Clinical trial results:
Determination of the rhIGF-1/rhIGFBP-3 Dose, Administered as a Continuous Infusion, Required to Establish and Maintain Longitudinal Serum IGF-1 Levels Within Physiological Levels in Premature Infants, to Prevent Retinopathy of Prematurity A Phase 2, Randomized Controlled, Assessor-blind, Dose-confirming, Pharmacokinetic, Safety and Efficacy, Multicenter Study

Summary

EudraCT number	2007-007872-40
Trial protocol	SE GB IT NL PL
Global end of trial date	30 March 2016

Results information

Result version number	v1 (current)
This version publication date	15 October 2016
First version publication date	15 October 2016

Trial information

Trial identification

Sponsor protocol code	ROPP-2008-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01096784
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Premacure AB, A Member of the Shire Group of Companies
Sponsor organisation address	300 Shire Way, Lexington, Massachusetts, United States, 02421
Public contact	Study Physician, Premacure AB, A Member of the Shire Group of Companies, ClinicalTransparency@shire.com
Scientific contact	Study Physician, Premacure AB, A Member of the Shire Group of Companies, ClinicalTransparency@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•To determine the effect of recombinant human insulin-like growth factor-1 (rhIGF-1)/recombinant human insulin-like growth factor binding protein-3 (rhIGFBP-3) on the severity of retinopathy of prematurity (ROP) as compared to the severity of ROP in an untreated control population.
•To evaluate the dose of rhIGF-1/rhIGFBP-3, administered by continuous intravenous (IV) infusion, required to reach and maintain a physiological range of serum IGF-1 of 28-109 microgram per liter (mcg/L), defined as the in utero levels of insulin-like growth factor-1 (IGF-1) for corresponding gestational age (GA) in a normal population.
•To determine serum concentrations of IGF-1 and associated pharmacokinetic parameters after continuous IV infusion of rhIGF-1/rhIGFBP-3.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Sweden: 24
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Italy: 56
Country: Number of subjects enrolled	Netherlands: 3
Worldwide total number of subjects	121
EEA total number of subjects	99

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	121
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in multiple centres in Italy, the Netherlands, Poland, Sweden, the United Kingdom and the United States between 19 September 2014 and 30 March 2016.

Pre-assignment

Screening details:

A total of 121 subjects were enrolled and randomized into the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Assessor blinded only for the primary endpoint.

Arms

Are arms mutually exclusive?	Yes
Arm title	rhIGF-1/rhIGFBP-3

Arm description:

Subjects received rhIGF-I/rhIGFBP-3 250 microgram per kilogram (mcg/kg) for 24 hours through continuous IV infusion from Day 0 up to 29 weeks 6 days of post-menstrual age (PMA).

Arm type	Experimental
Investigational medicinal product name	Mecasermin rinfabate
Investigational medicinal product code	
Other name	rhIGF-1/rhIGFBP-3
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rhIGF-I/rhIGFBP-3 250 mcg/kg for 24 hours through continuous IV infusion from Day 0 up to 29 weeks 6 days of PMA.

Arm title	Standard of Care (Control)

Arm description:

Subjects in this control group do not received any treatment other than the standard care.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	rhIGF-1/rhIGFBP-3	Standard of Care (Control)
Started	61	60
Completed	46	46
Not completed	15	14
Consent withdrawn by subject	2	1
Adverse event, non-fatal	11	9
Protocol Deviation	2	2

Administrative Decision	-	1
Other Unspecified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	rhIGF-1/rhIGFBP-3
Reporting group description:	
Subjects received rhIGF-I/rhIGFBP-3 250 microgram per kilogram (mcg/kg) for 24 hours through continuous IV infusion from Day 0 up to 29 weeks 6 days of post-menstrual age (PMA).	
Reporting group title	Standard of Care (Control)
Reporting group description:	
Subjects in this control group do not received any treatment other than the standard care.	

