Clinical trial results:
Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated With rhIGF 1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or who Received Standard Neonatal Care

Summary

EudraCT number	2014-003556-31
Trial protocol	SE GB NL PL IT
Global end of trial date	28 September 2021

Results information

Result version number	v1 (current)
This version publication date	18 April 2022
First version publication date	18 April 2022

Trial information

Trial identification

Sponsor protocol code	SHP607-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02386839
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, Massachusetts, United States, 02421
Public contact	Study Director, Shire, ClinicalTransparency@takeda.com
Scientific contact	Study Director, Shire, ClinicalTransparency@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000534-PIP03-17
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	28 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the long-term efficacy and safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (2007-007872-40).

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312 and the International Conference on Harmonisation (ICH) GCP guidelines. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	76
EEA total number of subjects	58

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	76

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:

This study was conducted at 16 sites from 26 March 2015 (first participant first visit) to 28 September 2021 (last participant last visit).

Pre-assignment

Screening details:

A total of 76 participants who previously treated with rhIGF 1/rhIGFBP-3 or Standard Neonatal Care in ROPP-2008-01 (2007-007872-40) study were enrolled in this long term safety and efficacy study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Antecedent Standard of Care

Arm description:

Participants who were treated with standard neonatal care in study ROPP-2008-01 (2007-007872-40).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Antecedent rhIGF-1/rhIGFBP-3

Arm description:

Participants who were treated with rhIGF-1/rhIGFBP-3 in study ROPP-2008-01 (2007-007872-40).

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:

Participants who received "rhIGF-1/rhIGFBP-3" in study ROPP-2008-01 (2007-007872-40) were enrolled to this study. No investigational product was administered in this study.

Number of subjects in period 1	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3
Started	36	40
Completed	20	25
Not completed	16	15
Adverse event, serious fatal	1	-
Other (Due to Covid 19 Pandemic)	-	1
Withdrawal by Subject	9	10
Other (unspecified)	1	-
Lost to follow-up	4	4

Other (Site Terminated by Sponsor)	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Antecedent Standard of Care
Reporting group description:	
Participants who were treated with standard neonatal care in study ROPP-2008-01 (2007-007872-40).	
Reporting group title	Antecedent rhIGF-1/rhIGFBP-3
Reporting group description:	
Participants who were treated with rhIGF-1/rhIGFBP-3 in study ROPP-2008-01 (2007-007872-40).	

Reporting group values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3	Total
Number of subjects	36	40	76
Age Categorical Units: Subjects			
Age continuous			
The age reported here is the corrected age. Corrected Age (weeks) was defined as Chronological Age (weeks) – 40 + Gestational Age (weeks) in this study.			
Units: weeks			
arithmetic mean	7.15	6.73	
standard deviation	± 5.622	± 6.224	-
Gender categorical Units: Participants			
Female	13	14	27
Male	23	26	49
Race (NIH/OMB) Units: Subjects			
Asian	4	0	4
Black or African American	5	1	6
White	26	34	60
Unknown or Not Reported	1	5	6
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	13	19
Not Hispanic or Latino	28	27	55
Unknown or Not Reported	2	0	2

End points

End points reporting groups

Reporting group title	Antecedent Standard of Care
Reporting group description:	
Participants who were treated with standard neonatal care in study ROPP-2008-01 (2007-007872-40).	
Reporting group title	Antecedent rhIGF-1/rhIGFBP-3
Reporting group description:	
Participants who were treated with rhIGF-1/rhIGFBP-3 in study ROPP-2008-01 (2007-007872-40).	

Primary: Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 6 Months Corrected age (CA)

End point title	Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 6 Months Corrected age (CA)[1]

End point description:

Standard age-appropriate methods were to assess visual acuity (how well a participant sees at different distances) with teller acuity cards, LEA symbols test and Charts. It was categorized as following: normal (measurable acuity greater than or equal to [>=] 20/40 or >=15 cycles/degree); below normal (20/200 less than or equal to [<=] measurable acuity less than [<] 20/40 or 3 cycles/degree <= measurable acuity <15 cycles/degree); poor (measurable acuity <=20/200 or <=3 cycles/degree). Corrected Age (weeks) was defined as Chronological Age (weeks) – 40 + Gestational Age (weeks) in this study. Enrolled set included all participants for whom written informed consent was obtained for this long-term outcome study. Here, "number of subjects analyzed"= subjects evaluable for this endpoint and "n=number analyzed" evaluable at specific categories.

End point type	Primary

End point timeframe:

At 6 Months CA

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	34		
Units: Participants				
Right Eye: Normal (n=24, 32)	0	0		
Right Eye: Below Normal (n=24, 32)	12	19		
Right Eye: Poor (n=24, 32)	12	13		
Left Eye: Normal (n=21, 32)	0	0		
Left Eye: Below Normal (n=21, 32)	14	18		
Left Eye: Poor (n=21, 32)	7	14		
Both Eyes: Normal (n=27, 34)	0	0		
Both Eyes: Below Normal (n=27, 34)	18	25		
Both Eyes: Poor (n=27, 34)	9	9		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 12 Months CA

End point title	Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 12 Months CA[2]

End point description:

Standard age-appropriate methods were to assess visual acuity (how well a participant sees at different distances) with teller acuity cards, LEA symbols test and Charts. It was categorized as following: normal (measurable acuity greater than or equal to [>=] 20/40 or >=15 cycles/degree); below normal (20/200 less than or equal to [<=] measurable acuity less than [<] 20/40 or 3 cycles/degree <= measurable acuity <15 cycles/degree); poor (measurable acuity <=20/200 or <=3 cycles/degree). Corrected Age (weeks) was defined as Chronological Age (weeks) – 40 + Gestational Age (weeks) in this study. Enrolled set included all participants for whom written informed consent was obtained for this long-term outcome study. Here, "number of subjects analyzed"= subjects evaluable for this endpoint and "n=number analyzed" evaluable at specific categories.

End point type	Primary

End point timeframe:

At 12 Months CA

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	36		
Units: Participants				
Right Eye: Normal (n=21, 32)	0	1		
Right Eye: Below Normal (n=21, 32)	21	26		
Right Eye: Poor (n=21, 32)	0	5		
Left Eye: Normal (n=21, 32)	0	1		
Left Eye: Below Normal (n=21, 32)	20	25		
Left Eye: Poor (n=21, 32)	1	6		
Both Eyes: Normal (n=24, 36)	0	1		
Both Eyes: Below Normal (n=24, 36)	23	33		
Both Eyes: Poor (n=24, 36)	1	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 20 Months CA

End point title	Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 20 Months CA[3]

End point description:

Standard age-appropriate methods were to assess visual acuity (how well a participant sees at different distances) with teller acuity cards, LEA symbols test and Charts. It was categorized as following: normal (measurable acuity greater than or equal to [>=] 20/40 or >=15 cycles/degree); below normal (20/200 less than or equal to [<=] measurable acuity less than [<] 20/40 or 3 cycles/degree <= measurable acuity <15 cycles/degree); poor (measurable acuity <=20/200 or <=3 cycles/degree). Corrected Age

(weeks) was defined as Chronological Age (weeks) – 40 + Gestational Age (weeks) in this study. Enrolled set included all participants for whom written informed consent was obtained for this long-term outcome study. Here, "number of subjects analyzed"= subjects evaluable for this endpoint and "n=number analyzed" evaluable at specific categories.

End point type	Primary

End point timeframe:

At 20 Months CA

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	33		
Units: Participants				
Right Eye: Normal (n=19, 29)	0	2		
Right Eye: Below Normal (n=19, 29)	17	23		
Right Eye: Poor (n=19, 29)	2	4		
Left Eye: Normal (n=20, 29)	0	1		
Left Eye: Below Normal (n=20, 29)	18	24		
Left Eye: Poor (n=20, 29)	2	4		
Both Eyes: Normal (n=23, 33)	0	1		
Both Eyes: Below Normal (n=23, 33)	20	30		
Both Eyes: Poor (n=23, 33)	3	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 24 Months CA

End point title	Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 24 Months CA[4]

End point description:

Standard age-appropriate methods were to assess visual acuity (how well a participant sees at different distances) with teller acuity cards, LEA symbols test and Charts. It was categorized as following: normal (measurable acuity greater than or equal to [>=] 20/40 or >=15 cycles/degree); below normal (20/200 less than or equal to [<=] measurable acuity less than [<] 20/40 or 3 cycles/degree <= measurable acuity <15 cycles/degree); poor (measurable acuity <=20/200 or <=3 cycles/degree). Corrected Age (weeks) was defined as Chronological Age (weeks) – 40 + Gestational Age (weeks) in this study. Enrolled set included all participants for whom written informed consent was obtained for this long-term outcome study. Here, "number of subjects analyzed"= subjects evaluable for this endpoint and "n=number analyzed" evaluable at specific categories.

