rhIGF-1/rhIGFBP-3 in Preterm Infants: A Phase 2 Randomized Controlled Trial

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Objective To investigate recombinant human insulin-like growth factor 1 complexed with its binding protein (rhIGF-1/rhIGFBP-3) for the prevention of retinopathy of prematurity (ROP) and other complications of prematurity among extremely preterm infants.

Study design This phase 2 trial was conducted from September 2014 to March 2016. Infants born at a gestational age of $23^{0/7}$ weeks to $27^{6/7}$ weeks were randomly allocated to rhIGF-1/rhIGFBP-3 (250 μg/kg/ 24 hours, continuous intravenous infusion from <24 hours of birth to postmenstrual age $29^{6/7}$ weeks) or standard neonatal care, with follow-up to a postmenstrual age of $40^{4/7}$ weeks. Target exposure was ≥70% IGF-1 measurements within 28-109 μg/L and ≥70% intended therapy duration. The primary endpoint was maximum severity of ROP. Secondary endpoints included time to discharge from neonatal care, bronchopulmonary dysplasia, intraventricular hemorrhage, and growth measures.

Results Overall, 61 infants were allocated to rhIGF-1/rhIGFBP-3, 60 to standard care (full analysis set); 24 of 61 treated infants achieved target exposure (evaluable set). rhIGF-1/rhIGFBP-3 did not decrease ROP severity or ROP occurrence. There was, however, a 53% decrease in severe bronchopulmonary dysplasia in the full analysis set (21.3% treated vs 44.9% standard care), and an 89% decrease in the evaluable set (4.8% vs 44.9%; $P = .04$ and $P = .02$, respectively) for severity distribution between groups. There was also a nonsignificant trend toward decrease in grades 3-4 intraventricular hemorrhage in the full analysis set (13.1% vs 23.3%) and in the evaluable set (8.3% vs 23.3%). Fatal serious adverse events were reported in 19.7% of treated infants (12/61) and 11.7% of control infants (7/60). No effect was observed on time to discharge from neonatal care/growth measures.

Conclusions rhIGF-1/rhIGFBP-3 did not affect development of ROP, but decreased the occurrence of severe bronchopulmonary dysplasia, with a nonsignificant decrease in grades 3-4 intraventricular hemorrhage. *(J Pediatr 2019;206:56-65).*

Trial registration ClinicalTrials.gov: NCT01096784.

Insulin-like growth factor-1 (IGF-1) is an important fetal growth regulator, with IGF-1 levels increasing with gestational age, particularly during the second and third trimesters of pregnancy.[1,2] After preterm birth, serum IGF-1 levels decrease rapidly and remain low for the first weeks of life relative to corresponding fetal levels in utero.[3,4]

Longitudinal studies have reported an association between lower serum IGF-1 levels at birth in extremely preterm infants and an increased risk of retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), neurodevelopmental

AE	Adverse event	PMA	Postmenstrual age
BPD	Bronchopulmonary dysplasia	rh	Recombinant human
ES	Evaluable set	ROP	Retinopathy of prematurity
FAS	Full analysis set	rhIGF-1/rhIGFBP-3	rhIGF-1 complexed with its binding protein rhIGFBP-3
IGF-1	Insulin-like growth factor-1	SAE	Serious AE
IVH	Intraventricular hemorrhage		
NEC	Necrotizing enterocolitis		

*List of additional members of the study team is available at www.jpeds.com (**Appendix 1**).

Detailed affiliations available at www.jpeds.com

Funded by Shire. Shire participated in the design of the study, the collection and analysis of data, and preparation of the clinical study report. D.L. and I.H-P. hold stock/stock options in Premalux AB, and received consulting fees from Shire. B.H. received consulting fees from Premacure AB and Shire. L.R. received consulting fees and research support from Shire. N.M. received consulting fees from Shire, and partial funding from the Department of Health's National Institute for Health Research Biomedical Research Centre's funding scheme at University College London Hospitals/University College London. K.B., F.B., J.H., O.M-N., M.vW., and L.S. received consulting fees from Shire. D.D. received consulting fees from Shire, and received consulting fees from Ipsen regarding other indications for IGF-1 therapies. N.B., A.T., M.H., E.J., A.M., and J-K.C. are employees of and own stock/stock options in Shire. M.T.'s university received consulting fees from Shire. A.H. holds stock/stock options in Premalux AB, and received consulting fees from Shire. C.D., A.M., P.R, and C.G. declare no conflicts of interest.

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impairment, and growth impairment.[5-9] Preclinical models also support associations between IGF-1 and complications of prematurity. In mice, IGF-1 absence delays normal retinal vascular development,[10] and recombinant human (rh)IGF-1 administration reduces risk of oxygen-induced retinopathy.[11] Additionally, rhIGF-1 administration in a hyperoxia-induced model of BPD decreases signs of disease in newborn rats.[12] Angiogenesis is an important process in both retinal and lung development,[10,13] and it may represent a common underlying mechanism affected by low IGF-1 levels in ROP and BPD.[10,14] In addition, IGF-1 is neuroprotective in rat pups affected by germinal matrix hemorrhage.[15] Together, these data suggest that ROP, BPD, brain injury/neurodevelopmental impairment, and growth restriction could be ameliorated by supplementing postnatal serum IGF-1 to corresponding fetal levels in extremely preterm infants.

We are investigating the use of rhIGF-1 complexed with its binding protein rhIGFBP-3 (rhIGF-1/rhIGFBP-3) to prevent complications of prematurity. Early clinical studies conducted between June 2010 and July 2013 demonstrated feasibility of rhIGF-1/rhIGFPB-3 infusion without safety concerns.[16,17] In the current study, we hypothesized that rhIGF-1/rhIGFBP-3 administration by continuous intravenous infusion would decrease the severity of ROP and other complications of prematurity.

Methods

This phase 2, multicenter, randomized, standard of care concurrent control, assessor-masked study evaluated the efficacy and safety of rhIGF-1/rhIGFBP-3 in decreasing the severity of ROP and other complications of prematurity (ClinicalTrials.gov: NCT01096784). The trial was conducted at 20 clinical sites in Italy, the Netherlands, Poland, Sweden, the United Kingdom, and the US. Study drug was administered from within 24 hours after birth until postmenstrual age (PMA) $29^{6/7}$ weeks, with follow-up evaluations up to a PMA of $40^{4/7}$ weeks (**Figure 1**). All infants' parents/guardians provided written informed consent. The study was reviewed/approved by relevant institutional review boards/independent ethics committees. Additional details on safety monitoring and interim analyses are provided in the Methods section of **Appendix 2** (available at www.jpeds.com). The study adhered to International Conference on Harmonization Good Clinical Practice guidelines and the tenets of the Declaration of Helsinki.

Patient Population

Infants with gestational age at birth of $23^{0/7}$-$27^{6/7}$ weeks were eligible for enrollment. Exclusion criteria included monozygotic twins, detectable gross malformation, known/suspected chromosomal abnormality, genetic disorder/syndrome, a persistent blood glucose level of <2.5 mmol/L or >10 mmol/L on the day of birth, anticipated need for administration of rh erythropoietin during treatment, a history of maternal diabetes requiring insulin, and clinically significant neurologic disease (germinal matrix hemorrhage allowed).

Randomization and Masking

Infants were allocated to rhIGF-1/rhIGFBP-3 or standard neonatal care (controls) in a 1:1. Dizygotic twins were randomized to the same study arm. Randomization was stratified by gestational age (<26, ≥26 weeks) centrally, using the permuted-block randomization approach. Investigators were not masked to treatment assignment, but certain assessments were masked. ROP stage was evaluated by 2 centralized independent pediatric ophthalmologists (and adjudicated by a third) and cranial ultrasound scans by a single central examiner.

Treatment Regimen

rhIGF-1/rhIGFBP-3 (mecasermin rinfabate, 50 μg/mL solution), a 1:1 molar ratio of the noncovalent complex of rhIGF-1 and rhIGFBP-3, was administered via continuous intravenous infusion through a central or peripheral line. Interruptions in the infusion of ≥1 hour were recorded. Standard care was determined based on the individual preterm infant's condition following local protocols. The Methods section in **Appendix 2** summarizes information on permitted and prohibited concomitant medications.

Dosing and Target IGF-1 Levels

rhIGF-1/rhIGFBP-3 dosing was standardized to 250 μg/kg/24 hours with the intention of maintaining serum IGF-1 levels within 28-109 μg/L, estimated as the normal physiologic intrauterine range based on prior literature.[18-20] The dose was decreased to 125 μg/kg/24 hours if the infant's serum IGF-1 levels exceeded the upper bound for 2 consecutively scheduled samples (plus a confirmatory sample 12 hours after the previous 2 consecutive samples). The Methods section in **Appendix 2** provides details on sampling intervals and methods for IGF-1 measurement.

Outcomes

The primary endpoint was maximum severity of ROP stage across all retinal examinations, based on retinal camera (RetCam, Clarity Medical Systems Inc, Pleasanton, California) images of the dilated fundus. ROP assessments were performed every 1-2 weeks between PMA 31 and 40 weeks. ROP was classified according to the International Classification.[21] For treatment, the recommendations of the Early Treatment for Retinopathy of Prematurity Cooperative Group were followed.[22] The International Classification is based on an ordinal scale with higher numbers indicating a more severe outcome: 0, 1, 2, 3, 3+, 4, and 5.

