Determination of Optimal Dosing of rhIGF-1/rhIGFBP-3 to Establish and Maintain Physiological Intrathecal Serum IGF-1 Levels in Preterm Infants

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PURPOSE

• Insulin-like growth factor 1 (IGF-1) replacement with recombinant human (rh)IGF-1/rhIGFBP-3 is being investigated for prevention of retinopathy of prematurity (ROP).
• A Phase 2 randomized, controlled, assessor-masked, multicenter study of rhIGF-1/rhIGFBP-3 (continuous intrathecal [IT] infusion) for prevention of ROP is being conducted in 4 sequential sections.

METHODS

Section D Dose Determination

• Normal intrathecal fetal serum IGF-1 levels were determined from published literature (N=174).1,4,10
  • 28–109 µg/L for gestational age (GA) 23–28 weeks.
• Serum IGF-1 in preterm infants was determined from data for untreated infants in Sections B/C of the Phase 2 study and published literature (N=137).1,5,6
  • 4–40 µg/L for GA 23–28 weeks.
• The model incorporated serum IGF-1 data from treated infants from the Phase 1 study and Sections A–C of the Phase 2 study in order to predict optimal dosing and duration of rhIGF-1/rhIGFBP-3 to reach targeted IGF-1 levels.

RESULTS

Interim PK Analysis With New 250 µg/kg/24 h Dose

Table 1 summarizes demographics and dosing for the 19 preterm infants included in the interim PK assessment.

• A treated infant received therapy for only 1 day.
  • For the 9 other infants, infusion duration was 13.6–34.5 days (total dose, 2.9–7.1 mg).
  • At baseline, mean (SD) serum IGF-1 was 19.2 (8.0) µg/L for treated and 15.4 (4.7) µg/L for control infants.

• Mean (SD) serum IGF-1 levels increased to 45.9 (19.6) µg/L at 12 hours in treated infants, and

• At regular intervals during treatment from 12 hours post baseline up to a PMA of 29 weeks + 6 days.

• Serum IGF-1 levels were measured using a validated radioimmunoassay at a central laboratory.

CONCLUSIONS

• In this interim PK assessment of the ongoing Phase 2 Section D study:
  • Serum IGF-1 levels were within targeted physiological intrathecal levels for the majority of measurements in infants treated with a standardized rhIGF-1/rhIGFBP-3 dose of 250 µg/kg/24 h continuous IT infusion.
  • In contrast, the majority of measurements in infants receiving standard care were below targeted levels.

This analysis validates the population PK model and confirms the appropriateness of the designed dosing regimen for Section D.