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

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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.

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 Michaelis-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 were 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 were compared with non-compartmental estimates.
- Population mean profiles with 95% confidence limits were simulated to support future studies.
- Large inter-individual variation, as reflected in simulated mean profiles with 95% confidence limits.

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.

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.