A prespecified key secondary endpoint was time between day of birth and day of discharge from neonatal care. Other secondary outcome measures included incidence of BPD and intraventricular hemorrhage (IVH) and assessment of growth (weight, length, and head circumference). BPD was assessed by need for oxygen use during the first 28 days after birth and by oxygen challenge testing at PMA of $36^{3/7}$ weeks.[23,24] Definitions of mild, moderate, and severe BPD were based on the National Institute of Child Health and Human Development criteria for preterm infants born before 32 weeks of gestation.[23] The presence of cerebral hemorrhage was assessed by cranial

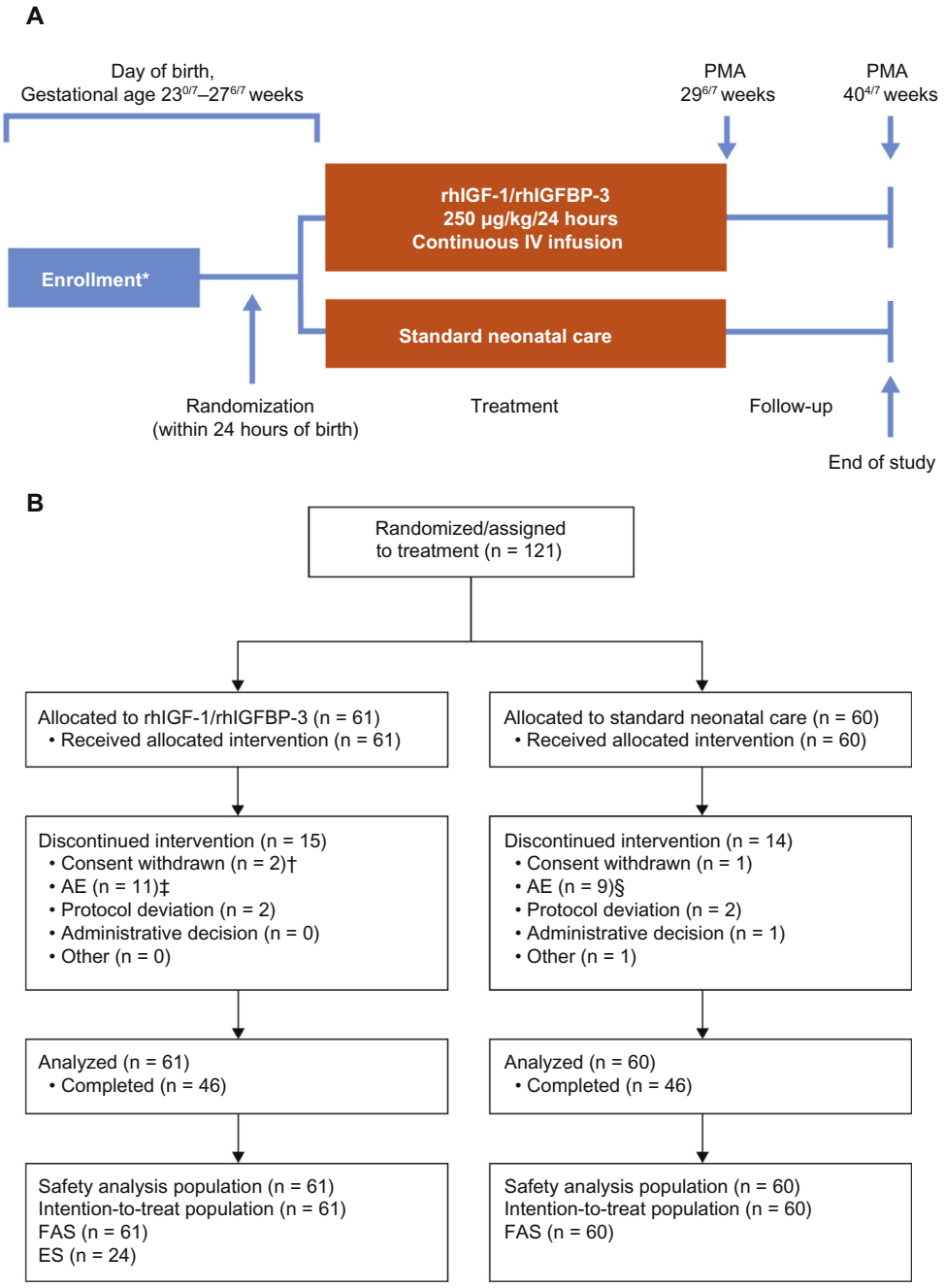

Figure 1. **A,** Study design and **B,** patient disposition. *Informed consent was obtained before birth or within 24 hours after birth. † One infant had an SAE with a fatal outcome, but the primary reason for discontinuation was withdrawal of consent. ‡ All infants discontinued owing to an SAE with fatal outcome. § Seven of 9 discontinuations were owing to SAEs with fatal outcome.

ultrasound scanning before study inclusion, at postnatal days 3, 7, 14, and 21 (±1 day), and at PMA 40 weeks (±4 days), and graded between 0 and 4 using the Papile/Bowerman scoring method.[25,26] Ultrasound images were graded by a single reader masked to study group. Brain volumetric measurements were performed on magnetic resonance images obtained at PMA 40 weeks and will be reported separately.

Safety Assessments

Adverse events (AEs) and serious AEs (SAEs) were recorded from receipt of informed consent until final study examination/sampling at PMA 40 weeks. Investigator Verbatim Terms describing AEs were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA; version 16.0) to MedDRA Preferred Terms (**Table I** [available at www.jpeds.com] for

reported Verbatim Terms for commonly observed AEs). The Methods section in **Appendix 2** describes other definitions and assessments of AEs.

Statistical Analyses

A sample size of 40 infants per treatment group (80 total) was estimated to provide 80% power (significance level, 5%) to demonstrate a statistically significant difference in distribution of ROP maximum severity between groups (primary endpoint). The ROP outcome stages in the current study were classified as 0, 1, 2, 3, and >3, which is the expected possible range of ROP stages that would be encountered in the study, based on analysis of Swedish infants screened for ROP from 2004 to 2008. Based on Swedish registry data,[27] the proportion of children with each ROP outcome for the control group is provided in **Table II** (available at www.jpeds.com). An estimated treatment effect among treated infants is also presented. The estimated treatment effect was calculated based on the following assumptions: For each outcome of the maximum severity of ROP stage, it is assumed that 25% of the children will not benefit from the treatment, 25% will have their maximum severity of ROP stage reduced by 1 level (eg, from 2 to 1), and 50% will have their maximum severity of ROP stage reduced 2 levels (eg, from 3+ to 2). The null hypothesis tested whether the distribution of maximum severity of ROP stage across all retinal examinations was the same for both treatment groups. Assuming a 30% nonevaluable/dropout rate, 120 infants (60 per group) were to be randomly assigned. The study was powered for the primary ROP endpoint only. A sample size of 80 evaluable infants was also estimated to provide adequate power for the key secondary endpoint (time to discharge from neonatal intensive care), but no power calculations were performed for BPD or IVH secondary endpoints. The Methods section in **Appendix 2** provides additional details on the statistical evaluation of all endpoints.

The intention-to-treat population included all enrolled infants assigned a randomization number. The full analysis set (FAS) was defined as all randomized infants receiving study drug or standard care. For rhIGF-1/rhIGFBP-3–treated infants, the FAS was the same as the intention-to-treat population because all randomized infants started treatment. The evaluable set (ES) included treated infants in the FAS who had ≥70% of serum IGF-1 levels within the target range (28-109 μg/L) and who received ≥70% of the intended duration of infusion of rhIGF-1/rhIGFBP-3 (overall infusion length excluding interruptions of ≥1 hour). For the standard care group, the FAS was also considered to be the ES. The safety population included randomized infants receiving study drug or standard care for whom ≥1 safety assessment was completed. The pharmacokinetic population included infants receiving study drug who had ≥1 blood samples drawn after administration.

Results

The first infant was enrolled September 19, 2014, and the last infant completed March 30, 2016. Overall, 121 infants were enrolled, of whom 29 did not complete the study (19 of 29 owing to death; **Figure 1**). Sixty-one infants received rhIGF-1/rhIGFBP-3 and 60 standard of care. Thirty-five of 61 treated infants (57.4%) and 32 of 60 control infants (53.3%) were born before 26 weeks gestational age (**Table III**). Mean average daily dose of rhIGF-1/rhIGFBP-3 was 248.1 μg/kg/24 hours (range, 131.1-250.0 μg/kg/24 hours); the total duration of exposure was 23.8 days (range, 0.1-45.3 days); the ratio of duration of exposure to expected duration (birth to $29^{6/7}$ weeks PMA) was 0.86 (range, 0.0-1.0); and the number of infusion interruptions of ≥1 hour was 4.0 per treated infant (range, 0-83 per treated infant). **Table IV** (available at www.jpeds.com) provides details on exposure by gestational age strata. Among treated infants, 52 of 61 received ≥70% of the expected treatment duration and 28 of 61 had ≥70% of IGF-1 levels within the target range. Overall target exposure (based on duration and IGF-1 level) was achieved for 24 of 61 treated infants (ES). The Results section in **Appendix 2** and **Figure 2** (available at www.jpeds.com) summarize information on attained serum IGF-1 levels.

