Lanreotide for the Prolonged Control of Carcinoid Syndrome in Somatostatin Analogue-Naive or Experienced Patients

INTRODUCTION
- Patients with neuroendocrine tumors (NET) who experience symptoms of carcinoid syndrome (CS) have a shorter life expectancy than those without a CS diagnosis. NETs commonly express somatostatin receptors and respond to treatment with the somatostatin analogue lanreotide. Lanreotide depot (30 mg) has been efficacious in reducing the risk of disease progression and improving symptoms.
- CS symptoms are variably distressing and have a significant negative impact on quality of life. Long-acting SSAs are recommended as first-line medical therapy for CS symptoms.
- Results from the double-blind phase of the multinational phase 3b ECLIPSE trial showed that lanreotide depot (30 mg) administered every 4 weeks for 42 weeks significantly reduced the mean percentage of days that short-acting octreotide rescue medication was used for control of breakthrough CS symptoms compared with placebo (37.3 vs. 86.8%, respectively, p<0.001).
- As expected due to study design, the average daily frequency of disha events was not significantly different between treatment. The average daily frequency of flushing events was lower for the lanreotide depot group but the result was not assessed for significance due to hierarchical testing being used. However in post-hoc analyses, improvements in average daily composite symptom score daily frequency were noted across non-interactive voice level response system were significantly greater for patients treated with lanreotide depot vs. placebo for flushing (p=0.001) and flushing and diarrhea (p=0.015).
- Lanreotide depot was well tolerated with no new safety signals identified during the double-blind phase and during the subsequent 12-week initial open-label (IO) phase.
- To further evaluate the impact of lanreotide depot on patients with CS symptoms in the ELECT study, we examined prospective data on the frequency of use of subcutaneous long-acting agonists (LAs) and other rescue medications during both the double-blind and IO treatment phases.
- We also assessed the impact of treatment with lanreotide depot on the frequency with which rescue medications were used within subgroups that were defined according to their prior exposure to SSA therapy.

METHODS

Patient Population
- Adults were included in the study if they had histologically confirmed diagnosis of carcinoid neuroendocrine tumor or a carcinoid tumor of unknown origin with liver metastases, a history of CS (flushing and/or diarrhea), and confirmed positive somatostatin-somatostatin receptor type 2 (SSTR2) activity. They also had an absence of tumor progression as documented by two sequential imaging scans 6 months apart (last scan within 6 months of study entry). Patients were recruited across Europe, North and South America, Asia, and Africa.
- Patients were either SSA-naïve or SSA-experienced (SSA prior subcutaneous dose of octreotide long-acting release (LAR) every 2 weeks or short-acting 30 mg daily as determined by the investigator).

Study Design and Treatment
- Patients were randomized to receive lanreotide depot (20 mg or 30 mg) placebo every 4 weeks over a 48-week double-blind (DB) phase followed by a 12-week IO phase in which they received lanreotide depot or lanreotide LAR (Figure 1).
- Throughout the study, patients were instructed to use so octreotide or other rescue medications such as octreotide 2 mg tablets and/or 12-hour IP as needed for control of breakthrough symptoms.
- After 24 weeks in the double-blind phase, patients rolled into the IO phase early if they self-assessed their disease as being under control for the last 4 weeks and were enrolled in a 24-hour cyclic between patients and the doses were 60 mg/12 mg for 12/1.25 mg/1.25 mg. The duration of the IO phase was 36 weeks for these patients.
- Patients reported their use of so octreotide and other rescue medications, and frequency and severity of symptoms of diarrhea and flushing, via daily interactive voice level response system.

Outcome Measures and Statistical Analysis
- Frequency with which so octreotide was used as rescue medication
  - During the double-blind phase (primary efficacy analysis endpoint), patients were assigned to the double-blind phase, and monitored every 4 weeks for CS symptoms and treatment-refractory events. The double-blind phase was continued until treatment withdrawal, death, or diagnosis of a second primary tumor, whichever occurred first. The frequency of rescue medication was assessed at the end of the double-blind phase for patients who had not withdrawn treatment or died during the double-blind phase. The frequency of rescue medication at baseline was used to calculate the statistical significance of treatment differences between treatment groups for time to next event reported - IOL phase = 7 months.
- Frequency with which other rescue medications were used - MPODs
  - Data were presented for the overall population and also by prior SSA therapy status (naive vs. prior use).

