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

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DISCLOSURES

Ann Hellström holds stock/stock options in Premalux AB and has received consulting fees from Shire. Boubou Hallberg has received consulting fees from Premacure AB and an unrestricted research grant from Baxter. Ingrid Hansen-Pupp holds stock/stock options in Premalux AB and has received consulting fees from Shire. Jou-Ku Chung and Norman Barton are employees of and hold stock/stock options in Shire. At the time of the study, Jyoti Sharma was an employee of and Gerald Fetterly a consultant to KinderPharm/PKPD Bioscience, who were paid consultants to Shire in relation to this study. Mary Ann Mascelli and Nerissa C. Kreher were employees of Shire at the time of the study and hold stock in Shire. David Ley holds stock/stock options in Premalux AB and has received consulting fees from Shire.

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PURPOSE

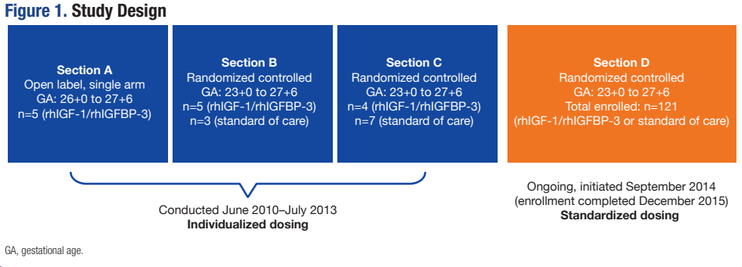
- Insulin-like growth factor 1 (IGF-1) replacement with recombinant human (rh)IGF-1/rhIGFBP-3 is being investigated for prevention of retinopathy of prematurity (ROP).
- A Phase 2 randomized, controlled, assessor-masked, multicenter study of rhIGF-1/rhIGFBP-3 (continuous intravenous [IV] infusion) for prevention of ROP is being conducted in 4 sequential sections[1] (**Figure 1**).
- Analysis of IGF-1 levels during an earlier Phase 1 dose-escalation study[2] and Sections A–C of the Phase 2 study indicated a need for a higher (and standardized) dose of rhIGF-1/rhIGFBP-3 to establish and maintain IGF-1 within physiological intrauterine levels in preterm infants.
- A population pharmacokinetic (PK) model was developed using data 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.
- Section D of the Phase 2 study, which is evaluating dosing/efficacy of rhIGF-1/rhIGFBP-3, was initiated using the predicted dose.
- We report serum IGF-1 levels for the first 10 infants treated in Section D.

METHODS

Section D Dose Determination

- Normal intrauterine fetal serum IGF-1 levels were determined from published literature (N=174).[3,4]
  - **~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 and 2 (Sections A–C) studies (N=19).
- Population PK simulations were performed at doses of 100, 250, 500, and 750 µg/kg/24 h for periods of 2, 4, 6, and 8 weeks.
- Simulations indicated that a dose of **250 µg/kg/24 h** administered by **continuous IV infusion** up to **~30 weeks postmenstrual age (PMA)** is needed to achieve IGF-1 levels within physiological intrauterine range.

Figure 1. Study Design



GA, gestational age.

Section D Dose Validation: Interim PK Analysis

- Section D was initiated using the predicted dose of 250 µg/kg/24 h administered by continuous IV infusion from birth up to a PMA of 29 weeks + 6 days.
- A review of serum IGF-1 data was conducted once 10 treated infants completed the dosing phase of the study to assess suitability of the dose regimen to reach and maintain serum IGF-1 target levels of 28–109 µg/L.
- Infant blood samples were taken at baseline (immediately before starting the infusion) 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.

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.
- 1 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 remained within target levels for all subsequent time points. In controls, mean serum IGF-1 remained below target levels for all time points (**Figure 2**).
- **Figure 3** shows individual serum IGF-1 measurements for all 19 preterm infants from day 0 up to a PMA of 29 weeks + 6 days.
- Overall, 88.8% of serum IGF-1 measurements were within target levels for treated infants (11.1% for controls; **Table 2**).

