively as gastroenteropancreatic (GEP)-NETs [3, 4]. Approximately 30% of GEP-NETs are considered to be functional tumors, characterized by hypersecretion of bioactive peptides and neuroamines leading to a range of hormone-associated symptoms such as general fatigue and muscle weakness, diarrhea, abdominal pain/cramping, skin reactions such as flushing, and, in some cases, cardiac valve fibrosis [2, 5–9]. However, many GEP-NETs are asymptomatic or non-specifically symptomatic; as such, most are diagnosed as locally advanced or metastatic [8, 10–13]. There is a need for safe and effective treatments to manage tumor growth and prolong progression-free survival (PFS) in patients with unresectable, metastatic GEP-NETs.

Somatostatin analogs (SSAs) are recommended for the treatment of hormone-related symptoms associated with NETs, and as a first-line option for the treatment of unresectable, metastatic GEP-NETs, according to the National Comprehensive Care Network (NCCN) treatment guidelines [2]. Lanreotide depot is an SSA indicated for the treatment of patients with GEP-NETs, with an approved dosing regimen of 120 mg every 28 days by deep subcutaneous injections [14]. The randomized, phase 3 CLARINET study demonstrated that PFS was significantly prolonged in patients treated with lanreotide depot compared with placebo [15].

Although clinical trials provide valuable objective information on the efficacy and safety of therapeutic agents, they often have very specific eligibility criteria. As a result, patients enrolled in clinical trials may not be representative of patients in the community setting. Real-world evidence (RWE) demonstrates the effectiveness and tolerability of treatments when they are used in clinical practice. In recent years, the Food and Drug Administration (FDA) has explored the potential benefits of using RWE as a key part of regulatory decisions regarding drug product effectiveness and safety [16]. However, RWE currently available on SSA utilization in the US consists largely of retrospective data, leaving a need for prospective real-world data [17, 18]. This non-interventional, prospective, observational study investigated the real-world effectiveness of lanreotide depot in patients with locally advanced or metastatic well-differentiated GEP-NETs in a US community oncology setting.

METHODS

Study Design and Endpoints

This prospective, non-interventional, observational study (NCT02730104) enrolled adult patients with locally advanced (inoperable), metastatic GEP-NETs treated with lanreotide depot 120 mg every 4 weeks in a US community oncology setting. Due to the observational nature of the study, the decision to prescribe lanreotide depot was required to have been made prior to, and independently from, the decision to enroll a patient in the study. Patients ≥ 18 years of age were enrolled in the study if they either planned to receive lanreotide depot or were already receiving lanreotide depot, provided that they had not experienced disease progression from the initiation of treatment. Patients were followed for a total duration of 24 months from the date of lanreotide depot initiation, regardless of whether treatment initiation occurred prior to or after enrollment in the study. Complete inclusion and exclusion criteria can be found in Supplementary Table 1.

The primary endpoint was clinically defined time to disease progression (TTDP). An exploratory analysis additionally assessed the PFS rates 12 and 24 months after lanreotide depot initiation, evaluated using Kaplan–Meier estimates. Progression was defined as at least one of the following: tumor growth (radiographic progression), new sites of metastatic...
disease, worsening clinical symptoms, or disease-related death, in conjunction with a treat-
ment change: treatment modification (dose increase, regimen change), treatment discon-
tinuation, or additional/other NET therapeutic intervention.

The secondary endpoints were rate of overall survival (OS) after 12 and 24 months and pa-
patient satisfaction with treatment via the Treatment Satisfaction Questionnaire for Medi-
cation (TSQM-9) [19]. TTDP, PFS, and OS were evaluated for the total study population as well as for subgroups based on primary tumor site. A safety analysis summarized treatment emergent adverse events (TEAEs) for all patients who received at least one dose of the study drug; all AEs considered to be related to lanreotide depot and all serious AEs (SAEs) were documented in the electronic case report form (eCRF) and reported to Ipsen Biopharmaceuticals. Patients were to be evaluated by their treating physician at a minimum of every 6 months from enrollment or initiation of lanreotide depot over a 24-month period, or more frequently, as best reflected routine clinical practice. If patients switched to a new anticancer therapy prior to disease progression or death (e.g., due to medication intolerance), they were censored and withdrawn from the study from the date of new treatment initiation. Patient demographics, including medical history, were collected at baseline upon study entry. Clinical characteristics were assessed and collected at each patient visit as appropriate; among these were radiologic assessment of disease progression, which was evaluated every 6 months, and AEs.

