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Original Research

Efficacy and safety of high-dose lanreotide autogel in patients with progressive pancreatic or midgut neuroendocrine tumours: CLARINET FORTE phase 2 study results

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KEYWORDS
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Abstract ***Introduction:*** This prospective, single-arm, phase 2 study assessed the efficacy and safety of lanreotide autogel (LAN) administered at a reduced dosing interval in patients with progressive neuroendocrine tumours (NETs) after LAN standard regimen.
Methods: Patients had metastatic or locally advanced, grade 1 or 2 midgut NETs or pancreatic NETs (panNETs) and centrally assessed disease progression on LAN 120 mg every 28 days. They were treated with LAN 120 mg every 14 days for up to 96 weeks (midgut cohort) or

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Somatostatin;
Lanreotide

48 weeks (panNET cohort). The primary end-point was centrally assessed progression-free survival (PFS). PFS by Ki-67 categories was analysed post hoc. Secondary end-points included quality of life (QoL) and safety.

Results: Ninety-nine patients were enrolled (midgut, N = 51; panNET, N = 48). Median (95% CI) PFS was 8.3 (5.6–11.1) and 5.6 (5.5–8.3) months, respectively. In patients with Ki-67 $\leq$ 10%, median (95% CI) PFS was 8.6 (5.6–13.8) and 8.0 (5.6–8.3) months in the midgut and panNET cohorts, respectively. Patients' QoL did not deteriorate during the study. There were no treatment-related serious adverse events and only two withdrawals for treatment-related adverse events (both in the panNET cohort).

Conclusions: In patients with progressive NETs following standard-regimen LAN, reducing the dosing interval to every 14 days provided encouraging PFS, particularly in patients with a Ki-67 $\leq$ 10% (post hoc); no safety concerns and no deterioration in QoL were observed. Increasing LAN dosing frequency could therefore be considered before escalation to less well-tolerated therapies.

1. Introduction

The somatostatin analogue (SSA) lanreotide autogel (LAN) at a dose of 120 mg every 28 days is an established therapy for advanced gastro-enteropancreatic neuroendocrine tumours (GEP-NETs) [1]. Its antiproliferative effects were demonstrated in the phase 3 CLARINET study, with significant improvements in progression-free survival (PFS) versus placebo in patients with GEP-NETs with a proliferation index (Ki-67) <10% [2].

European and US guidelines recommend increasing SSA dose (e.g. by reducing the dosing interval) as one option for controlling the worsening of specific symptoms in the absence of rapid radiological progression [3–5]. Patients with progressive disease on the standard LAN regimen may require escalation to other, substantially more toxic therapies, including molecular targeted agents, such as sunitinib (pancreatic NETs [panNETs] only) [6] or everolimus [7,8], peptide receptor radionuclide therapy (PRRT) [9] or even chemotherapy [10,11], which may negatively affect the quality of life (QoL).

The aim of CLARINET FORTE (NCT02651987; EudraCT: 2014-005607-24) was to assess the efficacy and safety of a reduced LAN dosing interval (120 mg every 14 days) in patients with progressive midgut NETs or panNETs following first-line standard-dose LAN treatment (120 mg every 28 days). When this study was designed, limited data were available to support the clinical benefit of increased frequency of prolonged-release SSAs to manage progressive NETs. Previous studies were retrospective or small prospective studies that assessed response rates [12].

2. Methods

This prospective, single-arm, open-label, exploratory, European phase 2 study investigated LAN 120 mg every 14 days by deep subcutaneous injection in patients with centrally assessed progressive midgut NETs or panNETs (Fig. 1). Eligibility criteria and study end-points are summarised in Table 1.

The study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice, independent ethics committee/institutional review board regulations and applicable local regulatory requirements. Written, informed consent was obtained from patients before enrolment.

Between study visits, home injection of LAN could be performed via a nurse network in countries where this was authorised by competent authorities (exceptions were Italy and Spain, where patients received all injections at the study site). Patients were treated until disease progression, death or unacceptable toxicity/tolerability occurred, for up to 96 weeks (midgut cohort) or 48 weeks (panNET cohort). If <25 events occurred in either cohort, patients not progressing by Week 96 (midgut) or 48 (panNET) could continue treatment until 25 events of disease progression, death or unacceptable toxicity/tolerability had occurred. Tumour assessments (response evaluation criteria in solid tumours v1.0 [13]) were performed centrally every 12 weeks by two radiologists (with third-reviewer adjudication if any disagreement).

A data safety monitoring board reviewed the early and steady-state safety profile of LAN (when 20 patients from both cohorts reached Week 4; and when 20 and then 50 patients from both cohorts reached Week 12) to advise if the study should continue as planned or recommend changes to trial conduct.

There was no formal sample size calculation as this was a pilot study; it was planned to include 100 patients in total (50 per cohort) a number that was considered sufficient to explore the efficacy of LAN at a reduced dosing interval. As a result of difficulty recruiting patients in the panNET cohort, recruitment was stopped