End point type	Primary

End point timeframe:

At 24 Months CA

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	33		
Units: Participants				
Right Eye: Normal (n=20, 31)	0	2		
Right Eye: Below Normal (n=20, 31)	17	25		
Right Eye: Poor (n=20, 31)	3	4		
Left Eye: Normal (n=20, 28)	0	2		
Left Eye: Below Normal (n=20, 28)	17	24		
Left Eye: Poor (n=20, 28)	3	2		
Both Eyes: Normal (n=23, 33)	1	5		
Both Eyes: Below Normal (n=23, 33)	19	24		
Both Eyes: Poor (n=23, 33)	3	4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 4.75 Years CA

End point title	Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 4.75 Years CA[5]

End point description:

Standard age-appropriate methods were to assess visual acuity (how well a participant sees at different distances) with teller acuity cards, LEA symbols test and Charts. It was categorized as following: normal (measurable acuity greater than or equal to [>=] 20/40 or >=15 cycles/degree); below normal (20/200 less than or equal to [<=] measurable acuity less than [<] 20/40 or 3 cycles/degree <= measurable acuity <15 cycles/degree); poor (measurable acuity <=20/200 or <=3 cycles/degree). Teller acuity card and at any location in the visual field). Corrected Age (weeks) was defined as Chronological Age (weeks) – 40 + Gestational Age (weeks) in this study. Enrolled set included all participants for whom written informed consent was obtained for this long-term outcome study. Here, "number of subjects analyzed"= subjects evaluable for this endpoint and "n=number analyzed" evaluable at specific categories.

End point type	Primary

End point timeframe:

At 4.75 Years CA

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: Participants				
Right Eye: Normal (n=15, 18)	11	15		
Right Eye: Below Normal (n=15, 18)	4	3		
Right Eye: Poor (n=15, 18)	0	0		
Left Eye: Normal (n=15, 18)	11	14		
Left Eye: Below Normal (n=15, 18)	4	4		

Left Eye: Poor (n=15, 18)	0	0		
Both Eyes: Normal (n=15, 18)	10	17		
Both Eyes: Below Normal (n=15, 18)	5	1		
Both Eyes: Poor (n=15, 18)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 5 Years CA

End point title	Number of Participants With Visual Acuity as Assessed by an Age-appropriate Method at 5 Years CA[6]

End point description:

Standard age-appropriate methods were used to assess visual acuity (how well a participant sees at different distances) with teller acuity cards, LEA symbols test and Charts. It was categorized as following: normal (measurable acuity >= 20/40 or >=15 cycles/degree); below normal (20/200 <= measurable acuity < 20/40 or 3 cycles/degree <= measurable acuity <15 cycles/degree); poor (measurable acuity <=20/200 or <=3 cycles/degree). Corrected Age (weeks) was defined as Chronological Age (weeks) – 40 + Gestational Age (weeks) in this study. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

At 5 Years CA

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: Participants				
Right Eye: Normal (n=14, 17)	9	11		
Right Eye: Below Normal (n=14, 17)	5	6		
Right Eye: Poor (n=14, 17)	0	0		
Left Eye: Normal (n=14, 17)	8	11		
Left Eye: Below Normal (n=14, 17)	6	6		
Left Eye: Poor (n=14, 17)	0	0		
Both Eyes: Normal (n=14, 17)	9	11		
Both Eyes: Below Normal (n=14, 17)	5	6		
Both Eyes: Poor (n=14, 17)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Oculomotor Examination (Motility) and Ocular Alignment (Assessed by Corneal Light Reflex and Cover Test) at 12 Months CA

End point title	Number of Participants With Oculomotor Examination (Motility) and Ocular Alignment (Assessed by Corneal Light Reflex and Cover Test) at 12 Months CA[7]

End point description:

Ocular alignment was assessed in primary gaze by comparing the position of the corneal light reflection in left eye and right eye (corneal light reflection assessment). Presence or absence of strabismus was recorded in primary gaze and in as many of the 9 positions of gaze as feasible with the cover test assessment of refixation movement. Extraocular muscle over action or deficiency was recorded. Ocular motility referred to eye movements governed by the 6 extraocular muscles in each eye. It was assessed by examiner observation of the participants ability to abduct, adduct, supra, and inferoduct each eye. Ocular alignment and motility included the presence or absence of strabismus (classified as Esotropia [inward turn of the eye], Exotropia [outward turn of the eye], Hypertropia [upward turn of the eye], Hypotropia [downward turn of the eye]) was recorded. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

At 12 Months CA

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	36		
Units: Participants				
Esotropia: Presence	1	4		
Esotropia: Absence	24	32		
Exotropia: Presence	0	0		
Exotropia: Absence	25	36		
Hypertropia: Presence	0	0		
Hypertropia: Absence	25	36		
Hypotropia: Presence	0	0		
Hypotropia: Absence	25	36		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Oculomotor Examination (Motility) and Ocular Alignment (Assessed by Corneal Light Reflex and Cover Test) at 24 Months CA

End point title	Number of Participants With Oculomotor Examination (Motility) and Ocular Alignment (Assessed by Corneal Light Reflex and Cover Test) at 24 Months CA[8]

End point description:

Ocular alignment was assessed in primary gaze by comparing the position of the corneal light reflection in left eye and right eye (corneal light reflection assessment). Presence or absence of strabismus was recorded in primary gaze and in as many of the 9 positions of gaze as feasible with the cover test assessment of refixation movement. Extraocular muscle over action or deficiency was recorded. Ocular motility referred to eye movements governed by the 6 extraocular muscles in each eye. It was assessed by examiner observation of the participants ability to abduct, adduct, supra, and inferoduct each eye.

Ocular alignment and motility included the presence or absence of strabismus (classified as Esotropia, Exotropia, Hypertropia, Hypotropia) was recorded. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

At 24 Months CA

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	34		
Units: Participants				
Esotropia: Presence	1	5		
Esotropia: Absence	22	29		
Exotropia: Presence	0	1		
Exotropia: Absence	23	33		
Hypertropia: Presence	0	0		
Hypertropia: Absence	23	34		
Hypotropia: Presence	0	0		
Hypotropia: Absence	23	34		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Oculomotor Examination (Motility) and Ocular Alignment (Assessed by Corneal Light Reflex and Cover Test) at 5-Years CA

End point title	Number of Participants With Oculomotor Examination (Motility) and Ocular Alignment (Assessed by Corneal Light Reflex and Cover Test) at 5-Years CA[9]

End point description:

Ocular alignment was assessed in primary gaze by comparing the position of the corneal light reflection in left eye and right eye (corneal light reflection assessment). Presence or absence of strabismus was recorded in primary gaze and in as many of the 9 positions of gaze as feasible with the cover test assessment of refixation movement. Extraocular muscle over action or deficiency was recorded. Ocular motility referred to eye movements governed by the 6 extraocular muscles in each eye. It was assessed by examiner observation of the participants ability to abduct, adduct, supra, and inferoduct each eye. Ocular alignment and motility included the presence or absence of strabismus (classified as Esotropia, Exotropia, Hypertropia, Hypotropia) was recorded. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

At 5-Years CA

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: Participants				
Esotropia: Presence	1	1		
Esotropia: Absence	13	16		
Exotropia: Presence	0	0		
Exotropia: Absence	14	17		
Hypertropia: Presence	0	0		
Hypertropia: Absence	14	17		
Hypotropia: Presence	0	0		
Hypotropia: Absence	14	17		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Nystagmus at 12 Months CA