Statistical Analysis

Statistical analyses were performed by US Oncology Research in accordance with Inter-
national Conference on Harmonization (ICH E9) guidelines, based on the pooled data from individual study sites. The planned sample size, 100 patients, was based on prior experience in conducting similar studies [20, 21]. Descriptive statistics, including mean, standard deviation, median, minimum, and maximum values, are presented for continuous variables, while numbers and percentages are presented for categorical variables. The Kaplan–Meier estimate was used for median TTDP, PFS, and OS, where the index date was the initiation of treatment with lanreotide depot, with patients then followed for a duration of 24 months. At each study visit, patients were given the opportunity to use the TSQM-9 to self-report treatment satisfaction on a seven-point scale from 'Extremely Dissatisfied' to 'Extremely Satisfied' across nine domains, covering aspects of treatment including convenience, effectiveness, and overall satisfaction with the medication. The scores were summarized using the worst score for each patient (in case a patient completed multiple questionnaires during a single visit) across all study visits, and descriptive statistics were applied. AEs were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.03) [22]. Incidence and type of AEs, including SAEs, were tabulated and summarized using descriptive statistics. All statistical analyses were performed using Statistical Analysis System (SAS) version 9.4 (Cary, NC, USA) [23].

Compliance with Ethics Guidelines

This study was non-interventional and therefore fell outside the scope of the European Union (EU) Directive 2001/20/EC and the EU Directive 2005/28/EC. As required by applicable local regulations, all legal regulatory aspects were covered, and approval was obtained from the appropriate regulatory bodies prior to study initiation. This study adhered to all local regulatory requirements applicable to non-interventional studies. Before initiating the study, written and dated approval/favorable opinion were obtained from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

This study complied with the EU Directive 95/46/EC of the European Parliament, and of the Council of 24 October 1995 on the protection of individuals with regards to the processing of personal data and on the free movement of such data. This study also followed the recommendations from the International Society
for Pharmacoepidemiology (ISPE), Good Pharmacoepidemiological Practice (GPP) Guidelines, April 2007.

Participants were given a full explanation, in lay terms, of the nature and purpose of this data collection at the enrollment visit. All assessments and procedures were conducted in accordance with routine medical practice, and therefore participation in the study did not convey any additional risk or burden for patients. However, participants were provided with information on the benefits and risks of their medical treatment. Participants were required to provide written informed consent to confirm that they allowed their medical data to be collected, analyzed, and shared with regulatory authorities. Informed consent was obtained prior to participant enrollment and prior to any data collection. Sufficient time was allowed for participants to discuss any questions with investigators.

RESULTS

A total of 100 patients were recruited to the study; 99 patients received at least one dose of study drug and were included in the analyses. Among all patients who received study treatment, 62.6% completed their treatment over the course of the study and 16.2% went off treatment due to progression of disease. The remaining 21.1% discontinued treatment due to the following reasons: patient request (5.1%), AEs (4.0%), investigator request (4.0%), lost to follow-up (3.0%), death (2.0%), and other reasons (3.0%). The mean age of included patients was 64.5 years, with men comprising 54.5% of the study population. Over half of patients (59.6%) had already started lanreotide treatment prior to enrollment in the study. At baseline, 21.2% and 37.0% of patients presented with flushing and diarrhea, respectively. Complete patient demographics and medical history are shown in Table 1. A list of prescribed concomitant medications is presented in Supplementary Table 2.