RESULTS

Patients
- A total of 321 patients participated in the double-blind phase (30 mg) who had not been treated with an SSA previously (Figure 2). A total of 30 patients continued into the IOL phase (60 mg/12 mg) who had been treated with a SSA previously.
- During the double-blind phase, 3 patients in the lanreotide depot treatment group and 3 in the placebo group withdrew Early withdrawal from the IO phase occurred for 3 patients in the placebo phase and placebo group, respectively. These patients were randomly assigned to treatment with lanreotide depot (30 mg) in the double-blind phase and placebo patients were randomly assigned to treatment with 60 mg/12 mg lanreotide depot in the IOL phase.
- Baseline demographic and clinical characteristics of patients in the IOL phase were similar to those of patients in the double-blind phase.

Use of Rescue Medications Between Previously SSA-Naïve and SSA-Experienced Subgroups
- No apparent differences in the use of rescue medications were observed between patients who were naïve vs. SSA therapy, and those who had received prior SSA therapy with the exception of patients treated with lanreotide depot. The use of placebo-treated patients in the double-blind phase both octreotide and other rescue medications and patients treated with lanreotide depot in the IOL phase either other rescue medications or both octreotide depot in the subgroup analysis were generally similar to those for the overall population (Figures 4a and 4b).

CONCLUSIONS
- The results of this study demonstrates that lanreotide depot was effective for the control of breakthrough CS symptoms in patients with NETs.
- The frequency with which rescue medications were used for the control of breakthrough CS symptoms was similar between lanreotide depot-treated patients who were previously naïve to SSA therapy and patients known to be responsive to SSA therapy.
- Taken together, these and previously published results confirm lanreotide depot’s safety and its potential for use in patients with NETs.

Conflicts of interest
- The authors have indicated that they have no conflicts of interest.

References
- The author has indicated that they have no additional relevant information to disclose.

Acknowledgements
- The author has indicated that they have no additional relevant information to disclose.

Figure 1. Study Design
- The figure shows the study design of the double-blind and initial open-label phases.

Figure 2. Frequency of Octreotide Use to Control Breakthrough CS Symptoms
- The figure illustrates the frequency of octreotide use to control breakthrough CS symptoms in the double-blind and initial open-label phases.

Figure 3. Frequency of Other Rescue Medications’ Use to Control Breakthrough CS Symptoms
- The figure presents the frequency of other rescue medications’ use to control breakthrough CS symptoms.

Figure 4. Frequency With Which so octreotide and b) Other Rescue Medications Were Used According to Prior SSA Therapy
- The figure displays the frequency with which so octreotide and other rescue medications were used according to prior SSA therapy.

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INTRODUCTION

- Patients with neuroendocrine tumors (NETs) who experience symptoms of carcinoid syndrome (CS) have a shorter life expectancy than those without a CS diagnosis.1 NETs commonly express somatostatin receptors and treatment with the long-acting somatostatin analog (LASSA) lanreotide depot/autogel at 120 mg has been confirmed as efficacious in reducing the risk of disease progression or death.2

- CS symptoms themselves are very distressing and have a significant negative impact on quality of life.3 Long-acting SSAs are recommended as first-line medical therapy for CS symptoms.4

- Results from the double-blind phase of the multinational phase 3 ELECT trial (NCT00774930) showed that lanreotide depot 120 mg administered every 4 weeks for 16 weeks significantly reduced the mean percentage of days that short-acting octreotide rescue medication was used for control of breakthrough CS symptoms compared with placebo (33.7 vs. 48.5%, respectively; p<0.017).5

- As expected due to study design, the average daily frequency of diarrhea events was not significantly different between treatments. The average daily frequency of flushing events was lower for the lanreotide depot group but this result was not assessed for significance due to hierarchical testing being used.6 However in post hoc analyses, improvements in average daily composite symptom scores (daily frequency x daily severity assessed via interactive voice (web) response system) were significantly greater for patients treated with lanreotide depot vs. placebo for flushing (p=0.030) and flushing and/or diarrhea (p=0.036).7

- Lanreotide depot was well tolerated with no new safety signals identified during the double-blind phase4 and during the subsequent 32-week initial open-label (IOL) phase.6

- To further evaluate the impact of lanreotide depot on patients’ relief of CS symptoms in the ELECT study, we examined prospective data on the frequency of use of subcutaneous (sc) octreotide and other rescue medications during both the double-blind and IOL treatment phases.

- We also examined the impact of treatment with lanreotide depot on the frequency with which rescue medications were used within subgroups that were defined according to their prior exposure to SSA therapy.