End point title	Number of Participants With Nystagmus at 12 Months CA[10]

End point description:

Nystagmus was observed during the ocular alignment assessments. Number of participants with presence and absence of nystagmus was reported at 12 Months CA. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

At 12 Months CA

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	36		
Units: Participants				
Nystagmus: Presence	1	2		
Nystagmus: Absence	24	34		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Nystagmus at 24 Months CA

End point title	Number of Participants With Nystagmus at 24 Months CA[11]

End point description:

Nystagmus was observed during the ocular alignment assessments. Number of participants with presence and absence of nystagmus was reported at 24 Months CA. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

At 24 Months CA

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	34		
Units: Participants				
Nystagmus: Presence	0	2		
Nystagmus: Absence	23	32		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Nystagmus at 5 Years CA

End point title	Number of Participants With Nystagmus at 5 Years CA[12]

End point description:

Nystagmus was observed during the ocular alignment assessments. Presence and absence of nystagmus was reported at 5 Years CA. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

At 5 Years CA

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: Participants				
Nystagmus: Presence	0	2		
Nystagmus: Absence	14	15		

Statistical analyses

No statistical analyses for this end point

Primary: Refraction With Cycloplegia as Assessed by Retinoscopy at 6 Months CA

End point title	Refraction With Cycloplegia as Assessed by Retinoscopy at 6 Months CA[13]

End point description:

Refraction was a measure of the lens power required for a focused image on the retina. Refraction with cycloplegia was measured and recorded in diopters for each eye individually (left eye and right eye). Refraction with cycloplegia performed as part of the corrective lens determination procedure included measurements of sphere, cylinder, axis, and prism for each individual eye (left eye and right eye). For sphere, the negative values are summarized as 'nearsighted', and the positive values are summarized as 'farsighted'. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint and "n=number analysed" evaluable at specific categories. Here, '99999' = mean and SD was not estimated.

End point type	Primary

End point timeframe:

At 6 Months CA

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	34		
Units: Diopter				
arithmetic mean (standard deviation)				
Right Eye: Sphere (Nearsighted) (n=6, 34)	-1.833 (± 1.0916)	-1.417 (± 1.4216)		
Right Eye: Sphere (Farsighted) (n=21, 34)	1.976 (± 1.2572)	1.838 (± 1.3256)		
Right Eye: Cylinder (n=24, 33)	0.875 (± 0.8534)	0.932 (± 0.8801)		
Right Eye: Axis (n=25, 33)	116.4 (± 58.03)	106.0 (± 52.87)		
Right Eye: Prism (n=0, 0)	99999 (± 99999)	99999 (± 99999)		
Left Eye: Sphere (Nearsighted) (n=6, 3)	-1.750 (± 0.9747)	-1.250 (± 0.9014)		
Left Eye: Sphere (Farsighted) (n=22, 34)	2.034 (± 1.2731)	1.831 (± 1.3494)		
Left Eye: Cylinder (n=25, 33)	0.820 (± 0.6395)	0.962 (± 0.8341)		
Left Eye: Axis (n=25, 33)	120.3 (± 52.27)	108.8 (± 54.18)		
Left Eye: Prism (n=0, 0)	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Primary: Refraction With Cycloplegia as Assessed by Retinoscopy at 12 Month CA

End point title	Refraction With Cycloplegia as Assessed by Retinoscopy at 12 Month CA[14]

End point description:

Refraction was a measure of the lens power required for a focused image on the retina. Refraction with cycloplegia was measured and recorded in diopters for each eye individually (left eye and right eye). Refraction with cycloplegia performed as part of the corrective lens determination procedure included measurements of sphere, cylinder, axis, and prism for each individual eye (left eye and right eye). For sphere, the negative values are summarized as 'nearsighted', and the positive values are summarized as 'farsighted'. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint and "n=number analysed" evaluable at specific categories. Here, '99999' = mean and SD was not estimated.

End point type	Primary

End point timeframe:

At 12 Months CA

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	30		
Units: Diopter				
arithmetic mean (standard deviation)				
Right Eye: Sphere (Nearsighted) (n=7, 4)	-1.564 (± 1.8752)	-2.438 (± 1.4773)		
Right Eye: Sphere (Farsighted) (n=18, 27)	2.042 (± 1.1796)	1.491 (± 1.0908)		
Right Eye: Cylinder (n=23, 27)	0.783 (± 0.7163)	0.926 (± 0.6423)		
Right Eye: Axis (n=23, 30)	86.0 (± 62.82)	105.7 (± 50.53)		
Right Eye: Prism (n=15, 25)	99999 (± 99999)	99999 (± 99999)		
Left Eye: Sphere (Nearsighted) (n=4, 5)	-2.875 (± 1.9203)	-2.500 (± 1.7048)		
Left Eye: Sphere (Farsighted) (n=21, 26)	1.857 (± 1.3171)	1.606 (± 1.1962)		
Left Eye: Cylinder (n=23, 27)	0.663 (± 0.6334)	0.851 (± 0.6795)		
Left Eye: Axis (n=22, 27)	107.3 (± 60.19)	112.6 (± 55.11)		
Left Eye: Prism (n=15, 25)	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Primary: Refraction With Cycloplegia as Assessed by Retinoscopy at 20 Month CA

End point title	Refraction With Cycloplegia as Assessed by Retinoscopy at 20 Month CA[15]

End point description:

Refraction was a measure of the lens power required for a focused image on the retina. Refraction with

cycloplegia was measured and recorded in diopters for each eye individually (left eye and right eye). Refraction with cycloplegia performed as part of the corrective lens determination procedure included measurements of sphere, cylinder, axis, and prism for each individual eye (left eye and right eye). For sphere, the negative values are summarized as 'nearsighted', and the positive values are summarized as 'farsighted'. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint and "n=number analysed" evaluable at specific categories. Here, '99999' = mean and SD was not estimated.

End point type	Primary

End point timeframe:

At 20 Months CA

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	31		
Units: Diopter				
arithmetic mean (standard deviation)				
Right Eye: Sphere (Nearsighted) (n=5, 5)	-2.350 (± 2.4083)	-1.700 (± 1.6808)		
Right Eye: Sphere (Farsighted) (n=18, 27)	1.903 (± 0.9931)	1.278 (± 0.8996)		
Right Eye: Cylinder (n=21, 27)	0.750 (± 0.6755)	0.778 (± 0.6841)		
Right Eye: Axis (n=23, 31)	105.0 (± 62.33)	122.8 (± 58.69)		
Right Eye: Prism (n=15, 22)	99999 (± 99999)	99999 (± 99999)		
Left Eye: Sphere (Nearsighted) (n=3, 5)	-3.500 (± 1.8028)	-2.600 (± 1.9733)		
Left Eye: Sphere (Farsighted) (n=20, 27)	1.800 (± 1.2237)	1.389 (± 1.1080)		
Left Eye: Cylinder (n=20, 29)	0.900 (± 0.8288)	0.681 (± 0.5665)		
Left Eye: Axis (n=21, 28)	117.8 (± 53.82)	110.1 (± 53.56)		
Left Eye: Prism (n=16, 23)	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Primary: Refraction With Cycloplegia as Assessed by Retinoscopy at 4.75 Years CA

End point title	Refraction With Cycloplegia as Assessed by Retinoscopy at 4.75 Years CA[16]

End point description:

Refraction was a measure of the lens power required for a focused image on the retina. Refraction with cycloplegia was measured and recorded in diopters for each eye individually (left eye and right eye). Refraction with cycloplegia performed as part of the corrective lens determination procedure included measurements of sphere, cylinder, axis, and prism for each individual eye (left eye and right eye). For sphere, the negative values are summarized as 'nearsighted', and the positive values are summarized as 'farsighted'.Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint

and “n=number analysed” evaluable at specific categories. Here, '99999' = mean and SD was not estimated because “n” was 1 for this category.