Overall, 24 patients experienced clinically defined progression. Too few patients experienced progression over the course of the study.

| Parameter                        | Patients (N = 99) |
|----------------------------------|------------------|
| **Sex**                          |                  |
| Female                           | 45 (45.5)        |
| Male                             | 54 (54.5)        |
| **Race**                         |                  |
| Caucasian                        | 90 (90.9)        |
| Asian                            | 3 (3.0)          |
| Black                            | 2 (2.0)          |
| Hispanic                         | 1 (1.0)          |
| Other                            | 3 (3.0)          |
| **ECOG**                         |                  |
| 0                                | 61 (61.6)        |
| 1                                | 36 (36.4)        |
| 2                                | 2 (2.0)          |
| **Primary tumor site**           |                  |
| GI                               | 63 (63.6)        |
| Pancreatic                       | 27 (27.3)        |
| Unknown                          | 9 (9.1)          |
| **Histology and staging**        |                  |
| Locally advanced                 | 10 (10.1)        |
| Metastatic                       | 40 (40.4)        |
| Well-differentiated neuroendocrine | 48 (48.5)    |
| Missing                          | 1 (1.0)          |
| **Grade**                        |                  |
| 1                                | 68 (68.7)        |
| 2                                | 31 (31.3)        |
| **Employment status**            |                  |
| Working full-time                | 33 (33.3)        |
| Working part-time                | 10 (10.1)        |
to reach the median TTDP; therefore, median TTDP is not reported. The 12-month and 24-month PFS rates were 88.2% (95% CI 79.6–93.3) and 73.7% (95% CI 63.1–81.7), respectively (Fig. 1a). OS rates were 92.3% (95% CI 84.6–96.3) at 12 months and 84.2% (95% CI 74.0–90.7) at 24 months (Fig. 1b). A total of 13 (13.1%) patients died over the course of the study. A complete summary of causes of death is presented in Supplementary Table 3.

The analysis by primary tumor sites demonstrated 24-month PFS rates of 77.5% (95% CI 63.7–86.6) for gastrointestinal (GI) tumors (n = 63), 60.8% (95% CI 39.3–76.8) for pancreatic tumors (n = 27) and 88.9% (95% CI 43.3–98.4) for tumors of unknown origin (n = 9; Fig. 2a). The 24-month rates of OS by subgroup were 79.0% (95% CI 64.7–88.0) for GI tumors, 91.6% (95% CI 70.4–97.8) for pancreatic tumors, and 100% for tumors of unknown origin (Fig. 2b).

A total of 83 patients answered the TSQM-9. The majority of patients (76/83; 91.6%) who answered the survey expressed at least some degree of satisfaction with the overall treatment. Of the 83 patients, 88.0% were somewhat, very, or extremely confident that the study medication was good for them (Table 2).

| Parameter                                      | Patients (N = 99) |
|------------------------------------------------|------------------|
| Homemaker                                      | 4 (4.0)          |
| On medical/disability leave                    | 4 (4.0)          |
| Retired                                        | 40 (40.4)        |
| Unemployed                                     | 2 (2.0)          |
| Other                                          | 4 (4.0)          |
| Missing                                        | 2 (2.0)          |
| Prior lanreotide depot                         |                  |
| Yes                                            | 59 (59.6)        |
| No                                             | 40 (40.4)        |
| Octreotide scan at screeninga                   |                  |
| Yes                                            | 26 (26.3)        |
| No                                             | 73 (73.7)        |
| Flushing at screening                           |                  |
| No                                             | 73 (73.7)        |
| Yes—Mild                                       | 12 (12.1)        |
| Yes—Moderate                                   | 8 (8.1)          |
| Yes—Severe                                     | 1 (1.0)          |
| Yes—Total                                      | 21 (21.2)        |
| Missing                                        | 5 (5.1)          |
| Diarrhea at screening                           |                  |
| No                                             | 59 (59.6)        |
| Yes—Mild                                       | 20 (20.2)        |
| Yes—Moderate                                   | 17 (17.2)        |
| Yes—Severe                                     | 1 (1.0)          |
| Yes—Total                                      | 38 (38.4)        |
| Missing                                        | 2 (2.0)          |
| Both flushing and diarrhea at screening         |                  |
| Missing                                        | 2 (2.0)          |
| Chromogranin A at screening (µg/ml)             |                  |
| Number of patients                             | 64 (64.6)        |
| Mean (SD)                                      | 578.3 (2111.0)   |

