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Lanreotide depot/autogel in intestinal and pancreatic neuroendocrine tumors according to body mass index: subgroup analyses from the CLARINET study

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Background

- Lanreotide depot (also known as autogel) is a long-acting somatostatin analog (SSA) that has recently been approved for the improvement of PFS in pancreatic and intestinal neuroendocrine tumors (NETs) in the US and EU.[1]
- In the latest NCCN guidelines, lanreotide has been positioned as first-line medical therapy for treating metastatic pancreatic and intestinal NETs.[2] Guidelines groups elsewhere in the world are currently considering their guidance.[3]
- These updates to guidelines are based on robust evidence from the CLARINET study, a pivotal randomized placebo-controlled trial, which clearly demonstrated antitumor effects.[4]
- This study continues to provide an invaluable data set for evaluating patient factors that might impact on individual treatment responses; the aim of this *post hoc* analysis was to characterize treatment effects of lanreotide within patient subgroups defined by baseline body mass index (BMI).

Methods

- The design of the CLARINET study has been described in detail previously.[4]
  - It was a 96-week, randomized, double-blind, placebo-controlled study conducted at 48 centers in 14 countries (ClinicalTrials.gov: NCT00353496; EudraCT 2005 004904-35).
  - Patients had: metastatic and/or locally advanced, well/moderately differentiated, non-functioning somatostatin receptor-positive NETs with a Ki-67 up to 10%; tumors originating in the pancreas, midgut, or hindgut, or of unknown origin.
  - Patients received lanreotide 120 mg (fixed dose) or placebo by deep subcutaneous injection once every 28 days for 96 weeks or until death/progressive disease (assessed using RECIST 1.0).
- *Post hoc* analyses were conducted to evaluate the efficacy (PFS) and safety (adverse events [AEs]) of lanreotide treatment according to patients' baseline BMI (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m²).
  - Median PFS and 95% confidence intervals (CIs) were determined using the Kaplan–Meier method, and hazard ratios (HRs) and CIs with the Cox proportional hazards model, with a single term for treatment (intent-to-treat population for both).
  - Summary statistics were used for AEs (safety population).
  - The PFS analyses investigated only consistency of treatment effects across subgroups as the study was not otherwise powered for such analyses.

Results

- In the CLARINET study, 101 patients were treated with lanreotide and 103 received placebo.[4] Baseline BMI data were available for 195 patients, only five (all placebo group) had BMI <18.5 kg/m² and subsequent analyses were not performed in this subgroup.
- Baseline characteristics of patients in the other three BMI subgroups are presented in **Table 1**. In the lanreotide group, median PFS was not reached in any of the BMI subgroups. In the placebo group, median PFS ranged from 13–24 months across the BMI subgroups (**Table 2**).
  - HRs favored lanreotide and were generally consistent with the overall population.
- AEs reported across the BMI subgroups in the lanreotide and placebo groups are summarized in **Table 3**.
  - Incidences of AEs overall were similar across BMI and treatment groups, although treatment-related AEs occurred more frequently in the lanreotide groups than in the placebo groups.
  - Most AEs (regardless of causality) were mild or moderate in intensity.
  - There was one serious treatment-related AE in the lanreotide group, in a patient with a BMI of 25 to <30 kg/m² (food poisoning).
  - Six patients withdrew as a result of AEs, three in the lanreotide group (all with a BMI of 18.5 to <25 kg/m²) due to intestinal obstruction, hepatic failure and sepsis and three in the placebo group (all with a BMI of 25 to <30 kg/m²) because of hypoglycemia, esophageal carcinoma and circulatory collapse.
  - The most frequently reported AEs are shown in **Table 4**. Of these, the most common was diarrhea.
  - Treatment-related AEs occurring in >5% of patients in any BMI strata or treatment group are shown in **Table 5**.

Table 1. Baseline demographic and disease characteristics of patients according to baseline BMI

