Population PK/PD modelling of the biomarker and progression free survival effects of Lanreotide Autogel® in patients with non-functioning gastroenteropancreatic neuroendocrine tumours

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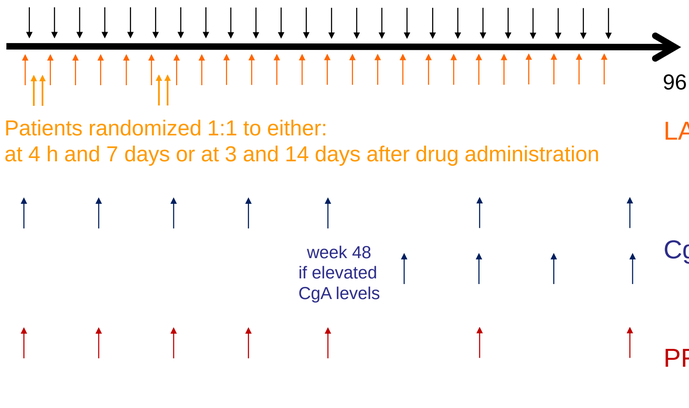
Background & Objectives

- Endocrine tumours are typically slow-growing tumours with an increasing incidence and usually located in the gastrointestinal tract or pancreas. These tumours secrete endocrine markers such as Chromogranin A (CgA), which has been reported to be a representative biomarker of tumour growth[1].
- Lanreotide Autogel®, a somatostatin analogue, has been recently approved for the improvement of progression-free survival in patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic NETs (GEP-NETs) [2].
- The aim of this work was to establish the relationship between serum concentrations of lanreotide, biomarker CgA serum levels and progression free survival (PFS).

Available data

Phase III, randomized, double-blind, placebo-controlled study[3].

4-weekly s.c. injections of:
Lanreotide Autogel 120 mg (LAN) (n=101) or **Placebo** (n=103)

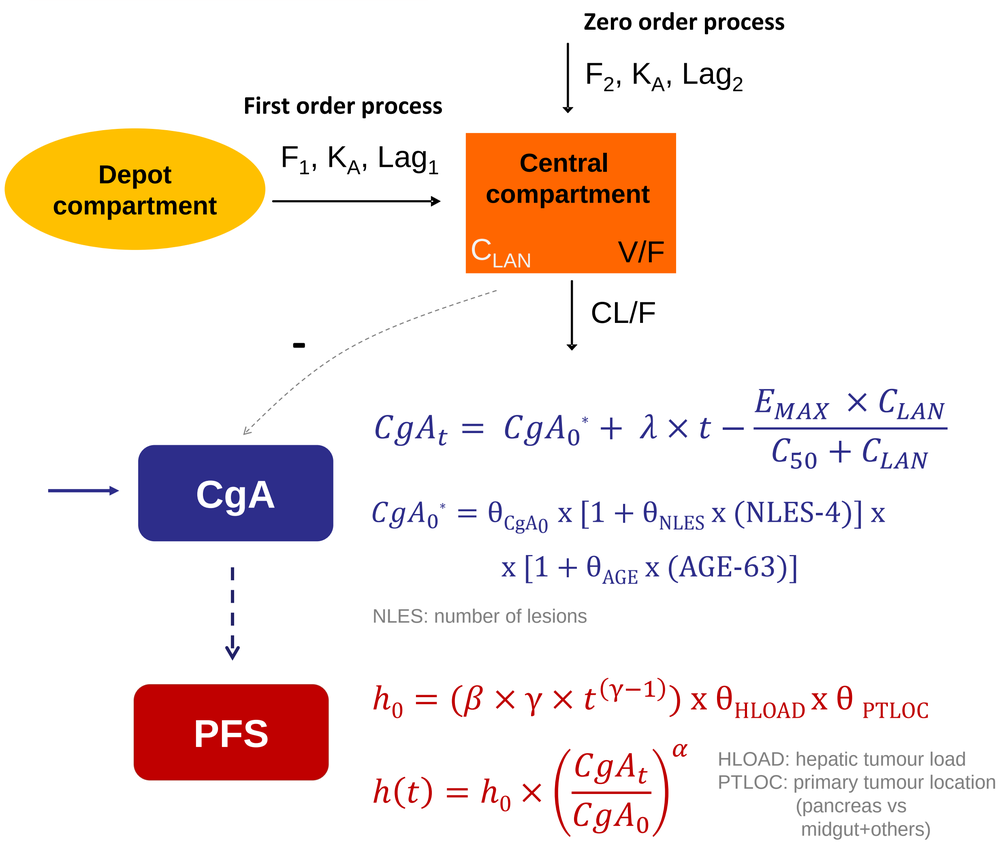


Modelling strategy

1. Development of PK model
2. Development of disease progression model (CgA concentrations from patients receiving placebo)
   - CgA observations Box-Cox transformed for the analysis
3. Use of PK Empirical Bayes Estimates to link LAN concentrations with CgA measurements
4. Joint modelling of CgA dynamics and parametric time-to-event model of PFS
   - Informative dropout → is there a relationship between CgA dynamics and PFS?
5. Step-wise covariate analysis on CgA and PFS:
   - Demographic (age, gender, race, body weight)
   - Disease-related (primary tumour location, hepatic tumour load, number of lesions and progressive disease status at baseline)
6. Model evaluation

Parameter estimation and model simulations were performed using NONMEM 7.2.