4Octreotide scan was the only imaging method recorded in the data set

ECOG Eastern Cooperative Oncology Group, GI gastrointestinal, SD standard deviation, 5-HIAA 5-hydroxyindoleacetic acid

A total of 83 patients answered the TSQM-9. The majority of patients (76/83; 91.6%) who answered the survey expressed at least some degree of satisfaction with the overall treatment. Of the 83 patients, 88.0% were somewhat, very, or extremely confident that the study medication was good for them (Table 2). Treatment-related AEs were experienced by 19/99 (19.2%) of patients; the majority were grades 1 and 2, with one patient experiencing grade 3 diarrhea (Table 3). Sixteen patients
experienced SAEs, none of which were determined to be related to the study drug (Table 3). Treatment was discontinued in four patients due to AEs (abdominal cramps, anorexia, nausea, and paroxysmal atrial fibrillation), two of whom died; one from cardiac arrest and one from progressive disease.

**DISCUSSION**

This prospective, observational study aimed to evaluate the effectiveness of lanreotide depot in patients with locally advanced, metastatic GEP-NETs. Patients treated with lanreotide depot demonstrated extended PFS and a high rate of OS, highlighting the effectiveness of lanreotide depot for the treatment of patients with GEP-NETs in a real-world setting. While previous RWE studies have evaluated the effectiveness of lanreotide depot retrospectively [24, 25], few
observational studies have prospectively evaluated the safety and effectiveness of lanreotide depot as a treatment for GEP-NETs. The design of our study likely minimized bias and increased the robustness of our data, as study outcomes were predetermined, and investigators were able to collect accurate and complete datasets in accordance with a protocol.

In line with our findings, several published RWE studies have suggested that lanreotide...
| Treatment satisfaction-1 | Extremely dissatisfied, n (%) | Very dissatisfied, n (%) | Dissatisfied, n (%) | Somewhat satisfied, n (%) | Satisfied, n (%) | Very satisfied, n (%) | Extremely satisfied, n (%) | Not answered, n (%) | Total, n |
|-------------------------|-------------------------------|-------------------------|---------------------|--------------------------|-----------------|---------------------|---------------------------|----------------------|---------|
| How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition? | 3 (3.6) | 1 (1.2) | 8 (9.6) | 17 (20.5) | 23 (27.7) | 19 (22.9) | 12 (14.5) | 0 (0) | 83 |
| How satisfied or dissatisfied are you with the way the medication relieves your symptoms? | 3 (3.6) | 2 (2.4) | 5 (6.0) | 23 (27.7) | 25 (30.1) | 15 (18.1) | 10 (12.0) | 0 (0) | 83 |
| How satisfied or dissatisfied are you with the amount of time it takes the medication to start working? | 3 (3.6) | 2 (2.4) | 4 (4.8) | 17 (20.5) | 30 (36.1) | 12 (14.5) | 15 (18.1) | 0 (0) | 83 |
| How easy or difficult is it to use the medication in its current form? | 2 (2.4) | 2 (2.4) | 5 (6.0) | 14 (16.9) | 27 (32.5) | 16 (19.3) | 17 (20.5) | 0 (0) | 83 |
| How easy or difficult is it to plan when you will use the medication each time? | 2 (2.4) | 1 (1.2) | 2 (2.4) | 10 (12.0) | 28 (33.7) | 20 (24.1) | 20 (24.1) | 0 (0) | 83 |
| How convenient or inconvenient is it to take the medication as instructed? | 2 (2.4) | 2 (2.4) | 6 (7.2) | 14 (16.9) | 26 (31.3) | 13 (15.7) | 20 (24.1) | 0 (0) | 83 |
| Taking all things into account, how satisfied or dissatisfied are you with this medication? | 1 (1.2) | 0 (0) | 6 (7.2) | 17 (20.5) | 27 (32.5) | 20 (24.1) | 12 (14.5) | 0 (0) | 83 |