End point type	Primary

End point timeframe:

At 4.75 Years CA

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: Diopter				
arithmetic mean (standard deviation)				
Right Eye: Sphere (Nearsighted) (n=1, 1)	-8.500 (± 99999)	-0.500 (± 99999)		
Right Eye: Sphere (Farsighted) (n=17, 15)	1.691 (± 1.1094)	1.383 (± 1.5465)		
Right Eye: Cylinder (n=16, 17)	0.593 (± 0.6505)	0.603 (± 0.6254)		
Right Eye: Axis (n=17, 17)	99.1 (± 69.95)	119.0 (± 56.05)		
Right Eye: Prism (n=17, 14)	0.02 (± 0.075)	0.00 (± 0.000)		
Left Eye: Sphere (Nearsighted) (n=1, 1)	-6.500 (± 99999)	-0.750 (± 99999)		
Left Eye: Sphere (Farsighted) (n=17, 15)	1.853 (± 1.2376)	1.517 (± 1.9966)		
Left Eye: Cylinder (n=15, 17)	0.717 (± 0.7126)	0.574 (± 0.5574)		
Left Eye: Axis (n=16, 17)	88.6 (± 65.64)	114.2 (± 55.17)		
Left Eye: Prism (n=15, 13)	0.02 (± 0.056)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Stereoacuity as Assessed With the Lang Stereotest At 5 Years CA

End point title	Number of Participants With Stereoacuity as Assessed With the Lang Stereotest At 5 Years CA[17]

End point description:

Stereoacuity, a measure of depth perception, was assessed using the Lang Stereotest. Number of participants with presence and absence of stereopsis (the ability to perceive depth and 3-dimensional structure) was reported. Enrolled set. Here, “number of subjects analysed”= subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

At 5 Years CA

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	17		
Units: Participants				
Participants with presence of stereopsis	13	16		
Participants with absence of stereopsis	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs)[18]

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. Safety Set included all participants in the Enrolled Set who have safety follow-up data in this long-term outcome study.

End point type	Primary

End point timeframe:

From start of study up to end of study (up to 6.5 years)

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	40		
Units: Participants	11	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Weight Z-score

End point title	Change From Baseline in Body Weight Z-score

End point description:

Body weight collected using calibrated scales (type of scale was dependent upon participant's age). Measure recorded to the nearest 0.1 kilogram (kg). Z-score based on participants chronological age and utilizing World Health Organization child growth standards by adjusting age and sex- matched means

and standard deviations (norm). Z-score is standard score that gives idea of how far from the mean a data point is. If Z-score is 0, it indicates that the data point's score is identical to the mean score. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Baseline is first assessment in the antecedent study (ROPP-2008-01 [2007-007872-40]).). Change from baseline in body weight Z-score at 6-month, 12-month, 24-month and 5-year CA were reported. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint and "n=number analysed" evaluable at specific time points..

End point type	Secondary

End point timeframe:

Baseline, 6 Months CA, 12 Months CA, 24 Months CA and 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	39		
Units: Z-score				
arithmetic mean (standard deviation)				
Change at 6 Months CA (n=28, 39)	4.40 (± 1.323)	4.30 (± 1.146)		
Change at 12 Months CA (n=26, 36)	5.08 (± 1.300)	4.88 (± 1.026)		
Change at 24 Months CA (n=25, 36)	5.17 (± 0.885)	4.99 (± 0.983)		
Change at 5 Years CA (n=19, 24)	5.80 (± 1.149)	5.60 (± 1.660)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height Z-score

End point title	Change From Baseline in Height Z-score

End point description:

Height was measured using Z-score. Z-score was calculated based on the participants chronological age and utilizing World Health Organization child growth standards by adjusting age and sex- matched means and standard deviations (norm). Baseline was defined as the first assessment in the antecedent study (ROPP-2008-01 [2007-007872-40]). Z-score is a standard score that gives an idea of how far from the mean a data point is. If a Z-score is 0, it indicates that the data point's score is identical to the mean score. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Change from baseline in Height Z-score at 6-month, 12-month, 24-month and 5-year CA were reported. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint and "n=number analysed" evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, 6 Months CA, 12 Month CA, 24 Months CA and 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	39		
Units: Z-Score				
arithmetic mean (standard deviation)				
Change at 6 Months CA (n=28, 39)	6.36 (± 1.711)	6.19 (± 1.215)		
Change at 12 Months CA (n=26, 36)	6.79 (± 1.747)	7.25 (± 1.155)		
Change at 24 Months CA (n=25, 36)	7.30 (± 2.029)	7.78 (± 1.376)		
Change at 5 Years CA (n=19, 24)	7.84 (± 1.856)	8.17 (± 1.505)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Head Circumference Z-score

End point title	Change From Baseline in Head Circumference Z-score

End point description:

Head circumference measured for all participants using a "lasso" type,non-stretchable measuring tape such as the Lasso-o tape.Z-score calculated based on participants chronological age and utilizing World Health Organization child growth standards by adjusting age,sex matched means and standard deviations (norm).Z-score is standard score that gives idea of how far from mean a data point is. If a Z-score is 0, it indicates that data point's score is identical to mean score.Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Baseline defined as first assessment in antecedent study (ROPP-2008-01 [2007-007872-40]).Change from baseline in Head Circumference Z-score at 6, 12 and 24-months reported. Enrolled set.Here,"number of subjects analysed"= subjects evaluable for this endpoint and "n=number analysed" evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline, 6 Months CA, 12 Months CA and 24 Months CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	39		
Units: Z-score				
arithmetic mean (standard deviation)				
Change at 6 Months CA (n=28, 39)	7.61 (± 1.535)	7.12 (± 1.576)		
Change at 12 Months CA (n=26, 36)	8.29 (± 1.472)	7.83 (± 1.567)		
Change at 24 Months CA (n=25, 35)	8.44 (± 1.415)	8.05 (± 1.692)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline (12 Months CA) in Cognitive Development as Assessed by Bayley Scales of Infant and Toddler Development (BSID-III) Composite Scores at 24 Months CA

End point title	Change from Baseline (12 Months CA) in Cognitive Development as Assessed by Bayley Scales of Infant and Toddler Development (BSID-III) Composite Scores at 24 Months CA

End point description:

The BSID-III was to assess cognitive, motor, and language skills, and applicable to children aged 1-42 months. There are 5 subscales, cognitive subscale (Ranges: 55-145) stands alone while 2 language subscales (expressive and receptive) combine to make a total language score (Ranges: 47-153) and 2 motor subtests (fine and gross motor) form combined motor scale (Ranges: 46-154). Positive value indicate improvement and negative value indicates worsening in cognitive development. The 12 Months CA considered as baseline for this outcome measure. Composite scores derived from various sums of subtest scaled scores and scaled to a metric with a mean of 100 and a standard deviation of 15 and range from 40 to 160. Higher values denote stronger skills and abilities in the domain, indicating better outcomes. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (12 Months CA), 24 Months CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	32		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Cognitive Composite Scores (n=23,32)	7.0 (± 18.45)	6.6 (± 21.27)		
Language Composite Scores (n=23,32)	2.4 (± 18.73)	-0.9 (± 15.79)		
Motor Composite Scores (n=23,32)	12.2 (± 23.54)	10.8 (± 18.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Development as Assessed by Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV) Full Scale at 5 Years CA

End point title	Cognitive Development as Assessed by Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV) Full Scale at 5 Years CA

End point description:

WPPSI-IV is measure of general cognitive development in children that has components of both verbal and nonverbal tasks. It is applicable to children aged 2 years +6 months to 7 years +7 months, is used to assess child's cognitive skills. Its test framework is organized into five Primary Index sub scales: Verbal Comprehension,Visual Spatial,Fluid Reasoning,Working Memory and Processing Speed. The Full Scale includes all sub scales at the Primary Index scale level, as well as any supplemental subtests that may be used to derive the Full Scale IQ. Composite scores derived from the sum of sub scaled scores with a mean of 100 and a standard deviation of 15. Composite score for Full Scale IQ and subscales (Verbal Comprehension,Visual Spatial,Fluid Reasoning,Working Memory and Processing Speed) ranges from 40 (extremely low) to 160 (very superior). Enrolled set. Here,"number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	14		
Units: Scores on a scale				
arithmetic mean (standard deviation)	97.3 (± 17.28)	91.6 (± 14.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Physical Examination

End point title	Number of Participants With Abnormal Physical Examination

End point description:

Physical examination includes general appearance; head and neck, eyes, ears, nose and throat; chest and lungs; endocrine, cardiovascular system, abdomen, genitourinary, skin and musculoskeletal system. Number of participants with abnormal physical examination were reported. Safety set included all participants in the Enrolled Set who have safety follow-up data in this long-term outcome study.

