Pharmacokinetic (PK) and Pharmacodynamic (PK/PD) Modeling of MOD-4023 in Growth Hormone (GH) Deficient Children

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• OPKO’s hGH, MOD-4023 contains a naturally-occurring peptide (C-terminal peptide)
• This molecular modification markedly increases GH’s residence in vivo
• In turn, this should allow less frequent dosing
• Aim: weekly dosing in children
Constraints in Pediatric Studies

- # of samples limited — necessitates sparse sampling
- In turn, population PK approach (mixed effects) needed
- NONMEM® software (gold standard) yields two sets of parameter estimates:
  - Individual, also known as post hoc
  - Population: “typical” (median) subject
Pediatric Phase 2 Study

- Treatment-naive GH-deficient children (N = 53)
- Age (years): 3-11
- Control: Genotropin, 0.034 mg/kg daily

**Dosing Regimen**

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<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
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**Sampling Regimen**

Dose escalation:
- Cohort 2: Week 3
- Cohort 3: Week 3, Week 5

MOD−4023:
- Cohort 1: 0.25 mg/kg
- Cohort 2: 0.48 mg/kg
- Cohort 3: 0.66 mg/kg

Sampling Block:
- 1
- 2
- 3

4 Samples / subject at 2\textsuperscript{nd} steady-state dose + Additional samples at monthly intervals
• Analysis uses IGF-1, not IGF-1 SDS (IGF-1 SDS is non-linear function of IGF-1)
• Assay: IDS-iSYS
MOD-4023 Pharmacokinetic Model

- 2-Compartment model with first-order elimination
- Parameters include apparent clearance (clearance / bioavailability)
- **Assay:** ELISA specific for MOD-4023
Combined (PK/PD) Model

Indirect model* (IGF-1 is not directly related to MOD-4023)

* Sun et al. JPET 1999 289:1523
Model Development: Adults with Extensive Sampling

Healthy Adults (Phase I)

GH-Deficient Adults (Phase II)

Fits are generally excellent
• Fits are generally good-excellent
• Apparent clearance is weight-proportional
• Baseline IGF-1 increases ~ 12% / year
• No other covariates affect PK or PK/PD
How should dosing be adjusted for body size?

- Systemic exposure (AUC) is a function of clearance / bioavailability (CL/F)
- Weight is the best predictor of CL/F (slightly better than allometric)
- No other covariates (e.g., age, height, organ function) influence exposure
- If goal is to maintain similar AUC at different ages, dosing should be weight-proportional; other covariates need not be considered
- Adequacy of exposure can be assessed by sampling IGF-1

Weight Normalize Initially, Then Monitor IGF-1/Adjust
Is MOD-4023’s residence time >> r-hGH? Weekly MOD-4023 vs. Daily r-hGH

MOD-4023 residence time is longer
Does MOD-4023 accumulate?

No accumulation with weekly dosing
When should samples be obtained to assess safety?: mean IGF-1 SDS

- IGF-1 profile simulated for each subject for Dose 6
- IGF-1 values mapped to IGF-1 SDS
- Mean over dosing interval calculated
- Mean compared to value at each day

Sample at Day 4 optimally describes mean IGF-1 SDS
Summary

• Weight-normalized *initial* dosing appropriate
• No other covariates need to be considered in *initial* dose selection
• PK and PK/PD models will guide dose adjustments
• MOD-4023 residence time >> r-hGH (supports longer interval between doses)
• Efficacy with weekly dosing being evaluated in phase 2/3 clinical trials