| Treatment satisfaction-2 | Not at all confident, n (%) | A little confident, n (%) | Somewhat confident, n (%) | Very confident, n (%) | Extremely confident, n (%) | Total, n |
|-------------------------|-------------------------------|-------------------------|--------------------------|---------------------|-----------------------------|---------|
| Overall, how confident are you that taking this medication is a good thing for you? | 2 (2.4) | 8 (9.6) | 28 (33.7) | 30 (36.1) | 15 (18.1) | 83 |
| How certain are you that the good things about your medication outweigh the bad things? | 6 (7.2) | 7 (8.4) | 25 (30.1) | 25 (30.1) | 20 (24.1) | 83 |
Table 3 Adverse events and serious adverse events

| Body system | AE term                        | AE grade | Total, n (%) |
|-------------|--------------------------------|----------|--------------|
|             | Treatment-related adverse events |          |              |
| Blood and lymphatic system disorders | Anemia | 2 | 1 (1.0) |
|             | Thrombocytopenia | 2 | 1 (1.0) |
| Cardiac disorders | Paroxysmal atrial fibrillation | 2 | 1 (1.0) |
| Gastrointestinal disorders | Abdominal pain | 1 | 2 (2.0) |
|             | Diarrhea | 1 | 4 (4.0) |
|             |          | 2 | 1 (1.0) |
|             |          | 3 | 1 (1.0) |
|             | Flatulence | 1 | 1 (1.0) |
|             |          | 2 | 1 (1.0) |
|             | Nausea | 1 | 2 (2.0) |
|             |          | 2 | 1 (1.0) |
|             | Vomiting | 1 | 1 (1.0) |
|             | Abdominal cramps | 2 | 1 (1.0) |
|             | Anorexia | 2 | 1 (1.0) |
| General disorders and administration site conditions | Fatigue | 1 | 3 (3.0) |
| Nervous system disorders | Dizziness | 1 | 1 (1.0) |
| Respiratory, thoracic, and mediastinal disorders | Pneumonitis | 2 | 1 (1.0) |
| Skin and subcutaneous tissue disorders | Granuloma injection site | 1 | 1 (1.0) |
|             | Serious adverse events |          |              |
| Cardiac disorders | Hypervolemia | 2 | 1 (1.0) |
|             | Myocardial infarction | 4 | 1 (1.0) |
|             | Cardiac arrest | 5 | 1 (1.0) |
|             | Heart disease congenital | 5 | 1 (1.0) |
| Gastrointestinal disorders | Bowel obstruction | 3 | 4 (4.0) |
|             |          | 4 | 1 (1.0) |
|             | Colitis | 3 | 1 (1.0) |
| Hepatobiliary disorders | Choledolithiasis | 3 | 1 (1.0) |
| Infections and infestations | Abscess | 3 | 1 (1.0) |
|             | Cellulitis | 3 | 1 (1.0) |
|             | Infection | 3 | 1 (1.0) |
Depot treatment is effective at controlling symptoms and disease progression in patients with NETs. One retrospective study evaluating patients with metastatic midgut NETs and carcinoid syndrome reported that lanreotide depot provided a reduction in daily frequency of diarrhea and flushing symptoms in 74% of patients, and 70% of patients demonstrated no radiological tumor progression throughout the study period [25]. Another study prospectively evaluated lanreotide treatment in patients with multiple endocrine neoplasia type 1 (MEN1) syndrome with one or more pancreatic NETs. Compared to patients not receiving lanreotide depot treatment, those receiving lanreotide depot had significantly longer median PFS ($p < 0.001$) [26]. An Italian retrospective database study investigated the effectiveness and tolerability of the four main therapeutic sequences recommended for grade 1 and 2 NETs: SSA standard dose to SSA high dose; SSA to everolimus; SSA to chemotherapy; and SSA to peptide receptor radionuclide therapy (PRRT) [27]. The study found that while PFS did not differ significantly between the groups, the sequences with SSA high dose or PRRT were better tolerated than those with everolimus or chemotherapy. A significantly lower number and severity of side effects ($p = 0.04$) and rate of dose reduction/discontinuation ($p = 0.03$) were observed in the SSA high dose and PRRT groups, suggesting that SSAs should be one of the preferred treatment options for NETs. Our study builds on these previous findings, demonstrating the effectiveness of an SSA, lanreotide depot, as a treatment for patients with a range of primary tumor sites.