Reporting group values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)	Total
Number of subjects	61	60	121
Age categorical Units: Subjects			

Age continuous			
Gestational age was mentioned.			
Units: weeks			
arithmetic mean	25.6	25.62	
standard deviation	± 1.207	± 1.397	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	22	21	43
Male	39	39	78

End points

End points reporting groups

Reporting group title	rhIGF-1/rhIGFBP-3
Reporting group description:	
Subjects received rhIGF-I/rhIGFBP-3 250 microgram per kilogram (mcg/kg) for 24 hours through continuous IV infusion from Day 0 up to 29 weeks 6 days of post-menstrual age (PMA).	
Reporting group title	Standard of Care (Control)
Reporting group description:	
Subjects in this control group do not received any treatment other than the standard care.	

Primary: Severity of Retinopathy of Prematurity (ROP) as Compared to the Severity of ROP in an Untreated Control Population

End point title	Severity of Retinopathy of Prematurity (ROP) as Compared to the Severity of ROP in an Untreated Control Population
End point description:	
ROP was measured by central exams with fundus photography. Maximum severity of ROP stage across all retinal examinations included International Classification of Retinopathy of Prematurity, a 5 stage system, for the classification of ROP with 7 different outcomes of the ROP stage in each retinal examination: 0, 1, 2, 3, 3+, 4, and 5. This is an ordinal scale with higher numbers indicating a more severe outcome. Full analysis set (FAS) included all randomized subjects who received the study drug and subjects in the control group who received Standard of Care.	
End point type	Primary
End point timeframe:	
From 31 weeks PMA up to 40 weeks PMA End of Study (EOS) +/- 4 days	

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Subjects				
ROP of Stage "0"	14	24		
ROP of Stage "1"	4	4		
ROP of Stage "2"	17	13		
ROP of Stage "3"	6	3		
ROP of Stage "3+"	6	6		
ROP of Stage "4"	0	0		
ROP of Stage "5"	0	0		
Missing	14	10		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Standard of Care (Control) v rhIGF-1/rhIGFBP-3

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0642
Method	CMH Row Mean Score Test

Secondary: Time to Discharge from Neonatal Intensive Care (TDNIC)

End point title	Time to Discharge from Neonatal Intensive Care (TDNIC)

End point description:

FAS with number of subjects evaluable for this outcome.

End point type	Secondary

End point timeframe:

Day 0 to 40 Weeks Post Menstrual Age (EOS)

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	31		
Units: Days				
median (full range (min-max))	82 (69 to 96)	74 (69 to 93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Bronchopulmonary Dysplasia (BPD)

End point title	Number of Subjects With Bronchopulmonary Dysplasia (BPD)

End point description:

Severity of BPD as mild, moderate and severe were based on the National Institute of Child Health and Human Development (NICHD) guidelines for preterm infants born at gestational age (GA) less than (<) 32 weeks. Mild: oxygen requirement during the first 28 days but in room air at PMA 36 weeks or discharge to home, whichever comes first. Moderate BPD: oxygen requirement during the first 28 days and oxygen <30 percent (%) at PMA 36 weeks or discharge to home, whichever comes first. Severe BPD: oxygen requirement during the first 28 days and oxygen greater than equal (≥)30% through head hood or nasal canula, or continuous positive airway pressure, or mechanical ventilation, or high flow nasal cannula ≥2 L/min at PMA 36 weeks or discharge to home, whichever comes first. FAS with number of subjects evaluable for this outcome.

End point type	Secondary

End point timeframe:

36 Weeks Post Menstrual Age

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: Subjects				
No BPD	4	4		
Mild	23	16		
Moderate	9	5		
Severe	10	22		
Unable to determine	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Change in Body weight

End point title	Rate of Change in Body weight

End point description:

The rate of change is the rate of specific body weight change per day in kilogram (kg). Population analysed was FAS.

End point type	Secondary

End point timeframe:

Day 0 to 40 Weeks Post Menstrual Age (EOS)

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: percentage of body weight				
number (confidence interval 95%)	0.021 (0.019 to 0.022)	0.023 (0.021 to 0.024)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Change in Length

End point title	Rate of Change in Length

End point description:

The rate of change is the length change per day in centimeter (cm). Population analysed was FAS.

