Lanreotide for the Prolonged Control of Carcinoid Syndrome in Somatostatin Analog-Naïve or Experienced Patients

Edward M. Wolin, MD[1], George A. Fisher, Jr, MD[2], Nilani Liyanage, MSc[3], Susan Pitman Lowenthal, MD[4], Beloo Mirakhur, MD[4], Rodney F. Pommier, MD[5], Montaser Shaheen, MD[6]*, Aaron I. Vinik, MD[7]

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

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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 (SSA) 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.[5] 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 ($p=0.036$).[6]
  - Lanreotide depot was well tolerated with no new safety signals identified during the double-blind phase[5] 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.[6]

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**).[5,6]
- 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 ≥4 weeks in the double-blind phase, patients rolled over into the IOL phase early if they self-administered sc octreotide for ≥21 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.

Outcome Measures and Statistical Analysis

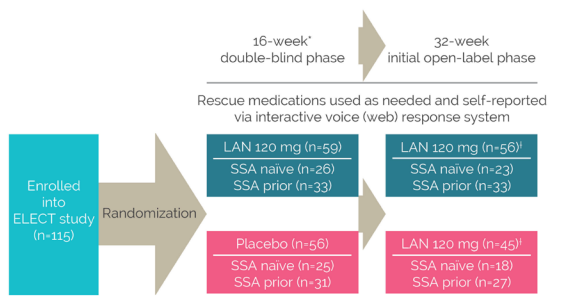
- Frequency with which sc octreotide was used as rescue medication:
  - Double-blind phase (primary efficacy analysis endpoint) – least squares (LS) mean percentage of usage days (MPUDs). Parametric analysis of covariance (ANCOVA), with adjustments for stratification factors and co-variates (octreotide usage, and daily averages of diarrhea and flushing events at baseline), was used to determine statistical differences between treatment groups as previously reported.[5]
  - 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 115 patients participated in the double-blind phase; 51 (44.3%) had not been treated with an SSA previously (**Figure 1**).[5] A total of 101 patients continued into the IOL phase; 60 (59.4%) had been treated with an SSA previously.[6]
- During the double-blind phase, 3 patients in the lanreotide depot treatment group and 11 in the placebo group withdrew.[5] Early rollover into the IOL phase occurred for 11 (18.6%) and 12 (21.4%) patients in the lanreotide depot and placebo groups, respectively.[5,6]
- The overall population in the double-blind phase had a mean age of 58.6 years. The majority had been symptomatic for ≥1 year (83 [72.2%]) and living with a diagnosis of CS for ≥1 year before starting treatment (74 [64.3%]).[5] 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).[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

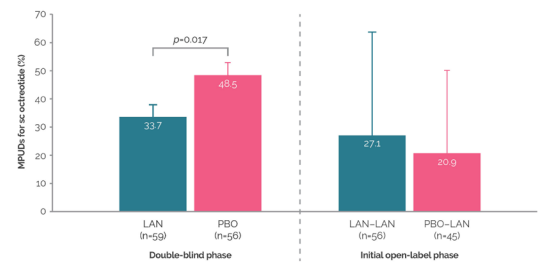


*Patients proceeded earlier to the initial open-label phase if they used sc octreotide for ≥21/28 days in the injection interval and doses were ≥300 µg for 14/21 days. †14 patients in total withdrew from the study during the double-blind phase.[5,6] LAN, lanreotide depot; SSA, somatostatin analog; SSA naïve, no prior SSA therapy; SSA prior, responsive to prior octreotide therapy.

Use of Rescue Medications in the Overall Population

- sc octreotide:
  - During the 16-week double-blind phase (and, as previously reported[5]), 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**).

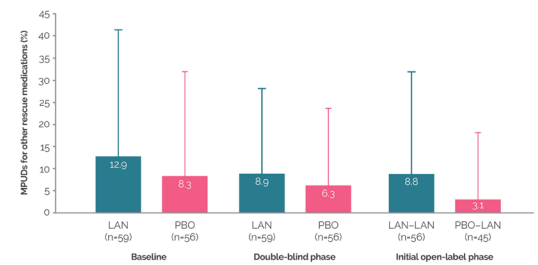
Figure 2. Frequency of Octreotide Use to Control Breakthrough CS Symptoms



Double-blind phase data are LS MPUDs (SE); initial open-label phase data are MPUDs (SD). *p*-value is derived from an ANCOVA adjusted for stratification factors and co-variates (octreotide usage, and daily averages of diarrhea and flushing events at baseline). ANCOVA, analysis of covariance; CS, carcinoid syndrome; LAN, lanreotide depot; LAN–LAN, patients randomized to lanreotide depot for the double-blind phase and continuing to receive lanreotide depot in the initial open-label phase; LS, least squares; MPUDs, mean percentage of usage days; PBO, placebo; PBO–LAN, patients randomized to placebo for the double-blind phase and switching to lanreotide depot in the initial open-label phase; sc, subcutaneous.

- Other rescue medications:
  - At baseline, MPUDs (standard deviation (SD)) were 12.9% (28.6%) with lanreotide depot and 8.3% (23.7%) 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 3.1%) (**Figure 3**).

