Lanreotide Autogel (Depot) Significantly Improves Tumor Progression-Free Survival in Patients with Non-functioning Gastroenteropancreatic Neuroendocrine Tumors: Results of the CLARINET Study

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Introduction

- Somatostatin analogs (SSAs) provide good symptom control in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs).
- SSAs also inhibit tumor growth in various experimental tumor types by direct and indirect mechanisms.[1,2]
- To date, evidence is based mostly on retrospective and prospective open-label studies.[3–6] Prior to CLARINET, PROMID was the only randomized placebo-controlled study conducted with octreotide LAR in midgut NETs.[7]
- The Controlled study of Lanreotide Antiproliferative Response In NET (CLARINET) is the only randomized placebo-controlled study with an SSA in gastrointestinal *and pancreatic* NETs (pNETs), strengthening the evidence for progression-free survival (PFS) benefits.
- CLARINET was a large 2-year international study (n=204, 14 countries) conducted with lanreotide Autogel (Depot in US) 120 mg (without dose titration). Patients had:
  - well-/moderately differentiated non-functioning NETs
  - 32% had Ki-67 >2%
  - 48% had hepatic tumor load >10%.

Methods

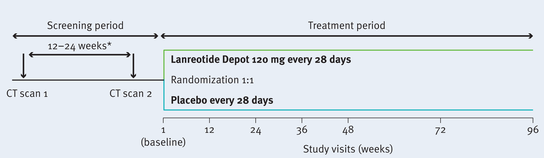
Patients

- Key inclusion criteria:
  - adults (≥18 years) with sporadic non-functioning NETs (or gastrinomas adequately controlled with proton-pump inhibitors for ≥4 months)
  - primary tumor localization in pancreas, midgut, hindgut, or unknown origin
  - NET confirmed centrally as well-/moderately differentiated and measurable according to response evaluation criteria in solid tumors (RECIST) criteria version 1.0
  - Ki-67 <10% (or mitotic index ≤2 mitosis/10 high power fields if Ki-67 not reliably quantified)
  - metastatic disease and/or locally advanced inoperable tumor (or documented refusal of surgery)
  - grade ≥2 with somatostatin receptor scintigraphy (Krenning scale).
- Key exclusion criteria:
  - treatment with interferon, chemoembolization, or chemotherapy within previous 6 months, radionuclide at any time, or SSA at any time (unless <15 days in duration and received >6 months previously)
  - major surgery related to NET within previous 3 months
  - multiple endocrine neoplasia.
- Patient withdrawals based on:
  - tumor progression according to RECIST criteria version 1.0 and confirmed centrally
  - investigator's clinical judgment, patient's own request, or adverse event (AE) possibly jeopardizing safety.

Design and treatment

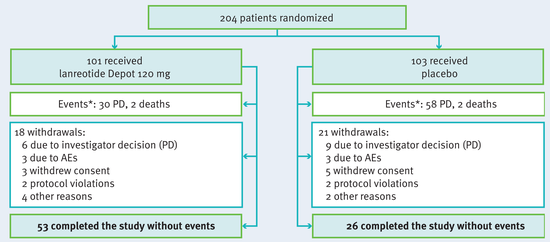
- A 96-week randomized double-blind placebo-controlled parallel-group phase 3 study (Figure 1) conducted in 14 countries (Austria, Belgium, Czech Republic, Denmark, France, Germany, India, Italy, Poland, Slovakia, Spain, Sweden, UK, USA).
- Patients randomized 1:1 to lanreotide Depot 120 mg or placebo, stratified by presence/absence of tumor progression and presence/absence of previous therapies.

Figure 1. Study design.



*If one or two scans performed up to 24 weeks before screening visit were available for central review, screening period was shortened. Scan 2 performed 12–24 weeks after scan 1 and randomization occurred within 4 weeks of scan 2. Clinicaltrials.gov (NCT00353496)/EudraCT (2005-004904-35). CT, computed tomography.

Figure 2. Patient disposition.



*2 deaths occurred in lanreotide group after withdrawal for another reason; and 2 deaths occurred and 2 PDs detected in placebo group after withdrawal for another reason.