End point type	Secondary

End point timeframe:

Day 0 to 40 Weeks Post Menstrual Age (EOS)

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: percentage of length				
number (confidence interval 95%)	0.141 (0.0132 to 0.149)	0.156 (0.147 to 0.164)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Change in Head Circumference

End point title	Rate of Change in Head Circumference

End point description:

The rate of change is the head circumference change per day in centimetre (cm). Population analysed was FAS.

End point type	Secondary

End point timeframe:

Day 0 to 40 Weeks Post Menstrual Age (EOS)

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: percentage of head circumference				
number (confidence interval 95%)	0.115 (0.109 to 0.121)	0.119 (0.113 to 0.125)		

Statistical analyses

No statistical analyses for this end point

Secondary: Brain Development as Assessed by Changes in Brain Volume

End point title	Brain Development as Assessed by Changes in Brain Volume

End point description:

Brain volume was measured using cerebral magnetic resonance imaging (MRI). Brain volume included cerebrospinal volume, gray matter volume, white matter volume, and total cerebellar volume. Population analysed was FAS. Here, n = number of subjects evaluable at each categories for the specific reporting groups.

End point type	Secondary

End point timeframe:

Week 40 PMA/ EOS +/- 4 days

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: cubic centimeter				
arithmetic mean (standard deviation)				
Cerebrospinal Fluid Volume (n = 45, 40)	87.94 (± 26.788)	93.7 (± 25.54)		
Gray Matter Volume (n = 45, 40)	206.34 (± 31.797)	221.98 (± 33.827)		
White Matter Volume (n = 45, 40)	110.23 (± 25.565)	117.62 (± 24.422)		
Total Cerebellar Volume (n = 45, 41)	18.27 (± 5.302)	19.2 (± 4.854)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Intraventricular Hemorrhage (IVH)

End point title	Percentage of Subjects With Intraventricular Hemorrhage (IVH)

End point description:

Development of intraventricular hemorrhage was assessed by cerebral ultrasound and coded as a binary endpoint (presence or absence of IVH). Population analysed was FAS.

End point type	Secondary

End point timeframe:

Day 0 to 40 Weeks Post Menstrual Age (EOS)

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: percentage of subjects				
number (not applicable)				
Yes	19.67	30		
No	80.33	70		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Curve for Maximum Severity of ROP Stage (AUC for ROP)

End point title	Area Under Curve for Maximum Severity of ROP Stage (AUC for ROP)

End point description:

Integration of the maximum severity of ROP stage and the duration of the time interval with respect to each retinal examination. AUC for the maximum severity of ROP was calculated using the trapezoidal rule. The area between each 2 visits was calculated by multiplying the average of the maximum severities of the 2 visits by the difference in days and analyzed using the van Elteren test. Population analysed was FAS with number of subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Day 0 to 40 Weeks Post Menstrual Age (EOS)

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	49		
Units: hour*microgram per liter				
arithmetic mean (standard deviation)	47.95 (± 47.384)	32.17 (± 40.151)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Maximum Severity of ROP Stage Greater Than Equal to 3 at any Time During the Study

End point title	Percentage of Subjects With Maximum Severity of ROP Stage Greater Than Equal to 3 at any Time During the Study

End point description:

ROP was measured by central exams with fundus photography. Maximum severity of ROP stage across all retinal examinations included International Classification of Retinopathy of Prematurity, a 5 stage system, for the classification of ROP with 7 different outcomes of the ROP stage in each retinal examination: 0, 1, 2, 3, 3+, 4, and 5. This is an ordinal scale with higher numbers indicating a more severe outcome. Population analysed was FAS.