METHODS

Patient Population

- Adults were included in the study if they had a histopathologically confirmed diagnosis of carcinoid (neuroendocrine) tumor or a carcinoid tumor of unknown location with liver metastases, a history of CS (flushing and/or diarrhea), and confirmed positive somatostatin-receptor status.5,6 They also had an absence of tumor progression as documented by two sequential imaging scans ≥3 months apart (last scan within 6 months of study entry). Patients were recruited from 13 countries spanning Europe, North and South America, Asia, and Africa.

- Patients were either SSA-naïve (SSA-naïve subgroup) or were responsive (SSA-prior subgroup) to conventional doses of octreotide (long-acting release ≥30 mg every 4 weeks or short-acting ≥600 μg daily) as determined by the investigator.5

Study Design and Treatment

- Patients were randomized to receive lanreotide depot 120 mg or placebo every 4 weeks over a 16-week duration (double-blind phase), followed by a 32-week IOL phase in which they received lanreotide depot 120 mg (Figure 1).10

- Throughout the study, patients were instructed to use sc octreotide or other rescue medications (such as loperamide 2-mg tablets and/or tincture of opium) as needed for control of breakthrough symptoms.

- After ≤1 weeks in the double-blind phase, patients rolled over into the IOL phase early if they self-administered sc octreotide for ≥2 days of the 28-day cycle between injections and the doses were ≥300 μg for 14/21 days. The duration of the IOL phase was then ≥32 weeks for these patients.

- Patients recorded their use of sc octreotide and other rescue medications, and frequency and severity of symptoms of diarrhea and flushing, via daily interactive voice (web) response system.
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Edward M. Wallin, MD, George A. Fisher, Jr, MD, Nilani Liyanage, MSc, Susan Pitman Lovernthal, MD, Belinda Mirakhor, MD, Rodney F. Pommier, MD, Montasser Shoheen, MD, and Aaron I. Vinik, MD

Division of Medical Oncology, John S. Leventhal, MD, Mount Sinai, New York, NY, USA

Department of Medical Oncology, Stanford University School of Medicine, Stanford, CA, USA

Ispen, Los Altos, CA, USA

Department of Medical Affairs, Ipsen, Eatontown, NJ, USA

Department of Surgical Oncology, Oregon Health & Science University, Portland, OR, USA

Affiliation subsequent to study conduct: University of Arizona, Tucson, AZ, USA

Outcome Measures and Statistical Analysis

- Frequency with which octreotide was used as rescue medication:
  - Double-blind phase (primary efficacy analysis endpoint) – least squares (LS) mean percentage of usage days (MPUDs). Parametric analysis of covariance (ANCOVA), with adjustments for stratification factors and co-variates (octreotide usage, and daily averages of diarrhea and flushing events at baseline), was used to determine statistical differences between treatment approaches as previously reported.1
  - IOL phase – MPUDs.
  - Frequency with which other rescue medications were used – MPUDs.
  - Data are presented for the overall population and also by prior SSA-therapy status (naïve vs. prior use).

RESULTS

Patients

- A total of 155 patients participated in the double-blind phase: 51 (44.3%) had not been treated with an SSA previously (Figure 1). A total of 101 patients continued into the IOL phase; 60 (59.4%) had been treated with an SSA previously.2
  - During the double-blind phase, 3 patients in the lanreotide depot treatment group and 11 in the placebo group withdrew.2 Early rollover into the IOL phase occurred for 11 (11.6%) and 12 (11.4%) patients in the lanreotide depot and placebo groups, respectively.3,4
  - The overall population in the double-blind phase had a mean age of 58.6 years. The majority had been symptomatic for at least 1 year (81% (72.2%)) and living with a diagnosis of CS for at least 1 year before starting treatment (79% (68.3%)).3 Baseline characteristics were similar between treatment groups, except there were slightly more men in the lanreotide depot group than in the placebo group (45.8% vs. 37.5%, respectively).3,5
  - Baseline demographic and clinical characteristics of patients in the IOL phase were similar to those of patients in the double-blind phase.6

Figure 1. Study Design

- Enrolled into ELECT study (n=155)
- Randomization
  - LAN 120 mg (n=59)
  - SSA naïve (n=26)
  - SSA prior (n=33)
  - LAN 120 mg (n=56)
  - SSA naïve (n=23)
  - SSA prior (n=33)
  - Placebo (n=60)
  - SSA naïve (n=25)
  - SSA prior (n=31)
  - LAN 120 mg (n=45)
  - SSA naïve (n=18)
  - SSA prior (n=27)