End point type	Secondary

End point timeframe:

From start of study drug administration up to end of study (up to 6.5 years)

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	40		
Units: Participants	13	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Diagnosed With Cerebral Palsy (CP) by Neurological Examination at 24 Months CA

End point title	Number of Participants Diagnosed With Cerebral Palsy (CP) by Neurological Examination at 24 Months CA

End point description:

A comprehensive neurological examination for the diagnosis of CP was conducted. The Amiel-Tison neurological examination framework was utilized for this assessment and it was conducted by trained

medical professionals. Number of Participants diagnosed with CP by neurological examination at 24 Months CA were reported. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At 24 Months CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	37		
Units: Participants	1	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (6 Months CA) in Child Behavior as Assessed by Vineland Adaptive Behaviour Scales (VABS-II)

End point title	Change From Baseline (6 Months CA) in Child Behavior as Assessed by Vineland Adaptive Behaviour Scales (VABS-II)

End point description:

The VABS-II was used to measure the personal and social skills of participants serially over time. This test measures the following 4 key domains: Communication, Daily Living Skills, Socialization, and Motor skills. The four domains (Communication, Daily Living Skills, Socialization, and Motor skills) have the same range and directionality as the adaptive behavior composite score (20-160). Higher scores indicate higher level of cognitive ability. A positive change value indicates improvement and negative value indicates worsening in adaptive functioning. The 6 months CA was considered as baseline for this outcome measure. Change from baseline (6 Months CA) in child behavior as assessed by VABS-II adaptive behavior composite was reported here. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint and "n=number analysed" evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline (6 Months CA), 12 Months CA, 24 Months CA, and 5 Year CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	30		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Change at 12 Months CA (n=22, 30)	-0.3 (± 14.50)	-1.5 (± 12.41)		
Change at 24 Months CA (n=20, 30)	7.8 (± 16.47)	0.8 (± 14.89)		
Change at 5 Years CA (n=13, 15)	-3.2 (± 20.92)	-3.9 (± 19.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Normal and Abnormal Hearing Screening Status

End point title	Number of Participants With Normal and Abnormal Hearing Screening Status

End point description:

Number of participants with any hearing status (normal and abnormal) were reported. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint and "n=number analysed" evaluable at specific time points.

End point type	Secondary

End point timeframe:

At 6 Months CA and 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	28		
Units: Participants				
At 6 Months CA: Normal Hearing (21, 28)	20	24		
At 6 Months CA: Abnormal Hearing (21, 28)	1	4		
At 5 Years CA: Normal Hearing (17, 21)	15	20		
At 5 Years CA: Abnormal Hearing (17, 21)	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Child Behaviour as Assessed by Child Behaviour Checklist (CBCL) Based on T-Score Clinical Categories

End point title	Number of Participants With Child Behaviour as Assessed by Child Behaviour Checklist (CBCL) Based on T-Score Clinical Categories

End point description:

CBCL(1½ to 5) a parent-reported outcome measure to assess behavioral, emotional, and social functioning of children aged 18-60 months. It composed of 99 items rated on Likert scale and include 7 syndrome scale under 2 domains (Internalizing and Externalizing Problems): Internalizing include syndromes of Emotionally Reactive,Anxious/Depressed,Somatic Complaints,and Withdrawn.

Externalizing include syndrome of Aggressive Behavior and Attention Problem. The 2 domains of all 7 scales combined to form total score range of 23 to 100. For each question, raw scores of all subscales converted to standardized T-scores. Higher T score indicate more behavior problems. For Internalization, Externalization and Total Behavior Problem, T-scores of less than 60 are non-clinical,60-63 are borderline,and 64 or more considered clinical. Enrolled set.Here,"number of subjects analysed"=subjects evaluable for this endpoint and"n=number analysed" evaluable at specific categories. Here, "M"=Months, "Y"=Years.

End point type	Secondary

End point timeframe:

At 24 Months CA and 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	34		
Units: Participants				
24 M: Internalizing:NonClinical(n=23,34)	23	32		
24 M: Internalizing:Borderline(n=23,34)	0	0		
24 M: Internalizing:Clinical(n=23,34)	0	2		
5 Y: Internalizing:NonClinical(n=19, 20)	15	15		
5 Y: Internalizing:Borderline(n=19,20)	1	2		
5 Y: Internalizing:Clinical(n=19,20)	3	3		
24 M: Externalizing:NonClinical(n=23,34)	21	32		
24 M: Externalizing:Borderline(n=23,34)	1	0		
24 M: Externalizing:Clinical(n=23,34)	1	2		
5 Y: Externalizing:NonClinical(n=19, 20)	16	17		
5 Y: Externalizing:Borderline(n=19, 20)	0	2		
5 Y: Externalizing:Clinical(n=19, 20)	3	1		
24 M: Total Behavior Problems:Clinical(n=23,34)	22	31		
24 M: Total Behavior Problems:NonClinical(n=23,34)	1	3		
24 M: Total Behavior Problems:Borderline(n=23,34)	0	0		
5 Y: Total Behavior Problems:Clinical(n=19,20)	14	17		
5 Y: Total Behavior Problems:NonClinical(n=19,20)	3	2		
5 Y: Total Behavior Problems:Borderline(n=19,20)	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Child Behavior as Assessed by Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) Based on Total Score

End point title	Child Behavior as Assessed by Attention-Deficit/Hyperactivity

	Disorder Rating Scale (ADHD-RS) Based on Total Score

End point description:

The ADHD-RS measures the behaviors of children with Attention-Deficit/Hyperactivity Disorder (ADHD). It consisted of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV criteria. Each item was scored on a 4-point scale ranging from 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0 to 54. Higher scores represent greater severity of ADHD symptoms. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Score on scale				
arithmetic mean (standard deviation)	11.9 (± 9.30)	8.3 (± 10.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Pulmonary Morbidity

End point title	Number of Participants With Pulmonary Morbidity

End point description:

Pulmonary morbidity was assessed with questions related to family history and smoking status as well as diagnosis of select pulmonary symptoms, conditions and related hospitalizations. Anyone living in the same home with participant smoke, Participants had asthma, wheezing, bronchopulmonary dysplasia (BPD) exacerbation or flare-up, Participants had bronchiolitis, bronchitis, or pneumonia diagnosed, Participants had to use oxygen at home, Participants had to visit emergency room or urgent care for respiratory problem, and Participants had to stay in a hospital overnight for respiratory problem were reported. Enrolled set. Here, "number of subjects analysed"= subjects evaluable for this endpoint and "n=number analysed" evaluable at specific categories. Here, "M"=Months, "Y"=Yes and "N"=No.

