

# POPULATION PHARMACOKINETIC MODELING OF THE COMPLEX RELEASE KINETICS OF OCTREOTIDE LAR: DEFINING SUB-POPULATIONS BY CLUSTER ANALYSIS

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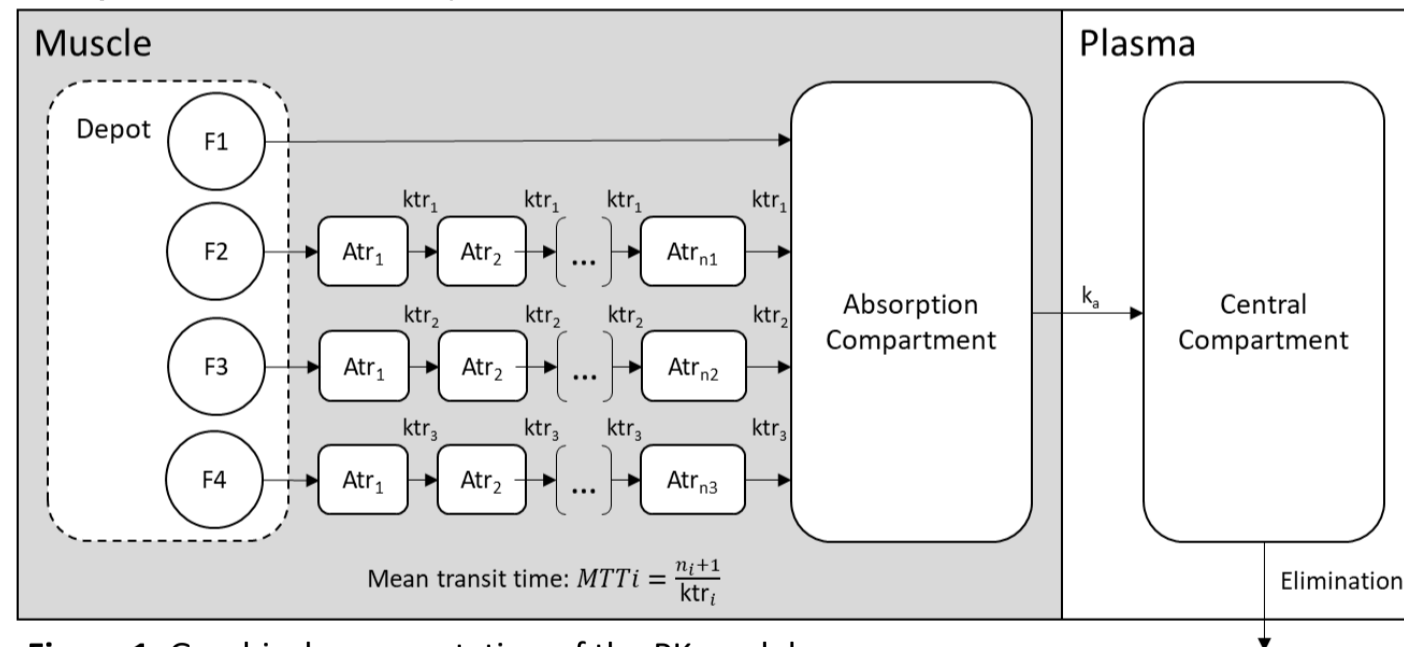


## Objectives

Octreotide long-acting repeatable (LAR) formulation is released from poly- (lactic-co-glycolic acid) (PLGA) microparticles in which it is encapsulated, by a slow, complex process controlled by the interplay between the drug, the formulation and the host. The aim of the study is to develop a population pharmacokinetic (PPK) model of Octreotide LAR in healthy volunteers which describes the highly variable, multiple peak absorption pattern of the pharmacokinetics of the drug, in individual and population levels. [1]

## Methods

**PK data:** Data were obtained from a phase 1, single dose PK study in 118 healthy volunteers following a single 30 mg intramuscular injection of Sandostatin® LAR Depot (octreotide acetate for injectable suspension, Novartis).



**Figure 1.** Graphical representation of the PK model.

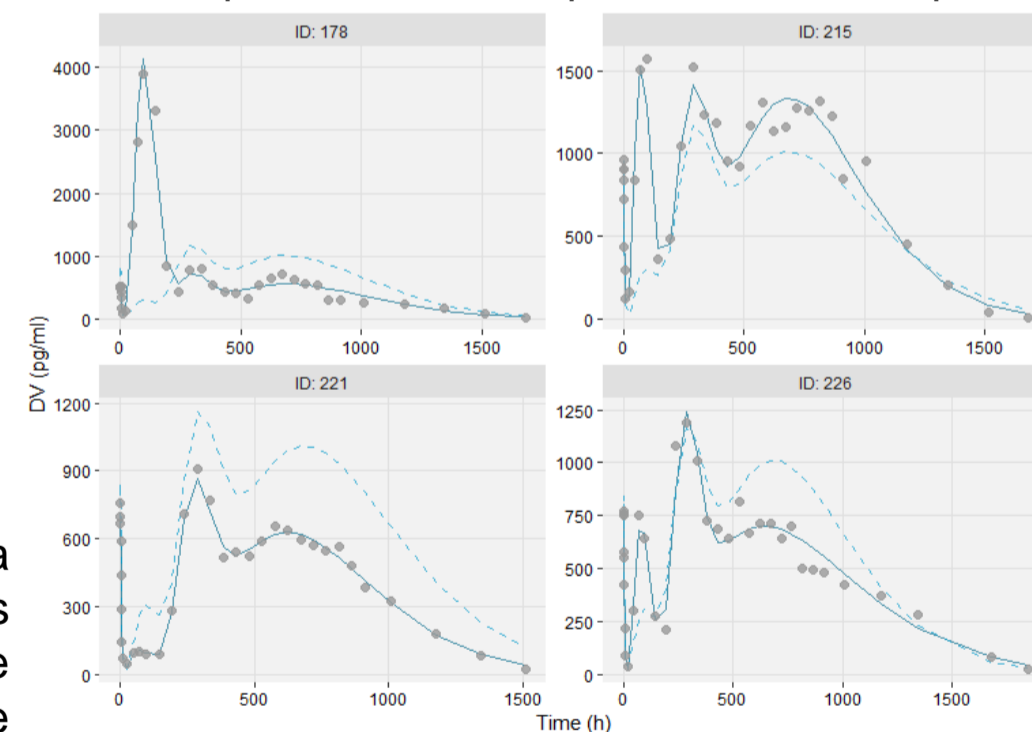
**Population PK model:** An empirical absorption model, coupled with a one-compartment distribution model with linear elimination, was developed to describe the typical PK profile. The initial burst phase was modeled as a first order process, defined by the absorption rate constant  $k_a$ . Three parallel delayed processes, using the transit compartment model, were employed to describe the three-phase absorption delays. [2] The input rate in the depot compartment was modeled as the weighted sum of the transit model function and the first-order absorption.

**Clustering:** A preprocessing step of the raw PK data was performed before PPK modeling i.e., cluster analysis, in order to identify subpopulations. We applied the shape-respecting variation of k-means clustering method implemented in R package kmlShape. [3]

This method, which was developed for the analysis of longitudinal data, takes into account the horizontal offset because modest variations on delays may be of limited importance, and yet account to large distances according to the classical k-means method. Normalization of the PK data allowed the identification of different patterns in release kinetics, without the influence of apparent clearance and total exposure. Cluster analysis results were handled as a categorical covariate and the inclusion in the final model was based on the likelihood ratio test and the overall performance of the PPK model to describe the data.

## Results

The cluster analysis allowed the identification of two different patterns in PK data. 87% of the subjects exhibit the typical multi-phase pattern of the initial burst followed by 3 delayed peaks. A sub-population (13% of the subjects) was characterized by an early, extended phase of absorption, followed by a slow delayed release phase, which corresponds to a small part of the total exposure.

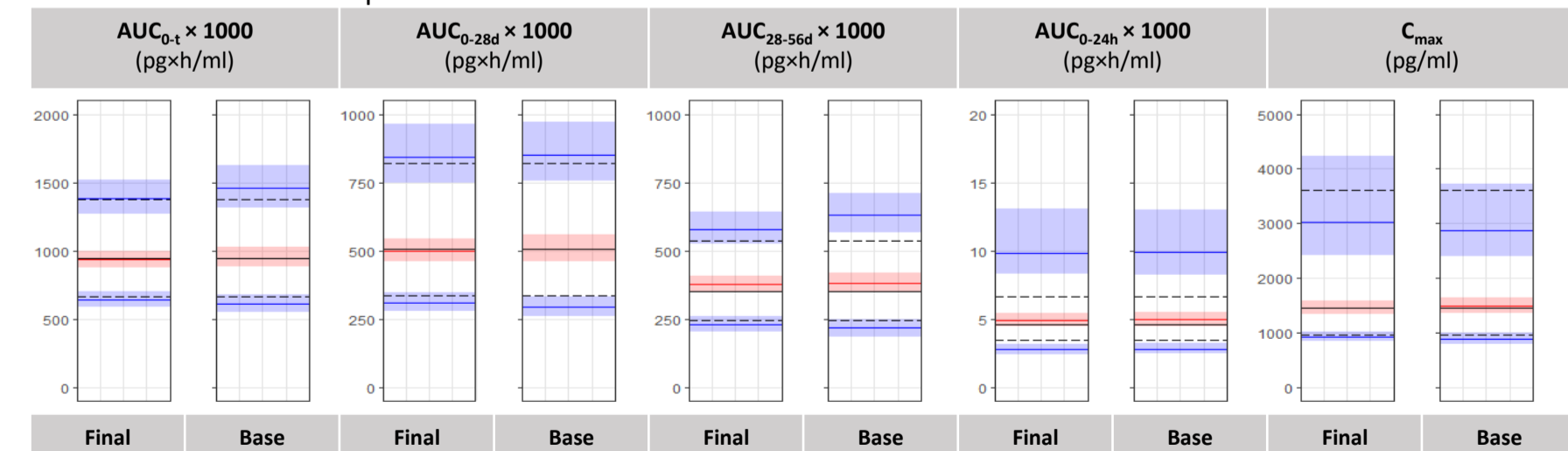


**Figure 2.** Individual plots of Observations vs PRED and IPRED showing the flexibility of the PPK model to predict for representative subjects. Solid line and dashed line indicate IPRED and PRED respectively.

The base model consisting of a simple one-compartment PK model with linear elimination, coupled with the empirical absorption model, successfully described the complex and highly variable individual PK profiles. The inclusion of the cluster-defined subpopulations as covariate of  $f_1$ ,  $f_2$  and CL allowed a better characterization of the observed heterogeneity and variability of the study and resulted in a drop in the objective function value,  $\Delta OFV = -115.158$ .

Parameter	Estimate (RSE%)	Workflow Bootstrap		
		Median	95% CI	RSE (%)
$k_a$	0.27 (2.2)	0.27	0.26 - 0.28	2
V	15.3 (7.7)	15.1	13.6 - 17.1	6
CL	32.7 (5.8)	32.6	30.8 - 34.8	3
Cluster effect:	-8.61 (34)	-9.24	-13.95 to -3.57	38
$Y_{F1}$	-5.18 (1.8)	-5.19	-5.24 to -5.11	1
$Y_{F2}$	-3.36 (7.9)	-3.34	-3.69 to -3.02	5
Cluster effect:	3.06 (33)	3.02	2.02 - 3.55	14
$Y_{F3}$	-1.54 (2.8)	-1.55	-1.65 to -1.44	4
Cluster effect:	-0.523 (26.8)	-0.47	-0.715 - 0.01	35
$Y_{MTT1}$	-0.421 (21.8)	-0.41	-0.562 to -0.253	20
MTT2	181 (3.3)	179	167 - 191	4
MTT3	506 (3.8)	508	481 - 534	3
N1	3.42 (15)	3.44	2.80 - 4.10	9
N2	17.9 (6)	18.0	15.9 - 20.3	7
N3	5.08 (5)	5.03	4.58 - 5.57	5
Proportional Residual Error	0.143 (1.3)	0.14	0.127 - 0.156	5
Additive Residual Error	28.4 (3.7)	28.8	23.6 - 35.2	10
Inter-individual Variability	Estimate (RSE%)	Median	95% CI	RSE (%)
$IIV_V$	39.4 (13) [16.3]	39.7	32.1 - 46.1	13
$IIV_{CL}$	28.2 (8) [1]	28.3	23.4 - 32.7	22
$IIV_{Y_{F1}}$	28.9 (7) [3.4]	28.1	13.9 - 48.2	50
$IIV_{Y_{F2}}$	128.8 (16) [4]	129.2	110.9 - 143.7	6
$IIV_{Y_{F3}}$	20.5 (18) [30.3]	21.1	14.1 - 37.2	25
$IIV_{Y_{MTT1}}$	60.1 (12) [12]	60.6	49.5 - 73.6	10
$IIV_{MTT2}$	17.3 (20) [17.6]	18.7	14.3 - 28.8	50
$IIV_{MTT3}$	20.2 (9) [1.7]	20.6	16.6 - 30.0	54
$IIV_{N1}$	71.2 (10) [22]	69.2	36.0 - 106.1	23
$IIV_{N2}$	26.2 (21) [31.2]	26.5	16.9 - 34.1	26
$IIV_N$	31.4 (12) [9.3]	31	24.2 - 42.2	14

**Table 1.** PPK model parameter estimates and "workflow bootstrap" results



**Figure 3.** VPC plots for PK metrics in the base and final model. Black lines denote the median, 10th and 90th percentiles of the observations. The shaded areas and colored lines represent the medians and 95% CI of the 1000 simulated datasets for the corresponding statistic measures of the observations

## References

- [1] Park et al. J. Control. Release 2019, 304, 125–134.
- [2] Savic et al. J. Pharmacokinet. Pharmacodyn. 2007, 34, 711–726.
- [3] Genolini et al. PLoS One 2016, 11, e0150738.

The performance of the final model was evaluated based on goodness-of-fit plots, visual predictive checks (VPCs) and bootstrap. Furthermore, the robustness of the analysis of the entire workflow was evaluated by using the bootstrap method. For each one of 200 resampled datasets, two steps were sequentially performed, i.e., the clustering and the model fitting step, using an semi-automated procedure coded in R and using PsN. VPCs comparing model predicted BE metrics to observed values calculated by NCA, showed that the final population PK model described better  $C_{max}$ ,  $AUC(0-t)$  and partial AUCs.

## Conclusions

The present model is the first to describe the multiple-peak absorption pattern observed after octreotide LAR administration and may be useful to provide insights and validate hypotheses regarding release from PLGA-based formulations. We proposed a workflow, showing that cluster analysis may be valuable in cases where subpopulations are present.



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