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Relationship Between Lanreotide Autogel, Chromogranin A and Progression-Free Survival in Patients with Gastroenteropancreatic Neuroendocrine Tumors

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Background: Antitumor efficacy and safety of lanreotide Autogel (Depot in US) in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) was demonstrated in the CLARINET study in which 204 patients received deep subcutaneous injections of lanreotide 120 mg (n=101) or placebo (n=103) every 4 weeks for 96 weeks. Plasma chromogranin A (CgA) may reflect tumor growth and could be a prognostic indicator for progression-free survival (PFS). We developed an integrated pharmacokinetic/pharmacodynamic (PK/PD) model for the effect of lanreotide Autogel on serum CgA and PFS in patients with nonfunctioning GEP-NETs.

Methods: Data from 810 lanreotide and 1298 CgA serum samples (n=632 placebo; n=666 lanreotide) were used. Of patients with available serum samples 76 experienced disease progression (n=49 placebo; n=27 lanreotide). The population approach in NONMEM v7.2 was used for analysis.

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Results: Lanreotide serum profiles were described by a one-compartment disposition model with absorption characterized by two parallel pathways following first- and zero-order kinetics. CgA levels increased continuously in the placebo group, reflecting disease progression as a function of time from

study initiation. A direct inhibitory relationship between lanreotide serum concentrations and CgA levels was described by the standard maximum effect (E_{MAX}) PD model.

The estimated lanreotide concentration required to achieve half-maximum effect (C_{50}) on CgA was 5.6 ng/mL (approximately nadir in NET patients on lanreotide 120 mg). Baseline target lesions and patient age correlated with baseline CgA levels. When PFS was treated as a time-to-event response and modelled by Weibull distribution, a decrease in CgA from baseline reduced progression hazard ($p<0.001$). Pancreatic tumor location and hepatic tumor load >25% were associated with a higher hazard of progression ($p<0.001$).

Conclusions: This is the first analysis to quantify the relationship between serum lanreotide, plasma CgA and PFS in patients with GEP-NET. Our results confirm the antitumor efficacy of lanreotide Autogel in these tumors.