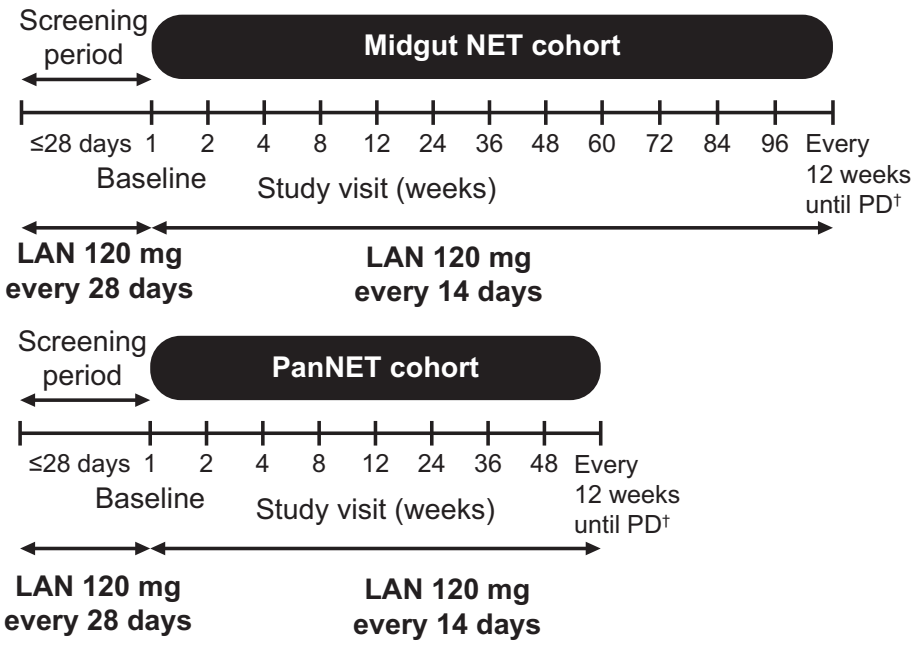

Fig. 1. Study design. †LAN 120 mg every 14 days was administered for 96 (midgut NETs) or 48 (panNETs) weeks (or until centrally assessed progressive disease, death, or unacceptable toxicity or tolerability), or longer if <25 events had occurred. LAN, lanreotide autogel; NET, neuroendocrine tumour; panNET, pancreatic NET; PD, progressive disease.

with 48 patients included, which did not impact study integrity. Statistical analyses were performed on the full analysis set, defined as all patients who received at least one dose of LAN 120 mg (Table 1). All efficacy analyses were conducted separately for the midgut and panNET cohorts. Univariate and multivariate analyses of predictive factors for PFS were conducted using a Cox proportional hazards model to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

3. Results

3.1. Patient disposition and baseline characteristics

Ninety-nine patients were enrolled (midgut cohort N = 51; panNET cohort N = 48; Fig. 2) from 25 European centres between 19/11/2015 and 24/10/2019 (supplementary appendix). At least one home injection was performed for 71.7% of patients (full analysis set).

Baseline demographic and disease characteristics are presented in Table 2. The proportion of patients with grade 2 tumours was lower in the midgut cohort (43.1%) than in the panNET cohort (75.0%). Most patients had liver metastases (midgut: 96.1%; panNET: 85.4%), but hepatic tumour load was ≤10% in over 60% of patients in both cohorts, and most had a Ki-67 ≤ 10% (midgut: 92.0%; panNET: 89.6%). The median duration of previous LAN treatment (standard-interval regimen) was 1.3 years (midgut) and 1.8 years (panNET).

3.2. Efficacy outcomes

Median (95% CI) PFS was 8.3 (5.6–11.1) and 5.6 (5.5–8.3) months in the midgut and panNET cohorts, respectively (Fig. 3A; Table S1). Four patients died and overall survival data were not mature. In the univariate analysis, predictive factors for PFS (p-value <0.2) in the midgut cohort were previous surgery of the primary tumour ('yes' versus 'no'; 2.14 [0.83–5.52]) and Ki-67 (<10% versus ≥10%; 2.26 [0.67–7.60]); in the multivariate analysis, neither variable was significant. In the panNET cohort, time from diagnosis to study entry (<3 versus ≥3 years; HR [95% CI] 0.49 [0.25–0.96]), time between prescreening and screening computed tomography (CT) scans (<12 versus ≥12 months; 0.47 [0.24–0.94]), Ki-67 (<10% versus ≥10%; 3.60 [1.39–9.32]) and symptoms at baseline (presence versus absence; 2.55 [0.89–7.28]) were significant (*a priori* univariate analysis; see Table S2). In the multivariate analysis, the time between the CT scans and baseline symptoms were significant; however, interactions were added in the model (due to the violation of proportional hazard assumption) and consequently, estimates provided by the adjusted models were not interpretable.

Table 1
Key eligibility criteria (A) and study end-points (B).

(A)

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Well-differentiated, SSTR2+, metastatic or locally advanced, unresectable, grade 1/2[a] (Ki-67 index ≤20%) midgut NETs or panNETs, with or without hormonal symptoms • Centrally assessed disease progression (RECIST 1.0) in the previous 2 years on the standard LAN regimen (120 mg every 28 days) for ≥24 weeks • ECOG performance status score ≤2	• Poorly differentiated grade 3 neuroendocrine neoplasms, or rapidly progressive NETs (within 12 weeks of standard LAN regimen initiation) • Previous chemotherapy, interferon, PRRT or molecular targeted therapy • Previous treatment with standard-dose octreotide LAR was permitted if it was discontinued for reasons other than progressive disease

(B)

End-point	Definition/measurement	Statistical analysis
Primary efficacy		
Median PFS	Time from first LAN injection (120 mg every 14 days) in the CLARINET FORTE study to progression or death from any cause as per RECIST 1.0	Kaplan–Meier method
Secondary efficacy		
Median OS	–	Kaplan–Meier method
Disease control rate	Proportion of patients who achieved complete response, partial response, or stable disease (RECIST 1.0)	Descriptive
Best overall response	Best response recorded from the initiation of treatment until disease progression	Descriptive
Duration of stable disease	Time from first LAN injection (120 mg every 14 days) in the CLARINET FORTE study to first occurrence of progressive disease	Kaplan–Meier method
Predictive factors of PFS	• Age (<65 years[b] versus ≥65 years) • Time from original diagnosis to study entry (<3 years[b] versus ≥3 years) • Duration of previous treatment with LAN 120 mg every 28 days (<1.3 years[b] versus ≥1.3 years for midgut NETs[c] and <1.8 years[b] versus ≥1.8 years for panNETs[c]) • Previous surgery of the primary tumour (yes[a] versus no) • Time interval between prescreening and screening CT scans (<12 months[b] versus ≥12 months) • Hepatic tumour load (≤25%[b] versus >25%) • Tumour grade (grade 1[b] versus grade 2) • Ki-67 (<10%[b] versus ≥10%) • Symptoms (diarrhoea or flushing at baseline: yes[b] versus no)	• Step 1: Each factor assessed for importance using univariate Cox proportional-hazards model • Factors were potentially associated with PFS if the p-value was <0.2 • Step 2: Each pre-selected parameter was tested with the other retained parameters at the 0.001 level to confirm that there was no strong link between them; if independence was not met ($p < 0.001$) and/or the correlation coefficient was moderate or high (i.e. ≥0.5), parameters were selected according to clinical and statistical relevance • Remaining variables were evaluated using multivariate analysis
Diarrhoea and flushing symptoms	Presence/absence of each symptom and by the total number of stools and flushing episodes during the 7 days prior to each visit (patient-reported)	Descriptive
Quality-of-life	• EORTC QLQ-C30 (v3.0) [24] • EORTC QLQ-GI.NET21 (2006) [25] • EQ-5D-5L (v1.0) [26] • Baseline, every 12 weeks, EOS	Scores derived according to standard algorithms recommended for their derivation [24–26]
Changes in tumour biomarkers (CgA, NSE and 5-HIAA)	• Baseline, every 12 weeks, EOS[d]	Descriptive