Table 1. Demographics and Dosing

Group	n	Sex	GA at Birth, wk+d	Birth Weight, kg	Total Dose, mg	Infusion Duration, d*
rhIGF-1/rhIGFBP-3	10	Female, n=5 Male, n=5	24+4 to 27+5	0.5–1.1	0.2–7.1	1–34.5
Standard Neonatal Care	9	Female, n=3 Male, n=6	23+3 to 27+6	0.6–1.2	NA	NA

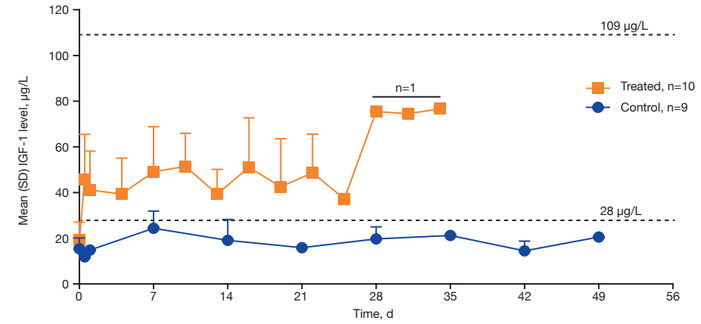
n, number of infants; GA, gestational age; NA, not applicable.
*Total duration of infusion, excluding the time for infusion interruptions.

Table 2. Proportion of Serum IGF-1 Measurements Within Target Range (28–109 µg/L)

IGF-1 Concentration, µg/L	Standard Neonatal Care n=9	rhIGF-1/rhIGFBP-3* n=10	rhIGF-1/rhIGFBP-3*,† n=9
<28, %	88.9	11.2	8.8
Total Within Target Range (28–109 µg/L), %	**11.1**	**88.8**	**91.2**
>109, %	0	0	0

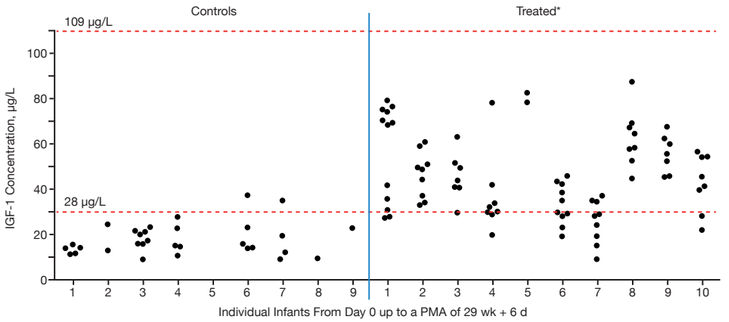
IGF-1, insulin-like growth factor 1.
*Predose data excluded.
†Excludes data from time points around infusion interruptions.

Figure 2. Serum IGF-1 Profile (Mean [SD]; Treated Versus Control Infants)



IGF-1, insulin-like growth factor 1.
Note: IGF-1 levels from treated infants on days 28, 31, and 34 were from only 1 infant, and therefore should be interpreted with caution.

Figure 3. Individual Serum IGF-1 Concentrations



IGF-1, insulin-like growth factor 1.
*Baseline (predose) values from treated infants are not included. One observation of 188 µg/L in 1 treated infant was excluded because of a sampling procedure error. All IGF-1 values for control infant #5 were below the lower limit of quantification and were not included in the population pharmacokinetic model (for control infants #8 and #9, only 1 IGF-1 measurement was above the lower limit of quantification). Treated infants #6 and #7 experienced frequent infusion interruptions.

CONCLUSIONS

- In this interim PK assessment of the ongoing Phase 2 Section D study:
  - Serum IGF-1 levels were within targeted physiological intrauterine levels for the majority of measurements in infants treated with a standardized rhIGF-1/rhIGFBP-3 dose of 250 µg/kg/24 h continuous IV infusion.
  - In contrast, the majority of measurements in infants receiving standard of care were below targeted levels.
- This analysis validates the population PK model and confirms the appropriateness of the designed dosing regimen for Section D.

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REFERENCES **1.** ClinicalTrials.gov. IGF-1/IGFBP3 Prevention of Retinopathy of Prematurity (NCT01096784). https://clinicaltrials.gov/ct2/show/NCT01096784. Accessed March 16, 2016. **2.** Löfqvist C, et al. *Arch Ophthalmol.* 2006;124(12):1711–8. **3.** Lassarre C, et al. *Pediatr Res.* 1991;29(3):219–25. **4.** Bang P, et al. *Pediatr Res.* 1994;36(4):528–36. **5.** Pérez-Muñuzuri A, et al. *Acta Paediatr.* 2010;99(4):519–25. **6.** Hellström A, et al. *Proc Natl Acad Sci U S A.* 2001;98(10):5804–8.