Furthermore, the high rates of PFS observed in this study (88.2% and 73.7% after 12 and 24 months, respectively) are broadly consistent with the results of previous clinical trials evaluating lanreotide depot. For example, the CLARINET phase 3 clinical trial reported a 24-month PFS rate of 65.1% for patients treated with lanreotide depot versus 33.0% for patients treated with placebo [15]. The CLARINET open-label extension (OLE) study and the CLARINET FORTE phase 2 study provided further evidence of the efficacy and safety of lanreotide treatment in this population. In CLARINET OLE, median (95% CI) PFS for patients receiving lanreotide depot was 38.5 months (95% CI 30.9–59.4), versus 19.0 months (95% CI 10.1–26.7) in placebo-treated patients [28]. The CLARINET FORTE study reported no treatment-related SAEs and no deterioration in quality of life for patients with progressive midgut or pancreatic NETs receiving an increased dosing.

### Table 3 continued

| Body system                              | AE term                              | AE grade | Total, $n$ (%) |
|------------------------------------------|--------------------------------------|----------|----------------|
| Musculoskeletal and connective tissue disorders | Bone fracture                        | 3        | 2 (2.0)        |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | Disease progression                   | 5        | 2 (2.0)        |
| Nervous system disorders                 | Syncope                              | 3        | 1 (1.0)        |
| Psychiatric disorders                    | Confusion                            | 3        | 1 (1.0)        |
| Renal and urinary disorders              | Kidney dysfunction                    | 3        | 1 (1.0)        |
|                                          | Nephrolithiasis                      | 3        | 1 (1.0)        |
| Vascular disorders                       | Hypotension                           | 3        | 1 (1.0)        |
|                                          | Subarachnoid hemorrhage               | 4        | 1 (1.0)        |

AE adverse event
frequency of lanreotide depot (every 14 days versus every 28 days), affirming the tolerability of lanreotide depot even when administered at shorter intervals [29]. Compared with real-world studies, data from clinical trials are considered to be more robust because their highly controlled design, including stricter eligibility criteria and data collection methods, reduces the risk of confounding factors. For example, the CLARINET trial excluded patients who had undergone surgery related to their NET within 3 months of study entry or had received chemotherapy within 6 months of entry, while these exclusion criteria were not present in our study. In addition, clinical trials typically use the response evaluation criteria in solid tumors (RECIST) as a standardized method for defining disease progression [30]. By contrast, our study introduced a more flexible definition of disease progression that identified worsening clinical symptoms, tumor growth without a specified increase in diameter, and treatment change as additional indications of progression beyond those described by RECIST. While clinical trial data are more robust, real-world studies can provide a more accurate representation of the patient population and their clinical management in the community. Notably, the rate of PFS observed in our study was comparable to the rates reported in clinical trials, indicating that lanreotide depot is effective in treating a broad range of patients in a real-world setting.