PK/PD model



$$CgA_t = CgA_0^* + \lambda \times t - \frac{E_{MAX} \times C_{LAN}}{C_{50} + C_{LAN}}$$

$$CgA_0^* = \theta_{CgA_0} \text{ x } [1 + \theta_{NLES} \text{ x } (NLES-4)] \text{ x } [1 + \theta_{AGE} \text{ x } (AGE-63)]$$

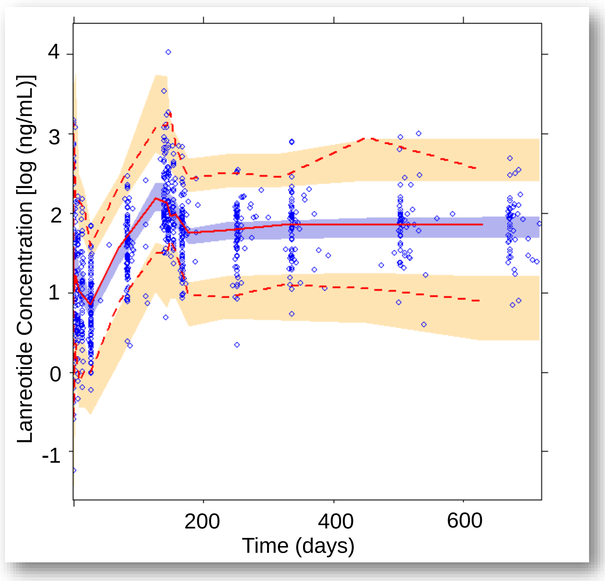
NLES: number of lesions

$$h_0 = (\beta \times \gamma \times t^{(\gamma-1)}) \text{ x } \theta_{HLOAD} \text{ x } \theta_{PTLOC}$$

$$h(t) = h_0 \times \left(\frac{CgA_t}{CgA_0}\right)^{\alpha}$$

HLOAD: hepatic tumour load
PTLOC: primary tumour location (pancreas vs midgut+others)

Model results



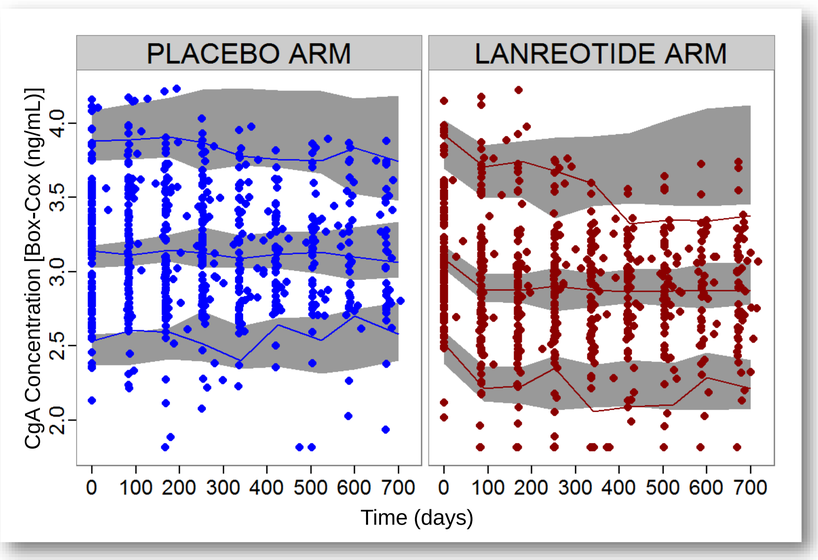


Figure 1: VPC of final Lanreotide PK model (left) and CgA PD Model including informative dropout (right)
Median (solid line), 2.5th and 97.5th percentiles (dashed lines) of observed data compared to 95% predicition intervals (shaded area) for the median, 2.5th and 97.5th percentiles based on 500 simulations.

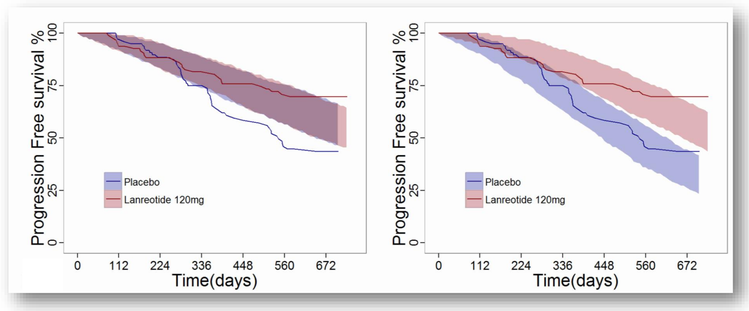


Figure 2: VPC for Kaplan-Meier PFS curve for base Weibull hazard (left) and Weibull hazard modulated by CgA ratio from baseline (right)
The observed Kaplan-Meier for placebo and lanreotide arms (solid line) is compared to the 95% prediction interval (shaded areas) based on 500 simulations

