

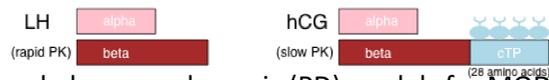
# Year 2 Pharmacokinetic and Pharmacodynamic Modeling of Long-Acting Human Growth Hormone (MOD-4023) in Growth Hormone Deficient Children

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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.



At ESPE2015 (Barcelona), we reported pharmacokinetic (PK) and pharmacodynamic (PD) models for MOD-4023 and its effect on IGF-1 (and IGF-1 SDS) from clinical trial CP-4-004 (treatment-naive GH-deficient children aged 3-11 years receiving subcutaneous MOD-4023 weekly for up to one year). Thirty-eight (38) of the forty-two (42) subjects in that trial have now continued treatment through at least Year 2. We now report whether the model developed from data obtained during Year 1 predicts the time course of MOD-4023, IGF-1, and IGF-1 SDS during Year 2.

Key elements from the Year 1 analysis were:

- Apparent clearance was proportional to weight (supporting OPKO's decision to administer initial doses based on weight).
- No other covariates affected systemic pharmacokinetics in children.
- An indirect pharmacodynamic model proposed by Sun *et al.* (MOD-4023 concentration [Cp] affects IGF-1 input; sigmoid Emax relationship between Cp and effect) fit the IGF-1 data well. Calculations were performed using IGF-1 values rather than IGF-1 SDS because IGF-1 SDS is a non-linear transform of IGF-1.
- Baseline IGF-1 (the trough of the IGF-1 profile during each dosing interval) increased ~ 21% per hour, consistent with known increases in IGF-1 with maturation.

## METHODS

During Year 2, samples were obtained at months 3, 6, 9, and 12 typically 4 days post-dose. MOD-4023 and IGF-1 concentrations were determined using electrochemiluminescence and IDS-iSYS assays, respectively. The individual (*post hoc*) parameters from the model for Year 1 were applied to predict MOD-4023 and IGF-1 concentrations at each sampling time in Year 2. IGF-1 SDS was calculated from IGF-1 concentrations using Bidlingmaier's table (2) that account for age and gender. Comparisons between observed and predicted values were explored graphically.

## RESULTS

Data from a representative subject are shown in **Figure 1**. Observed values are displayed vs. predicted values in **Figure 2**. Individual and median of the ratio between observed and predicted values (MOD-4023, IGF-1) or difference (IGF-1 SDS) for each set of samples is displayed in **Figure 3**.

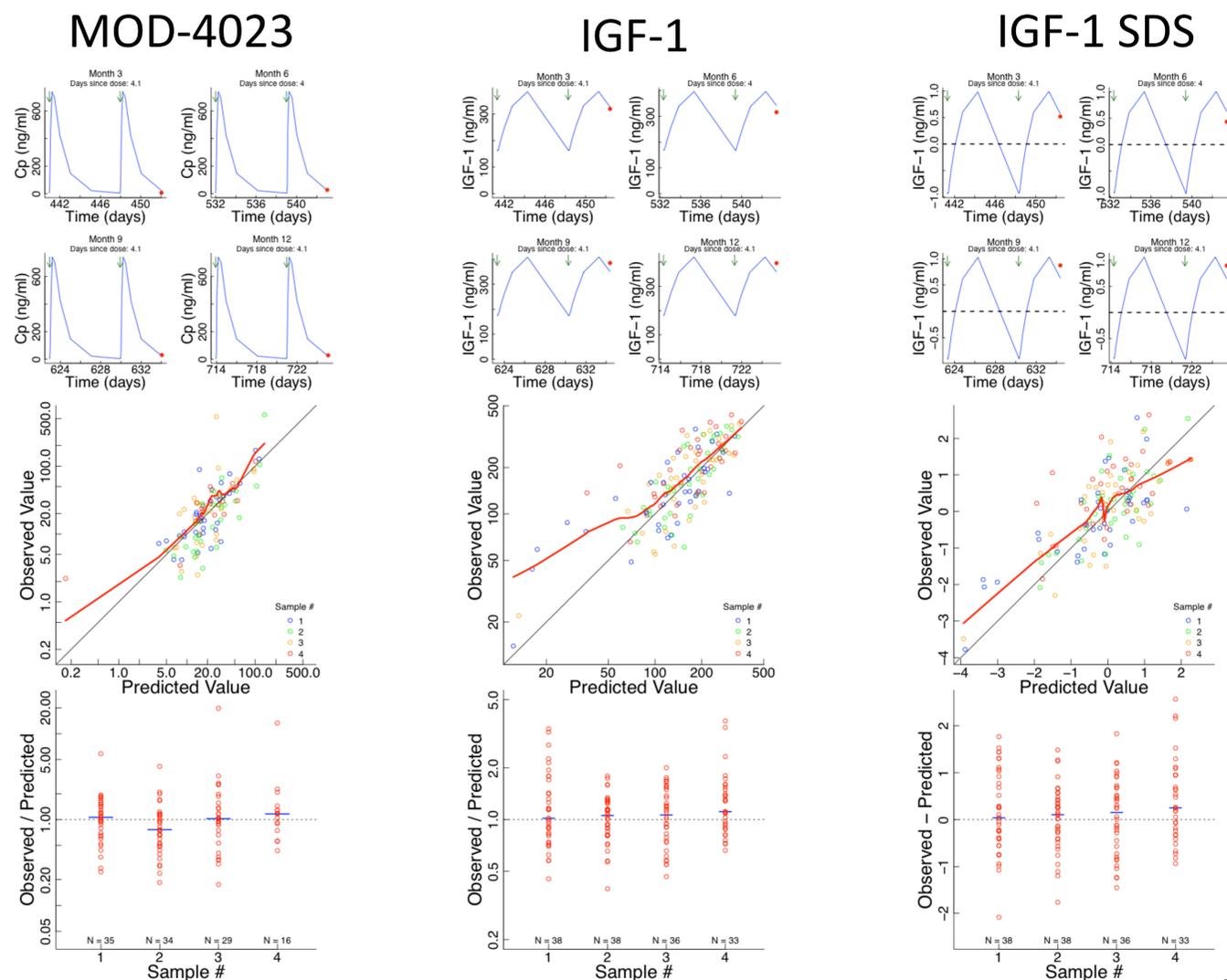
The model from Year 1 generally predicted the Year 2 data in an unbiased manner. Differences between predictions and observations were moderate in magnitude. Deviations between observed and predicted MOD-4023 Cp were largest at low Cp, possibly a result of a larger coefficient of variation of the assay at low Cp values. For IGF-1 and IGF-1 SDS, deviations were also largest at low values. For IGF-1 SDS, the deviation between predictions and observations was largest at Sample 4 (12 months), approximately 0.5 SDS units.

## CONCLUSIONS

PK and PD models developed from Year 1 data for MOD-4023 treatment in children generally predicted Year 2 MOD-4023, IGF-1, and IGF-1 SDS in an unbiased manner. However, variability was moderate.

## REFERENCES

1. Sun *et al.* JPET 1999; 289:1523
2. Bidlingmaier *et al.* J Clin Endocrinol Metab 2014; 99:1712



**Figure 1.** Values at each of 4 sampling periods for a representative subject. The blue line is the profile predicted from Year 1 data. The red circle is the measured value. Arrows indicate doses.

**Figure 2.** Observed vs. predicted values at each of the 4 (color-coded) sampling times. The red line (Supersmoother) generally tracks the line of identity.

**Figure 3.** Individual values and mean of ratio (MOD-4023, IGF-1) or difference (IGF-1 SDS) for each set of samples.

### Disclosure Statement

DMF: Consultant, OPKO Biologics. Nothing to Disclose: MJM, SV, RK, GH.

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