The mortality rate and safety profile of our study were comparable to those of other studies evaluating lanreotide depot as a treatment for NETs. The low mortality rate was expected due to the slow-growing nature of GEP-NETs, with patients generally having prolonged survival even after disease progression has occurred. Other studies investigating SSAs to treat NETs have shown that median survival after disease progression can range from 12 to over 60 months [31–34]. Furthermore, treatment-related AEs were experienced by 19.2% of patients, the majority of which were mild or moderate (grades 1 or 2), and no SAEs were determined to be treatment-related. The phase 3 ELECT study, which evaluated the efficacy and safety of lanreotide depot, found that 26% of patients in the lanreotide depot group experienced TEAEs [35]. In the CLARINET study, a higher proportion of patients receiving lanreotide depot (50%) experienced treatment-related AEs; however, the low rate of SAEs (3%) is consistent with our findings [15]. Additionally, a review of 40 publications evaluating the safety and tolerability of lanreotide depot determined that the most frequently reported AEs were abdominal pain, diarrhea, and cholelithiasis [36]. This is in line with our study, which found that abdominal pain/cramping and diarrhea were the most frequently experienced treatment-related AEs. Finally, in our analysis, 4.0% of patients discontinued treatment due to AEs, generally aligning with previous findings: in an analysis of SSAs to treat metastatic NETs, 8.6% discontinued treatment due to side effects [36, 37], while the ELECT study had a slightly lower rate of discontinuation due to AEs, at 1.7% [35, 36]. These results indicate that lanreotide depot is generally well tolerated in both clinical trials and a real-world setting, with patients typically experiencing mild or moderate AEs and few SAEs, as well as relatively low rates of discontinuation due to AEs.

Patient satisfaction and confidence with treatment were also assessed, in line with the FDA’s emphasis on patient autonomy and centricity [16]. Patient satisfaction questionnaires, such as the TSQM-9, allow patients receiving treatment to self-report on a range of factors, including convenience of the medication, symptom relief, and the ability of the medication to treat the condition. In our study, the majority of patients (> 80%) expressed satisfaction with their treatment, with 88.0% of patients specifically expressing satisfaction with the way the medication relieved their symptoms. As patients with GEP-NETs regularly experience a multitude of debilitating symptoms, including fatigue, diarrhea, abdominal discomfort, and trouble sleeping, alleviation of symptoms is a critical factor in patient satisfaction [38–40]. Confidence with the medication was also high; 88.0% of patients expressed that they felt somewhat, very, or extremely confident that taking lanreotide depot was good for them, and 84.3% felt that the good aspects of the
medication outweighed the bad. The satisfaction scores obtained in our analysis align with the findings of previous studies, which generally report high rates of satisfaction in patients receiving lanreotide depot [41, 42]. Importantly, high patient satisfaction has been linked to better treatment adherence and persistence [43]. Therefore, the patient satisfaction results of our study indicate that real-world patients who receive lanreotide depot are likely to have good rates of adherence, which is a critical factor in ensuring the effectiveness of treatments in a real-world setting [44].

A relatively low proportion (26.3%) of patients in the study had received an octreotide scan at screening. Under European Society for Medical Oncology (ESMO) clinical practice guidelines, it is strongly recommended that patients with GEP-NETs undergo SSA radiolabeled imaging to assist with localization of both primary and metastatic tumors [45]. Historically, the primary imaging method has been somatostatin receptor scintigraphy (Octreoscan) [46], with 68Ga-labeled PET imaging increasingly used in recent years [47]. The low percentage of patients who had received an octreotide scan prior to entry in this study has several potential implications. Firstly, community-based treatment programs may not always have access to diagnostic techniques such as octreotide scans, or such scans may not be consistently utilized in clinical practice. In these cases, it may be difficult for tumors to be localized and treated effectively; where resources allow, imaging should be used to facilitate accurate GEP-NETs diagnosis. Secondly, it is also possible that octreotide scans were performed for more than 26.3% of patients and were simply underreported. With the increasing importance of real-world studies, it is crucial that data are reported as comprehensively and accurately as possible to ensure that studies' findings closely reflect real-world clinical practice.