End point type	Secondary

End point timeframe:

Every 1-2 weeks starting at 31 weeks PMA/ EOS +/- 4 days

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: percentage of subjects				
number (not applicable)				
Yes	25.53	18		
No	74.47	82		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Event (TEAE) and Treatment Emergent Serious Adverse Event (TESAE)

End point title	Number of Subjects with Treatment Emergent Adverse Event (TEAE) and Treatment Emergent Serious Adverse Event (TESAE)

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. TEAE was defined as the onset of any AE or if the severity of a pre-existing AE worsened any time on or after the date of first dose of investigational product. Safety analysis set (SAF) included all randomized subjects who received the study drug and subjects in the control group who received standard of care, and for whom at least 1 safety assessment was completed.

End point type	Secondary

End point timeframe:

Day 0 to 40 Weeks Post Menstrual Age (EOS)

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Subjects				
Subjects with TEAE	60	60		
Subjects with TESAE	48	37		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Serum IGF-1 concentrations Falling Withing Target Range After Infusion of rhIGF-1/rhIGFBP-3

End point title	Percentage of Serum IGF-1 concentrations Falling Withing Target Range After Infusion of rhIGF-1/rhIGFBP-3

End point description:

Serum samples were collected from treated and control subjects for quantification of IGF-1 using validated immunoassays. Target range of serum IGF-1 was 28-109 mcg/L. Population analysed was FAS.

End point type	Secondary

End point timeframe:

Day 0 to 40 Weeks Post Menstrual Age (EOS)

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: percentage of serum concentration				
number (not applicable)	66.23	6.28		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations of IGFBP-3 After Intravenous (IV) Infusion of rhIGF-1/rhIGFBP-3

End point title	Serum Concentrations of IGFBP-3 After Intravenous (IV) Infusion of rhIGF-1/rhIGFBP-3

End point description:

Population analysed was FAS. Here n = number of subjects evaluable at each categories for the specific reporting groups.

End point type	Secondary

End point timeframe:

Day 0 to Week 40 PMA/EOS +/- 4 days

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: number				
arithmetic mean (standard deviation)				
DAY 0 (N = 60, 60)	494.2 (± 200.38)	469.9 (± 180.52)		
WEEK 40 (N = 47, 46)	830.1 (± 200.17)	882.1 (± 274.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentrations of Acid Labile Sub-unit (ALS) After Intravenous (IV) Infusion of rhIGF-1/rhIGFBP-3

End point title	Serum concentrations of Acid Labile Sub-unit (ALS) After

	Intravenous (IV) Infusion of rhIGF-1/rhIGFBP-3

End point description:

Population analysed was FAS. Here, n = number of subjects evaluable at each categories for the specific reporting groups.

End point type	Secondary

End point timeframe:

Day 0 to Week 40 PMA/ EOS +/- 4 days

End point values	rhIGF-1/rhIGFBP-3	Standard of Care (Control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: microgram per liter				
arithmetic mean (standard deviation)				
DAY 7 (N = 60, 60)	411.9 (± 237.91)	500.3 (± 350.59)		
WEEK 40 (N = 47, 46)	1804.6 (± 629.61)	2114.3 (± 941.94)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 0 upto 4 days from PMA 40 Weeks	
Adverse event reporting additional description:	
Event desc	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	nil
Dictionary version	16.0

Reporting groups	
Reporting group title	rhIGF-I/rhIGFBP-3
Reporting group description:	
Subjects received rhIGF-I/rhIGFBP-3 250 mcg/kg for 24 hours through continuous IV infusion from Day 0 up to 29 weeks 6 days of PMA.	
Reporting group title	Standard of Care (Control)
Reporting group description:	
Subjects in this control group do not received any treatment other than the standard care.	