Table III. Demographic characteristics and maternal/perinatal histories

Characteristics	Standard care (n = 60)	rhIGF-1/rhIGFBP-3 FAS (n = 61)	rhIGF-1/rhIGFBP-3 ES (n = 24)
Sex, no. (%)			
Male	39 (65.0)	39 (63.9)	14 (58.3)
Female	21 (35.0)	22 (36.1)	10 (41.7)
Gestational age group, no. (%)			
<26 wk	32 (53.3)	35 (57.4)	10 (41.7)
≥26 wk	28 (46.7)	26 (42.6)	14 (58.3)
Gestational age			
Mean, wk	$25^{4/7}$	$25^{4/7}$	$25^{7/7}$
±SD, d	±10	±8	±9
SGA, no. (%)	10 (16.7)	11 (18.0)	NA
Weight at birth			
Mean, kg	0.804	0.780	0.847
SD, kg	0.174	0.183	0.192
Race, no. (%)			
Asian	5 (8.3)	4 (6.6)	1 (4.2)
Black or African American	9 (15.0)	5 (8.2)	3 (12.5)
White	42 (70.0)	49 (80.3)	19 (79.2)
Other	4 (6.6)	3 (4.9)	1 (4.2)
Mode of delivery, no. (%)			
Vaginal	27 (45.0)	25 (41.0)	10 (41.7)
Cesarean	33 (55.0)	36 (59.0)	14 (58.3)
Maternal infections, no. (%)	14 (23.3)	11 (18.0)	3 (12.5)
Clinical chorioamnionitis, no. (%)	6 (10.0)	10 (16.4)	2 (8.3)
Maternal antibiotics, no. (%)	38 (63.3)	32 (52.5)	12 (50.0)
Antenatal steroids, no. (%)	60 (100.0)	61 (100.0)	24 (100.0)
Fertility therapy, no. (%)	9 (15.0)	10 (16.4)	2 (8.3)
IVF	7 (11.7)	10 (16.4)	2 (8.3)
Ovulation stimulation	2 (3.3)	0	0
Preterm labor, no. (%)	53 (88.3)	50 (82.0)	19 (79.2)
Preterm premature rupture of membranes, no. (%)	20 (33.3)	18 (29.5)	8 (33.3)
Preeclampsia, no. (%)	5 (8.3)	7 (11.5)	2 (8.3)

IVF, in vitro fertilization; *NA*, not available; *SGA*, small for gestational age.

Primary Endpoint: ROP

Considering the FAS, 25.5% of rhIGF-1/rhIGFBP-3–treated infants developed ROP stage ≥3 vs 18.0% of controls; there

Table V. Maximum severity of ROP stage, severity of BPD, and IVH by grades (FAS and ES)

	Standard care (n = 60)	rhIGF-1/rhIGFBP-3	
		FAS (n = 61)	ES (n = 24)
ROP			
Infants with ROP examination, no.	50	47	22
Infants with maximum severity of ROP of stage, no. (%)			
0	24 (48.0)	14 (29.8)	8 (36.4)
1	4 (8.0)	4 (8.5)	2 (9.1)
2	13 (26.0)	17 (36.2)	8 (36.4)
3	3 (6.0)	6 (12.8)	2 (9.1)
3+	6 (12.0)	6 (12.8)	2 (9.1)
4	0	0	0
5	0	0	0
≥3	9 (18.0)	12 (25.5)	4 (18.2)
Missing, no.*	10	14	2
P value†		.06	.24
BPD			
Infants with BPD assessment, no.	49	47	21
Severity of BPD, no. (%)			
No BPD	4 (8.2)	4 (8.5)	2 (9.5)
Mild	16 (32.7)	23 (48.9)	13 (61.9)
Moderate	5 (10.2)	9 (19.1)	5 (23.8)
Severe	22 (44.9)	10 (21.3)	1 (4.8)
Unable to determine	2 (4.1)	1 (2.1)	0
P value†		.04‡	.02‡
IVH			
IVH grade, no. (%)			
0-1	42 (70.0)	49 (80.3)	20 (83.3)
2	4 (6.7)	4 (6.6)	2 (8.3)
3	9 (15.0)	6 (9.8)	2 (8.3)
4	5 (8.3)	2 (3.3)	0
P value†		.14	.18

*The majority (11/12 treated [FAS] and 5/7 control infants) of infants who died in this study had died before the first scheduled ROP assessment at week 31. Other reasons for not being evaluated included withdrawal of consent and difficulties in capturing quality RetCam images.
†Cochran–Mantel–Haenszel row mean score test.
‡Difference in the distribution of BPD severity seen between the rhIGF-1/rhIGFBP-3 (FAS or ES) and standard care groups is statistically significant.

was no statistically significant difference between the 2 groups in distribution of maximum severity of ROP ($P = .06$; **Table V**). In the ES, similar proportions of treated vs control infants had ROP of stage ≥3 (18.2% vs 18.0%, respectively; $P = .24$ for severity distribution between groups). A breakdown by gestational age strata for ROP/other endpoints is presented in **Table VI**, **Table VII**, and **Table VIII** (available at www.jpeds.com). The number of infants who received treatment for ROP was similar between treatment groups: standard of care, 7 (all laser therapy); rhIGF-1/rhIGFBP-3, 7 (6 laser therapy, 1 anti-vascular endothelial growth factor only).

Post hoc analysis of IGF-1 levels by ROP severity (<3, ≥3) across weeks after birth showed a clear separation for mean IGF-1 profiles between treated and control infants; in the rhIGF-1/rhIGFBP-3 group, an association of higher serum IGF-1 with less severe ROP was observed (**Figure 3**, A).

Key Secondary Endpoint: Time to Discharge From Neonatal Care

In the overall population (FAS), the median time to discharge was 82 days (range, 55-115 days) in the rhIGF-1/rhIGFBP-3 group and 74 days (range, 51-107 days) among controls. The difference between groups was not statistically significant ($P = .37$). In the ES, median time to discharge was 74 days in both study arms ($P = .43$).

Secondary Endpoints

A statistically significant difference in distribution of BPD severity was observed between groups (FAS, $P = .04$; ES, $P = .02$; **Table V**), with an apparent shift toward milder BPD cases with treatment. In the FAS, 21.3% of infants with BPD assessments (10/47) in the rhIGF-1/rhIGFBP-3 group had severe BPD vs 44.9% of controls (22/49). The difference between treatment groups was more pronounced in the ES, with 4.8% of treated infants (1/21) with severe BPD vs 44.9% of controls.

The BPD analyses did not include the 19 all-cause deaths that occurred in the study, including 12 deaths (20%) in the rhIGF-1/rhIGFBP-3 group and 7 deaths (12%) in the standard care group. We conducted post hoc analyses for BPD that included all-cause deaths during the study period. In the additional analyses, deaths were grouped with severe BPD. These analyses showed that, when deaths were included, the trend for a decrease in severe BPD among treated infants remained (37.3% in rhIGF-1/rhIGFBP-3 group vs 51.8% in the standard of care group **Table IX** [available at www.jpeds.com]).

In this study, we observed a shift in the distribution of severity of BPD, which was most evident in the difference between groups in the percentage of subjects with severe BPD. If moderate cases were combined with severe cases and deaths, 52.5% of the rhIGF-1/rhIGFBP-3 group (31/59) and 60.7% of the standard care group (34/56) had BPD. When early deaths (within the first 14 days) were excluded, as suggested by Higgins et al in the 2016 National Institute of Child Health and Human Development [NICHD] workshop,[28] 31.5% of the rhIGF-1/rhIGFBP-3 group (17/54) vs 50.0% of the standard of care group (27/54) had severe BPD.

Post hoc analysis of IGF-1 levels by BPD severity (mild, moderate, severe) across weeks after birth showed a clear separation for mean IGF-1 profiles between treated and control infants, with a higher serum IGF-1 associated with less severe BPD in the treated group (**Figure 3**, B).

A smaller proportion of infants in the rhIGF-1/rhIGFBP-3 group had severe IVH (grades 3-4) than among controls (**Table V**): FAS, 13.1% vs 23.3%, respectively; ES, 8.3% vs 23.3%, respectively (not statistically significant). The numbers of IVH events were too small to explore an exposure-response relationship between IGF-1 levels and IVH grade.

rhIGF-1/rhIGFBP-3 treatment did not affect rates of change of length, weight, or head circumference compared with standard of care (**Figure 4** [available at www.jpeds.com]). Similar results were seen in both the FAS and ES.

Safety

All infants had ≥1 treatment-emergent AEs, with the exception of 1 infant in the rhIGF-1/rhIGFBP-3 group. For 13.1% of treated infants (8/61), treatment-emergent AEs were considered possibly related to study drug. The most common events overall (related or unrelated) were patent ductus arteriosus