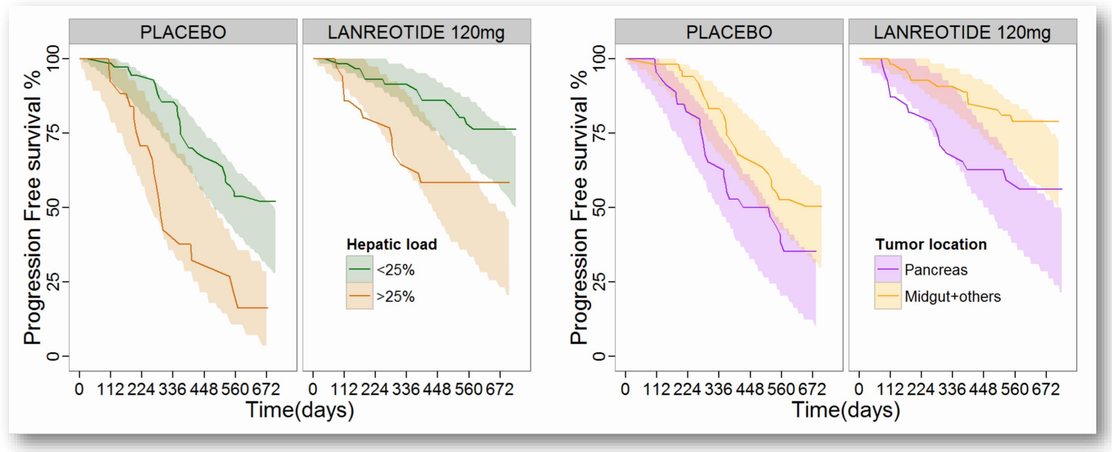


Figure 3: VPC of final PFS model for Kaplan-Meier PFS curve
The observed Kaplan-Meier (solid line) is compared to the 95% prediction interval (shaded areas) based on 500 simulations

Model Simulations

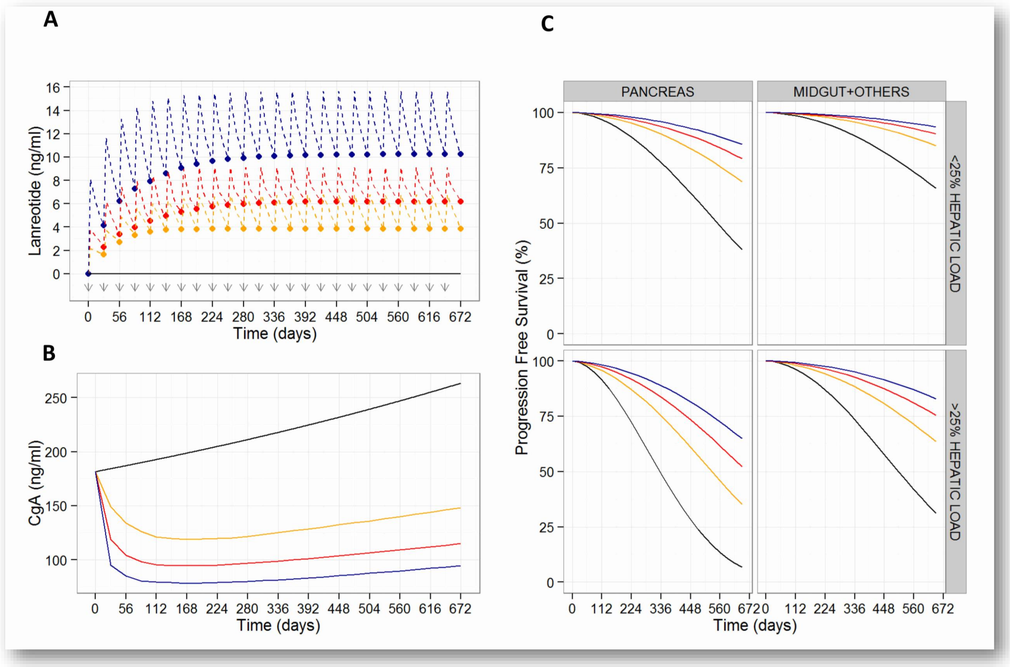


Fig. 4: Simulations illustrating link between LAN, CgA & PFS
A: *Lanreotide profiles after 4-weekly 120mg injections (gray arrows). Red dashed line represents typical LAN profile and blue and yellow dashed lines depict 97.5th and 2.5th LAN concentrations given interpatient variability. Dots depict trough concentrations, which were used to simulate CgA profiles*
B: *Simulated CgA levels corresponding to LAN concentrations in A*
C: *Simulated PFS curves according to pre-dose CgA levels in B for the two prognostic factors included in the final model*

Conclusions

✓ A model linking in a mechanistic way drug exposure, biomarker and clinical endpoint could be established in patients with non-functioning GEP-NETs receiving lanreotide Autogel®.

✓ The proposed model could provide the basis to develop a framework which enables disease monitoring in patients with GEP-NETs based on biomarker levels, as it has been recently applied to small cell lung cancer patients[4].

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