Serious adverse events	rhIGF-I/rhIGFBP-3	Standard of Care (Control)	
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 61 (78.69%)	37 / 60 (61.67%)	
number of deaths (all causes)	12	7	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Neonatal hypotension			
subjects affected / exposed	2 / 61 (3.28%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vena cava thrombosis			

subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infantile apnoeic attack			
subjects affected / exposed	5 / 61 (8.20%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal aspiration			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal respiratory distress syndrome			
subjects affected / exposed	3 / 61 (4.92%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal respiratory failure			
subjects affected / exposed	7 / 61 (11.48%)	9 / 60 (15.00%)	
occurrences causally related to treatment / all	0 / 11	0 / 13	
deaths causally related to treatment / all	0 / 2	0 / 3	
Pleurisy			

subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	2 / 61 (3.28%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary interstitial emphysema syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Pco2 increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Patent ductus arteriosus			
subjects affected / exposed	13 / 61 (21.31%)	14 / 60 (23.33%)	
occurrences causally related to treatment / all	0 / 13	0 / 14	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac disorders			
Bradycardia neonatal			

subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac hypertrophy			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage neonatal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion neonatal			
subjects affected / exposed	2 / 61 (3.28%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intraventricular haemorrhage neonatal			
subjects affected / exposed	7 / 61 (11.48%)	8 / 60 (13.33%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 5	0 / 3	
Periventricular leukomalacia			

subjects affected / exposed	4 / 61 (6.56%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Coagulation disorder neonatal			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia neonatal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinopathy of prematurity			
subjects affected / exposed	5 / 61 (8.20%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal perforation			
subjects affected / exposed	1 / 61 (1.64%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Intra-Abdominal haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Intussusception			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meconium ileus			
subjects affected / exposed	2 / 61 (3.28%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising enterocolitis neonatal			
subjects affected / exposed	6 / 61 (9.84%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 0	
Volvulus			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure neonatal			
subjects affected / exposed	3 / 61 (4.92%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Infections and infestations			
Citrobacter sepsis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enterococcal sepsis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 61 (1.64%)	3 / 60 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	

Group b streptococcus neonatal sepsis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal pneumonia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis neonatal			
subjects affected / exposed	7 / 61 (11.48%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Serratia sepsis			
subjects affected / exposed	3 / 61 (4.92%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	9 / 61 (14.75%)	7 / 60 (11.67%)	
occurrences causally related to treatment / all	0 / 10	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lactic acidosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	rhIGF-I/rhIGFBP-3	Standard of Care (Control)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 61 (95.08%)	60 / 60 (100.00%)	
Vascular disorders			
Neonatal hypotension			
subjects affected / exposed	23 / 61 (37.70%)	15 / 60 (25.00%)	
occurrences (all)	33	27	
Pregnancy, puerperium and perinatal conditions			
Jaundice neonatal			
subjects affected / exposed	28 / 61 (45.90%)	30 / 60 (50.00%)	
occurrences (all)	34	38	
Poor weight gain neonatal			
subjects affected / exposed	3 / 61 (4.92%)	4 / 60 (6.67%)	
occurrences (all)	3	4	
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	9 / 61 (14.75%)	4 / 60 (6.67%)	
occurrences (all)	15	5	
Infusion site extravasation			
subjects affected / exposed	1 / 61 (1.64%)	3 / 60 (5.00%)	
occurrences (all)	1	8	
Oedema peripheral			
subjects affected / exposed	9 / 61 (14.75%)	1 / 60 (1.67%)	
occurrences (all)	11	1	

Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	8 / 61 (13.11%)	1 / 60 (1.67%)	
occurrences (all)	9	2	
Respiratory, thoracic and mediastinal disorders			
Atelectasis neonatal			
subjects affected / exposed	3 / 61 (4.92%)	4 / 60 (6.67%)	
occurrences (all)	3	4	
Bronchopulmonary dysplasia			
subjects affected / exposed	34 / 61 (55.74%)	37 / 60 (61.67%)	
occurrences (all)	37	42	
Bronchospasm			
subjects affected / exposed	2 / 61 (3.28%)	8 / 60 (13.33%)	
occurrences (all)	2	11	
Hypocapnia			
subjects affected / exposed	2 / 61 (3.28%)	4 / 60 (6.67%)	
occurrences (all)	3	5	
Infantile apnoeic attack			
subjects affected / exposed	26 / 61 (42.62%)	16 / 60 (26.67%)	
occurrences (all)	42	32	
Neonatal hypoxia			
subjects affected / exposed	14 / 61 (22.95%)	13 / 60 (21.67%)	
occurrences (all)	17	21	
Neonatal respiratory acidosis			
subjects affected / exposed	10 / 61 (16.39%)	5 / 60 (8.33%)	
occurrences (all)	30	11	
Neonatal respiratory failure			
subjects affected / exposed	9 / 61 (14.75%)	5 / 60 (8.33%)	
occurrences (all)	11	5	
Neonatal respiratory distress syndrome			
subjects affected / exposed	27 / 61 (44.26%)	32 / 60 (53.33%)	
occurrences (all)	31	41	
Neonatal tachypnoea			
subjects affected / exposed	2 / 61 (3.28%)	4 / 60 (6.67%)	
occurrences (all)	2	5	