The inclusion of patients with diverse types of GEP-NETs, including GI, pancreatic, and unknown primary origin, was a key strength of this study. While the incidence of NETs is increasing overall, the percentage classified as tumors of unknown primary origin is decreasing, which may reflect advances in tumor identification techniques [1, 48]. Tumors of unknown primary origin are estimated to account for 10–22% of GEP-NETs [48, 49], which is slightly higher than the 9.1% of patients in our study. As the incidence and relative rate of GEP-NETs primary tumors changes over time, it is important to evaluate medications across a range of primary tumor sites to ensure that all patients receive effective care and disease management. In our study, lanreotide depot was shown to be effective in treating all included primary tumor types, indicating that our results are broadly applicable to the overall population of patients with GEP-NETs.

The results of this study should be interpreted in light of several limitations. While similar RWE studies have used comparable sample sizes [20, 21], the numbers of patients in each primary tumor type subgroup in the exploratory analysis were low. Patients in this study were recruited from the US Oncology Research sample, which may also have limited generalizability to other populations (e.g., patients in academic institutions, other geographic locations), and RWE does not always mirror clinical recommendations, which can make it difficult to accurately interpret all collected data. Additionally, this 2-year study only allowed for a relatively short timeframe to measure disease progression in GEP-NETs. For instance, although we were able to analyze the exploratory objective (PFS), too few patients experienced disease progression within the course of the study to calculate median duration for TTDP (the primary endpoint). Furthermore, while 75 of the 99 total patients did not experience disease progression within the 2-year study, only 15 patients were considered ‘at risk’ (i.e., had neither experienced disease progression nor been censored for any other reason) at 24 months, indicating that a large proportion of the study population was censored. In a longer study, more patients would likely experience disease progression prior to the end of the study, potentially resulting in fewer patients being censored at their final study visit. Indeed, the CLARINET OLE study
found that the median PFS among patients treated with lanreotide depot was 38.5 months [28], suggesting that a longer prospective, observational study may be necessary to evaluate TTDP for patients in a community setting. Results for control of flushing and diarrhea from the current study have also not been reported, as a high proportion of patients presented without these symptoms at baseline (73.7% and 59.6%, respectively), which prevented meaningful analysis of these endpoints. Finally, the study did not include a comparator drug or placebo group against which lanreotide depot could be directly compared.

CONCLUSIONS

This study has demonstrated the effectiveness and tolerability of lanreotide depot in a real-world setting. Lanreotide depot was associated with prolonged PFS and OS in patients with GEP-NETs, in line with previous studies. Additionally, the medication was well tolerated, and the majority of patients reported satisfaction with their treatment. These results suggest that findings from stringent clinical trial populations are applicable to a more diverse group of patients in the community. Future RWE studies with an extended duration may be useful to explore the longer-term safety and effectiveness of lanreotide depot, especially in terms of TTDP and survival rate, in a real-world setting.

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Compliance with Ethics Guidelines. This study was non interventional and therefore fell outside the scope of the European Union (EU) Directive 2001/20/EC and the EU Directive 2005/28/EC. As required by applicable local regulations, all legal regulatory aspects were covered, and approval was obtained from the appropriate regulatory bodies prior to study initiation. This study adhered to all local regulatory requirements applicable to non-interventional studies. Before initiating the study, written and dated approval/favorable opinion were obtained from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

This study complied with the EU Directive 95/46/EC of the European Parliament, and of the Council of 24 October 1995 on the protection of individuals with regards to the processing of personal data and on the free movement of such data. This study also followed the recommendations from the International Society for Pharmacoepidemiology (ISPE), Good Pharmacoepidemiological Practice (GPP) Guidelines, April 2007.

Participants were given a full explanation, in lay terms, of the nature and purpose of this data collection at the enrollment visit. All assessments and procedures were conducted in accordance with routine medical practice, and therefore participation in the study did not convey any additional risk or burden for patients. However, participants were provided with information on the benefits and risks of their medical treatment. Participants were required to provide written informed consent to confirm that they allowed their medical data to be collected, analyzed, and shared with regulatory authorities. Informed consent was obtained prior to participant enrollment and prior to any data collection. Sufficient time was allowed for participants to discuss any questions with investigators.

Data Availability. Where patient data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

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