1 Patients proceeded earlier to the initial open-label phase if they used sc octreotide for ≥ 18 days in the injection interval and doses were ≥ 300 μg for ≥ 18 days. 4 Patients in total withdrew from the study during the double-blind phase: 1) LAN, lanreotide depot: SSA, somatostatin analog; SSA-naïve, no prior SSA therapy; SSA prior, response to prior octreotide therapy.
Lanreotide for the Prolonged Control of Carcinoid Syndrome in Somatostatin Analog-Naïve or Experienced Patients

Edward M. Wolin, MD; George A. Fisher, Jr, MD; Nilani Liyanage, MSc; Susan Pitman Lowenthal, MD; Belo Mirakhur, MD; Rodney F. Pommier, MD; Montasser Shoaheen, MD*; Aaron I. Vinik, MD*

*Division of Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; †Department of Medical Oncology, Stanford University School of Medicine, Stanford, CA, USA; ‡Ipsen, Les Lilas, France; §Department of Medical Affairs, Ipsen, London Ridge, NJ, USA; ††Department of Surgical Oncology, Oregon Health & Science University, Portland, OR, USA; *‡Department of Internal Medicine, University of New Mexico Comprehensive Cancer Center, Albuquerque, NM, USA; ‡‡Department of Medicine, Eastern Virginia Medical School, Norfolk, VA, USA

Affiliation subsequent to study conduct: University of Arizona, Tucson, AZ, USA

Use of Rescue Medications in the Overall Population

- sc octreotide:
  - During the 16-week double-blind phase (and, as previously reported1), the LS MPUDs in the lanreotide depot group was significantly lower than that for placebo (Figure 2).
  - During the 32-week IOL phase, the MPUDs decreased in patients continuing treatment with lanreotide depot and in those switching from placebo to lanreotide depot (Figure 2).

- Other rescue medications:
  - At baseline, MPUDs (standard deviation [SD]) were 3.2% (2.6%) with lanreotide depot and 8.3% (3.7%) with placebo. No significant decreases were observed from baseline with lanreotide depot or placebo in the double-blind phase (Figure 3).
  - MPUDs remained relatively unchanged among patients continuing treatment with lanreotide depot in the IOL phase but decreased among patients switching from placebo to lanreotide depot (6.3% to 3.3%) (Figure 3).

Figure 2. Frequency of Octreotide Use to Control Breakthrough CS Symptoms

Figure 3. Frequency of Other Rescue Medication Use to Control Breakthrough CS Symptoms
Use of Rescue Medications Between Previously SSA-Naive and SSA-Experienced Subgroups

- No apparent differences in the use of rescue medications were observed between patients who were naïve to SSA therapy and those who had received prior SSA therapy, with the exception of placebo-treated patients in the double-blind phase (both octreotide and other rescue medications) and of patients switching from placebo to lanreotide in the IOI phase (other rescue medications) (Figure 4). Trends in MPUs for rescue medications in the subgroups were generally similar to those for the overall population (Figures 2–4).

Conclusions

- The results of this analysis demonstrated that lanreotide depot was effective for the prolonged control of CS symptoms in patients with NETs.
- The frequency with which rescue medications were used for the control of breakthrough CS symptoms was similar between lanreotide-treated patients who were previously naïve to SSA therapy and in patients known to be responsive to SSAs.
- Taken together, these and previously published results confirm lanreotide depot 120 mg administered monthly via deep sc injection is associated with a reduced need for rescue medications to control breakthrough CS symptoms for up to a year in both SSA-experienced and SSA-naive patients with NETs.

References


Conflicts of interest

EHK is a consultant/advisor for Advanced Accelerator Applications, Ipsen, Lexicon, and Novartis. GAJ is a consultant/advisor for Genentech/Roche, Ipsen, and Merck; stock ownership in Seattle Genetics (family member); honoraria from Genentech, Ipsen, and Merck; research funding to institution from Amgen (Biotech, Epizyme), Forty Seven, Genentech/Roche, Merck, Neneleve Genetix, Novartis, and Wellcome Trust; and BH (employee of Ipsen) stock ownership in Ipsen. SPL is consultant/advisor for Merck, Roche Pharmaceuticals, and Novartis; EK, JF, and KJ (employee of Medtronic) have no competing interests to disclose.

AM is a member of speakers bureaus for Merck and Lexicon; consultant/advisor for chrysalis, Jadus, Pharma, Ipsen, Janvier, Merck, Pembrolizumab, and Veredos Science; research funding to institution from Impella Medical; Novartis, Veredos Science, and Yttrium Medical travel, accommodation, expenses from Ipsen; O’Mara, Pembrolizumab, and Pfizer, Regeneron, and Veredos Science.

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