Study endpoints

- Primary endpoint – PFS (time to death or disease progression confirmed centrally according to RECIST criteria) within 96 weeks of first study treatment.
  - primary analysis with intention-to-treat (ITT) population (i.e., all randomized patients).
  - analyses of effects of baseline covariates (e.g., primary tumor localization, tumor grade, hepatic tumor load; ITT analyses).
- Secondary endpoints included % patients alive and without tumor progression at 48 and 96 weeks; time to progression; overall survival (time from randomization to death due to any cause); tumor biomarkers; safety. (Of these secondary endpoints, data for overall survival and safety are presented here.)

Results

Patient disposition and baseline characteristics

- A total of 204 patients received treatment: lanreotide Depot 120 mg (n=101) vs. placebo (n=103) (Figure 2).
- Treatment groups were well-matched for baseline characteristics (Table 1).

PFS (primary endpoint)

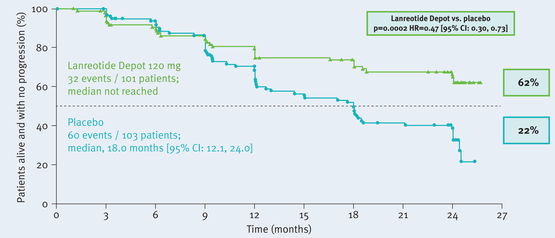
- Primary analysis – lanreotide Depot 120 mg significantly prolonged PFS vs. placebo: median PFS not reached vs. 18 months, respectively (hazard ratio [HR] 0.47 [95% confidence interval (CI): 0.30, 0.73], P=0.0002; Figure 3).

Table 1. Baseline demographic and disease characteristics.

	Lanreotide Depot 120 mg (n=101)	Placebo (n=103)
Men, n (%)	53 (52)	54 (52)
Age, mean (SD) in years	63 (10)	62 (11)
Time since diagnosis, mean (SD) in months	33 (46)	34 (41)
Primary tumor resected, n (%)	40 (40)	39 (38)
NET origin, n (%)		
Pancreas*	42 (42)	49 (48)
Midgut	33 (33)	40 (39)
Hindgut	11 (11)	3 (3)
Unknown/other	15 (15)	11 (11)
Tumor progression, n (%)	4 (4)	5 (5)
Prior treatment, n (%)	16 (16)	16 (16)
Tumor grade, n (%)		
G1 (Ki-67 0–2%)	69 (68)	72 (70)
G2 (Ki-67 3–10%)	32 (32)	29 (28)
Unknown	0	2 (2)
Hepatic tumor load, n (%)		
0%†	16 (16)	18 (17)
0–10%	33 (33)	40 (39)
10–25%	13 (13)	17 (17)
25–50%	23 (23)	12 (12)
>50%	16 (16)	16 (16)
Chromogranin A, n (%)		
≤1 × ULN	33 (33)	34 (33)
1–2 × ULN	25 (25)	18 (17)
>2 × ULN	41 (41)	48 (47)
Unknown	2 (2)	3 (3)

Data from the intention-to-treat population. No statistically significant differences in baseline characteristics between treatment groups were observed. *Two patients in each group had gastrinomas; †patients with no liver metastases, had metastases in one or more of lymph nodes, peritoneum, retroperitoneum, pancreas, and mediastinum. Ki-67, tumor proliferation index; NET, neuroendocrine tumor; ULN, upper limit of normal.

Figure 3. Lanreotide Depot 120 mg significantly prolonged PFS compared with placebo (primary analysis of primary endpoint).



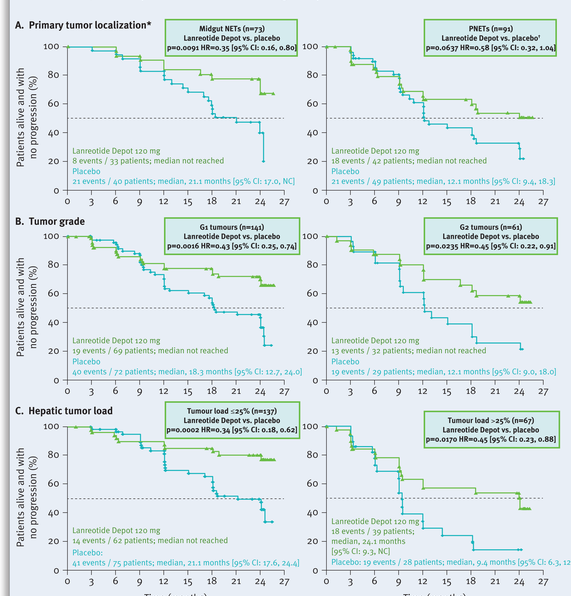
Analysis based on intention-to-treat population with centrally assessed disease progression or death as events. The survival curves were compared via the stratified logrank test, with stratification for presence/absence of tumor progression at baseline and presence/absence of previous therapy. Hazard ratio (HR) derived from Cox proportional hazards model.
CI, confidence interval; PFS, progression-free survival.

