Optimal Sampling of IGF-1 during Weekly Administration of a Long-Acting Human Growth Hormone (MOD-4023)

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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 shown 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.

During Phase 3 clinical trials and following future approval of MOD-4023 for clinical use, IGF-1 SDS values will be used to assess safety of weekly therapy and to determine any potential need for dose adjustment. During the one-week dosing interval, IGF1 (and resulting IGF-1 SDS) values fluctuate. Therefore, it is important to understand the relationship between IGF1 values obtained at different timepoints in the dosing interval to the peak and mean IGF-1 SDS during the dosing interval. We used pharmacokinetic (PK) and pharmacodynamic (PD) modeling and simulation to determine the optimal time to sample IGF-1.

METHODS: TRIAL DESIGN

In clinical trial CP-4-004, treatment-naive GH-deficient children aged 3-11 years received subcutaneous MOD-4023 weekly for up to one year. Sparse samples (MOD-4023, IGF-1) were obtained after the second steady state dose and at later timepoints.

METHODS: PHARMACOKINETIC / PHARMACODYNAMIC SIMULATION

• For each subject, the time course of MOD-4023 and IGF-1 was simulated following 11 weekly doses. The dose escalation scheme employed in the trial was implemented, followed by equal-sized steady state doses.
• IGF-1 SDS values estimated based on IGF-1 values, age, and gender, using Bidlingmaier’s reference tables (2)
• For each subject, the simulated values for each of MOD-4023 and IGF-1 SDS were examined to determine:
  — mean values over the dosing interval (determined using linear trapezoids)
  — peak values
  — values at each of Day 1 (24 hours post-dose) through Day 7 (end of dosing interval)
• Graphics were prepared to examine the relationship between the values at each day vs. peak / mean values

RESULTS

Peak IGF-1 SDS: Samples obtained on Day 2 (48 hours post-dose) predicted peak IGF-1 SDS well (Figure 1): correlation was high (r > 0.99) and deviation from the line of unity was minimal. Values obtained on all other days (Day 4 displayed) underestimated peak IGF-1 SDS. However, there was a strong linear relationship between the value on any day and peak IGF-1 SDS; the r value and intercept/slope for those relationships are displayed in Table 1.

Mean IGF-1 SDS: Samples obtained on Day 4 (96 hours post-dose) predicted mean IGF-1 SDS well (Figure 2): correlation was high (r > 0.99) and deviation from the line of unity was minimal. Values obtained on all Day 2 (displayed) and Day 3 overestimated mean IGF-1 SDS whereas those obtained on Days 6 or 7 underestimated mean IGF-1 SDS. However, there was a strong linear relationship between the value on any day and mean IGF-1 SDS; the r value and intercept/slope for those relationships are displayed in Table 2.

CONCLUSIONS

• IGF-1 SDS, determined from an IGF-1 sample obtained at Day 2, provides a direct estimate of peak IGF-1 SDS. In contrast, a sample at Day 4 provides a direct estimate of mean IGF-1 SDS.
• Samples obtained at other days can be used to estimate peak or mean IGF-1 SDS using the linear relationships displayed in Table 1 and Table 2.
• These values of peak and/or mean IGF-1 SDS can be used to adjust dosing of MOD-4023.
• Similar results (not reported) were obtained from a study in GH-deficient adults (CP-4-003).

REFERENCES


Disclosure Statement

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

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