Figure 3. Frequency of Other Rescue Medication* Use to Control Breakthrough CS Symptoms



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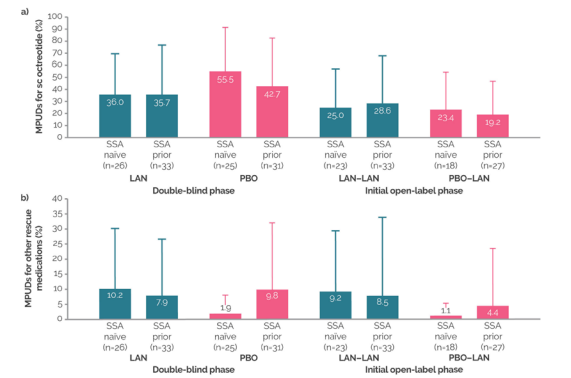
Use of Rescue Medications Between Previously SSA-Naïve and SSA-Experienced Subgroups

- No apparent differences in the use of rescue medications were observed between patients who were naïve 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 IOL phase (other rescue medications) (**Figure 4**). Trends in MPUDs for rescue medications in the subgroups were generally similar to those for the overall population (**Figures 2–4**).

Figure 4. Frequency With Which a) sc Octreotide and b) Other Rescue Medications* Were Used According to Prior SSA Therapy



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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[5,6] 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-naïve patients with NETs.

Conflicts of interest

EMW: consultant/advisor for Advanced Accelerator Applications, Ipsen, Lexicon, and Novartis. **GAF:** 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 Aduro Biotech, EpicentRx, Forty Seven, Genentech/Roche, Merck, NewLink Genetics, Novartis, and XBiotech. **NL and BM:** employees of Ipsen; stock ownership in Ipsen. **SPL:** consultant of Ipsen; stock ownership in Pfizer. **RFP:** travel, accommodation, expenses, honoraria, consultant/advisor, and member of speakers' bureau for Novartis; travel, accommodation, consultant/advisor, and honoraria from Ipsen. **MS** has no competing interests to disclose. **AIV:** member of speakers' bureau for Merck and Lexicon; consultant/advisor for Alnylam, Astellas Pharma, Ipsen, Janssen, Merck, Pamlab, and VeroScience; research funding (to institution) from Impeto Medical, Novo Nordisk, VeroScience, and ViroMed; travel, accommodation, expenses from Ipsen, Janssen, Merck, Pamlab, Pfizer, Regeneron, and VeroScience.

Acknowledgements

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Presented at the North American Neuroendocrine Tumor Society (NANETS), Seattle, Washington, USA, October 4–6, 2018.

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- 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 115 patients participated in the double-blind phase; 51 (44.3%) had not been treated with an SSA previously (**Figure 1**).[5] A total of 101 patients continued into the IOL phase; 60 (59.4%) had been treated with an SSA previously.[6]
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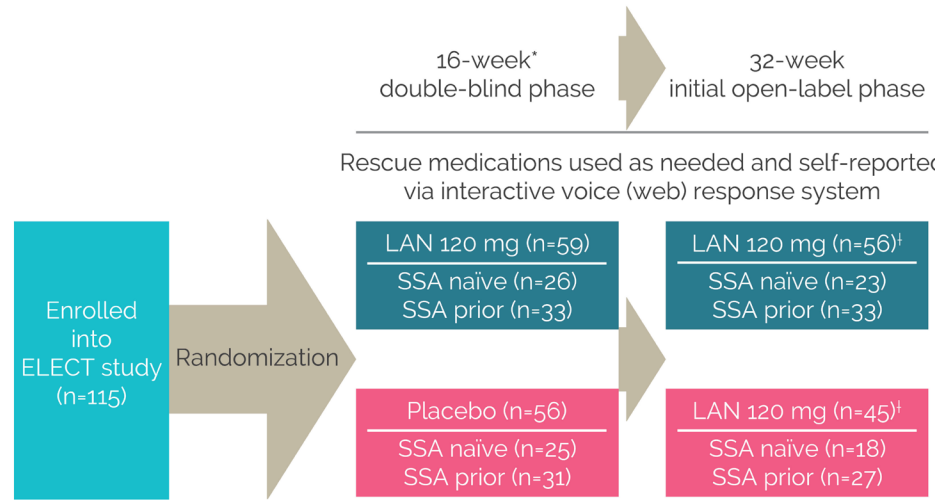

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Figure 2. Frequency of Octreotide Use to Control Breakthrough CS Symptoms