BMI subgroup*	18.5–<25		25–<30		≥30	
	LAN (n=34)	PBO (n=38)	LAN (n=38)	PBO (n=29)	LAN (n=24)	PBO (n=27)
BMI, kg/m²	22.5 (1.8)	22.1 (1.7)	27.5 (1.4)	27.0 (1.5)	33.9 (3.4)	34.5 (3.7)
Male:female, n (%)	15:19 (44:56)	18:20 (47:53)	26:12 (68:32)	19:10 (66:35)	10:14 (42:58)	15:12 (56:44)
Age, years	64.1 (11.6)	64.1 (10.2)	65.0 (8.2)	64.1 (10.9)	59.5 (9.0)	57.6 (11.0)
Time since diagnosis, months	33.0 (51.9)	46.7 (52.7)	32.5 (42.1)	19.1 (17.1)	33.2 (49.3)	25.0 (21.3)
Prior therapy, n (%)	1 (3)	5 (13)	11 (29)	7 (24)	3 (13)	2 (7)
Progression at baseline, n (%)	1 (3)	1 (3)	2 (5)	2 (7)	1 (4)	0 (0)
Location of primary tumor, n (%)	14 (41)	18 (47)	16 (42)	11 (38)	7 (29)	13 (48)
Pancreas	13 (38)	14 (37)	9 (24)	15 (52)	11 (46)	9 (33)
Midgut	5 (15)	1 (3)	3 (8)	1 (3)	3 (13)	1 (4)
Hindgut	2 (6)	5 (13)	10 (26)	2 (7)	3 (13)	4 (15)
Other / unknown						
Tumor grade, n (%)	26 (77)	23 (61)	25 (66)	22 (76)	13 (54)	19 (70)
Grade 1 (Ki67 0–2%)	8 (24)	13 (34)	13 (34)	7 (24)	11 (46)	8 (30)
Grade 2 (Ki67 3–10%)						
Hepatic tumor load, n (%)	17 (50)	19 (50)	22 (58)	18 (62)	9 (38)	16 (59)
≤10%	5 (15)	6 (16)	0 (0)	5 (17)	7 (29)	4 (15)
>10, ≤25%	12 (35)	13 (34)	16 (42)	6 (21)	8 (33)	7 (26)
>25%						
Previous chemotherapy for NF-NET, n (%)	1 (3)	5 (13)	9 (24)	6 (21)	3 (13)	2 (7)
Primary tumor resection, n (%)	15 (44)	18 (47)	15 (40)	10 (35)	9 (38)	7 (26)

Data are mean (±SD) or n (%) as stated. *In kg/m²; BMI <18.5 kg/m² omitted as n=5.
BMI, body mass index; LAN, lanreotide; NF-NET, nonfunctioning neuroendocrine tumor; PBO, placebo.

Table 2. Median PFS for lanreotide vs. placebo according to baseline BMI

BMI subgroup*	Treatment group	Events n (%)	PFS median [95% CI] months†	Log rank *p* value	HR [95% CI]
18.5–<25.0	**LAN (n=34)** **PBO (n=38)**	11 (32.42) 27 (71.1)	NR 13.0 [12.0, 18.2]	0.0016	0.330 [0.161, 0.673]
25.0–<30.0	**LAN (n=38)** **PBO (n=29)**	12 (31.6) 12 (41.4)	NR 24.4 [18.0, NR]	0.3860	0.705 [0.316, 1.573]
≥30.0	**LAN (n=24)** **PBO (n=27)**	8 (33.3) 16 (59.3)	NR 17.6 [9.0, 24.5]	0.0572	0.446 [0.190, 1.047]

*In kg/m²; BMI <18.5 kg/m² omitted as n=5. †Data in months are approximated based on 4 weeks per month. BMI, body mass index; CI, confidence interval; HR, hazard ratio for progressive disease or death with LAN vs. PBO; LAN, lanreotide; NR, not reached; PBO, placebo; PFS, progression-free survival.

Table 3. Adverse event profile for lanreotide and placebo according to baseline BMI

BMI subgroup*	18.5–<25.0		25.0–<30.0		≥30.0	
	LAN (n=34)	PBO (n=38)	LAN (n=38)	PBO (n=29)	LAN (n=24)	PBO (n=27)
Any AE, n (%)	30 (88.2)	35 (92.1)	32 (84.2)	26 (89.6)	22 (91.7)	24 (88.9)
Severe/moderate/mild/missing (%)	32.4/29.4/23.5/2.9	31.6/39.5/21.1/0	15.8/55.3/13.2/0	34.5/41.4/13.8/0	25.0/45.8/16.7/4.2	22.2/51.9/14.8/0
Treatment-related AEs, n (%)	17 (50.0)	8 (21.0)	18 (47.4)	10 (34.5)	12 (50.0)	9 (33.3)
SAEs, n (%)	9 (26.5)	14 (36.8)	8 (21.0)	9 (31.0)	4 (16.7)	6 (22.2)
Treatment-related SAEs, n (%)	0	0	1 (2.6)†	0	1 (4.2)	1 (3.7)
Withdrawals due to AEs, n (%)	3 (8.8)	0	0	3 (10.3)	0	0

*In kg/m²; BMI <18.5 kg/m² omitted as n=5; †Withdrawal due to food poisoning. AE, adverse event; BMI, body mass index; LAN, lanreotide; PBO, placebo; SAE, serious adverse event.