Table 1 (*continued*)

(B)		
End-point	Definition/measurement	Statistical analysis
	• CgA responders (reduction ≥30% in first year in those with levels >ULN), post-hoc analysis	
Safety		
TEAEs SAEs TRAEs	• Graded according to NCI CTCAE (version 4.03, 14 June 2010) • Coded using MedDRA (version 22.0)	Descriptive
Post hoc		
PFS and DCR according to Ki-67 categories	• ≤2% (PFS) • ≤5% (DCR) • ≤10% • >10%	Descriptive
Early occurrence of TRAEs (up to week 12)		Descriptive
Correlation between urinary/plasma 5-HIAA		Spearman correlation co-efficient

CgA, chromogranin A; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation into the Research and Treatment of Cancer; EOS, end of study; EQ-5D-5L, EuroQoL 5 dimensions, 5 levels; 5-HIAA, 5-hydroxyindoleacetic acid; NET, neuroendocrine tumour; LAN, lanreotide autogel; LAR, long-acting release; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; NSE, neuron-specific enolase; OS, overall survival; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-GI.NET21, Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumour 21; RECIST, Response Evaluation Criteria In Solid Tumours; SAE, serious adverse event; SSTR2, somatostatin receptor type 2; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; ULN, upper limit of normal.

[a] World Health Organization 2010.
[b] Reference group.
[c] Median treatment duration in CLARINET FORTE.
[d] Baseline, Week 12 and EOS only for urinary 5-HIAA.

In the midgut cohort, PFS in patients with Ki-67 values ≤2% (n = 29), ≤10% (n = 47) and >10% (n = 4) were 8.4 (5.3–11.1), 8.6 (5.6–13.8) and 5.5 (2.6; not estimable) months, respectively (post-hoc analysis; Fig. 4A). Values in the panNET cohort were 5.6 (2.8–8.3) (n = 12), 8.0 (5.6–8.3) (n = 43) and 2.8 (2.8–2.9) months (n = 5), respectively (Fig. 4B).

Disease control rate (i.e. complete response, partial response or stable disease) was 58.8% (Week 24), 33.3% (Week 48) and 31.4% (end of study) in the midgut cohort, and 43.8% (Week 24) and 22.9% (Week 48) in the panNET cohort (Table 3A). Two partial responses were achieved in the midgut NET cohort (3.9% of patients; Table 3B). The best overall response was stable

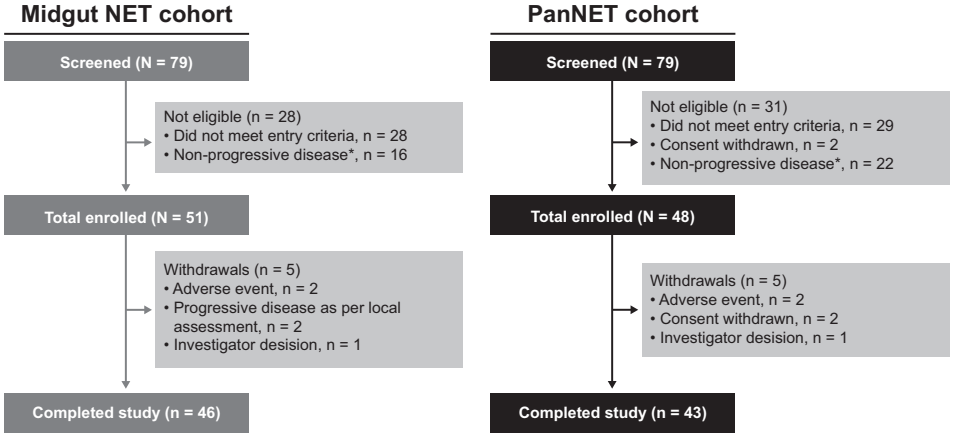

Fig. 2. Patient disposition. Because of difficulty in recruiting patients in the panNET cohort, recruitment was stopped just before the target of 50 was reached, which did not impact the study integrity. Patients who complete all scheduled visits, or who had progressed or died were considered to have completed the study. The number of patients excluded after screening as they did not have centrally confirmed disease progression (RECIST v1.0) was 16 in the midgut cohort and 22 in the panNET cohort. AE, adverse event; NET, neuroendocrine tumour; panNET, pancreatic NET; RECIST, Response Evaluation Criteria in Solid Tumours.

Table 2
Baseline demographics and disease characteristics (full analysis set).