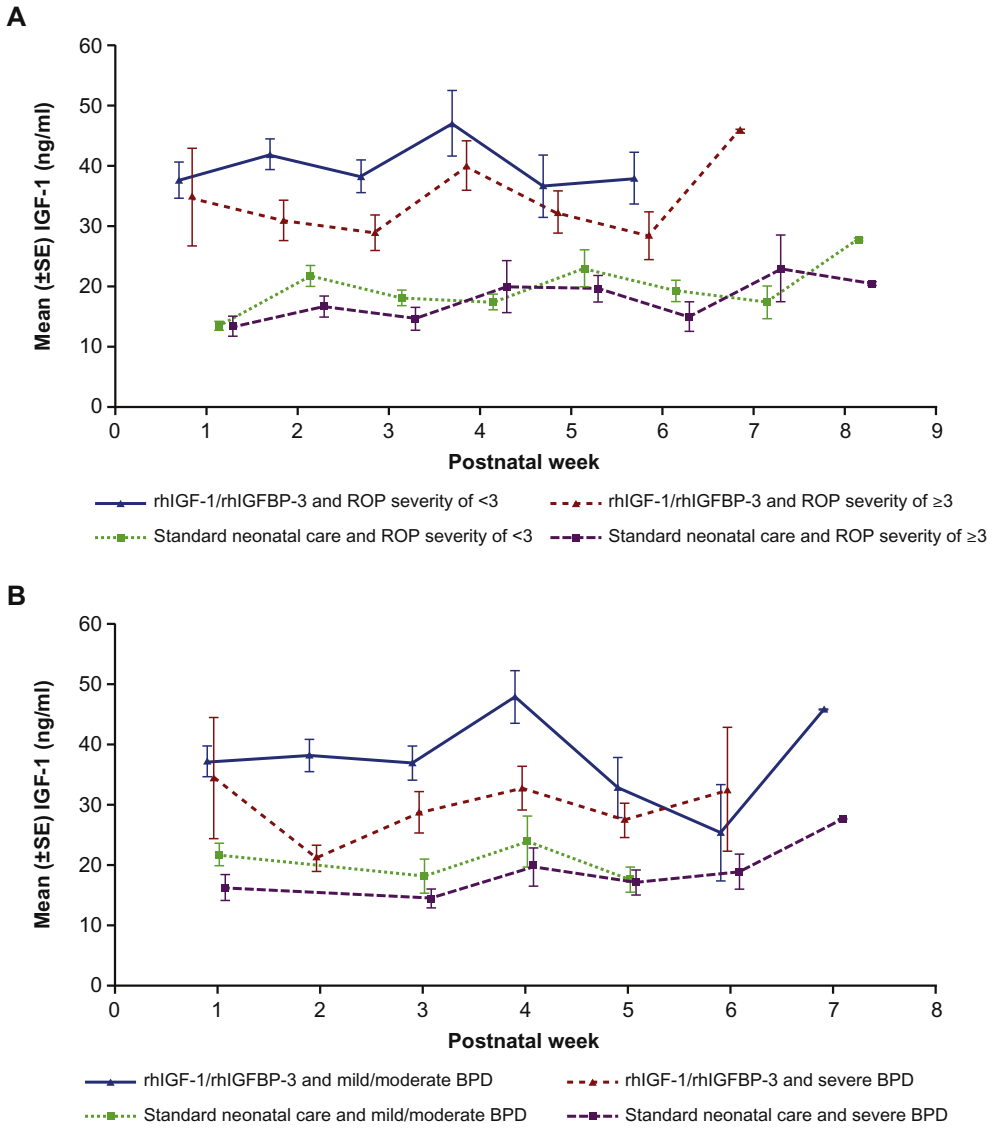

Figure 3. IGF-1 levels by **A,** ROP severity* and **B,** BPD severity† by postnatal week. *Mean (±SE) serum IGF-1 levels and ROP severity (<3, ≥3) in the rhIGF-1/rhIGFBP-3 and standard neonatal care groups by postnatal week. †Mean (±SE) serum IGF-1 levels and BPD severity (mild, moderate, or severe) in the rhIGF-1/rhIGFBP-3 and standard neonatal care groups by postnatal week. Note: If an infant had multiple IGF-1 levels in a day, then IGF-1 level was averaged for the day.

(90.2% of treated infants vs 85.0% of controls) and neonatal anemia (75.4% vs 73.3%, respectively; **Table X**; available at www.jpeds.com). Additionally, 78.7% of treated infants (48/61) and 61.7% of control infants (37/60) had SAEs.

Fatal SAEs were reported in 19.7% of treated infants (12/61) and 11.7% of control infants (7/60); none were considered treatment related (**Table XI**). The imbalance of deaths was concentrated in the subgroup born at a gestational age of <26 weeks and driven by 1 iatrogenic death owing to a misplaced umbilical catheter (which caused intra-abdominal hemorrhage leading to multiorgan failure), 1 infant with severe respiratory distress with onset before study drug infusion, and 3 more cases of necrotizing enterocolitis (NEC). Overall, NEC AEs (fatal and nonfatal) were balanced between groups (6 infants [9.8%] in the treated group vs 5 infants [8.3%] in the standard care group). Further explorations revealed no apparent differences in modes of delivery, transfusions, sepsis events, antibiotic/probiotic use, or nutrition between infants with NEC who died and those who survived. In addition to NEC (which can be misclassified as a bowel perforation), 1 infant who died in the rhIGF-1/rhIGFBP-3 group had an intestinal perforation and 2 infants who died in the standard care group had intestinal perforations. Overall, including nonfatal cases, there was 1 case of intestinal perforation in the rhIGF-1/rhIGFBP-3 group, compared with 5 in the standard of care group. A full summary of safety data, including severe AEs,

Table XI. Fatal treatment-emergent SAEs (preferred terms)

	Standard care		rhIGF-1/rhIGFBP-3	
	Gestational age <26 wk	Gestational age ≥26 wk	Gestational age <26 wk	Gestational age ≥26 wk
Total deaths, no.	4	3	8	4
Days since birth				
≤7	2 IVH Neonatal respiratory failure	0	3 Neonatal respiratory failure Pulmonary hemorrhage IVH	2 Pulmonary hypertension *Escherichia* sepsis*
>7 and ≤14	0	0	0	0
>14 and ≤28	2 Renal failure neonatal† *Citrobacter* sepsis	1 Staphylococcal sepsis‡	4 Sepsis neonatal§ Renal failure neonatal† NEC neonatal NEC neonatal	1 Renal failure neonatal†
>28	0	2 Neonatal respiratory failure Intestinal obstruction	1 Neonatal respiratory failure¶	1 NEC neonatal

*Early-onset sepsis owing to *Escherichia coli*.
†Verbatim Terms under the Preferred Term "renal failure neonatal" were "renal insufficiency" and "acute renal failure."
‡Catheter-related sepsis owing to *Staphylococcus epidermidis*.
§Sepsis owing to *Enterococcus faecalis*, *Staphylococcus aureus*, and *Staphylococcus haemolyticus*.
¶Verbatim terms under the preferred term "neonatal respiratory failure" were "respiratory insufficiency" and "respiratory failure."

and AEs of interest is provided in the Results section in **Appendix 2**.

Discussion

This study did not meet the primary endpoint of reducing maximum severity of ROP. However, there was a marked decrease in the proportion of rhIGF-1/rhIGFBP-3–treated infants who developed severe BPD, and a shift in patterns of BPD severity to milder cases; a similar trend was observed for IVH but was not statistically significant. rhIGF-1/rhIGFBP-3 was well-tolerated in this study; there were no safety signals. The overall results of this study support continued evaluation of rhIGF-1/rhIGFBP-3 for the prevention of complications of prematurity in extremely preterm infants.

Although a trend toward higher serum IGF-1 in rhIGF-1/rhIGFBP-3–treated infants with no or lower stages of ROP was observed, the reason for lack of overall effect on ROP is not clear. It may be that the dosing regimen of rhIGF-1/rhIGFBP-3 requires further optimization. Alternatively, practice variability in RetCam assessments may have limited the observed treatment effect. A further consideration is the variation between sites in target oxygen saturation measures and compliance with these levels. This consideration is particularly important in light of findings from 5 landmark clinical trials, published shortly before commencement of the current study, which studied the effects of targeting lower (85%-89%) vs higher (91%-95%) oxygen saturation targets on neurodevelopmental impairment and severe ROP in extremely preterm infants.[29-31] The US Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) associated a lower oxygenation target of 85%-90%, as compared with a higher target of 91%-95%, with increased mortality and decreased ROP among survivors.[29] Combined findings from the Benefits of Oxygen Saturation Targeting II (BOOST II) trials,[30] conducted in the UK, Australia, and New Zealand, were largely consistent with the SUPPORT study. The investigators reported increased mortality in the lower oxygen target group vs the higher (among infants with revised oximeter software) and a lower rate of severe ROP in the lower saturation range vs the higher (among infants in the total study population).[30] Conversely, the Canadian Oxygen Trial (COT) found no significant difference in mortality or the incidence of severe ROP between the lower and higher oxygen target groups.[31] Findings from the SUPPORT and BOOST II trials led to changes in neonatal clinical practice, where the risk of ROP needed to be considered against the risk of increased mortality, with the result that many centers across countries adopted higher oxygen target ranges. More recent studies have reported increased rates and severity of ROP among extremely preterm infants after changing from lower to higher oxygen target ranges.[32,33] It is possible that higher oxygen target ranges used in centers in the current study may have affected the observed incidences of ROP in the study population.

The key secondary endpoint of time to discharge from neonatal care also was not statistically different between groups. However, it is difficult to draw conclusions from these data because assessment of length of stay in intensive care is easily confounded. There also was a lack of effect of rhIGF-1/rhIGFBP-3 on growth measures, which could have been confounded by nutritional differences across sites; unfortunately, nutrition data were not recorded consistently, precluding further analysis of a potential effect.

By contrast, the shift in severity distribution of BPD was marked and suggests a hypothesis-generating trend with higher serum IGF-1. The rate of IVH events was too low to evaluate correlations with IGF-1 levels, but a similar trend toward a decrease in grades 3-4 IVH in the ES vs the FAS was observed. Although it remains unclear why such a marked effect was seen

for BPD relative to ROP, these observations support the hypothesis that increasing serum IGF-1 levels can decrease the severity of complications of prematurity.

An analysis of the achieved serum IGF-1 levels indicates that attainment of target levels could be further optimized to potentially improve outcomes. An interim pharmacokinetic analysis in the first 10 treated infants supported the appropriateness of the 250 μg/kg/24 hours dose to achieve IGF-1 target levels.[20] However, in the treated population, although the proportion of IGF-1 measurements within target was substantially greater than among controls, fewer than one-half of infants (28/61 [45.9%]) achieved ≥70% of IGF-1 measurements within the target range (see the Results section in **Appendix 2**). It is possible that the slightly lower than anticipated target attainment could relate to technical aspects of drug administration or that intercurrent proinflammatory states could have led to fluctuations in IGF-1 levels.[34] Alternatively, these observations may point to a need for further dose optimization.