End point type	Secondary

End point timeframe:

At 6 Months CA, 12 Months CA and 24 Months CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	39		
Units: Participants				
6M:Same home with participant smoke:Y(n=28,39)	6	7		
6M:Same home with participant smoke:N(n=28,39)	22	32		

6M:Asthma,wheeze,BPDexacerbation flare:Y(n=28,39)	8	4		
6M:Asthma,wheeze,BPDexacerbation flare:N(n=28,39)	20	35		
6M:Bronchiolitis,bronchitis,pneumonia:Y (n=28,39)	4	5		
6M:Bronchiolitis,bronchitis,pneumonia:N (n=28,39)	24	34		
6M:Used oxygen at home:Y(n=28,39)	8	5		
6M:Used oxygen at home:N(n=28,39)	20	34		
6M:Emergency respiratory problem:Y(n=28,39)	5	7		
6M:Emergency respiratory problem:N(n=28,39)	23	32		
6M:Hospitalovernightrespiratoryproblem :Y(n=28,39)	5	7		
6M:Hospitalovernightrespiratoryproblem :N(n=28,39)	23	32		
12M:Same home with participant smoke:Y(n=26,35)	3	5		
12M:Same home with participant smoke:N(n=26,35)	23	30		
12M:Asthma,wheeze,BPDexacerbation flare:Y(n=26,35)	4	7		
12M:Asthma,wheeze,BPDexacerbation flare:N(n=26,35)	22	28		
12M:Bronchiolitis,bronchitis,pneumonia: Y(n=26,35)	1	5		
12M:Bronchiolitis,bronchitis,pneumonia: N(n=26,35)	25	30		
12M:Used oxygen at home:Y(n=26,35)	2	0		
12M:Used oxygen at home:N(n=26,35)	24	35		
12M:Emergency respiratory problem:Y(n=26,35)	3	7		
12M:Emergency respiratory problem:N(n=26,35)	23	28		
12M:Hospitalovernightrespiratoryproble m:Y(n=26,35)	1	4		
12M:Hospitalovernightrespiratoryproble m:N(n=26,35)	25	31		
24M:Same home with participant smoke:Y(n=25,36)	3	3		
24M:Same home with participant smoke:N(n=25,36)	22	33		
24M:Asthma,wheeze,BPDexacerbation flare:Y(n=25,36)	4	8		
24M:Asthma,wheeze,BPDexacerbation flare:N(n=25,36)	21	28		
24M:Bronchiolitis,bronchitis,pneumonia: Y(n=25,36)	2	1		
24M:Bronchiolitis,bronchitis,pneumonia: N(n=25,36)	23	25		
24M:Used oxygen at home:Y(n=25,36)	1	0		
24M:Used oxygen at home:N(n=25,36)	24	36		
24M:Emergency respiratory problem:Y(n=25,36)	5	5		

24M:Emergency respiratory problem:N(n=25,36)	20	31		
24M:Hospitalovernightrespiratoryproblem:Y(n=25,36)	2	0		
24M:Hospitalovernightrespiratoryproblem:N(n=25,36)	23	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Child Behavior as Assessed by Social Communication Questionnaire (SCQ) Based on Total Score

End point title	Child Behavior as Assessed by Social Communication Questionnaire (SCQ) Based on Total Score

End point description:

SCQ instrument to evaluate communication skills and social functioning in child with autism or autism spectrum disorders (ASD).
The SCQ has 40 dichotomous (yes, no) items. Each scored item receives a value of 1 point for "abnormal behavior" and 0 point for "absence of abnormal behavior/normal behavior." The SCQ yields a total score ranging from 0 to 39, with higher scores representing more social communication impairment. Enrolled set. Here,"number of subjects analysed"= subjects evaluable for this endpoint

End point type	Secondary

End point timeframe:

At 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Score on scale				
arithmetic mean (standard deviation)	5.9 (± 6.80)	5.2 (± 7.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Survival Status

End point title	Number of Participants With Survival Status

End point description:

Survival status was assessed by number participants who died and were censored during the study. Safety set included all participants in the Enrolled Set who have safety follow-up data in this long-term outcome study.

End point type	Secondary

End point timeframe:

From start of study drug administration up to end of study (up to 6.5 years)

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	40		
Units: Participants				
Participants who Died	1	0		
Participants who were Censored	35	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (3 Months CA) in Pediatric Quality of Life Inventory (PedsQL™) Scale: Infant Scale

End point title	Change From Baseline (3 Months CA) in Pediatric Quality of Life Inventory (PedsQL™) Scale: Infant Scale

End point description:

The PedsQL was a generic health related quality of life instrument designed specifically for a pediatric population. PedsQL infant scale encompasses 5 dimensions of functioning (Physical Functioning, Physical Symptoms, Emotional Functioning, Social Functioning, and Cognitive Functioning). The infant for ages 1-12 months (36 Items); for ages 13-24 months (45 Items) rated on a 5-point Likert scale (0 to 4). Overall total scores were calculated as average of all dimensional sub-score items of Infant scale, ranging from 0 to 100 where 0=100 (Never), 1=75 (almost never), 2=50 (sometimes), 3=25 (often), and 4=0 (almost always). Higher scores indicate improved quality of life. A negative value indicates decreased quality of life. Enrolled set. Here,"number of subjects analysed"= subjects evaluable for this endpoint. and "n=number analysed" evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline (3 Months CA) up to 6 Months CA, 12 Months CA and 24 Months CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	38		
Units: Score on scale				
arithmetic mean (standard deviation)				
Change at 6 Months CA: Total Score (n=28, 38)	-1.10 (± 10.056)	-0.60 (± 11.088)		
Change at 12 Months CA: Total Score (n=25, 36)	-0.16 (± 12.875)	-0.57 (± 11.902)		
Change at 24 Months CA: Total Score (n=3, 7)	7.84 (± 7.339)	-4.82 (± 14.205)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (24 Months CA) in Pediatric Quality of Life Inventory (PedsQL™) Scale: Generic Core Scale (GCS) Total Score

End point title	Change From Baseline (24 Months CA) in Pediatric Quality of Life Inventory (PedsQL™) Scale: Generic Core Scale (GCS) Total Score

End point description:

The PedsQL was a generic health related quality of life instrument designed specifically for a pediatric population. The GCS encompasses 4 dimensions of functioning (physical, emotional, social, school). The GCS that apply to toddler for 2-4 years of age (21 Items) rated on a 5-point Likert scale (0 to 4); and Young Child for 5-7 years of age (23 Items) rated on a 3-point Likert scale (0, 2, 4). Overall total scores were calculated as average of all dimensional sub-score items of GCS (Toddler and young children's) ranging from 0 to 100 where 0=100 (Never), 1=75 (almost never), 2=50 (sometimes), 3=25 (often), and 4=0 (almost always). Higher scores indicate improved quality of life. A negative value indicates decreased quality of life. Enrolled set. Here,"number of subjects analysed"= subjects evaluable for this endpoint. and "n=number analysed" evaluable at specific time points.

End point type	Secondary

End point timeframe:

Baseline (24 Months CA), up to 3 Years CA, 4 Years CA and 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	22		
Units: Score on scale				
arithmetic mean (standard deviation)				
Change at 3 Years CA: Total Score (n=19, 22)	0.62 (± 12.220)	-1.13 (± 8.533)		
Change at 4 Years CA: Total Score (n=19, 18)	1.50 (± 14.376)	-3.46 (± 7.917)		
Change at 5 Years CA: Total Score (n=16, 15)	-4.96 (± 15.561)	-4.49 (± 8.225)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Health Status Measured by the Health Status Classification System-Preschool (HSCS-PS)

End point title	Number of Participants With Health Status Measured by the Health Status Classification System-Preschool (HSCS-PS)

End point description:

HSCS-PS: validated instrument for age 2.5 - 5 years, composed of 12 domains (Vision, Hearing, Speech, Mobility, Dexterity, Self-care, Emotion, Learn/Remember, Think/Problem Solve, Pain, General Health, Behavior) with up to 6 levels (0-5). The 12 dimensions grouped into 4 categories: neurosensory (vision and hearing), motor (mobility, dexterity, and self-care), learning/remembering (speech, learn/remember, think/problem solve), and quality of life (emotion, pain, general health, behavior). For each category, data were recorded into following levels: no problem (scoring 0 on any attribute); mild problem (scoring 1 on scale of 0 to 3, or 1 to 2 on scale of 0 to 5 for any attribute);moderate/severe problem (scoring > 1 on scale of 0 to 3, or >2 on a scale of 0 to 5 for any attribute). Higher numbers indicating better child's health status. Enrolled set. Here,"number of subjects analysed"= subjects evaluable for this endpoint. and "n=number analysed" evaluable at specific timepoints.