Table 4. Adverse events reported by ≥10% of patients in the overall CLARINET study population according to baseline BMI

BMI subgroup*	Incidence of AE, n (%)					
	18.5–<25.0		25.0–<30.0		≥30.0	
	LAN (n=34)	PBO (n=38)	LAN (n=38)	PBO (n=29)	LAN (n=24)	PBO (n=27)
Gastrointestinal disorders						
Diarrhea	8 (23.5)	14 (36.8)	13 (34.2)	10 (34.5)	11 (45.8)	9 (33.3)
Abdominal pain	6 (17.6)	8 (21.1)	10 (26.3)	6 (20.7)	7 (29.2)	3 (11.1)
Constipation	6 (17.6)	8 (21.1)	4 (10.5)	2 (6.9)	1 (4.2)	2 (7.4)
Vomiting	5 (14.7)	2 (5.3)	4 (10.5)	5 (17.2)	6 (25.0)	1 (3.7)
Flatulence	3 (8.8)	4 (10.5)	5 (13.2)	4 (13.8)	4 (16.7)	1 (3.7)
Nausea	3 (8.8)	9 (23.7)	5 (13.2)	4 (13.8)	5 (20.8)	1 (3.7)
General disorders						
Fatigue	6 (17.6)	7 (18.4)	2 (5.3)	4 (13.8)	2 (8.3)	3 (11.1)
Musculoskeletal and connective tissue disorders						
Arthralgia	4 (11.8)	1 (2.6)	2 (5.3)	3 (10.3)	3 (12.5)	2 (7.4)
Back pain	3 (8.8)	6 (15.8)	5 (13.2)	2 (6.9)	2 (8.3)	2 (7.4)
Metabolism and nutrition disorders						
Decreased appetite	6 (17.6)	4 (10.5)	2 (5.3)	3 (10.3)	2 (8.3)	2 (7.4)
Nervous system disorders						
Headache	6 (17.6)	4 (10.5)	4 (10.5)	2 (6.9)	5 (20.8)	4 (14.8)
Hepatobiliary disorders						
Cholelithiasis	4 (11.8)	2 (5.3)	4 (10.5)	1 (3.4)	4 (16.7)	3 (11.1)
Vascular disorders						
Hypertension	3 (8.8)	0	7 (18.4)	2 (6.9)	3 (12.5)	3 (11.1)

*In kg/m²; BMI <18.5 kg/m² omitted as n=5. AE, adverse event; BMI, body mass index; LAN, lanreotide; PBO, placebo.

Table 5. Treatment-related adverse events reported by ≥5% of patients in the overall CLARINET study population according to baseline BMI

BMI subgroup*	Incidence of TRAE, n (%)					
	18.5–<25.0		25.0–<30.0		≥30.0	
	LAN (n=34)	PBO (n=38)	LAN (n=38)	PBO (n=29)	LAN (n=24)	PBO (n=27)
Gastrointestinal disorders						
Diarrhea	7 (20.6)	3 (7.9)	9 (23.7)	3 (10.3)	7 (29.2)	3 (11.1)
Abdominal pain	4 (11.8)	1 (2.6)	4 (10.5)	0	6 (25.0)	1 (3.7)
Flatulence	3 (8.8)	1 (2.6)	2 (5.3)	3 (10.3)	3 (12.5)	1 (3.7)
Nausea	2 (5.9)	1 (2.6)	2 (5.3)	1 (3.4)	3 (12.5)	0
Vomiting	2 (5.9)	0	1 (2.6)	0	2 (8.3)	0
Metabolism and nutrition disorders	0	0	3 (7.9)	0	2 (8.3)	0
Hyperglycemia						
General disorders/administration site conditions	2 (5.9)	1 (2.6)	1 (2.6)	2 (6.9)	4 (16.7)	0
Injection site pain						
Investigations	5 (14.7)	0	1 (2.6)†	1 (3.4)†	1 (4.2)	0
Pancreatic enzymes decreased						
Hepatobiliary disorders	4 (11.8)	0	3 (7.9)	0	3 (12.5)	3 (11.1)
Cholelithiasis						
Nervous system disorders	3 (8.8)	0	1 (2.6)	1 (3.4)	1 (4.2)	1 (3.7)
Headache						

*In kg/m²; BMI <18.5 kg/m² omitted as n=5. †Recorded as pancreatic insufficiency in this stratum.
BMI, body mass index; LAN, lanreotide; PBO, placebo; TRAE, treatment-related adverse event

Conclusions

- In this subgroup analyses of data from the CLARINET study, antitumor effects of lanreotide were observed in patients in all BMI categories examined.
- Lanreotide also had a favorable safety/tolerability profile regardless of patient BMI; no new major safety signals dependent on BMI categorization were identified
- These results suggest, irrespective of their BMI, lanreotide should be expected to offer a positive benefit:risk ratio to patients with pancreatic and intestinal NETs.

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