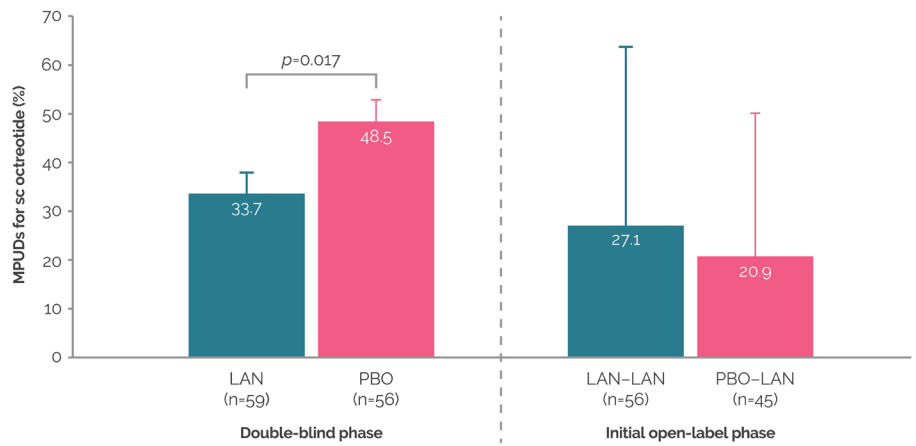

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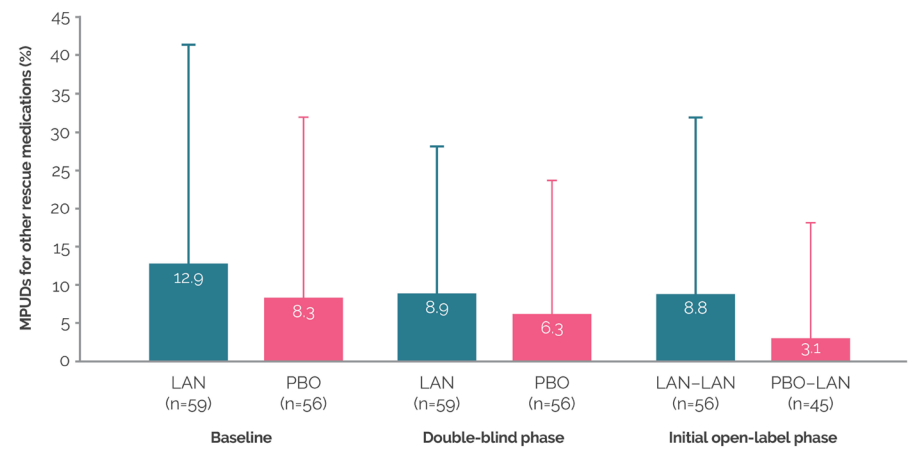
Figure 3. Frequency of Other Rescue Medication* Use to Control Breakthrough CS Symptoms



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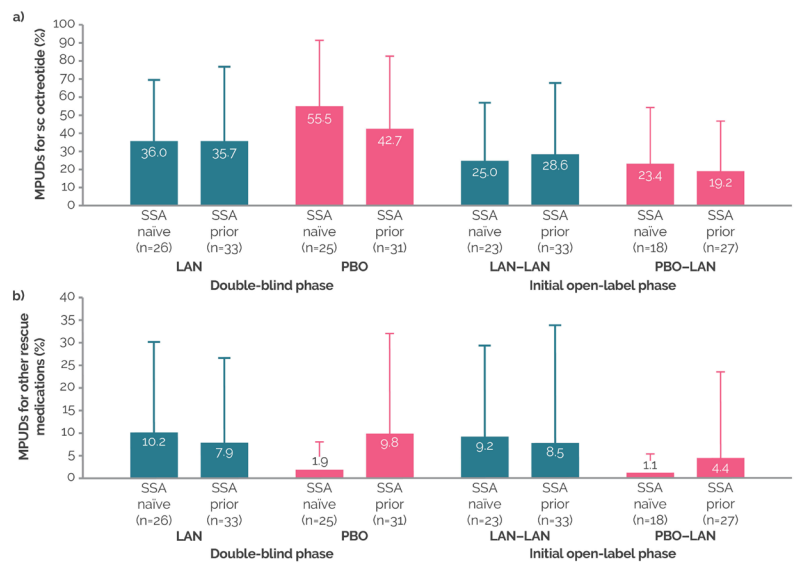

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- The results of this analysis demonstrated that lanreotide depot was effective for the prolonged control of CS symptoms in patients with NETs.
- The frequency with which rescue medications were used for the control of breakthrough CS symptoms was 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[5,6] 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-naïve patients with NETs.

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Conflicts of interest

EMW: consultant/advisor for Advanced Accelerator Applications, Ipsen, Lexicon, and Novartis. **GAF:** 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 Aduro Biotech, EpicentRx, Forty Seven, Genentech/Roche, Merck, Newlink Genetics, Novartis, and XBiotech. **NL and BM:** employees of Ipsen; stock ownership in Ipsen. **SPL:** consultant of Ipsen; stock ownership in Pfizer. **RFP:** travel, accommodation, expenses, honoraria, consultant/advisor, and member of speakers' bureau for Novartis; travel, accommodation, consultant/advisor, and honoraria from Ipsen. **MS** has no competing interests to disclose. **AIV:** member of speakers' bureau for Merck and Lexicon; consultant/advisor for Alnylam, Astellas Pharma, Ipsen, Janssen, Merck, Pamlab, and VeroScience; research funding (to institution) from Impeto Medical, Novo Nordisk, VeroScience, and ViroMed; travel, accommodation, expenses from Ipsen, Janssen, Merck, Pamlab, Pfizer, Regeneron, and VeroScience.

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