End point type	Secondary

End point timeframe:

At 24 Months CA, 3 Years CA, 4 Years CA and 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	35		
Units: Participants				
24M:Neurosensory:No Problem(n=24,35)	21	30		
24M:Neurosensory:Mild(n=24,35)	3	4		
24M:Neurosensory:Moderate/severe(n=24,35)	0	1		
24M:Motor:No Problem(n=24,35)	19	21		
24M:Motor:Mild(n=24,35)	3	9		
24M:Motor:Moderate/severe(n=24,35)	2	5		
24M:Learning/Remembering:No Problem(n=24,35)	10	10		
24M:Learning/Remembering: Mild(n=24,35)	6	13		
24M:Learning/Remembering: Moderate/severe(n=24,35)	8	12		
24M:Quality of life:No Problem(n=24,35)	11	21		
24M:Quality of life: Mild(n=24,35)	11	11		
24M:Quality of life: Moderate/severe(n=24,35)	2	3		
3Y:Neurosensory:No Problem(n=24,33)	20	28		
3Y:Neurosensory:Mild(n=24,33)	2	3		
3Y:Neurosensory:Moderate/severe(n=24,33)	2	2		
3Y:Motor:No Problem(n=24,33)	16	16		
3Y:Motor:Mild(n=24,33)	4	13		
3Y:Motor:Moderate/severe(n=24,33)	4	4		
3Y:Learning/Remembering:No Problem(n=24,33)	13	17		
3Y:Learning/Remembering: Mild(n=24,33)	6	11		
3Y:Learning/Remembering: Moderate/severe(n=24,33)	5	5		
3Y:Quality of life:No Problem(n=24,33)	13	21		
3Y:Quality of life: Mild(n=24,33)	9	8		

3Y:Quality of life: Moderate/severe(n=24,35)	2	4		
4Y:Neurosensory:No Problem(n=23,27)	21	23		
4Y:Neurosensory:Mild(n=23,27)	2	4		
4Y:Neurosensory:Moderate/severe(n=23,27)	0	0		
4Y:Motor:No Problem(n=23,27)	16	16		
4Y:Motor:Mild(n=23,27)	5	8		
4Y:Motor:Moderate/severe(n=23,27)	2	3		
4Y:Learning/Remembering:No Problem(n=23,27)	16	12		
4Y:Learning/Remembering: Mild(n=23,27)	4	11		
4Y:Learning/Remembering: Moderate/severe(n=23,27)	3	4		
4Y:Quality of life:No Problem(n=23,27)	13	17		
4Y:Quality of life: Mild(n=23,27)	8	9		
4Y:Quality of life: Moderate/severe(n=23,27)	2	1		
5Y:Neurosensory:No Problem(n=19,20)	16	17		
5Y:Neurosensory:Mild(n=19,20)	3	3		
5Y:Neurosensory:Moderate/severe(n=19,20)	0	0		
5Y:Motor:No Problem(n=19,20)	13	14		
5Y Motor:Mild(n=19,20)	5	5		
5Y:Motor:Moderate/severe(n=19,20)	1	1		
5Y:Learning/Remembering:No Problem(n=19,20)	10	12		
5Y:Learning/Remembering: Mild(n=19,20)	7	7		
5Y:Learning/Remembering: Moderate/severe(n=19,20)	2	1		
5Y:Quality of life:No Problem(n=19,20)	11	15		
5Y:Quality of life: Mild(n=19,20)	8	4		
5Y:Quality of life: Moderate/severe(n=19,20)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Status Measured by the Health Utilities Index (HUI) Mark 2 and 3

End point title	Health Status Measured by the Health Utilities Index (HUI) Mark 2 and 3

End point description:

The HUI is a family of generic health profiles and preference-based systems used for measuring health status, reporting HRQoL, and producing utility scores. The HUI2 score includes 6 attributes: Sensation, Mobility, Cognition, Self-Care, Emotion, and Pain with up to 5 levels of severity (higher numbers indicate worse level of severity). The HUI3 score includes 8 attributes: Vision, Hearing, Speech, Cognition, Ambulation, Dexterity, Emotion, and Pain with up to 6 levels to indicate the severity (with higher numbers indicating worse levels). HUI2/3 single-attribute scores of morbidities are defined on a scale such the worst level has a score of 0.00 and the best level has a score of 1.00. HUI mark 2 and 3 Overall utility score was reported. Enrolled set. Here,"number of subjects analysed"= subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Score on scale				
arithmetic mean (standard deviation)				
HUI2 Overall Utility Score	0.929 (± 0.1246)	0.867 (± 0.2115)		
HUI3 Overall Utility Score	0.893 (± 0.1960)	0.852 (± 0.2665)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Care Resource Use (HCRU)

End point title	Health Care Resource Use (HCRU)

End point description:

The total number of private office/hospital outpatient visits of health care resource at 3 Months CA, 6 Months CA, 12 Months CA, 24 Months CA, 3 Years CA, 4 Years CA and 5 Years CA were reported. Enrolled set. Here,"number of subjects analysed"= subjects evaluable for this endpoint. and "n=number analysed" evaluable at specific time points.

End point type	Secondary

End point timeframe:

At 3 Months CA, 6 Months CA, 12 Months CA, 24 Months CA, 3 Years CA, 4 Years CA and 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	39		
Units: Visits				
arithmetic mean (standard deviation)				
At 3 Months CA (n=29, 39)	9.8 (± 6.48)	8.3 (± 7.67)		
At 6 Months CA (n=28, 37)	15.5 (± 16.06)	10.3 (± 9.40)		
At 12 Months CA (n=25, 36)	25.0 (± 23.81)	22.5 (± 33.95)		
At 24 Months CA (n=25, 35)	20.1 (± 31.95)	30.0 (± 40.92)		
At 3 Years CA (n=24, 31)	22.8 (± 41.38)	34.8 (± 55.25)		
At 4 Years CA (n=20, 23)	21.8 (± 39.00)	41.2 (± 69.93)		
At 5 Years CA (n=16, 15)	15.7 (± 39.80)	32.7 (± 51.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Care Resource Utilization (HCRU): Number of Visits to Emergency Department

End point title	Health Care Resource Utilization (HCRU): Number of Visits to Emergency Department

End point description:

Number of visits to the emergency department at 3 Months CA, 6 Months CA, 12 Months CA, 24 Months CA, 3 Years CA, 4 Years CA and 5 Years CA were reported. Enrolled set. Here,"number of subjects analysed"= subjects evaluable for this endpoint. and "n=number analysed" evaluable at specific categories. Here, '99999' = SD was not estimated.

End point type	Secondary

End point timeframe:

At 3 Months CA, 6 Months CA, 12 Months CA , 24 Months CA, 3 Years CA, 4 Years CA and 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: Visits				
arithmetic mean (standard deviation)				
At 3 Months CA (n=6, 7)	2.5 (± 1.87)	1.6 (± 1.13)		
At 6 Months CA (n=5, 10)	2.2 (± 2.17)	1.3 (± 0.67)		
At 12 Months CA (n=9, 13)	1.6 (± 0.73)	2.2 (± 1.14)		
At 24 Months CA (n=15, 17)	2.1 (± 1.39)	1.4 (± 0.61)		
At 3 Years CA (n=11, 14)	2.5 (± 2.38)	1.6 (± 0.84)		
At 4 Years CA (n=7, 6)	1.9 (± 1.46)	1.7 (± 0.82)		
At 5 Years CA (n=3, 1)	1.7 (± 0.58)	1 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Care Resource Utilization (HCRU): Duration of Hospitalization

End point title	Health Care Resource Utilization (HCRU): Duration of Hospitalization

End point description:

The participants, duration of hospitalizations at 3 Months CA, 6 Months CA, 12 Months CA, 24 Months CA, 3 Years CA, 4 Years CA and 5 Years CA were reported. Enrolled set. Here,"number of subjects analysed"= subjects evaluable for this endpoint. and "n=number analysed" evaluable at specific time

points.