Pulmonary haemorrhage			
subjects affected / exposed	4 / 61 (6.56%)	0 / 60 (0.00%)	
occurrences (all)	4	0	
Pulmonary hypertension			
subjects affected / exposed	6 / 61 (9.84%)	9 / 60 (15.00%)	
occurrences (all)	6	11	
Pulmonary oedema neonatal			
subjects affected / exposed	6 / 61 (9.84%)	1 / 60 (1.67%)	
occurrences (all)	7	1	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 61 (8.20%)	6 / 60 (10.00%)	
occurrences (all)	6	6	
C-Reactive protein increased			
subjects affected / exposed	5 / 61 (8.20%)	4 / 60 (6.67%)	
occurrences (all)	6	5	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	6 / 61 (9.84%)	9 / 60 (15.00%)	
occurrences (all)	6	10	
Patent ductus arteriosus			
subjects affected / exposed	53 / 61 (86.89%)	45 / 60 (75.00%)	
occurrences (all)	67	57	
Cardiac disorders			
Neonatal tachycardia			
subjects affected / exposed	4 / 61 (6.56%)	0 / 60 (0.00%)	
occurrences (all)	8	0	
Bradycardia neonatal			
subjects affected / exposed	13 / 61 (21.31%)	5 / 60 (8.33%)	
occurrences (all)	18	6	
Nervous system disorders			
Convulsion neonatal			
subjects affected / exposed	3 / 61 (4.92%)	3 / 60 (5.00%)	
occurrences (all)	3	3	
Cerebral ventricle dilatation			

subjects affected / exposed	0 / 61 (0.00%)	3 / 60 (5.00%)	
occurrences (all)	0	3	
Intraventricular haemorrhage neonatal			
subjects affected / exposed	11 / 61 (18.03%)	18 / 60 (30.00%)	
occurrences (all)	13	19	
Periventricular leukomalacia			
subjects affected / exposed	1 / 61 (1.64%)	3 / 60 (5.00%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Coagulation disorder neonatal			
subjects affected / exposed	9 / 61 (14.75%)	8 / 60 (13.33%)	
occurrences (all)	10	12	
Anaemia neonatal			
subjects affected / exposed	46 / 61 (75.41%)	44 / 60 (73.33%)	
occurrences (all)	210	157	
Neutropenia neonatal			
subjects affected / exposed	5 / 61 (8.20%)	0 / 60 (0.00%)	
occurrences (all)	5	0	
Thrombocytopenia neonatal			
subjects affected / exposed	12 / 61 (19.67%)	9 / 60 (15.00%)	
occurrences (all)	15	13	
Eye disorders			
Retinopathy of prematurity			
subjects affected / exposed	39 / 61 (63.93%)	37 / 60 (61.67%)	
occurrences (all)	106	89	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	5 / 61 (8.20%)	4 / 60 (6.67%)	
occurrences (all)	5	4	
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 61 (11.48%)	6 / 60 (10.00%)	
occurrences (all)	9	6	
Impaired gastric emptying			
subjects affected / exposed	1 / 61 (1.64%)	3 / 60 (5.00%)	
occurrences (all)	1	3	
Inguinal hernia			

subjects affected / exposed	9 / 61 (14.75%)	11 / 60 (18.33%)	
occurrences (all)	10	11	
Umbilical hernia			
subjects affected / exposed	3 / 61 (4.92%)	6 / 60 (10.00%)	
occurrences (all)	3	6	
Vomiting neonatal			
subjects affected / exposed	2 / 61 (3.28%)	3 / 60 (5.00%)	
occurrences (all)	2	5	
Hepatobiliary disorders			
Hyperbilirubinaemia neonatal			
subjects affected / exposed	12 / 61 (19.67%)	14 / 60 (23.33%)	
occurrences (all)	14	18	
Neonatal cholestasis			
subjects affected / exposed	2 / 61 (3.28%)	6 / 60 (10.00%)	
occurrences (all)	2	6	
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	5 / 61 (8.20%)	3 / 60 (5.00%)	
occurrences (all)	5	4	
Musculoskeletal and connective tissue disorders			
Growth retardation			
subjects affected / exposed	1 / 61 (1.64%)	3 / 60 (5.00%)	
occurrences (all)	1	3	
Osteopenia			
subjects affected / exposed	6 / 61 (9.84%)	9 / 60 (15.00%)	
occurrences (all)	6	9	
Infections and infestations			
Fungal skin infection			
subjects affected / exposed	3 / 61 (4.92%)	3 / 60 (5.00%)	
occurrences (all)	6	6	
Neonatal pneumonia			
subjects affected / exposed	1 / 61 (1.64%)	3 / 60 (5.00%)	
occurrences (all)	1	3	
Pneumonia bacterial			
subjects affected / exposed	4 / 61 (6.56%)	5 / 60 (8.33%)	
occurrences (all)	4	6	

Rhinitis			
subjects affected / exposed	4 / 61 (6.56%)	3 / 60 (5.00%)	
occurrences (all)	5	6	
Sepsis neonatal			
subjects affected / exposed	16 / 61 (26.23%)	15 / 60 (25.00%)	
occurrences (all)	33	29	
Staphylococcal sepsis			
subjects affected / exposed	9 / 61 (14.75%)	12 / 60 (20.00%)	
occurrences (all)	14	16	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	4 / 61 (6.56%)	8 / 60 (13.33%)	
occurrences (all)	5	9	
Feeding disorder neonatal			
subjects affected / exposed	1 / 61 (1.64%)	3 / 60 (5.00%)	
occurrences (all)	1	4	
Hypercalcaemia			
subjects affected / exposed	4 / 61 (6.56%)	4 / 60 (6.67%)	
occurrences (all)	5	8	
Hyperglycaemia			
subjects affected / exposed	24 / 61 (39.34%)	28 / 60 (46.67%)	
occurrences (all)	41	55	
Hypernatraemia			
subjects affected / exposed	6 / 61 (9.84%)	11 / 60 (18.33%)	
occurrences (all)	7	13	
Hypoalbuminaemia			
subjects affected / exposed	5 / 61 (8.20%)	4 / 60 (6.67%)	
occurrences (all)	6	5	
Hypocalcaemia			
subjects affected / exposed	8 / 61 (13.11%)	6 / 60 (10.00%)	
occurrences (all)	20	6	
Hypoglycaemia neonatal			
subjects affected / exposed	18 / 61 (29.51%)	19 / 60 (31.67%)	
occurrences (all)	22	27	
Hypokalaemia			

subjects affected / exposed	14 / 61 (22.95%)	11 / 60 (18.33%)	
occurrences (all)	24	18	
Hypophosphataemia			
subjects affected / exposed	2 / 61 (3.28%)	4 / 60 (6.67%)	
occurrences (all)	2	5	
Hypovolaemia			
subjects affected / exposed	1 / 61 (1.64%)	3 / 60 (5.00%)	
occurrences (all)	1	4	
Metabolic acidosis			
subjects affected / exposed	17 / 61 (27.87%)	22 / 60 (36.67%)	
occurrences (all)	43	46	
Neonatal hyponatraemia			
subjects affected / exposed	23 / 61 (37.70%)	22 / 60 (36.67%)	
occurrences (all)	43	39	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported