Pharmacokinetic / Pharmacodynamic Modeling of MOD 4023 (Long-Acting Human Growth Hormone) in Growth Hormone Deficient Children

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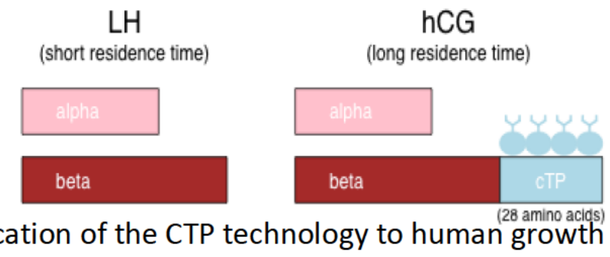
INTRODUCTION

OPKO Biologics is developing long-acting versions of existing therapeutic proteins utilizing CTP technology. This technology fuses the C-terminus peptide of human chorionic gonadotropin (hCG) to one or both ends of a target protein. CTP technology has been validated clinically and proven as a safe and efficient way to increase the half-life of several therapeutic proteins while maintaining their biological activity.



MOD-4023, application of the CTP technology to human growth hormone (hGH), is being developed for the treatment of short stature in children. The goal is to develop a product that allows weekly dosing while maintaining a small clinically-tolerable injection volume.

Pharmacokinetic (PK) and pharmacodynamic (PD, based on IGF-1) characteristics of MOD-4023 have been studied in three clinical trials, one in healthy adults, one in GH-deficient adults, and one in GH-deficient children. Data from adults were used to develop and validate PK and PD models; these models were then applied to the data in children. The goal is to develop models to assist in dose selection, dose adjustment and design of clinical trials.

METHODS: CLINICAL TRIAL DESIGNS

CP-4-001: 24 healthy adults received single subcutaneous (SC) injections of placebo (N=6) or 4, 7, or 21 mg MOD-4023 (N = 6/group). Samples (MOD-4023, IGF-1) were obtained through 14 days post-dose.

CP-4-003: 54 GH-deficient adults received weekly or every-other-week SC injections of MOD-4023 for 4 weeks. Doses ranged from 18.5%-123.4% of their weekly r-hGH dose. Samples were obtained for 7 days after dose 4.

CP-4-004: 52 Treatment-naive GH-deficient children aged 3-11 years received SC MOD-4023 weekly (**Figure 1**) or r-HGH (N=11), 0.034 mg/kg, daily for up to one year. For MOD-4023, sparse samples were obtained after the second steady state dose (**Figure 2**) and at later timepoints. r-HGH was sampled after dose 1.

METHODS: PHARMACOKINETIC / PHARMACODYNAMIC ANALYSIS

- Mixed-effects (population) methods with NONMEM (Icon Development Solutions) were needed because of sparse sampling in children
- PK model: Linear 2-compartment model with first-order absorption and absorption lag
- PD model:
  - Indirect model (Sun *et al*. JPET 1999; 289:1523-32) relates drug concentration to IGF-1 input (**Figure 3)**; sigmoid Emax relationship between drug concentration and effect
  - Based on IGF-1 rather than IGF-1 SDS (IGF-1 SDS is non-linear function of IGF-1)
  - IGF-1 SDS values estimated using reference tables (Bidlingmaier *et al.* J Clin Endocrinol Metab 2014; 99:1712)
- Body size, age, gender, organ function evaluated as covariates for all PK and PD parameters
- Results from optimal models used to evaluate accumulation, time to steady state, comparison to r-hGH

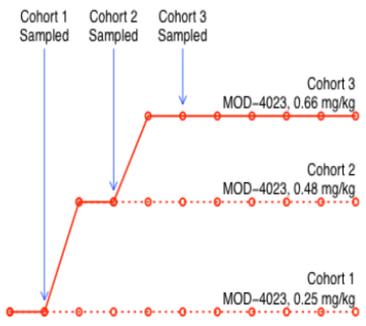


Figure 1. Dose escalation for MOD-4023.

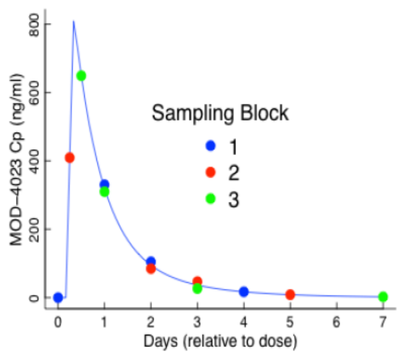


Figure 2. Sampling regimen for MOD-4023.

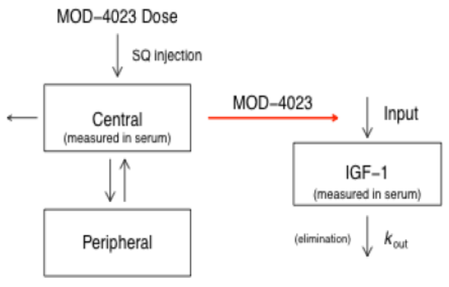


Figure 3. Indirect PK/PD Model.

RESULTS

- Adults: Fit of the PK model to MOD-4023 and the PD model to IGF-1 was good-to-excellent (not shown)
- Children:
  - Fits generally good-to-excellent (**Figure 4**)
  - Weight-normalized approach preferred over allometric scaling (**Figure 5**)
  - Time-related change in PD (baseline IGF-1 increases over time) results in IGF-1 increasing over time (not shown)
  - Steady state conditions for PK reached by second dose; no accumulation (**Figure 6**)
  - Residence time of MOD-4023 markedly longer than r-hGH (**Figure 7**)
  - IGF-1 SDS values in Cohorts 2 and 3 stabilize around the target value of zero (not shown)

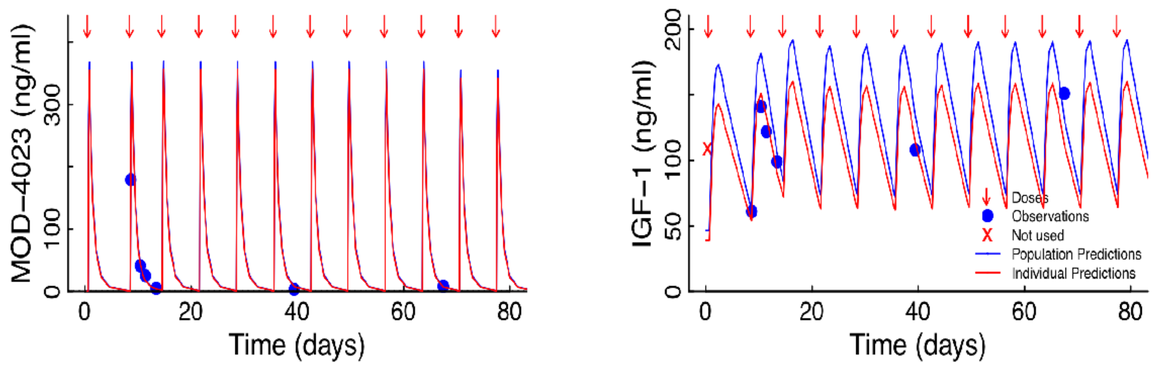


Figure 4. Representative fit of the models to the PK data (left) and PD data (right).

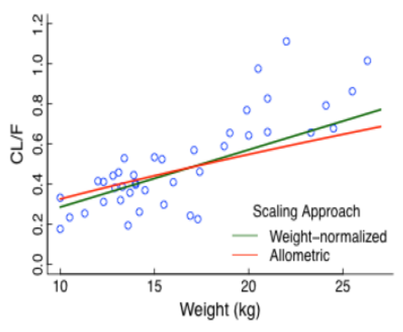


Figure 5. *Post hoc* (individual values) for apparent clearance are displayed against weight. The weight-normalized fit is preferred.

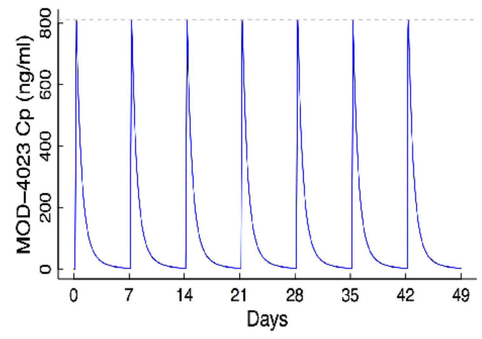


Figure 6. Simulations based on the optimal model for MOD-4023 show that steady state conditions are reached by the second dose and that there is no accumulation.

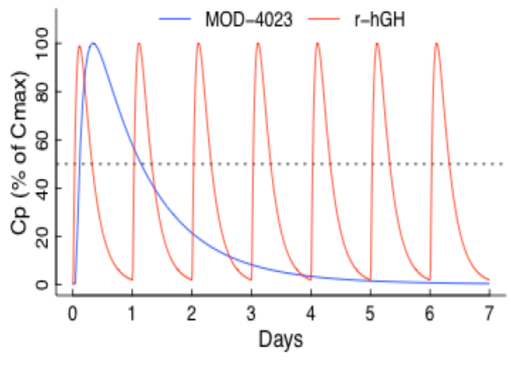


Figure 7. Simulations based on the optimal models for MOD-4023 and r-hGH show that residence time for MOD-4023 is markedly longer than that for r-hGH.

CONCLUSIONS

- Weight-normalized dosing is appropriate to maintain comparable exposures in children over a range of weights
- MOD-4023 has a longer residence time than r-hGH, leading to a prolonged increase in IGF-1. This supports weekly dosing
- MOD-4023 reaches steady state rapidly with no accumulation
- IGF-1 SDS values stabilize around 0 (the target value) for the two higher MOD-4023 cohorts, comparable to daily r-hGH
- Model can guide dose adjustments in both Phase 3 and clinical practice and can aid in clinical trial design

OPKO Biologics

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