	Midgut NET n = 51	PanNET n = 48
Age, mean (SD), years	67.1 (8.2)	63.3 (10.6)
Male, n (%)	29 (56.9)	20 (41.7)
BMI, mean (SD), kg/m^2	25.0 (3.5)	25.8 (5.1)
ECOG performance status, n (%)		
0 (normal activity)	39 (76.5)	39 (81.3)
1 (restricted activity)	11 (21.6)	9 (18.8)
2 (in bed ≤50% of the time)	1 (2.0)	0
Time from diagnosis to study entry, median (95% CI), years	3.0 (1.7–4.0)	4.4 (2.4–6.0)
Duration of prior LAN exposure, median (95% CI), years	1.3 (1.0–1.9)	1.8 (1.4–2.5)
<6 months, n (%)	3 (5.9)	4 (8.3)
6–12 months, n (%)	16 (31.4)	6 (12.5)
12–24 months, n (%)	15 (29.4)	16 (33.3)
≥24 months, n (%)	17 (33.3)	22 (45.8)
Previous surgery of primary tumour, n (%)	12 (23.5)	22 (45.8)
Tumour grade, n (%)		
Grade 1	29 (56.9)	12 (25.0)
Grade 2	22 (43.1)	36 (75.0)
Proliferation index (Ki-67), n (%)		
≤2%	29 (58.0)	12 (25.0)
>2–5%	7 (14.0)	5 (10.4)
>5–10%	10 (20.0)	26 (54.2)
>10%	4 (8.0)	5 (10.4)
Missing, n	1	0
Hepatic tumour load (centrally assessed), n (%)		
0%	2 (3.9)	7 (14.6)
>0–10%	33 (64.7)	30 (62.5)
>10–25%	7 (13.7)	4 (8.3)
>25%	9 (17.6)	7 (14.6)
Somatostatin receptor expression		
Krenning scale, n (%)		
Grade 1	4 (8.5)	0
Grade 2	4 (8.5)	6 (12.5)
Grade 3	15 (31.9)	10 (20.8)
Grade 4	21 (44.7)	28 (58.3)
NA – PET scan with gallium	3 (6.4)	4 (8.3)
Missing, n	4	0
SSTR2 heterogeneity[a], n (%)	22 (43.1)	20 (41.7)
Lesions negative or weakly positive, n (%)[b]	7 (31.8)	6 (30.0)
Location, n (%)[c]		
Liver	4 (57.1)[d]	3 (50.0)
Pancreas	1 (14.3)	0
Bone	3 (42.9)	2 (33.3)
Other	4 (57.1)	2 (33.3)
Tumour biomarkers >ULN[e]		
CgA, n (%)	30 (68.2)	10 (22.7)
Missing, n	7	4
NSE, n (%)	21 (41.2)	23 (47.9)
Missing, n	0	0
Plasma 5-HIAA, n (%)	25 (80.6)	6 (15.8)
Missing, n	20	10

5-HIAA, 5-hydroxyindoleacetic acid; CgA, chromogranin A; BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; NA, not applicable; NET, neuroendocrine tumour; NSE, neuron-specific enolase; panNET, pancreatic NET; PD, progressive disease; PET, positron emission tomography; SD, standard deviation; SSTR2, somatostatin receptor type 2.

[a] According to SSTR imaging, based on coexistence of negative or weakly positive lesions.

[b] Denominator is number of patients with heterogeneously positive SSTR2 expression.

[c] Denominator is number of patients with negative or weakly positive lesions (multiple locations for one patient possible).

[d] One patient with a negative/weakly positive lesion in the liver also had a target lesion in the liver and had PD during the study - this may have negatively impacted PFS range of the midgut cohort, but not median PFS.

[e] Denominator is number of patients with biomarker data available at baseline. CgA ULN: 100 ng/mL, NSE ULN: 16.3 ng/mL, plasma 5-HIAA ULN: 22 ng/mL.

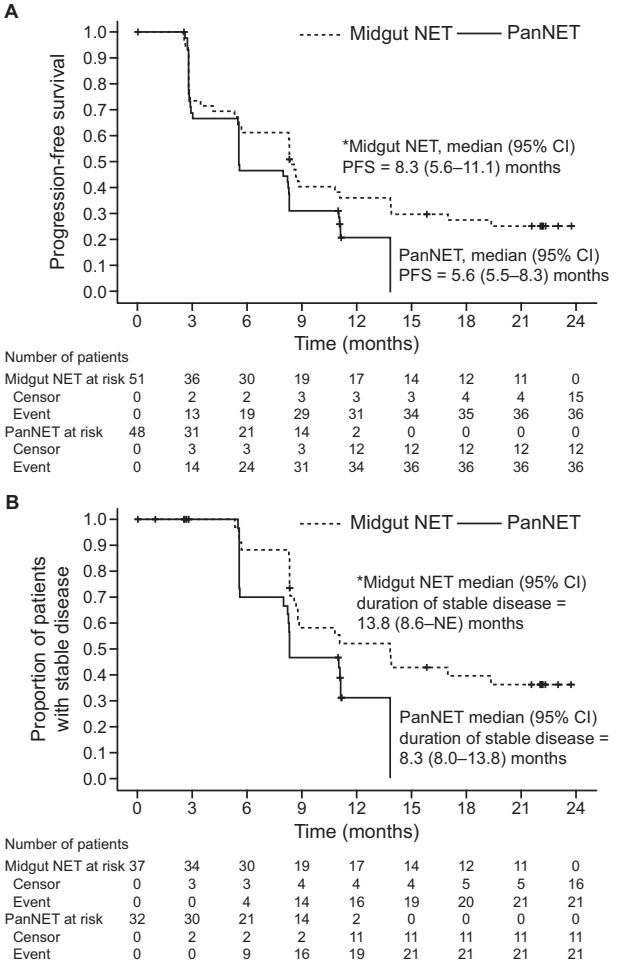

Fig. 3. PFS by cohort (**A**), duration of stable disease by cohort (**B**) (full analysis set). Duration of stable disease was defined as the time from first injection of LAN every 14 days until the first occurrence of progressive disease by central assessment. ∗Data from one patient may have negatively impacted the range of the PFS of the midgut NET cohort, but not the median PFS. CI, confidence interval; Ki-67, proliferation index; NE, not estimable; NET, neuroendocrine tumour; panNET, pancreatic NET, PFS, progression-free survival.

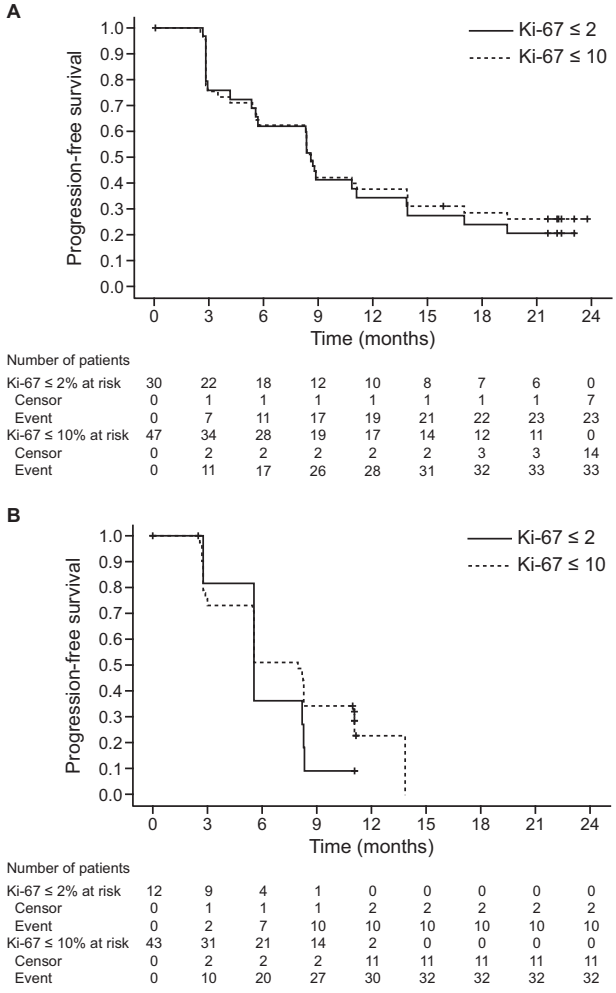

Fig. 4. Post-hoc analyses: PFS by Ki-67, in the midgut NET cohort (**A**), and in the panNET cohort (**B**) (full analysis set). Ki-67 categories are not exclusive; patients with Ki-67 ≤ 2% are included in the ≤10% category. CI, confidence interval; NET, neuroendocrine tumour; panNET, pancreatic NET, PFS, progression-free survival.

disease for 68.6% and 66.7% of patients in the midgut and panNET cohorts, respectively (Table 3B). The median (95% CI) duration of stable disease was 13.8 (8.6–not estimable) and 8.3 (8.0–13.8) months in the midgut and panNET cohorts, respectively (Fig. 3B).

At baseline, 27 (54.0%) and 11 (22.9%) patients in the midgut and panNET cohorts, respectively, had diarrhoea and/or flushing; incidence rates did not worsen with time in either cohort. Among patients with data available at baseline and early withdrawal/end of the study, seven patients in the midgut cohort who had diarrhoea at baseline no longer had it at early withdrawal/end of the study; the corresponding number in the panNET cohort was 1, but most patients in this cohort did not have diarrhoea at baseline (Table S3).

No deterioration in QoL was observed in either cohort based on the results of all three questionnaires (EORTC QLQ-C30; EORTC QLQ-GI.NET21; EQ-5D-5L) (Fig. 5, Figs. S1–S3). Mean (SD) changes in the EQ-5D-5L index and EQ-5D-5L visual analogue scores at end of study/early withdrawal visit were −0.00 (0.11) and −1.76 (9.34), respectively, in the midgut cohort, and −0.04 (0.12) and −1.90 (14.8), respectively, in the panNET cohort.

The percentages of patients with baseline biomarker levels >upper limit of normal (ULN) are summarised in Table 2. Chromogranin A response rates (defined as a reduction of ≥30% in the first year in those with baseline > ULN) were 36.7% (95% CI 19.9–56.1) and 30.0% (6.7–65.2) in the midgut and panNET cohorts, respectively. Median (95% CI) changes in plasma 5-hydroxyindoleacetic acid (5-HIAA) levels (× ULN) at weeks 12 and 24 were 0.25 (−0.86–12.26) and 0.27 (−1.75–9.66), respectively, in the

Table 3
Disease control rate (A) and best overall response (B) (full analysis set).

(A)		
Disease control rate,[a] % [95% CI]	Midgut NET, N = 51	PanNET, N = 48
All patients		
Week 24	58.8 [44.2–72.4]	43.8 [29.5–58.8]
Week 48	33.3 [20.8–47.9]	22.9 [12.0–37.3]
EOS	31.4 [19.1–45.9]	–
Ki-67 category[b]		
≤5%	n = 45	n = 33
Week 24	60.0 [44.3–74.3]	45.5 [28.1–63.6]
Week 48	37.8 [23.8–53.5]	27.3 [13.3–45.5]
≤10%	n = 47	n = 43
Week 24	59.6 [44.3–73.6]	48.8 [33.3–64.5]
Week 48	36.2 [22.7–51.5]	25.6 [13.5–41.2]
>10%	n = 5	n = 5
Week 24	50.0 [6.8–93.2]	0 [0–52.2]
Week 48	0 [0–60.2]	–
(B)		
Best overall response,[c] % [95% CI]	Midgut NET, N = 51	PanNET, N = 48
Partial response	3.9 [0.5–13.5]	0.0 [0.0–7.4]
Stable disease	68.6 [54.1–80.9]	66.7 [51.6–79.6]
Progressive disease	23.5 [12.8–37.5]	31.3 [18.7–46.3]
Not evaluable	2.0 [0.0–10.4]	0.0 [0.0–7.4]

CI, confidence interval; EOS, end of study; Ki-67, proliferation index; NET, neuroendocrine tumour; panNET, pancreatic NET; RECIST, Response Evaluation Criteria In Solid Tumours.
[a] Complete response, partial response or stable disease (RECIST v1.0, central review).
[b] Post-hoc analysis.
[c] According to RECIST v1.0 (central review); there were no complete responses in either cohort.

midgut cohort and 0.01 (−0.54–1.25) and 0.01 (−0.33–0.25), respectively, in the panNET cohort. There was a strong correlation (Spearman correlation: 0.896; $p < 0.001$) between 24-h urinary and plasma 5-HIAA in the midgut cohort (post-hoc analysis; data not shown).

3.3. Safety outcomes

Treatment-emergent adverse events were reported for 94.1% and 85.4% of patients in the midgut and panNET cohorts, respectively; most cases (80.0% and 84.8%, respectively) were grade 1 or grade 2 in intensity (Table 4). Treatment-related adverse events (TRAEs) were reported by 51.0% and 37.5%, respectively (Table 4). Most TRAEs occurred in the first 12 weeks in both cohorts (post-hoc analysis; Table 4). Excluding diarrhoea, the most common TRAE was abdominal pain (Table 4). Treatment-related steatorrhoea (midgut n = 1; grade 1) and hyperglycemia (no history of diabetes; midgut n = 1; panNET n = 1; both grade 1) were reported.

Two patients (both panNET cohort) withdrew from the study because of TRAEs (liver damage, n = 1; fatigue, abdominal pain and diarrhoea, n = 1). Serious adverse events were reported in 18.2% patients (midgut, 25.5%; panNET, 10.4%) (Table 4); none were considered treatment-related by the investigator. Three treatment-emergent adverse events led to death in the midgut cohort (pulseless electrical activity, intestinal obstruction, general health deterioration); none were considered treatment-related by the investigator.

4. Discussion

CLARINET FORTE assessed efficacy and safety of LAN 120 mg every 14 days in patients with disease progression during previous LAN treatment at the approved dosing interval of 28 days. These are the first prospective data on a 14-day LAN dosing regimen. The median PFS was 8.3 and 5.6 months in the midgut and panNET cohorts, respectively. Stable disease as the best response was achieved in more than two-thirds of patients in each cohort; furthermore, two patients from the midgut cohort achieved a partial response. In patients with stable disease, there was a long duration of response, particularly in those with midgut NETs (13.8 months). Approximately one-third and one-quarter of patients in the midgut and panNET cohorts, respectively, had stable disease lasting more than 1 year. Overall, these results demonstrate the durable benefit of LAN 120 mg every 14 days. Importantly, prevention of further significant progression was achieved after most patients had already received LAN every 28 days for >1 year. LAN every 14 days was well tolerated and the safety profile was consistent with the approved standard 28-day dosing interval [1] and previous clinical trials [2]. There was no deterioration in QoL in either cohort, including QLQ GI.NET21 subscales for endocrine symptoms and diarrhoea. The lack of improvement for these subscales was not unexpected, given that most patients did not have symptoms of carcinoid syndrome at baseline.

At the time CLARINET FORTE was initiated, data were lacking on the efficacy and safety of escalated SSA dosing regimens (increased dose per injection or reduced dosing interval) for managing progressive NETs. Since then, several retrospective analyses have been conducted, all with the inherent limitations of this type of analysis and in the context of NETs, and lack of central assessment of tumour progression [12,14–16]. Data have also been published from the phase 3, open-label NETTER-1 study, designed to evaluate the efficacy and safety of PRRT for progressive midgut NETs with a control arm of high-dose octreotide long-acting release (LAR; 60 mg every 4 weeks) [9].

Patients in CLARINET FORTE had slowly progressing NETs (based on the duration of previous therapy with LAN every 28 days: ≥12 months in 79% of patients), and most had good physical status (Eastern Cooperative Oncology Group performance scale score ≤1) and a Ki-67 index ≤10%. In addition, many patients had low tumour hepatic involvement, which would

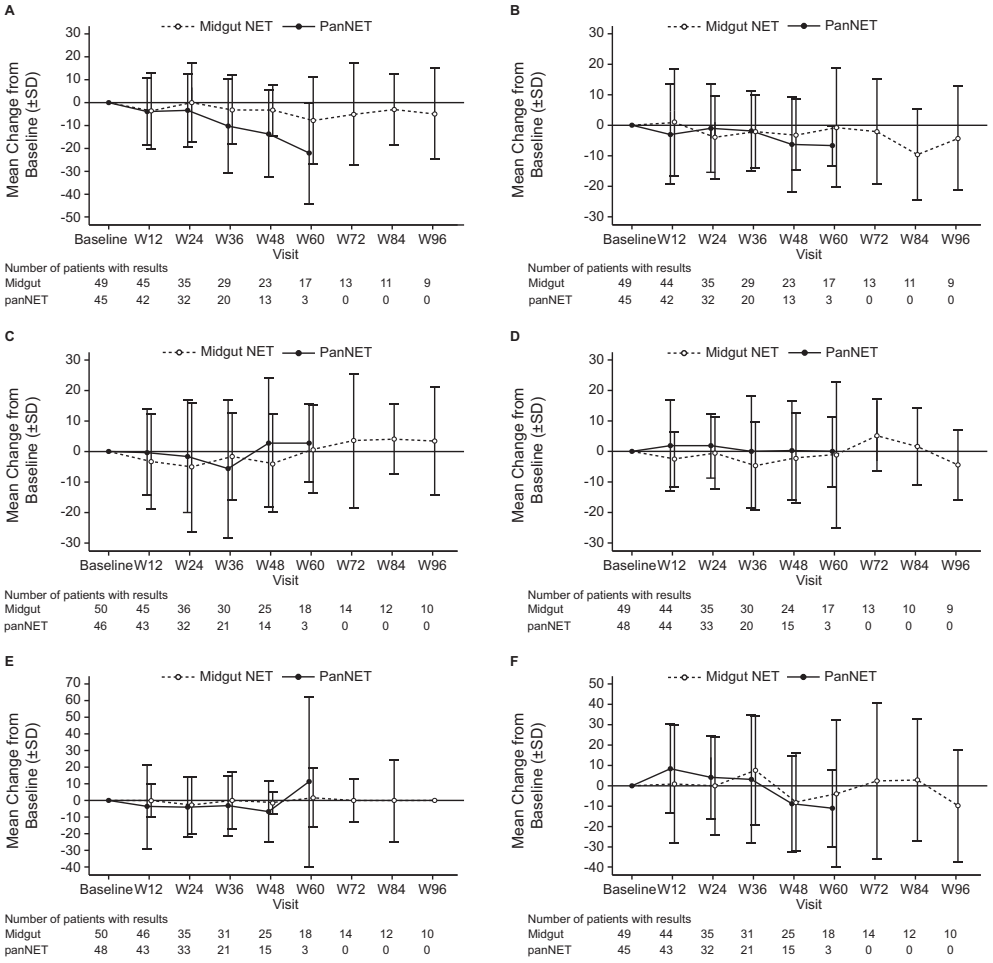

Fig. 5. Mean change from Baseline in QLQ GI.NET21 endocrine symptoms scale (**A**), GI symptoms scale (**B**), and QLQ-C30 transformed scores global health status/QoL (**C**), physical functioning scale (**D**), constipation scale (**E**), and diarrhoea scale (**F**) (full analysis set). For all QLQ GI.NET21 scales, a high score is equivalent to worse or more problems. For functional scales, a higher value reflects a better level of function, but for symptoms scales, a higher value reflects worse symptoms; high score for the global health status represents a high QoL. NET, neuroendocrine tumour; panNET, pancreatic NET; QLQ-C30, QoL Questionnaire Core 30; QLQ-GI.NET21, QoL Questionnaire Gastrointestinal Neuroendocrine Tumour 21; SD, standard deviation.

influence the decision to increase the LAN dose or switch to another treatment option. Somatostatin receptor type 2 (SSTR2)-positivity was an inclusion criterion, and most patients (>75%) had a Krenning Scale grade of 3 or 4.

In the midgut NET cohort, median PFS was similar to that of the NETTER-1 study octreotide LAR high-dose arm in patients with advanced, progressive, SSTR2+ midgut NETs (8.4 months [95% CI 5.8–9.1]) [9]. However, patients treated with octreotide LAR had less severe disease with respect to tumour grade (grade 1 tumours: 72%; grade 2 tumours: 28%) compared with the midgut NET population in the CLARINET FORTE study [9].

Median PFS in the panNET cohort was lower in this study than that reported in other studies in patients with progressive panNETs treated with everolimus (11.0 months [95% CI 8.4–13.9]) or sunitinib (11.4 months [95% CI 7.4–19.8]) [6,7] and was similar to results from the placebo arms of those studies (4.6 months [95% CI 3.1–5.4] and 5.5 months [95% CI 3.6–7.4], respectively). However, comparisons should be made with caution because of differences in study design, patient populations' treatment history and challenges associated with comparing patients' biological profiles. For example, patients were eligible for inclusion in the everolimus study if they had any progressive disease, but in contrast to the CLARINET FORTE study, this did not have to be confirmed using response evaluation criteria in solid tumours [6,7].

Of note, PFS in patients with panNETs and Ki-67 $\leq$ 10% was 8.0 months, compared with 2.8 months in those with Ki-67 > 10% (post-hoc). PFS in the midgut cohort was 8.6 and 5.5 months in the Ki-67 $\leq$ 10% and >10% subgroups, respectively. The Cox proportional-hazards model indicated that a higher Ki-67 ($\geq$10% versus <10%) was a significant univariate predictor of shorter PFS in both cohorts. However, as a result of to the small number of patients with Ki-67 > 10%, these data should be interpreted with caution.

Table 4
Summary of safety data (full analysis set).

AEs	n (%)		
	Midgut NET, N = 51	PanNET, N = 48	Overall, N = 99
All TEAEs	48 (94.1)	41 (85.4)	89 (89.9)
Intensity of TEAEs			
Grade 1	45 (88.2)	41 (85.4)	86 (86.9)
Grade 2	31 (60.8)	15 (31.3)	46 (46.5)
Grade 3	13 (25.5)	9 (18.8)	22 (22.2)
Grade 4	3 (5.9)	1 (2.1)	4 (4.0)
Grade 5	3 (5.9)	0	3 (3.0)
Missing	1	1	2
TRAEs	26 (51.0)	18 (37.5)	44 (44.4)
Intensity of TRAEs			
Grade 1	21 (41.2)	16 (33.3)	37 (37.4)
Grade 2	9 (17.6)	4 (8.3)	13 (13.1)
Grade 3	0	1 (2.1)	1 (1.0)
Grade 4	0	0	0
Grade 5	0	0	0
Missing	0	0	0
TEAEs leading to withdrawal	4 (7.8)	2 (4.2)	6 (6.1)
TRAEs leading to withdrawal	0	2 (4.2)	2 (2.0)
TEAEs leading to death[a]	3 (5.9)	0	3 (3.0)
Serious AEs[b]	13 (25.5)	5 (10.4)	18 (18.2)
Treatment-related TEAEs reported in the first 12 weeks of treatment[c]			
Any event	18 (35.3)	14 (29.2)	32 (32.3)
Gastrointestinal disorders	14 (27.5)	9 (18.8)	23 (23.2)
Abdominal distension	3 (5.9)	0	3 (3.0)
Abdominal pain[d]	5 (9.8)	4 (8.3)	9 (9.1)
Diarrhoea	8 (15.7)	7 (14.6)	15 (15.2)
Flatulence	1 (2.0)	0	1 (1.0)
General disorders and administration site conditions	6 (11.8)	3 (6.3)	9 (9.1)
Hepatobiliary disorders	1 (2.0)	0	1 (1.0)
Cholelithiasis	1 (2.0)	0	1 (1.0)
Most common (≥5% in either cohort) treatment-related TEAEs overall			
Abdominal distention	3 (5.9)	0	3 (3.0)
Abdominal pain[d]	6 (11.8)	5 (10.4)	11 (11.1)
Diarrhoea	12 (23.5)	7 (14.6)	19 (19.2)
Flatulence	4 (7.8)	1 (2.1)	5 (5.1)
Cholelithiasis/bile duct stones	3 (5.9)	0	3 (3.0)

AE, adverse event; NET, neuroendocrine tumour; panNET, pancreatic NET; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

[a] Midgut NET cohort deaths (grade 5): pulseless electrical activity, n = 1; intestinal obstruction, n = 1; general health deterioration, n = 1; all deaths were considered unrelated to treatment by the investigator. One death in the panNET cohort was not counted as an event, as progressive disease occurred before death.

[b] None of the serious AEs were treatment-related.

[c] Post-hoc analyses of selected system organ class/preferred term with significant number of events, not all preferred terms are presented for each system organ class.

[d] Includes the preferred terms: abdominal pain and abdominal pain, upper. Data are displayed as number of patients (% of patients).

A recent retrospective analysis of above-label doses of octreotide LAR (30 mg/3 weeks) or LAN (120 mg/3 weeks) administered to 105 patients with advanced, progressive GEP-NETs on standard treatment included a multivariate analysis in which Ki-67 5–20% was independently associated with PFS duration (HR: 3.96 [95% CI 1.18–13.32] versus Ki-67 <3%; p = 0.03) [16]. Our data suggest that patients with panNET and Ki-67 ≤ 10% might benefit from increased SSA dose when experiencing the progressive disease. Further prospective studies might help define the most useful Ki-67 cutoff threshold.

Other studies support an increase in SSA dose to control progressive disease, including two retrospective studies of patients with progressive GEP-NETs treated with LAN or octreotide LAR at increased administered doses or reduced dosing intervals [14,16]. In addition, a prospective phase 2 study of dose escalation of LAN (180 mg every 28 days) in 32 patients with progressive thoracic or GEP-NETs reported a disease control rate of 47% at 12 months and median time to progression of 11 months [17]. High-dose LAN was well-tolerated in each study.

In the present study, most TRAEs were grade 1 and withdrawals due to AEs were minimal. Furthermore, AE frequency and type were similar to those reported with LAN 120 mg every 28 days in the CLARINET and CLARINET open-label extension studies [2,18], and the safety profile was consistent with previous real-world studies conducted worldwide over many years [19,20]. There was no deterioration of QoL throughout the study; in fact, there were some improvements over time in some QoL measures, although it is possible this may have been influenced by patients with progressive disease leaving the study. QoL and drug safety profiles are generally more favourable with LAN than with alternative treatments, such as molecular targeted therapies (sunitinib and everolimus) [6,7,21], chemotherapy [10,11] or PRRT [22]. SSAs have an excellent tolerability profile, and side-effects are rarely severe, while sunitinib and everolimus have been associated with severe TRAEs, and treatment discontinuation or dose adjustment is not uncommon [23]. PRRT, while considered to be highly effective, is associated with both immediate and long-term TRAEs [23].

Potential study limitations include lack of comparator, local rather than central Krenning scale assessment, and the small sample size (as expected for a pilot study). Study strengths include the prospective, international, multicenter design, inclusion of two patient cohorts (midgut and panNET), and central assessment of tumour response. Further investigation to better define subgroups of patients who benefit most from LAN 120 mg every 14 days is warranted.

5. Conclusion

LAN 120 mg at a reduced dosing interval (every 14 days) provided clinically meaningful PFS in a population of patients with midgut NETs or panNETs with Ki-67 ≤ 10%, a low hepatic tumour load and prior long-term exposure to standard-dose LAN (before experiencing progressive disease). Most TRAEs were

mild, withdrawals due to TRAEs were minimal, and the safety profile was similar to that observed with LAN 120 mg every 28 days. Thus, the combined efficacy and safety data indicate that LAN 120 mg every 14 days may delay the need for more aggressive, less tolerable therapies, meaning that these patients could remain on a more tolerable first-line standard of care for longer.

Author contributions

Study concepts MP, PR.
Study design MP, PR, AH.
Data acquisition MP, JCB, CLB, IB, TS, UFP, JC, FP, PR.
Quality control of data and algorithms AH.
Data analysis and interpretation All authors.
Statistical analysis AH.
Manuscript preparation All authors.
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Role of study sponsor

Ipsen provided financial support for the conduct of the research and preparation of the article, and was involved in the study design, collection, analysis and interpretation of data, writing of the report and in the decision to submit the article for publication.

Data sharing

Where patient data can be anonymised, 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.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

MP: participated in advisory boards for, and received honoraria from, Ipsen, Novartis, Pfizer, AAA, Riemser, Lexicon and Boehringer-Ingelheim.

JBC: received honoraria for lectures during Polish scientific congress meetings from Ipsen.

CLB: consultant for Ipsen, Pfizer and Novartis; received research funding from Ipsen and Novartis.

IB: consultant and advisor for Pfizer, Novartis and Ipsen; received research funding from Novartis, Ipsen, Bayer and Celgene.

TS: received honoraria and remuneration for a consulting/advisory role; remuneration for travel, accommodation and expenses from Ipsen.

UFP: advisory role or expert testimony at Ipsen; honoraria and scientific research funding from Ipsen and Novartis.

JC: reports the payment of study fees from Ipsen for the SPINET and FORTE studies to his institution, and has received payment for lectures from Ipsen.

FP: received honoraria for speaker/advisory role from Novartis, for advisory role from Ipsen, for consulting from Advanced Accelerator Applications, and travel/accommodation from Pfizer

XMTT and **AH** are employees of Ipsen.

PR: scientific advisory roles for Novartis, Ipsen, AAA, ITM and Keocyt.

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Appendix A. Supplementary data

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