The observed safety profile of rhIGF-1/rhIGFBP-3 was encouraging. There was an imbalance in deaths between the treatment arms concentrated in the subgroup with a gestational age of <26 weeks; however, careful evaluation of the causes of death by an independent data monitoring committee did not raise safety concerns (see the Results section in **Appendix 2**). With regard to other safety considerations, despite the duration of intravenous infusion, data collected to date across rhIGF-1/rhIGFBP-3 clinical trials have shown no signs of an increase in pathogen-confirmed sepsis. Also in the current study, the proportion of infants with hypoglycemia was similar between groups. Of note, rhIGF-1/rhIGFBP-3 was associated with a lower incidence of hyperglycemia relative to standard care, suggesting possible improvements in glycemic control. A previous phase of the study (B/C) found that rhIGF-1/rhIGFBP-3 was well-tolerated in extremely preterm infants and that the incidence of AEs was similar for infants treated with rhIGF-1/rhIGFBP-3 vs control infants.[35] Further, consistent with the current trial, rates of hypoglycemia were similar between groups in the phase B/C study. These outcomes will be of interest for further investigation.

The limitations of this study included the smaller than anticipated number of infants eligible for inclusion in the ES, albeit an arbitrary a priori definition. Another limitation was the randomization by gestational age centrally and not by study site, which resulted in an imbalance between gestational age strata at high enrolling sites, and may have been an additional confounder. Additionally, there were technical challenges to performing certain assessments (eg, RetCam) and variability of practices across and within sites. The analysis of AEs was limited by some reporting inconsistency, largely owing to a lack of international consensus on defining and classifying AEs in infants based on their severity. A further consideration is that infants who died were not included in the analyses, and this factor may have had an impact on our findings related to the degree of difference in severe BPD between the 2 groups. However, post hoc analyses showed similar, although attenuated, results when all-cause death was included with severe BPD as an outcome. Although the prevalence of ROP, BPD, and IVH was comparable with the observed prevalence in the extremely preterm population,[36,37] the sample size was relatively small. The latter limitation obviously precludes the evaluation of a possible confounding effect of mortality on differences in respiratory morbidity between study groups at a gestational age of 36 weeks. A larger investigation that examines a higher dose IGF-I with more standardized and harmonized approaches to safety assessments is needed to clarify this issue, including the evaluation of treatment effects on NEC. Preclinical models indicate that IGF-I supplementation and subsequent enhancement of vascular endothelial growth factor receptor-2 signaling may have a preventive effect on development of NEC.[38-42] Higher levels of plasma IGF-1 were also associated with reduced incidence of NEC in a prospective analysis of very low birth weight infants in the NIRTURE study.[43] The administration of IGF-1/IGFBP3 would not be expected to increase the risk of NEC.

Of note, there were additional protocol limitations associated with the methodology used to assess presence of IVH (a single reader of cranial ultrasound examinations, grading only by the Papile/Bowerman method[25,26]), which may have impacted the frequency of the various grades seen in both treatment groups. Post hoc analyses are ongoing using an adjudicated reader and 2 additional scoring methods[44,45] for the assessment of ultrasound scans to evaluate whether the frequency of the various grades varied as a function of the scoring method; details of the comparison (also including magnetic resonance imaging data) will be reported separately.

Based on the results of this study and given the clear unmet need for therapies to decrease the overall morbidity burden in extremely preterm infants,[46-49] continued investigation of rhIGF-1/rhIGFBP-3 for the prevention of complications of prematurity is planned in a larger clinical trial. The protocol for this study is in development, with the prevention of the onset of chronic lung disease (indicated by reductions in respiratory complications) at a corrected age of 12 months as the primary endpoint, and a decrease in the severity of BPD at a PMA of 36 weeks and IVH severity at a PMA of 40 weeks as separate key secondary endpoints. Of importance, long-term outcomes after short-term exposure to rhIGF-1/rhIGFBP-3 also are being investigated in an extension study (PEDAL; NCT02386839) over 5 years. ■

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Appendix 2

Methods

Safety Monitoring. A clinical study monitor ensured that the investigation was conducted according to protocol design and regulatory requirements through frequent site visits and communications. Infant safety was monitored on a continuous basis until the last infant completed the last scheduled study visit/assessment, and quarterly safety review meetings were held throughout the study. Safety data collected during the trial were reported annually to competent authorities in the form of a Development Safety Update Report. Additionally, an independent data monitoring committee provided an ongoing review and assessment of safety data. A special data monitoring committee meeting was to be convened if the safety-related stopping rules (ie, if a death occurred that was considered possibly or probably related to the study drug) were met.

Interim Analyses. Two interim analyses were planned and conducted. The first was an analysis of dosing/target attainment conducted when 10 treated infants had completed the rhIGF-1/IGFBP-3 dosing phase of the study (reported previously by Chung et al[1]). In the second, a conditional power analysis was performed on unmasked data when 60 infants had completed the study or withdrew early. The analysis was performed by an external independent statistician to assess the appropriateness of the sample size and assumptions made regarding the distribution of the maximum severity of ROP.

Concomitant Medications. Predefined medications (including hydrocortisone, betamethasone, dexamethasone, ibuprofen, dopamine, dobutamine, epinephrine, budesonide, furosemide, nitric oxide, Curosurf/other surfactants, indomethacin, and other medications given to treat AEs) and

procedures administered to infants from time of informed consent through to a PMA of $40^{4/7}$ weeks were regarded as permitted. Treatment with fresh frozen plasma, which is associated with a short-term increase of serum concentrations of IGF-1,[2] was permitted and recorded. Anti-vascular endothelial growth factor medication and rh erythropoietin were prohibited. Delivery of parenteral/enteral nutrition (including glucose) was performed according to local guidelines.

IGF-1 Blood Sampling. Blood samples for IGF-1 measurement were obtained at baseline (predose), 12 hours ± 30 minutes, and 24 hours ± 30 minutes after the infusion started, then every 72 ± 1 hours until a PMA of $29^{6/7}$ weeks, and then 1 hour ± 30 minutes after the infusion stopped for treated infants. Controls were tested at baseline (day of birth), 12 hours ± 30 minutes, 24 hours ± 30 minutes, and then every 168 ± 1 hours after baseline until a PMA of $29^{6/7}$ weeks. Additional sampling occurred at PMA 32, 36, and 40 weeks. IGF-1 was determined locally by a validated ELISA (Mediagnost GmbH, Reutlingen, Germany), and in a central laboratory by radioimmunoassay (PPD Laboratories, Richmond, Virginia).[3]

Safety Assessments. Hypoglycemia was defined within the trial as plasma glucose levels of <2.5 mmol/L measured during predefined schedules of blood glucose monitoring (see Blood Glucose Monitoring section), and from blood glucose measurements performed on clinical indication. Hyperglycemia was defined as plasma glucose levels of >10 mmol/L. Echocardiography was interpreted by a pediatric cardiologist to define presence of clinically significant patent ductus arteriosus on postnatal days 2 and 4, and according to clinical judgment after these time points. All infants were assessed for tonsillar hypertrophy by visual examination of their tonsils during a weekly physical examination and at term age (PMA of 40 weeks) by a pediatric specialist.

Blood Glucose Monitoring.

rhIGF-1/rhIGFBP-3 Group. For infants who were fed every 2 hours or who were fed intravenously or through continuous enteral feed, blood glucose measurement was performed every 4 hours during the first 72 hours (days 1-3) after starting infusion with rhIGF-1/rhIGFBP-3. For infants who were fed every 3 hours, blood glucose was measured every 3 hours during the first 72 hours (days 1-3) after starting infusion with rhIGF-1/rhIGFBP-3. During days 4-7, blood glucose was measured every 6 hours for those infants who were fed either every 2 or every 3 hours. After the first 7 days of the infusion, blood glucose was analyzed twice daily until the completion of infusion (PMA of $29^{6/7}$ weeks). Thereafter, blood glucose was measured weekly until the end of the study. If blood glucose was <3 mmol/L during ongoing rhIGF-1/rhIGFBP-3 infusion and more frequent monitoring was deemed necessary based on the clinical judgment of the investigator, a blood glucose sample was then taken every hour until a blood glucose of ≥3 mmol/L was reached. Clinical sites had specific protocols in place to monitor hypoglycemia.

Standard Neonatal Care Group. Blood glucose was analyzed every 6 hours for the first 7 days. Thereafter, it was analyzed twice daily until a PMA of $29^{6/7}$ weeks, provided that blood was available for sampling. If blood was not available, the sample collection interval was increased. After PMA $29^{6/7}$ weeks, blood glucose was measured weekly until the end of the study.

Statistical Analyses. The primary endpoint between the 2 groups was analyzed using a generalized Cochran–Mantel–Haenszel row means score statistic with modified ridit scores adjusting for gestational age strata. This statistical test generates an estimate of an association between an exposure and an outcome after adjusting for or taking into account confounding factors. The sample size of 80 evaluable infants also was to provide adequate power for the key secondary endpoint of time to discharge from neonatal care, for which the difference between the 2 treatment groups was tested using the stratified version of the Wilcoxon rank-sum test and adjusted for gestational age status. In the event of death, time to discharge was imputed using the median value of all infants with available data within each gestational age strata. The comparison between treatment groups for ordered category of BPD (absent, mild, moderate, severe) at PMA 36 weeks was made using Cochran–Mantel–Haenszel row mean score statistics with modified ridit scores adjusting for gestational age strata. The grade of the hemorrhage (grades 1-4) was summarized descriptively by treatment group and gestational age strata. The difference in the distribution of IVH severity seen between the rhIGF-1/rhIGFBP-3 (FAS or ES) and standard care groups was analyzed in a post hoc analysis using Cochran–Mantel–Haenszel row mean score statistics. Weight, length, and head circumference were analyzed separately, using a linear mixed-model repeated measurement analysis over all postbaseline visits, with change from baseline in each parameter as the outcome variable. The model included treatment time (days), treatment by time interaction, gestational age strata as a fixed effect, infant as a random effect, and baseline value as covariate. Time (days) was calculated relative to the date of the baseline assessment and was used as a continuous covariate.

Results

Serum IGF-1 Levels. For rhIGF-1/rhIGFBP-3–treated infants, 66.2% of IGF-1 measurements were within the targeted physiological intrauterine range (28-109 μg/L) vs 6.3% for the standard care group (predose data and data after the end of the final infusion were excluded). Very few IGF-1 measurements (1.5%) in treated infants were above the upper bound of the targeted range. **Figure 2** shows the mean (SD) serum IGF-1 concentrations over the duration of the study in both the rhIGF-1/rhIGFBP-3 and standard care groups; mean concentrations were within target range during the infusion period for treated infants and below range for the standard care group. The onset of endogenous IGF-1 production was estimated between weeks 30 and 32 (corresponding approximately with cessation of treatment), after which both groups had mean IGF-1 levels within the target range.

Additional Safety Results.

Severe AEs. In the rhIGF-1/rhIGFBP-3 vs standard care groups, 73.8% of infants (45/61) vs 65.0% of infants (39/60) experienced SAEs, respectively. Only 1 treated infant (1.6%) had 2 SAEs considered possibly related to study drug (1 AE of IVH and 1 separate AE of apnea).

Discontinuations Owing to AEs. A total of 20 infants (11 [18%] in the rhIGF-1/rhIGFBP-3 group and 9 [15%] in the standard care group) discontinued the study owing to treatment-emergent AEs, which were fatal SAEs in 90% of infants (18/20). One additional infant in the treated group had an SAE with fatal outcome, but the primary reason for discontinuation was withdrawal of consent.

AEs of Interest. The frequency of pathogen-confirmed sepsis was similar between the rhIGF-1/rhIGFBP-3 and standard care groups (65.9% vs 67.4%, respectively). Coagulase-negative staphylococcal sepsis was reported in similar percentages of infants in each group: 36.4% vs 37.2% in the rhIGF-1/rhIGFBP-3 and standard care groups, respectively. Hypoglycemia occurred in a similar proportion in each group: 29.5% of infants (18/61) in the rhIGF-1/rhIGFBP-3 group had AEs of hypoglycemia (considered possibly related to treatment for 4 infants) vs 31.7% (19/60) in the standard care group. Additionally, 39.3% of infants (24/61) in the rhIGF-1/rhIGFBP-3 group had AEs of hyperglycemia vs 48.3% (29/60) in the standard care group (**Table VIII**). There were no cases of intracranial hypertension or tonsillar hypertrophy in either group.

References

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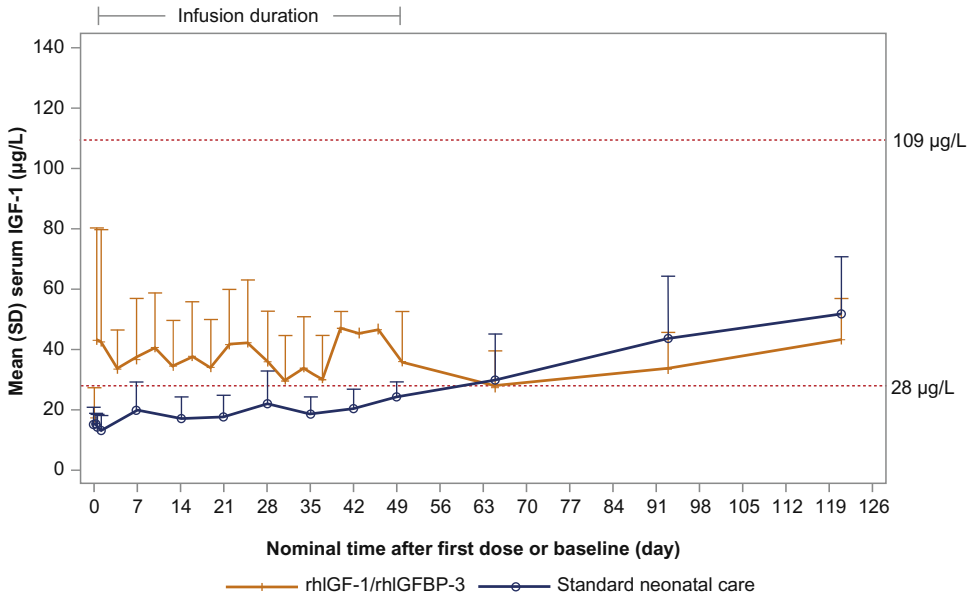

Figure 2. Mean (SD) serum IGF-1 concentrations over time in infants in the standard neonatal care and rhIGF-1/rhIGFBP-3 groups (n = 121).

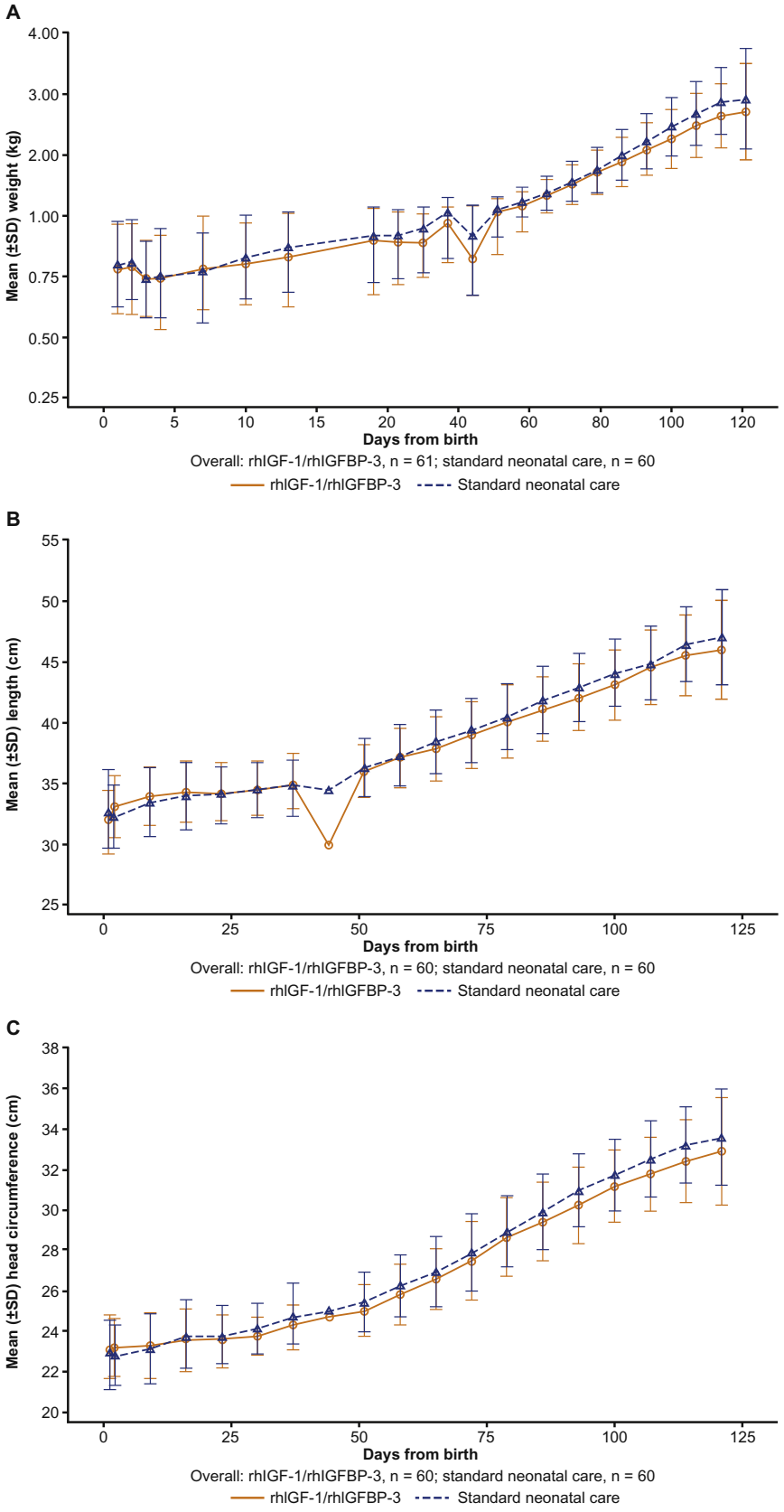

Figure 4. **A,** Average weight, **B,** length, and **C,** head circumference by treatment group (FAS).

Table I. Verbatim terms reported in relation to common treatment-emergent AEs

AE/preferred term	Verbatim terms
Patent ductus arteriosus	"Persistent ductus arteriosus," "patent ductus arteriosus that requires treatment," "patent ductus arteriosus that need treatment," "PDA," "large PDA," "large patent ductus arteriosus," "patent ductus arteriosus, moderately hemodynamically significant," "patent ductus arteriosus, minor hemodynamically significant," "PDA of 3.4 mm detected on first ECHO," "reopening of ductus arteriosus," "reopening of patent ductus arteriosus," "big patent ductus arteriosus," "small patent ductus arteriosus," "patent ductus arteriosus, hemodynamically significant," "patent ductus arteriosa without any clinical significance," "small PDA again," "homonymic significant patent ductus arteriosus," "patent ductus arteriosus (PDA)," "small closing patent ductus arteriosus," "patent ductus arteriosus 2.1 mm," "patent ductus arteriosus with shunt pulsating flow pattern," "PDA prior to treatment," "patent ductus arteriosus from echocardiogram," "PDA observed on echocardiogram"
Anemia neonatal	"Anemia," "anemi," "anemia requiring transfusion," "anaemia," "anaemia of prematurity," "anemie," "tired, pale, listless due to anemia," "anaemia needed transfusion," "neonatal anaemia," "anemia of prematurity," "symptomatic anemia"
Neonatal respiratory distress syndrome	"Respiratory distress syndrome," "RDS," "respiratory distress," "hyaline membrane disease," "infant respiratory distress syndrome," "respiratory distress/hyaline membrane disease"
Jaundice neonatal	"Jaundice," "jaundiced," "neonatal jaundice," "icterus," "jaundice requiring phototherapy," "intermittent jaundice," "jaundice requiring treatment with phototherapy"
Infantile apneic attack	"Apnéas," "apneas," "apnéa," "apnea of prematurity," "apnea," "apnoea," "prematurity apnea," "apnoea crisis," "recurrent apnea," "recurrent apnoeas," "sudden and severe apnoea," "severe apnoea," "apnea episode," "apnea neonatal," "crisis of apnea"
Neonatal hypotension	"Hypotension," "low blood pressure," "hypotension (low blood pressure)," "systemic hypotension," "hypotensive (mean 21)," "intermittent hypotension," "hypotension (intermittent)," "hypotension, MAP 26"
Hyperglycemia	"Hyperglycemia," "hyperglycaemia," "hyperglucemia," "hyperglicemia," "hyperglycemia (intermittent)," "hyperglycemia, blood glucose 26 mmol, insulin infusion commenced," "hyperglycemia, blood glucose 58 mmol stat dose of insulin given," "hyperglycemia, blood glucose 45 mmol, insulin infusion concentration and dose increased"
Neonatal hyponatremia	"Hyponatremia," "hyponatremi," "low natrium," "hyponatriemia," "hyponatraemia," "mild hyponatremia," "severe hyponatremia"
Sepsis neonatal	"Suspected sepsis, blood cultures negative," "suspected septicemia," "suspected sepsis," "sepsis," "sepsis (blood culture negative)," "sepsis due to Enterococcus faecalis, Staphilococcus aureus, and Staphilococcus haemoliticus," "late onset neonatal sepsis," "late onset sepsis," "suspected sepsis not confirmed (CRP negative)," "suspected sepsis (blood culture and tracheal aspiration were negative, the adverse event was not confirmed," "suspected sepsis (clinical instability, elevation of CRP but blood and CSF cultures were negative)," "clinical sepsis (desaturations, elevation of CRP but blood culture was negative)," "suspected sepsis (recurrent apneas but blood culture and CRP were negative)," "suspected sepsis (blood culture was negative) for clinical instability (desaturations)," "sepsis (etiology unknown, blood culture was negative)," "clinical sepsis (PCR, blood culture negative)," "possibility to sepsis, no bacteria found in blood culture," "presumed sepsis (blood cultures negative after 6 days)," "sepsis presumed, no growth on blood culture or nasopharyngeal aspirate," "presumed sepsis, blood cultures negative," "sepsis of unknown etiology," "suspected sepsis, not confirmed," "suspected sepsis, not confirmed, etiology unknown," "neonatal septicemia, staphylococcus capitis grown from blood culture," "possible sepsis, cultures negative," "suspected sepsis, rising infection parameters, no bacteria detected in cultures," "early onset sepsis," "presumed long line sepsis, cultures negative," suspected sepsis due to severe desaturations," "suspected sepsis (CSF and blood cultures were negative)," "clinical sepsis, etiology unknown (cultures remained negative)," "sepsis presumed in line with routine neonatal care of extreme premature baby, antibiotics stopped when sepsis ruled out," "sepsis suspected and therefore treated with antibiotics but blood cultures negative after 6 days," "sepsis suspected, blood cultures showed no growth after 6 days incubation," "sepsis (no growth from blood cultures after 6 days incubation, no other source of infection suspected)," "sepsis suspected, no sepsis confirmed," "suspected sepsis (in line with routine preterm neonatal care) (blood cultures negative after 6 days) antibiotics stopped," "presumed sepsis, no confirmed on blood cultures," "central line associated blood stream infection from PICC line," "clinical sepsis (bloody stool), and blood cultures negative"
Hypoglycemia neonatal	"Hypoglycemia," "asymptomatic hypoglycaemia," "hypoglicemia," "hypoglycaemia," "hypoglycaemia as peripheral venous line delivering TPN was leaking," "hypoglycaemia (intermittent)," "hypoglycaemia, asymptomatic," "hypoglycaemia, 1.8," "hypoglycaemia, 1.6," "hypoglycaemia (1.0 mmol/l at 6 pm)"
Metabolic acidosis	"Metabolic acidosis," "metabolic acidosis on blood gas"
Staphylococcal sepsis	"Septicemia: stafyloccus epidermidis," "staphylococcus epidermis in the blood," "coagulase negative staphylococci septicaemia," "sepsis (staphylococcus epidermidis)," "sepsis due to Bacillus Amyloliquefaciens and Staphilococcus Epidermidis," "sepsis due to staphylococcus epidermidis," "sepsis by staphylococcus aureus," "sepsis by oxacillin-resistant staphylococcus epidermis," "sepsis by Staphilococcus Aureus," "sepsis by Staphilococcus epidermidis probably originated by a skin lesion," "sepsis by staphylococcus warneri," "sepsis by MRSA," "sepsis from staphylococcus capitis," "sepsis from staphylococcus epidermidis," "coagulase-negative staphylococcal sepsis," "positive blood culture-staphylococcus epidermidis," "neonatal septicaemia, staphylococcus capitis grown from blood culture," "positive blood culture, staphylococcus epidermidis," "mild sepsis (Staphylococcus epidermidis)," "septicemia with coagulase negative staphylococci," "sepsis staph aureus and KNS," "staphylococcus sepsis," "sepsis due to staphylococcus epidermidis and staphylococcus warneri," "sepsis from staphylococcus capitis and epidermidis," "staphylococcus aureus bacteraemia sepsis," "sepsis by methicillin-resistant staphylococcus aureaus (MRSA)," "clinical sepsis by staphylococcus capitis oxacilline resistant," "sepsis staphylococcus haemolitycus," "sepsis from Staphylococcus Haemolitycus," "sepsis, blood cultures Staphyloccus capitis positive," "blood cultures showed mixed coagulase negative staphylococci," "sepsis, confirmed coag neg staph from blood cultures," "sepsis suspected, confirmed Staphylococcis capitis," "presumed sepsis, coagulase negative staph isolated from aerobic bottle after 1 day incubation," "sepsis, Staphylococcus pettenkoferi," "sepsis confirmed, Staphylococcus aureus and Staphylococcus epidermitis," "positive blood culture staphylococci epidermidis," "positive blood culture (gram positive cocci) Staphylococcus Epidermidis," "sepsis (positive blood culture Staphylococcus epidermidis noted)," "coagulase negative staphylococci septicaemia," "sepsis from staphylococcus epidermidis catheter associated"
Neonatal hypoxia	"Increasing need of oxygen," "oxygen saturation decreased," "neonatal hypoxia," "repeated desaturations," "low saturation," "poor saturations and blood gases," "desaturations," "episodes of desaturations," "desaturation crisis," "frequent desaturations," "persistent need of oxygen in nCPAP with clinical instability (frequent desaturations)," "persistent need of oxygen in CPAP," "persistent need of oxygen," "prolonged need of oxygen," "hypoxia," "desaturation, need of increased oxygen," "increased need of oxygen," "oxygen saturation dips," "necessity of nCPAP at 28 days of life without oxygen," "oxygenation problems due to PIE," "respiratory step up (increase in the oxygen requirement)," "profound desaturation after a feed," "desaturation following a feed," "poor oxygen saturation," "oxygen desaturations," "desaturation associated with feeding," "low oxygen saturation (14%)"

(*continued*)

Table I. Continued

AE/preferred term	Verbatim terms
Neonatal respiratory failure	"Respiratory insufficiency," "respiratory crisis," "pulmonary insufficiency," "respiratory failure, ventilator dependent," "respiratory failure unable to ventilate," "reintubation for impending respiratory failure," "respiratory instability," "respiratory failure unable to ventilate infant," "respiratory failure"
Hypokalemia	"Hypokalemia," "ipokaliemia," "hypokalaemia," "hypokalemi," "hypopotassemia"
Bradycardia neonatal	"Bradycardia," "bradycardia episodes," "bradycardia (mean heart rate 56.3 bpm)," "bradycardia (heart rate <60 bpm)"
Hyperbilirubinemia neonatal	"Hyperbilirubinemia," "hyperbilirubinemi," "hyperbillirubin," "hyperbillirubinemi," "hyperbilirubinaemia," "conjugated hyperbilirubaemia"
Pulmonary hypertension	"Persistent pulmonary hypertension," "pulmonary hypertension," "Persistent pulmonary hypertension of the newborn," "severe pulmonary hypertension on study echocardiogram"

CPAP, continuous positive airway pressure; *CRP*, C-reactive protein; *CSF*, cerebrospinal fluid; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *nCPAP*, nasal continuous positive airway pressure; *PICC*, peripherally inserted central catheter; *PIE*, pulmonary interstitial emphysema.

Table II. Anticipated distribution of the maximum severity of ROP (standard care and rhIGF-1/ rhIGFBP-3 groups) used for calculation of sample size*

ROP	0	1	2	3	>3	Total
Standard care (%)	26	15	24	18	17	100
rhIGF-1/rhIGFBP-3 (%)	49	19	19	9	4	100

*Standard care group distribution based on registry data (Austeng. *Arch Ophthalmol*. 2009;127:1315-9); estimated treatment effect in the rhIGF-1/rhIGFBP-3 group based on the following assumptions: For each outcome of the maximum severity of ROP stage, it is assumed that 25% of the children will not benefit from the treatment, 25% will have their maximum severity of ROP stage reduced by 1 level (eg, from 2 to 1), and 50% will have their maximum severity of ROP stage reduced 2 levels (eg, from 3+ to 2).

Table IV. rhIGF-1/rhIGFBP-3 exposure (safety analysis set)

Variables	rhIGF-1/rhIGFBP-3 Overall population (n = 61)	Gestational age <26 wk (n = 35)	Gestational age ≥26 wk (n = 26)
Total duration of exposure, d*			
Mean	23.8	27.4	18.9
Range	0.1-45.3	0.1-45.3	1.8-26.7
Ratio of duration of exposure to expected duration, d†			
Mean	0.86	0.85	0.88
Range	0.0-1.0	0.0-1.0	0.6-1.0
Overall dose, μg/kg‡			
Mean	5907.5	6849.8	4639.0
Range	16.0-11,321.9	16.0-11,321.9	460.9-6664.1
Average daily dose, μg/kg/24 hours§			
Mean	248.1	250.0	245.4
Range	131.1-250.0	250.0-250.0	131.1-250.0
Interruptions, no.			
Mean	4.0	5.7	1.6
Range	0-83	0-83	0-9
Length interruptions, h			
Mean	7.5	10.2	3.9
Range	0.0-52.6	0.0-52.6	0.0-30.8

*Total duration of exposure defined as (study medication end date – study medication start date) – duration of interruptions.
†Ratio of duration of exposure to expected duration defined as total duration of exposure / (29 weeks × 7 + 6 days) or the last day in the study–(birth weeks × 7 + day) + 1.
‡Total dose (μg/kg) defined as the sum of weight-adjusted doses during the exposure.
§Average daily dose (μg/kg/24 hours) defined as overall dose/total duration of exposure across the entire study.

Table VI. Maximum severity of ROP stage across all examinations by a central pediatric ophthalmologist by gestational age strata (FAS and ES)

Gestational age groups	Standard care (n = 32)	rhIGF-1/rhIGFBP-3 FAS (n = 35)	rhIGF-1/rhIGFBP-3 ES (n = 10)
<26 wk			
Infants with ROP examination, no.	26	25	9
Infants with maximum severity of ROP of stage, no. (%)			
0	8 (30.8)	5 (20.0)	2 (22.2)
1	2 (7.7)	2 (8.0)	0
2	9 (34.6)	7 (28.0)	4 (44.4)
3	2 (7.7)	5 (20.0)	1 (11.1)
3+	5 (19.2)	6 (24.0)	2 (22.2)
4	0	0	0
5	0	0	0
≥3	7 (26.9)	11 (44.0)	3 (33.3)
Missing	6	10	1
≥26 wk	n = 28	n = 26	n = 14
Infants with ROP examination, no.	24	22	13
Infants with maximum severity of ROP of stage, no. (%)			
0	16 (66.7)	9 (40.9)	6 (46.2)
1	2 (8.3)	2 (9.1)	2 (15.4)
2	4 (16.7)	10 (45.5)	4 (30.8)
3	1 (4.2)	1 (4.5)	1 (7.7)
3+	1 (4.2)	0	0
4	0	0	0
5	0	0	0
≥3	2 (8.3)	1 (4.5)	1 (7.7)
Missing	4	4	1

Table VII. Severity of BPD by gestational age strata (FAS and ES)

Gestational age groups	Standard care (n = 32)	rhIGF-1/ rhIGFBP-3 FAS (n = 35)	rhIGF-1/ rhIGFBP-3 ES (n = 10)
<26 wk			
Infants with BPD assessment, no.	25	25	8
Severity of BPD, no. (%)			
No BPD	1 (4.0)	1 (4.0)	0
Mild	5 (20.0)	10 (40.0)	4 (50.0)
Moderate	4 (16.0)	7 (28.0)	3 (37.5)
Severe	14 (56.0)	6 (24.0)	1 (12.5)
Unable to determine	1 (4.0)	1 (4.0)	0
≥26 wk			
n	28	26	14
Infants with BPD assessment, no.	24	22	13
Severity of BPD, no. (%)			
No BPD	3 (12.5)	3 (13.6)	2 (15.4)
Mild	11 (45.8)	13 (59.1)	9 (69.2)
Moderate	1 (4.2)	2 (9.1)	2 (15.4)
Severe	8 (33.3)	4 (18.2)	0
Unable to determine	1 (4.2)	0	0

Table VIII. Percentage of infants with IVH by grade and gestational age strata (FAS and ES)

Gestational age groups	Standard care (n = 32)	rhIGF-1/ rhIGFBP-3 FAS (n = 35)	rhIGF-1/ rhIGFBP-3 ES (n = 10)
<26 wk			
IVH grade, no. (%)			
0-1	20 (62.5)	27 (77.1)	9 (90.0)
2	3 (9.4)	3 (8.6)	1 (10.0)
3	6 (18.8)	3 (8.6)	0
4	3 (9.4)	2 (5.7)	0
≥26 wk			
n	28	26	14
IVH grade, no. (%)			
0-1	22 (78.6)	22 (84.6)	11 (78.6)
2	1 (3.6)	1 (3.8)	1 (7.1)
3	3 (10.7)	3 (11.5)	2 (14.3)
4	2 (7.1)	0	0

Table IX. Post hoc analysis of BPD including all-cause death in the severe BPD category

	Standard care (n = 60)		rhIGF-1/rhIGFBP-3 FAS (n = 61)	
Infants with BPD assessment or death, no.*	56†		59†	
Severity of BPD	No. (%)	95% CI	No. (%)	95% CI
No BPD/mild	20 (35.7)	(24.5-48.8)	27 (45.8)	(33.7-58.3)
Moderate	5 (8.9)	(3.9-19.3)	9 (15.3)	(8.2-26.5)
Severe/death	29 (51.8)	(39.0-64.3)	22 (37.3)	(26.1-50.1)
Unable to determine	2 (3.6)	(1.0-12.1)	1 (1.7)	(0.3-9.0)

*There were 19 all-cause deaths that occurred during the study, 12 deaths in the rhIGF-1/rhIGFBP-3 group and 7 deaths in the standard care group.
†Four infants in the standard care group and 2 infants in the rhIGF-1/rhIGFBP-3 FAS were withdrawn from the study before being assessed for BPD.

Table X. Most common treatment-emergent AEs (preferred terms, occurring in ≥20% in any treatment group)

AEs	Standard care (n = 60) Infants, no. (%)	Standard care (n = 60) Events, no.	rhIGF-1/rhIGFBP-3 (n = 61) Infants, no. (%)	rhIGF-1/rhIGFBP-3 (n = 61) Events, no.
Patent ductus arteriosus	51 (85.0)	71	55 (90.2)	80
Anemia neonatal	44 (73.3)	157	46 (75.4)	210
Neonatal respiratory distress syndrome	34 (56.7)	49	29 (47.5)	34
Jaundice neonatal	30 (50.0)	38	28 (45.9)	34
Infantile apneic attack	17 (28.3)	35	27 (44.3)	48
Neonatal hypotension	18 (30.0)	30	25 (41.0)	35
Hyperglycemia	29 (48.3)	58	24 (39.3)	41
Neonatal hyponatremia	22 (36.7)	39	23 (37.7)	43
Sepsis neonatal*	15 (25.0)	30	23 (37.7)	41
Hypoglycemia neonatal	19 (31.7)	28	18 (29.5)	22
Metabolic acidosis	22 (36.7)	46	17 (27.9)	48
Staphylococcal sepsis	19 (31.7)	25	16 (26.2)	24
Neonatal hypoxia†	13 (21.7)	22	14 (23.0)	17
Neonatal respiratory failure‡	14 (23.3)	18	14 (23.0)	22
Hypokalemia	11 (18.3)	18	14 (23.0)	24
Bradycardia neonatal§	5 (8.3)	6	13 (21.3)	19
Hyperbilirubinemia neonatal	14 (23.3)	18	12 (19.7)	14
Pulmonary hypertension	12 (20.0)	14	8 (13.1)	8

Events of ROP, BPD, and IVH also were reported as treatment-emergent AEs in some but not all cases; however, they are not included in the table because these are efficacy outcomes.
*Verbatim terms include suspected/presumed sepsis and some microbiologically confirmed cases of sepsis, but do not encompass all cases of sepsis (nonspecific term). See **Table I** for a list of reported verbatim terms under the preferred term "sepsis neonatal."
†See **Table I** for verbatim terms reported under the preferred term "neonatal hypoxia."
‡See **Table I** for verbatim terms reported under the preferred term "neonatal respiratory failure."
§Frequency in rhIGF-1/rhIGFBP-3 group at least twice that of the standard care group.