Population Pharmacokinetic Model for Human Growth Hormone in Adult Patients in Chronic Dialysis vs. Healthy Subjects

T Klitgaard[1,✉], JN Nielsen[1], MS Fitsios[1], and M Lange[2]

[1]Novo Nordisk A/S Bagsvaerd, Denmark;[2]Clinical Research, Novo Nordisk Inc., Princeton, US. ✉ tkt@novonordisk.com

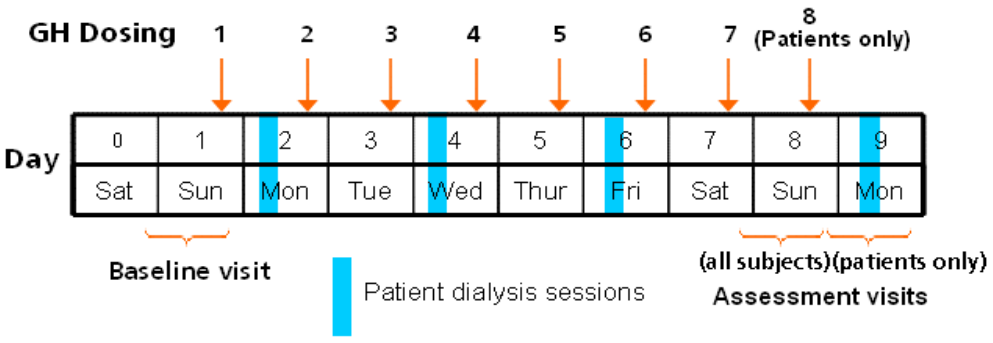
Background and Objectives

- Recombinant human Growth Hormone (rhGH) may be beneficial in treating adult patients in chronic dialysis (APCD pts.). Since both the kidneys and the liver are reported to play a role in GH clearance, pharmacokinetics could be significantly influenced by renal function impairment, with possible implications on accumulation and, in turn, efficacy and safety.
- Objective: To develop a population pharmacokinetic (popPK) model for rhGH in APCD pts. and healthy volunteers (HVs), to support the design of future clinical trials.

Trial design and subjects

- **Design:** Open, non-randomized, single-center, parallel-group study over 8-9 days.
- **Subjects:** 11 APCD pts., 10 matched healthy controls.
- **Dose:** 50 µg/kg/day rhGH s.c. for 7 days. ERSD pts. had an extra dose on Day 8 and 4 dialysis sessions over the 9 day period.

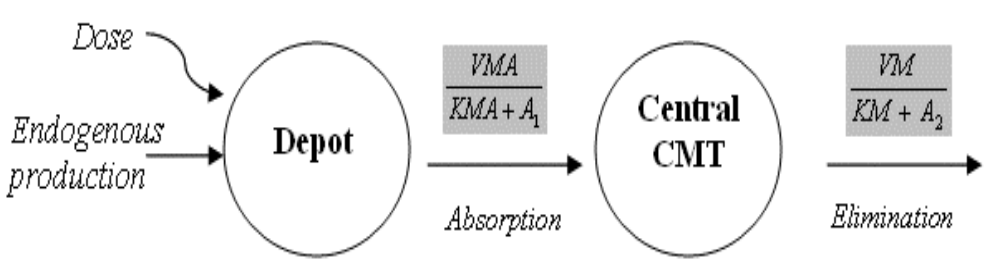
Figure 1. Trial Design



Methods

- Analysis was performed in NONMEM V. First order conditional (FOCE) estimation method with INTERACTION was used.
- The following structural models were evaluated:
  - One- and two- compartment (CMT) models with first-order (FO) absorption and elimination
  - One CMT models with FO absorption and Michaelïs-Menten (MM) type of elimination
  - One CMT models with FO absorption and MM elimination + parallel FO elimination
  - One CMT models with MM absorption and elimination +/- parallel FO elimination
  - All above +/- individual absorption lag time or +/- absorption delay CMT
- Covariates APCD/HV, Gender, Weight, and Dialysis Flow rate (APCD pts. only) were tested on key model parameters.
- Exponential error models used for inter-individual variability. Combined error model used for residual error.
- Model performance was evaluated with a simplified posterior predictive check: 1000 trials were simulated and distributions of mean, geometric mean, and standard deviation of AUC0-24h and Cmax were compared with non-compartmental estimates.
- Population mean profiles with 95% confidence limits were simulated for each of the two groups of subjects.

Figure 2. Final Model

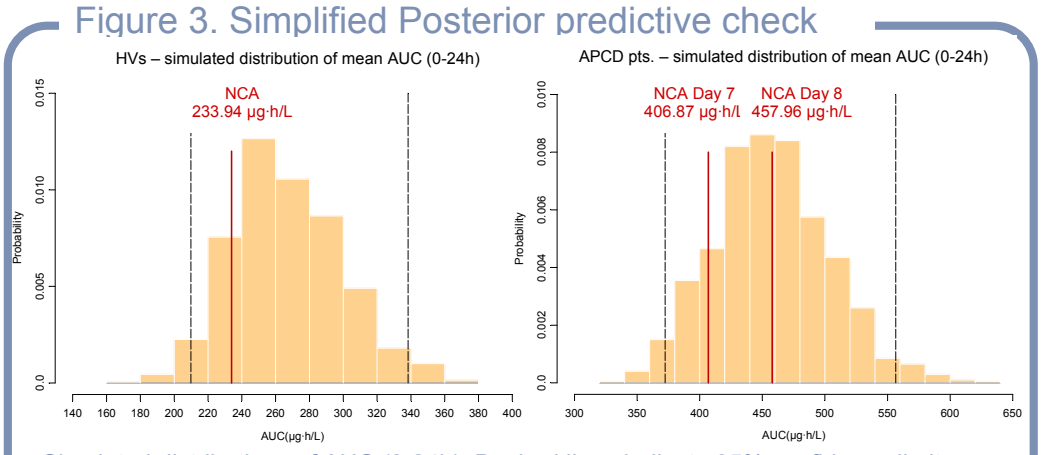


One CMT model with MM absorption and elimination, and an individual baseline level of endogenous hGH. A1: Drug amount in depot, A2: Drug amount in central compartment, VMA, VM: Max absorption, elimination rate, KMA, KM: Amount for half-max absorption, elimination rate

Results

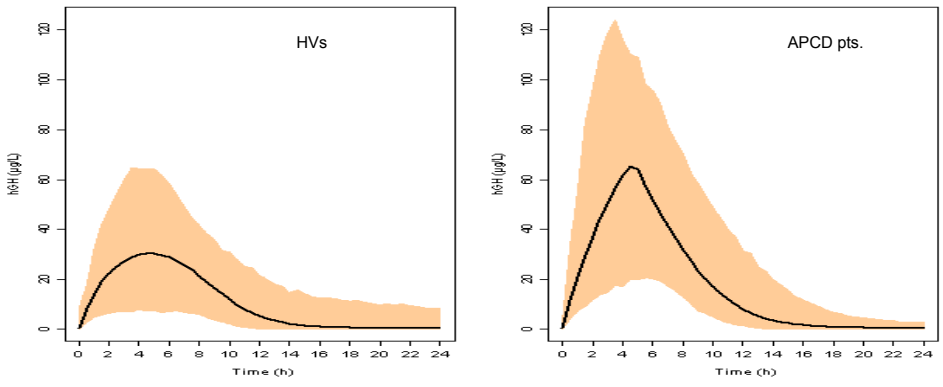
- Final model was a one CMT model with MM-absorption and MM-elimination The latter possibly describes both a FO (renal) and a MM (hepatic) elimination (could not be separated).
- Statistically significant ($p<0.001$) differences in parameters for absorption (KMA) and elimination (VM) for HVs vs. APCD pts.
- A posterior predictive check indicated acceptable performance for simulation purposes, to support future studies.
- Large inter-individual variation, as reflected in simulated mean profiles with 95% confidence limits.

Figure 3. Simplified Posterior predictive check



Simulated distributions of AUC (0-24h). Dashed lines indicate 95% confidence limits. NCA: Results from the non-compartmental analysis.

Figure 4. Population mean hGH profiles



Population mean hGH profiles for HVs (left) and APCD patients (right) on day 7, with 95 % confidence limits. Dose: 50 µg/kg/day for 7 days Based on 1000 simulated subjects in each group.

Table 1. Final model parameters

Parameter	Population Mean	Uncertainty of estimate (% CV of pop mean)	Variability (% CV between subjects)
KMA – HVs (µg/kg)	18.8	44.1	179†
KMA – APCD pts. (µg/kg)	1.06	68.0	179†
VMA (µg/kg/h)	11.3	9.82	46.3†
KM (µg/kg)	18.9	12.6	27.2
VM – HVs (µg/kg/h)	13.0	11.5	-
VM – APCD pts. (µg/kg/h)	9.37	8.38	-
V/f (L/kg)	0.450	5.93	27.5
BASE (µg/L)	0.520	11.3	53.4
q_1 – residual error model†	0.129	7.26	-
q_2 – residual error model†	0.945	13.5	-

BASE: Baseline level of drug , VMA, VM: Maximum absorption, elimination rate, KMA, KM: Amount corres-ponding to half-maximum absorption, elimination rate, %CV of mean: Standard error for mean estimate*100/mean estimate, %CV between subjects: Standard error of individual estimates*100/mean estimate´. †KMA and VMA were correlated with a correlation coefficient of 0.647, †† Estimated parameters in the residual error model $Y_{observed} = f + \sqrt{\theta_1^2 f^2 + \theta_2^2} \cdot \varepsilon$ where f is the model predicted, individual Y and $\varepsilon \sim N(0,1)$.

Conclusions

- A popPK model of hGH was developed for APCD pts. and HVs.
- Absorption and elimination were found to be different in the HVs and APCD pts.
- Simplified posterior predictive check of the model showed an acceptable performance for simulation purposes.