- Lanreotide Depot significantly prolonged PFS vs. placebo for:
  - midgut NETs (and approached significance with lanreotide for pNETs) (Figure 4a)
  - grade 1 and grade 2 tumors (Figure 4b)
  - high and low baseline hepatic tumor loads (Figure 4c).

Secondary endpoints

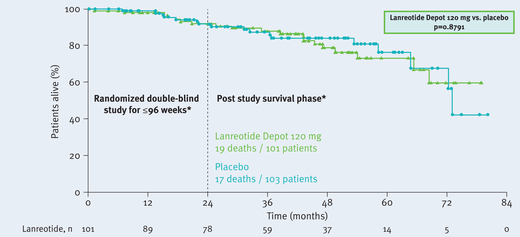
- No difference in overall survival between treatment groups (Figure 5).
- Treatment well tolerated, with no treatment-related deaths and few withdrawals due to adverse events (AEs) (Table 2).

Figure 4. Lanreotide Depot 120 mg prolonged PFS in midgut NETs and pNETs, in G1 and G2 tumors, and in patients with low or high hepatic tumor load.



*Results based on centrally assessed disease progressions only. †pNET analysis repeated with addition of withdrawals for disease progression based on investigator assessment despite a central assessment of stable disease: lanreotide, 20 events and median of 24 months; placebo, 35 events and median of 12 months; p=0.0496). Tumor location was formal subgroup analysis, and grade and hepatic tumor load were exploratory subgroup analyses. p-values from unstratified log-rank tests and HRs from Cox proportional hazards model. CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival; pNETs, pancreatic neuroendocrine tumors.

Figure 5. No treatment difference for overall survival over 2 years.



Data are from the intention-to-treat population; P-value derived from log-rank test. CI, confidence interval.
*Survival was followed throughout the randomized study for patients on study medication for up to 96 weeks or until early withdrawal / PD, and then continued to be followed during the post-study survival phase (when the patient may or may not have continued or switched to lanreotide).

Table 2. Adverse events.

	Lanreotide Depot 120 mg (n=101)	Placebo (n=103)
Any treatment-emergent AE	89 (88)	93 (90)
Related to treatment	50 (50)	29 (28)
Severe : moderate : mild	26 (26) : 46 (46) : 17 (17)	32 (31) : 44 (43) : 17 (17)
Any serious AE*	25 (25)	32 (31)
Related to treatment†	3 (3)	1 (1)
Withdrawals due to treatment-emergent AEs	3 (3)	3 (3)
Related to treatment	1 (1)§	0
Treatment-related AEs occurring in ≥10% of patients	11 (11)	3 (3)
Diarrhea	26 (26)	9 (9)
Abdominal pain	14 (14)	2 (2)
Cholelithiasis	10 (10)	3 (3)

Data are number (%) patients with treatment-emergent AEs from the safety population. *Serious AEs are defined as AEs that result in disability/incapacity, hospitalization, death, or are life-threatening; †seven events in lanreotide group – hyperglycemia, diabetes mellitus, nausea, vomiting, abdominal pain, biliary fistula, cholelithiasis; one event in placebo group – bile duct stenosis; §hepatic failure. AE, adverse event.

Conclusions

- **PFS substantially prolonged with lanreotide Depot 120 mg vs. placebo for metastatic well-/moderately differentiated GEP-NETs, with 53% relative risk reduction for progression or death.**
- **PFS prolonged with lanreotide Depot 120 mg vs. placebo:**
  - **significantly in patients with grade 1 and grade 2 tumors**
  - **significantly in patients with low and high HTL.**
- **Safety profile consistent with previous studies.**
- **CLARINET provides new evidence for the antiproliferative effects of lanreotide Depot, which may support its place in treatment algorithms.**

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