End point type	Secondary

End point timeframe:

At 3 Months CA, 6 Months CA, 12 Months CA , 24 Months CA, 3 Years CA, 4 Years CA and 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: Days				
arithmetic mean (standard deviation)				
At 3 Months CA (n=9, 11)	12.9 (± 31.27)	5.5 (± 4.55)		
At 6 Months CA (n=9, 12)	6.4 (± 4.56)	7.4 (± 5.98)		
At 12 Months CA (n=5, 9)	7.2 (± 7.76)	9.0 (± 11.87)		
At 24 Months CA (n=7, 4)	4.1 (± 5.01)	2.5 (± 1.73)		
At 3 Years CA (n=4, 5)	4.3 (± 3.30)	4.8 (± 6.87)		
At 4 Years CA (n=2, 3)	3.5 (± 3.54)	4.0 (± 3.61)		
At 5 Years CA (n=0, 0)	0.00 (± 0.000)	0.00 (± 0.000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Care Resource Utilization (HCRU): Number of Participants who Required Prescription Eyeglasses and Educational Support

End point title	Health Care Resource Utilization (HCRU): Number of Participants who Required Prescription Eyeglasses and Educational Support

End point description:

Number of participants who required prescription eyeglasses and educational support at 3 Months CA, 6 Months CA, 12 Months CA, 24 Months CA, 3 Years CA, 4 Years CA and 5 Years CA were reported. Enrolled set. Here,"number of subjects analysed"= subjects evaluable for this endpoint. and "n=number analysed" evaluable at specific time points.

End point type	Secondary

End point timeframe:

At 3 Months CA, 6 Months CA, 12 Months CA, 24 Months CA, 3 Years CA, 4 Years CA and 5 Years CA

End point values	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	39		
Units: Participants				
3 Months:Used Eyeglasses:Yes(n=32,39)	0	0		
3 Months:Used Eyeglasses:No(n=32,39)	32	39		

6 Months:Used Eyeglasses:Yes(n=28,39)	0	0		
6 Months:Used Eyeglasses:No(n=28,39)	28	39		
12 Months:Used Eyeglasses:Yes(n=26,36)	0	1		
12 Months:Used Eyeglasses:No(n=26,36)	26	35		
24 Months:Used Eyeglasses:Yes(n=25,36)	1	2		
24 Months:Used Eyeglasses:No(n=25,36)	24	34		
3 Years:Used Eyeglasses:Yes(n=24,33)	3	7		
3 Years:Used Eyeglasses:No(n n=24,33)	21	26		
4 Years:Used Eyeglasses:Yes(n=23,27)	2	5		
4 Years:Used Eyeglasses:No(n=23,27)	21	22		
5 Years:Used Eyeglasses:Yes(n=19,20)	3	4		
5 Years:Used Eyeglasses:No(n=19,20)	16	16		
3 Months:Educational Support:Yes(n=32,39)	0	0		
3 Months:Educational Support:No(n=32,39)	32	39		
6 Months:Educational Support:Yes(n=28,39)	0	1		
6 Months:Educational Support:No(n=28,39)	28	38		
12 Months:Educational Support:Yes(n=26,36)	0	1		
12 Months:Educational Support:No(n=26,36)	26	35		
24 Months:Educational Support:Yes(n=25,36)	0	0		
24 Months:Educational Support:No(n=25,36)	25	36		
3 Years:Educational Support:Yes(n=24,33)	1	4		
3 Years:Educational Support:No(n=24,33)	23	29		
4 Years:Educational Support:Yes(n=23,27)	5	3		
4 Years:Educational Support:No(n=23,27)	18	24		
5 Years:Educational Support:Yes(n=19,20)	3	5		
5 Years:Educational Support:No(n=19,20)	16	15		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study up to end of study (6.5 years)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Antecedent Standard of Care
Reporting group description:	
Participants who were treated with standard neonatal care in study ROPP-2008-01 (2007-007872-40).	
Reporting group title	Antecedent rhIGF-1/rhIGFBP-3
Reporting group description:	
Participants who were treated with rhIGF-1/rhIGFBP-3 in study ROPP-2008-01 (2007-007872-40).	

Serious adverse events	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 36 (8.33%)	2 / 40 (5.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Sudden infant death syndrome			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar hypertrophy			
subjects affected / exposed	2 / 36 (5.56%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Antecedent Standard of Care	Antecedent rhIGF-1/rhIGFBP-3	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 36 (13.89%)	2 / 40 (5.00%)	
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	5 / 36 (13.89%)	2 / 40 (5.00%)	
occurrences (all)	5	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2016	Protocol Amendment 1: Removed the Refraction with Cycloplegia assessment performed at the 24-month and the 5-year visits. Added the 20-month visit with the following assessments: visual acuity, corrective lens determination (including refraction with cycloplegia), assessment of participation in other clinical studies. Added the 4.75-year visit with the following assessments: visual acuity and corrective lens determination (including refraction with cycloplegia). Clarified the term "Pulmonary Morbidity Assessment" throughout the protocol for consistency by replacing "Questionnaire" with "Assessment." Updated list of Target Medical Events to be captured in the study to ensure all events with a potential impact to the primary and secondary endpoint are tracked. AEs related to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP 2008 01, Section D). AEs related to procedures performed in this study (Study SHP 607 201). Specified targeted medical events regardless of causality. Only the following SAEs will be collected (Fatal SAEs regardless of causality, SAEs related to ROP, SAEs related to congenital malformations not identified at birth which may impact neurocognitive development, Captured SAEs from the end-of–study visit in ROPP-2008-01 Section D and the start of the SHP-607-201 study for safety purpose, Added "When possible, subject's parents or legally authorized representative(s) should be consented at the end of study visit for the ROPP-2008-01. However, SAEs that the subject experiences between ROPP-2008-001 end-of-study visit and the start of the SHP-607-201, will be reported by the Investigator." Added "SAEs that the subject experiences between ROPP-2008-001 end-of-study visit and the start of the SHP-607-201 will be reported by the Investigator."
21 February 2017	Protocol Amendment 2: Added pulmonary morbidity assessments to be conducted during phone interviews at the 30-month, 3-year, 3.5-year, 4-year, and 4.5-year CA visits, Provided the pulmonary morbidity assessments at clinical site visits for the 6-month,12-month, 24-month, and 5-year CA visits and phone interviews for the 30-month, 3-year, 3.5-year, 4-year, and 4.5-year CA visits, Added cerebral MRI to the 5-year CA visit, Added hearing assessment history at the 5-year CA visits, Added blood pressure, heart rate, and respiratory rate measurements at the 5-year CA Visit, Clarified that if informed consent is not obtained at or before the 3-month visit in Study ROPP-2008-01 for inclusion in this study (SHP607-201), the subject may still be enrolled until they turn 2 years +3 months CA, Clarified that for subjects enrolled between the ages of 9 months CA and 2 years +3 months CA, missed procedures such as neurocognitive assessments, abdominal ultrasounds, and echocardiograms are not required, Clarified that for consented patients, additional biomarker analysis may be performed on prior collected blood samples from Study ROPP-2008-01.
11 May 2017	Protocol Amendment 3: Added hearing assessment history to the 6-month CA visit. Added language explaining that cerebral magnetic resonance imagining (MRI) procedures are optional. Language was also added explaining that the nature, scope, risks, benefits, and potential sedation associated with cerebral MRI will be explained to the subject and subject's parent(s) or legally authorized representative(s). Added cerebral MRI to the 5-year CA visit. Added medications, survival assessment, assessment of participation in other clinical studies and adverse events, including targeted medical events to the 30 months, 3.5 years, 4.5 years CA visits conducted by telephone. Clarified that age equivalent scores and standard scores will be summarized for Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), Wechsler Preschool and Primary Scale of Intelligence (WPPSI), and Vineland Adaptive Behavior Scales, Second Edition (VABS-II). Removed the pulmonary morbidity assessments from the appendices as they will be provided in the Study Operations Manual. Administrative errors were corrected throughout the protocol.

09 April 2018	Protocol Amendment 4: Updated Medical Monitor and Shire Global Drug Safety contact information. Added pulmonary function testing to be performed at selected sites that have access to personnel with expertise in performing pediatric spirometry. Added assessment of Health Utilities Index Mark 2 and Mark 3 (HUI2/3) to the 5 year CA visit. Removed assessment of optical coherence tomography (OCT) at the 5 year CA visit. Updated the status of Section D of Study ROPP-2008-01 since the study has now been completed. Clarified that if the Initial Visit does not occur at or before 40 weeks CA, the subject may still be enrolled until they turn 2 years CA +3 months. Removed language stating that any abnormal change in physical examination findings will be recorded as an adverse event (AE).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported