Clinical trial results:
A Prospective, Randomized, Double-Blind, Phase 3 Study Comparing rhBSSL and Placebo Added to Infant Formula or Pasteurized Breast Milk During 4 Weeks of Treatment in Preterm Infants Born Before Week 32 of Gestational Age

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2010-023909-35
Trial protocol	GB BE SE DE HU FR CZ PL ES IT Outside EU/EEA
Global end of trial date	15 May 2014

Results information

Result version number	v2 (current)
This version publication date	14 July 2016
First version publication date	27 June 2015
Version creation reason	• New data added to full data set 1) Results for the period 12-24 months corrected age has been added as analysis of these endpoints has now been finalized. 2) Link to publication added. 3) Correction of wrongful allocation of data within the "Adverse Events" section caused by EudraCT software issues.

Trial information

Trial identification

Sponsor protocol code	BVT.BSSL-030

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01413581
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swedish Orphan Biovitrum AB (publ)
Sponsor organisation address	Tomtebodavägen 23A, Solna, Stockholm, Sweden, SE-112 76
Public contact	Anna Olsson, Swedish Orphan Biovitrum AB (publ), 46 8 697 20 00, anna.olsson@sobi.com
Scientific contact	Kristina Timdahl, Swedish Orphan Biovitrum AB (publ), 46 8 697 20 00, kristina.timdahl@sobi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000822-PIP01-09
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate that rhBSSL improves growth in preterm infants as compared with placebo when administered in infant formula or PBM.

Protection of trial subjects:

The study will be conducted according to the International Conference on Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice ensuring that the rights, safety and well-being of patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki. The conduct of the study in neonatology intensive care units allowed for the continuous monitoring of patient safety and the accessibility to any necessary therapeutic measures. Furthermore the blood volume to be drawn from the preterm infants was strictly controlled. Serum levels of possible rhBSSL antibodies was determined at Baseline, at the end of treatment (Day 29), and 3 months after the start of treatment and followed further if antibodies were detected. Each individual patient with a positive anti-drug antibody response was checked for immune related adverse events (and vice versa).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 87
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Belgium: 42
Country: Number of subjects enrolled	Czech Republic: 49
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 108
Country: Number of subjects enrolled	Italy: 46
Country: Number of subjects enrolled	Russian Federation: 3

Worldwide total number of subjects	415
EEA total number of subjects	412

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	415
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:

74 study centres in Europe participated in the trial and patients were randomised at 54 of them. First patient was screened on July 26 2011 and last patient randomised on 3 June 2013.

Pre-assignment

Screening details:

After informed consent was collected from the parents/legally authorised representatives, patients entered a screening period of a maximum of seven days. The screening and baseline visit could also take place on the same date. A total of 415 patients were randomized and treatment was initiated in 412 patients.

Period 1

Period 1 title	Overall study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	rhBSSL Full Analysis Set

Arm description:

Patients received rhBSSL Day 1 (Baseline) as soon as possible after randomization (either on the day of randomization or the day after). The administration of rhBSSL continued for 4 weeks. Follow-up visits occurred at 3 months after the first dose of study drug and at 12 months corrected age.

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.

Arm type	Experimental
Investigational medicinal product name	Recombinant Human Bile-Salt-Stimulated Lipase
Investigational medicinal product code	rhBSSL
Other name	Recombinant Human Bile-Salt-Stimulated Lipase (rhBSSL)
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Enteral use

Dosage and administration details:

15 mg of rhBSSL (sterile powder for oral solution) will be reconstituted in 1mL of sterile water before addition to 100 mL pasteurised breast milk of infant formula. The food volume should be in the range of 150-180 mL/kg/day. Each feeding during the 4 week treatment period should contain study drug.

Arm title	Placebo Full Analysis Set

Arm description:

Patients received placebo Day 1 (Baseline) as soon as possible after randomization (either on the day of randomization or the day after). The administration of placebo continued for 4 weeks. Follow-up visits occurred at 3 months after the first dose of study drug and at 12 months corrected age.

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS due to lack of body weight data.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Enteral use , Oral use

Dosage and administration details:

Placebo will be reconstituted in 1mL of sterile water before addition to 100 mL pasteurised breast milk of infant formula. The food volume should be in the range of 150-180 mL/kg/day. Each feeding during the 4 week treatment period should contain study drug.

Number of subjects in period 1[1]	rhBSSL Full Analysis Set	Placebo Full Analysis Set
Started	206	204
Initiated Treatment	206	204
In the study at Day 29	204	204
Completed	179	186
Not completed	27	18
Adverse event, serious fatal	2	1
Parents decision	-	1
Consent withdrawn by subject	7	7
Not possible for parents to come to visit	-	1
Adverse event, non-fatal	2	-
Patient moved	1	-
Lost to follow-up	14	7
Not possible to schedule visit with parents	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 415 patients were randomly assigned to treatment (rhBSSL=207, placebo=208). Treatment was initiated in 412 patients (rhBSSL=207, placebo=205). The full analysis set (FAS) was used as the primary population for the analyses of the primary and secondary efficacy variables and it is the FAS that baseline characteristics are described for. 410 patients were included in the FAS (rhBSSL=206, placebo=204). Exclusion from the FAS was due to lack of body weight data post baseline.

Period 2

Period 2 title	Extended f-u to 24 months corrected age
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	rhBSSL EES

Arm description:

At the 12 months corrected age visit the parents/primary caregivers were to be asked to consent to an extended follow-up to 24 months corrected age. The extended follow-up included telephone visits at 15, 18 and 21 months corrected age and a visit at 24 months corrected age. The extension efficacy set (EES) was the primary analysis set and consisted of all patients who signed an ICF to have data collected in the extension portion of the study, and had at least one efficacy assessment at the 24-months CA visit.

Of the 179 patients treated with rhBSSL who performed the 12-months CA visit, 133 consented to continue with the extended follow-up and 35 of these completed the 24-months CA visit. The remaining 98 were withdrawn from the study upon request from the sponsor

Arm type	Experimental
Investigational medicinal product name	Recombinant Human Bile-Salt-Stimulated Lipase
Investigational medicinal product code	rhBSSL
Other name	Recombinant Human Bile-Salt-Stimulated Lipase (rhBSSL)
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Enteral use

Dosage and administration details:

15 mg of rhBSSL (sterile powder for oral solution) will be reconstituted in 1mL of sterile water before addition to 100 mL pasteurised breast milk of infant formula. The food volume should be in the range of 150-180 mL/kg/day. Each feeding during the 4 week treatment period should contain study drug.

Arm title	Placebo EES

Arm description:

At the 12 months corrected age visit the parents/primary caregivers were to be asked to consent to an extended follow-up to 24 months corrected age. The extended follow-up included telephone visits at 15, 18 and 21 months corrected age and a visit at 24 months corrected age. The extension efficacy set (EES) was the primary analysis set and consisted of all patients who signed an ICF to have data collected in the extension portion of the study, and had at least one efficacy assessment at the 24-months CA visit.

Of the 186 patients treated with placebo who performed the 12-months CA visit, 133 consented to continue with the extended follow-up and 37 of these completed the 24-months CA visit. One patient reached the 24 months CA but did not perform the visit. The remaining 95 were withdrawn from the study; 1 was lost to follow-up, 1 withdrew consent and 93 upon request from the sponsor

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Enteral use , Oral use

Dosage and administration details:

Placebo will be reconstituted in 1mL of sterile water before addition to 100 mL pasteurised breast milk of infant formula. The food volume should be in the range of 150-180 mL/kg/day. Each feeding during the 4 week treatment period should contain study drug.

Number of subjects in period 2[2]	rhBSSL EES	Placebo EES
Started	35	37
Completed	35	37

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Of the 365 pts performing the 12-months CA visit, 266 consented to an extended fu to 24 months CA, one pt reached the 24 months CA but did not perform the visit, 72 completed the 24-months CA visit and 193 were withdrawn (1 lost to follow-up, 1 consent withdrawn, 101 sponsor request). The extension efficacy set (EES) was the primary analysis set for efficacy and consisted of all pts who consented to the extended fu and had at least one efficacy assessment at the 24-months CA visit (72 pts)

Baseline characteristics

Reporting groups	
Reporting group title	rhBSSL Full Analysis Set

Reporting group description:

Patients received rhBSSL Day 1 (Baseline) as soon as possible after randomization (either on the day of randomization or the day after). The administration of rhBSSL continued for 4 weeks. Follow-up visits occurred at 3 months after the first dose of study drug and at 12 months corrected age.

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.

Reporting group title	Placebo Full Analysis Set

Reporting group description:

Patients received placebo Day 1 (Baseline) as soon as possible after randomization (either on the day of randomization or the day after). The administration of placebo continued for 4 weeks. Follow-up visits occurred at 3 months after the first dose of study drug and at 12 months corrected age.

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS due to lack of body weight data.

Reporting group values	rhBSSL Full Analysis Set	Placebo Full Analysis Set	Total
Number of subjects	206	204	410
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	206	204	410
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at time of randomization			
Units: weeks			
arithmetic mean	3.18	3.23	
standard deviation	± 1.528	± 1.457	-
Gender categorical			
Units: Subjects			
Female	104	117	221
Male	102	87	189
Feeding regimen			
Number of patients receiving their study medication together with PBM and formula respectively			
Units: Subjects			

Pasteurized breast milk	79	76	155
Formula	127	128	255
Size for gestational age			
An infant who had a birth weight that was above the 10th percentile for the gestational age on the gender-specific intrauterine growth curves was defined as AGA. An infant with a birth weight at or below the 10th percentile was defined as SGA (Olsen, Groveman et al. 2010).			
Units: Subjects			
Small for gestational age (SGA)	32	30	62
Appropriate for gestational age (AGA)	174	174	348
Gestational Age at Time of Birth			
Units: Weeks			
arithmetic mean	28.75	28.83	
standard deviation	± 1.666	± 1.729	-
Baseline Body Weight			
Units: gram(s)			
arithmetic mean	1384.9	1387.6	
standard deviation	± 265.19	± 263	-
Baseline Body Length			
Units: cm			
arithmetic mean	39.76	39.49	
standard deviation	± 2.727	± 2.374	-
Head Circumference at Baseline			
Units: cm			
arithmetic mean	27.85	27.78	
standard deviation	± 1.61	± 1.663	-

Subject analysis sets

Subject analysis set title	rhBSSL Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF consisted of a total of 412 patients who received at least one dose of study drug; 212 patients were included in the rhBSSL group and 200 patients were included in the placebo group. Five patients randomized to placebo treatment were included in the rhBSSL group since they incorrectly had received ≥2 vials of rhBSSL

Subject analysis set title	Placebo Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF consisted of a total of 412 patients who received at least one dose of study drug; 212 patients were included in the rhBSSL group and 200 patients were included in the placebo group. Five patients randomized to placebo treatment were included in the rhBSSL group since they incorrectly had received ≥2 vials of rhBSSL

Subject analysis set title	rhBSSL Full Analysis Set, PBM Strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.
79 patients treated with rhBSSL and included in the FAS received PBM (Pasteurized breast milk)

Subject analysis set title	Placebo Full Analysis Set, AGA strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS due to lack of body weight data.
174 patients treated with placebo and included in the FAS were classified as appropriate for gestational age (AGA)

Subject analysis set title	rhBSSL Full Analysis Set, Formula Strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.
127 patients treated with rhBSSL and included in the FAS received Infant Formula

Subject analysis set title	Placebo Full Analysis Set, PBM strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS due to lack of body weight data.
76 patients treated with placebo and included in the FAS received PBM (Pasteurized breast milk)

Subject analysis set title	Placebo Full Analysis Set, Formula strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS due to lack of body weight data.
128 patients treated with placebo and included in the FAS received Infant Formula

Subject analysis set title	rhBSSL Full Analysis Set, SGA Strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.
32 patients treated with rhBSSL and included in the FAS were classified as small for gestational age (SGA)

Subject analysis set title	rhBSSL Full Analysis Set, AGA Strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.
174 patients treated with rhBSSL and included in the FAS were classified as appropriate for gestational age (AGA)

Subject analysis set title	Placebo Full Analysis Set, SGA strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS

due to lack of body weight data.
30 patients treated with placebo and included in the FAS were classified as small for gestational age (SGA)

Subject analysis set title	rhBSSL Extension safety set: 12 to 24 months CA
Subject analysis set type	Safety analysis

Subject analysis set description:

The extension safety set (ESAF) consisted of all patients who signed an ICF to have data collected in the extension portion of the study and who were included in the safety set in the main study. Patients in the placebo group that incorrectly received two or more kits with rhBSSL were included in the rhBSSL group.

Subject analysis set title	Placebo Extension safety set: 12 to 24 months CA
Subject analysis set type	Safety analysis

Subject analysis set description:

The extension safety set (ESAF) consisted of all patients who signed an ICF to have data collected in the extension portion of the study and who were included in the safety set in the main study. Patients in the rhBSSL group that incorrectly received no kit with rhBSSL were included in the placebo group.

Reporting group values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set	rhBSSL Full Analysis Set, PBM Strata
Number of subjects	212	200	79
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	212	200	79
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at time of randomization			
Units: weeks			
arithmetic mean	3.21	3.18	
standard deviation	± 1.552	± 1.429	±
Gender categorical			
Units: Subjects			
Female	107	115	
Male	105	85	
Feeding regimen			
Number of patients receiving their study medication together with PBM and formula respectively			
Units: Subjects			
Pasteurized breast milk	80	77	
Formula	132	123	
Size for gestational age			
An infant who had a birth weight that was above the 10th percentile for the gestational age on the gender-specific intrauterine growth curves was defined as AGA. An infant with a birth weight at or below the 10th percentile was defined as SGA (Olsen, Groveman et al. 2010).			
Units: Subjects			
Small for gestational age (SGA)	34	30	
Appropriate for gestational age (AGA)	178	170	

Gestational Age at Time of Birth			
Units: Weeks			
arithmetic mean	28.74	28.86	
standard deviation	± 1.675	± 1.731	±
Baseline Body Weight			
Units: gram(s)			
arithmetic mean	1386.8	1383.1	
standard deviation	± 268.9	± 258.85	±
Baseline Body Length			
Units: cm			
arithmetic mean	39.75	39.48	
standard deviation	± 2.718	± 2.364	±
Head Circumference at Baseline			
Units: cm			
arithmetic mean	27.86	27.77	
standard deviation	± 1.605	± 1.664	±

Reporting group values	Placebo Full Analysis Set, AGA strata	rhBSSL Full Analysis Set, Formula Strata	Placebo Full Analysis Set, PBM strata
Number of subjects	174	127	76
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	174	127	76
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at time of randomization			
Units: weeks			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			
Feeding regimen			
Number of patients receiving their study medication together with PBM and formula respectively			
Units: Subjects			
Pasteurized breast milk			
Formula			
Size for gestational age			
An infant who had a birth weight that was above the 10th percentile for the gestational age on the gender-specific intrauterine growth curves was defined as AGA. An infant with a birth weight at or below the 10th percentile was defined as SGA (Olsen, Groveman et al. 2010).			
Units: Subjects			
Small for gestational age (SGA)			

Appropriate for gestational age (AGA)			

Gestational Age at Time of Birth			
Units: Weeks			
arithmetic mean			
standard deviation	±	±	±
Baseline Body Weight			
Units: gram(s)			
arithmetic mean			
standard deviation	±	±	±
Baseline Body Length			
Units: cm			
arithmetic mean			
standard deviation	±	±	±
Head Circumference at Baseline			
Units: cm			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	Placebo Full Analysis Set, Formula strata	rhBSSL Full Analysis Set, SGA Strata	rhBSSL Full Analysis Set, AGA Strata
Number of subjects	128	32	174
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	128	32	174
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at time of randomization			
Units: weeks			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			
Feeding regimen			
Number of patients receiving their study medication together with PBM and formula respectively			
Units: Subjects			
Pasteurized breast milk			
Formula			
Size for gestational age			
An infant who had a birth weight that was above the 10th percentile for the gestational age on the gender-specific intrauterine growth curves was defined as AGA. An infant with a birth weight at or below			

the 10th percentile was defined as SGA (Olsen, Groveman et al. 2010).			
Units: Subjects			
Small for gestational age (SGA)			
Appropriate for gestational age (AGA)			
Gestational Age at Time of Birth			
Units: Weeks			
arithmetic mean			
standard deviation	±	±	±
Baseline Body Weight			
Units: gram(s)			
arithmetic mean			
standard deviation	±	±	±
Baseline Body Length			
Units: cm			
arithmetic mean			
standard deviation	±	±	±
Head Circumference at Baseline			
Units: cm			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	Placebo Full Analysis Set, SGA strata	rhBSSL Extension safety set: 12 to 24 months CA	Placebo Extension safety set: 12 to 24 months CA
Number of subjects	30	135	131
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	30		
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 65-84 years	0		
85 years and over	0		
Age continuous			
Age at time of randomization			
Units: weeks			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			
Feeding regimen			
Number of patients receiving their study medication together with PBM and formula respectively			
Units: Subjects			
Pasteurized breast milk			
Formula			

Size for gestational age			
An infant who had a birth weight that was above the 10th percentile for the gestational age on the gender-specific intrauterine growth curves was defined as AGA. An infant with a birth weight at or below the 10th percentile was defined as SGA (Olsen, Groveman et al. 2010).			
Units: Subjects			
Small for gestational age (SGA) Appropriate for gestational age (AGA)			
Gestational Age at Time of Birth Units: Weeks arithmetic mean standard deviation	±	±	±
Baseline Body Weight Units: gram(s) arithmetic mean standard deviation	±	±	±
Baseline Body Length Units: cm arithmetic mean standard deviation	±	±	±
Head Circumference at Baseline Units: cm arithmetic mean standard deviation	±	±	±

End points

End points reporting groups

Reporting group title	rhBSSL Full Analysis Set

Reporting group description:

Patients received rhBSSL Day 1 (Baseline) as soon as possible after randomization (either on the day of randomization or the day after). The administration of rhBSSL continued for 4 weeks. Follow-up visits occurred at 3 months after the first dose of study drug and at 12 months corrected age.

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.

Reporting group title	Placebo Full Analysis Set

Reporting group description:

Patients received placebo Day 1 (Baseline) as soon as possible after randomization (either on the day of randomization or the day after). The administration of placebo continued for 4 weeks. Follow-up visits occurred at 3 months after the first dose of study drug and at 12 months corrected age.

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS due to lack of body weight data.

Reporting group title	rhBSSL EES

Reporting group description:

At the 12 months corrected age visit the parents/primary caregivers were to be asked to consent to an extended follow-up to 24 months corrected age. The extended follow-up included telephone visits at 15, 18 and 21 months corrected age and a visit at 24 months corrected age. The extension efficacy set (EES) was the primary analysis set and consisted of all patients who signed an ICF to have data collected in the extension portion of the study, and had at least one efficacy assessment at the 24-months CA visit.

Of the 179 patients treated with rhBSSL who performed the 12-months CA visit, 133 consented to continue with the extended follow-up and 35 of these completed the 24-months CA visit. The remaining 98 were withdrawn from the study upon request from the sponsor

Reporting group title	Placebo EES

Reporting group description:

At the 12 months corrected age visit the parents/primary caregivers were to be asked to consent to an extended follow-up to 24 months corrected age. The extended follow-up included telephone visits at 15, 18 and 21 months corrected age and a visit at 24 months corrected age. The extension efficacy set (EES) was the primary analysis set and consisted of all patients who signed an ICF to have data collected in the extension portion of the study, and had at least one efficacy assessment at the 24-months CA visit.

Of the 186 patients treated with placebo who performed the 12-months CA visit, 133 consented to continue with the extended follow-up and 37 of these completed the 24-months CA visit. One patient reached the 24 months CA but did not perform the visit. The remaining 95 were withdrawn from the study; 1 was lost to follow-up, 1 withdrew consent and 93 upon request from the sponsor

Subject analysis set title	rhBSSL Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF consisted of a total of 412 patients who received at least one dose of study drug; 212 patients were included in the rhBSSL group and 200 patients were included in the placebo group. Five patients randomized to placebo treatment were included in the rhBSSL group since they incorrectly had received ≥2 vials of rhBSSL

Subject analysis set title	Placebo Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF consisted of a total of 412 patients who received at least one dose of study drug; 212 patients were included in the rhBSSL group and 200 patients were included in the placebo group. Five patients randomized to placebo treatment were included in the rhBSSL group since they incorrectly had received ≥2 vials of rhBSSL

Subject analysis set title	rhBSSL Full Analysis Set, PBM Strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.
79 patients treated with rhBSSL and included in the FAS received PBM (Pasteurized breast milk)

Subject analysis set title	Placebo Full Analysis Set, AGA strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS due to lack of body weight data.
174 patients treated with placebo and included in the FAS were classified as appropriate for gestational age (AGA)

Subject analysis set title	rhBSSL Full Analysis Set, Formula Strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.
127 patients treated with rhBSSL and included in the FAS received Infant Formula

Subject analysis set title	Placebo Full Analysis Set, PBM strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS due to lack of body weight data.
76 patients treated with placebo and included in the FAS received PBM (Pasteurized breast milk)

Subject analysis set title	Placebo Full Analysis Set, Formula strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS due to lack of body weight data.
128 patients treated with placebo and included in the FAS received Infant Formula

Subject analysis set title	rhBSSL Full Analysis Set, SGA Strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.
32 patients treated with rhBSSL and included in the FAS were classified as small for gestational age (SGA)

Subject analysis set title	rhBSSL Full Analysis Set, AGA Strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. All 207 patients randomized to the rhBSSL group started treatment but one patient was excluded from the FAS due to lack of body weight data.
174 patients treated with rhBSSL and included in the FAS were classified as appropriate for gestational age (AGA)

Subject analysis set title	Placebo Full Analysis Set, SGA strata
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all patients randomly assigned to treatment who had at least one dose of study medication, an assessment of body weight at baseline, and at least one body weight assessment post baseline. The patients were grouped according to randomized treatment. Of the 208 patients that was randomized to the placebo group, 3 did not start treatment and one patient was excluded from the FAS due to lack of body weight data.
30 patients treated with placebo and included in the FAS were classified as small for gestational age (SGA)

Subject analysis set title	rhBSSL Extension safety set: 12 to 24 months CA
Subject analysis set type	Safety analysis

Subject analysis set description:

The extension safety set (ESAF) consisted of all patients who signed an ICF to have data collected in the extension portion of the study and who were included in the safety set in the main study. Patients in the placebo group that incorrectly received two or more kits with rhBSSL were included in the rhBSSL group.

Subject analysis set title	Placebo Extension safety set: 12 to 24 months CA
Subject analysis set type	Safety analysis

Subject analysis set description:

The extension safety set (ESAF) consisted of all patients who signed an ICF to have data collected in the extension portion of the study and who were included in the safety set in the main study. Patients in the rhBSSL group that incorrectly received no kit with rhBSSL were included in the placebo group.

Primary: Growth Velocity during 4 weeks of treatment

End point title	Growth Velocity during 4 weeks of treatment

End point description:

The primary efficacy variable is growth velocity in grams per kilogram per day during 4 weeks of treatment. The primary efficacy measurement (growth velocity) was made by frequent (at least 3 times per week) measurements of the infant’s weight during treatment.
If a patient withdrew before Day 29 then growth velocity was derived using weight assessments up to their last available assessment.
In order to calculate growth velocity, the natural log-transformed value of the baseline and all post baseline weight assessments for each patient was calculated. A linear regression model was then fitted for each patient with a response variable of log(weight) and a predictor variable of time. Growth velocity for each patient was estimated as the slope arising from the regression model, and needed to be multiplied by 1000 for conversion into the desired unit.

End point type	Primary

End point timeframe:

Baseline to Week 4

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set	rhBSSL Full Analysis Set, PBM Strata	Placebo Full Analysis Set, AGA strata
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	206	204	206	204
Units: g/kg/day				
arithmetic mean (standard deviation)	17.394 (± 3.53)	17.201 (± 3.3579)	16.333 (± 3.0247)	17.302 (± 3.3092)

End point values	rhBSSL Full Analysis Set, Formula Strata	Placebo Full Analysis Set, PBM strata	Placebo Full Analysis Set, Formula strata	rhBSSL Full Analysis Set, SGA Strata
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	206	204	204	206
Units: g/kg/day				
arithmetic mean (standard deviation)	18.054 (± 3.6694)	15.875 (± 2.7538)	17.989 (± 3.4448)	18.547 (± 3.7442)

End point values	rhBSSL Full Analysis Set, AGA Strata	Placebo Full Analysis Set, SGA strata		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	206	204		
Units: g/kg/day				
arithmetic mean (standard deviation)	17.182 (± 3.4588)	16.615 (± 3.6314)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline weight included as a covariate.

PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.493
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.214

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.828

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA) and the interaction between treatment and feeding regimen, with baseline weight included as a covariate.

PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	Placebo Full Analysis Set, PBM strata v rhBSSL Full Analysis Set, PBM Strata
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.371
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.629
upper limit	1.37

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA) and the interaction between treatment and feeding regimen, with baseline weight included as a covariate

PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set, Formula Strata v Placebo Full Analysis Set, Formula strata
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.119
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0.898

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA) and the interaction between treatment and size for gestational age, with baseline weight included as a covariate.

PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set, SGA Strata v Placebo Full Analysis Set, SGA strata
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.951
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.381
upper limit	3.521

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA) and the interaction between treatment and size for gestational age, with baseline weight included as a covariate.

PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set, AGA Strata v Placebo Full Analysis Set, AGA strata
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.757
upper limit	0.567

Secondary: Body Weight: Change from Baseline at 4 Weeks

End point title	Body Weight: Change from Baseline at 4 Weeks

End point description:

Change from baseline = post baseline value — baseline value.

End point type	Secondary

End point timeframe:

Baseline and Week 4. Baseline is defined as last non-missing measurement prior to dosing.

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	204		
Units: gram(s)				
arithmetic mean (standard deviation)	860.5 (± 226.35)	845.4 (± 223.24)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline weight included as a covariate.
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.304
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	18.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.9
upper limit	54

Secondary: Body Weight: Change from Baseline at 3 Months

End point title	Body Weight: Change from Baseline at 3 Months

End point description:

End point type	Secondary

End point timeframe:

Baseline and Month 3. Baseline is defined as last non-missing measurement prior to dosing.

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	182		
Units: gram(s)				
arithmetic mean (standard deviation)	2813.5 (± 567.2)	2823.8 (± 540.34)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline weight included as a covariate.
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	Placebo Full Analysis Set v rhBSSL Full Analysis Set
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-101.9
upper limit	106.6

Secondary: Body Weight at 12 Months Corrected Age

End point title	Body Weight at 12 Months Corrected Age

End point description:

End point type	Secondary

End point timeframe:

12 Months Corrected Age visit

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	169		
Units: gram(s)				
arithmetic mean (standard deviation)	9077.1 (± 1334.25)	8845.9 (± 1239.8)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline weight included as a covariate.
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	197.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.3
upper limit	448.1

Secondary: Head Circumference: Change from Baseline at 4 Weeks

End point title	Head Circumference: Change from Baseline at 4 Weeks

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 4. Baseline is defined as last non-missing measurement prior to dosing.

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	202		
Units: cm				
arithmetic mean (standard deviation)	4.09 (± 1.038)	4.07 (± 1.075)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Change from baseline = post baseline value — baseline value.

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline weight included as a covariate.

PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.655
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.24

Secondary: Head Circumference: Change from Baseline at 3 Months

End point title	Head Circumference: Change from Baseline at 3 Months

End point description:

Change from baseline = post baseline value — baseline value

End point type	Secondary

End point timeframe:

Baseline and Month 3. Baseline is defined as last non-missing measurement prior to dosing.

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	180		
Units: cm				
arithmetic mean (standard deviation)	9.57 (± 1.499)	9.54 (± 1.266)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline head circumference included as a covariate.
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.3

Secondary: Head Circumference at 12 Months Corrected Age

End point title	Head Circumference at 12 Months Corrected Age

End point description:

End point type	Secondary

End point timeframe:

12 Months Corrected Age

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	167		
Units: cm				
arithmetic mean (standard deviation)	45.63 (± 1.811)	45.37 (± 1.724)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline weight included as a covariate.

PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set

Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.51

Secondary: Body Length: Change from Baseline at 4 Weeks

End point title	Body Length: Change from Baseline at 4 Weeks

End point description:

Change from baseline = post baseline value — baseline value.

End point type	Secondary

End point timeframe:

Baseline and Week 4. Baseline is defined as last non-missing measurement prior to dosing.

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	203		
Units: cm				
arithmetic mean (standard deviation)	4.44 (± 1.494)	4.5 (± 1.442)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline body length included as a covariate.

PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.982
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.27

Secondary: Body Length: Change from Baseline at 3 Months

End point title	Body Length: Change from Baseline at 3 Months

End point description:

Change from baseline = post baseline value — baseline value.

End point type	Secondary

End point timeframe:

Baseline and Month 3. Baseline is defined as last non-missing measurement prior to dosing.

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	181		
Units: cm				
arithmetic mean (standard deviation)	13.29 (± 2.406)	13.37 (± 2.112)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline body length included as a covariate.
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.43

Secondary: Body Length at 12 Months Corrected Age

End point title	Body Length at 12 Months Corrected Age

End point description:

End point type	Secondary

End point timeframe:

12 Months Corrected Age

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	169		
Units: cm				
arithmetic mean (standard deviation)	74.31 (± 4.128)	73.49 (± 3.724)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline weight included as a covariate.

PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	Placebo Full Analysis Set v rhBSSL Full Analysis Set
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	1.43

Secondary: Time from First Dose to 150 mL/kg/day of Enteral Feeding Volume

End point title	Time from First Dose to 150 mL/kg/day of Enteral Feeding Volume

End point description:

Time to 150 mL/kg/day of Enteral Feeding (days) = Date 150 mL/kg/day enteral feeding reached or exceeded — Date of first dose

The summary statistics presented are based on a time to event analysis. Patients who do not reach 150 mL/kg/day of enteral feeding are censored at their last day of feeding.

End point type	Secondary

End point timeframe:

Time from First Dose to 150 mL/kg/day of Enteral Feeding Volume

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	204		
Units: day				
median (inter-quartile range (Q1-Q3))	2 (1 to 7)	1 (1 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Restriction

End point title	Growth Restriction

End point description:

Growth restriction is defined as a growth velocity of less than 15 g per kilogram bodyweight per day during the 4-week treatment period

End point type	Secondary

End point timeframe:

Baseline to Week 4

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	204		
Units: Patients with growth restriction	50	58		

Statistical analyses

Statistical analysis title	Logistic regression model

Statistical analysis description:

Adjusted percentage of patients with growth restriction, odds ratio and p-value obtained from a logistic regression model with treatment, feeding regimen (PBM or infant formula), and size for gestational age category (SGA/AGA) as explanatory variables.
Odds ratio is defined as rhBSSL / Placebo.
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set

Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.312
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.24

Secondary: Time to Discharge

End point title	Time to Discharge

End point description:

Time to Discharge (days) = [Date of discharge — Date of first dose]

End point type	Secondary

End point timeframe:

Time to Discharge

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	204		
Units: day				
arithmetic mean (standard deviation)	41.3 (± 12.82)	41.3 (± 19)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of variance model including factors for treatment, feeding regimen (PBM or Infant formula) and size for gestational age category (SGA or AGA).
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.933
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	2.9

Secondary: Time to Readiness for Discharge

End point title	Time to Readiness for Discharge

End point description:

Time to Readiness for Discharge (days) = [Date of Readiness for Discharge — Date of First Dose].

In order to have achieved readiness for discharge, a date must be recorded for 'Ability to suckle feed','Ability to self-regulate body temperature', and 'Ability to self-regulate cardiorespiratory function' in the eCRF (missing dates will be replaced by date of discharge), while date of 'Sustained weight gain' is derived. A sustained pattern of weight gain is defined as the first day after the start of treatment when the patient has sustained a weight of 1.8 kg for three days.

End point type	Secondary

End point timeframe:

Time to Readiness for Discharge

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	204		
Units: day				
arithmetic mean (standard deviation)	31.5 (± 15.29)	30.6 (± 18.39)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Analysis uses analysis of variance model including factors for treatment, feeding regimen (PBM or Infant formula) and size for gestational age category (SGA or AGA).
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.688
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	3.8

Secondary: Re-admission to Hospital Within 1 Month of Discharge

End point title	Re-admission to Hospital Within 1 Month of Discharge
End point description:	
Number of patients with re-admission to hospital within 1 month of discharge	
End point type	Secondary
End point timeframe:	
Discharge unyil 1 month of discharge.	

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	204		
Units: Patients	22	19		

Statistical analyses

Statistical analysis title	Logistic regression

Statistical analysis description:

Adjusted percentage of patients with re-admission to hospital within 1 month of discharge, odds ratio and p-value obtained from a logistic regression model with treatment, feeding regimen (PBM or infant formula), and size for gestational age category (SGA/AGA) as explanatory variables. Odds ratio is defined as rhBSSL / Placebo.

Comparison groups	Placebo Full Analysis Set v rhBSSL Full Analysis Set
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.659
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	2.21

Secondary: Feeding Utilization

End point title	Feeding Utilization

End point description:

Feeding utilization variable (α) which is defined by the differential equation
(dm/dt)=αV(t), t>=1
where
• α is the efficiency in feeding utilization (g/L)
• V(t) is the volume (ml/kg) at time t
• m is the weight (g) and
• t is the time (day)
For each patient all daily feeding volumes between Day 1 and Week 4 and the corresponding body weight values on these days (where missing body weight values will be imputed) will be used to derive nonlinear ordinary least square (OLS) parameter estimates for α, separately for each patient. α will be constrained to be ≥ 0, and the initial value will be set to 0.5. The equation for weight will be fitted by a static model. The model is an appropriate simplification of the mathematical model of weight change with adaption in [Thomas, 2009].
The computed α is an estimate of the metabolic efficiency.

End point type	Secondary

End point timeframe:

Day 1 and Week 4

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	204		
Units: g/L				
arithmetic mean (standard deviation)	113.94 (± 23.625)	109.72 (± 23.286)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis uses analysis of covariance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA), with baseline weight included as a covariate. If a patient withdraws before Day 29 then feeding utilization was derived using weight values and feeding volumes up to their last available assessment.
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.347
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	8.574

Secondary: DHA Concentration in S-TG at 4 weeks

End point title	DHA Concentration in S-TG at 4 weeks
End point description: DHA = Docosahexaenoic acid S-TG = Serum triglycerine fraction	
End point type	Secondary
End point timeframe: 4 weeks	

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	124		
Units: µg/mL				
arithmetic mean (standard deviation)	6.41 (± 3.292)	6.51 (± 3.738)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Analysis uses analysis of variance model including factors for treatment, feeding regimen (PBM or Infant formula) and size for gestational age category (SGA or AGA)

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.952
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.83

Secondary: DHA Concentration in S-PC at 4 weeks

End point title	DHA Concentration in S-PC at 4 weeks
End point description: DHA = Docosahexaenoic acid S-PC = Serum phosphatidylcholine fraction	

End point type	Secondary

End point timeframe:

4 weeks

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	133		
Units: µg/mL				
arithmetic mean (standard deviation)	34.95 (± 10.149)	35.15 (± 9.789)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Analysis uses analysis of variance model including factors for treatment, feeding regimen (PBM or Infant formula) and size for gestational age category (SGA or AGA).

Comparison groups	Placebo Full Analysis Set v rhBSSL Full Analysis Set
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.921
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	2.24

Secondary: AA Concentration in S-TG at 4 weeks

End point title	AA Concentration in S-TG at 4 weeks

End point description:

AA = Arachidonic acid.
S-TG = Serum triglycerine fraction

End point type	Secondary

End point timeframe:

4 weeks

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	124		
Units: µg/mL				
arithmetic mean (standard deviation)	10.41 (± 4.628)	10.45 (± 5.665)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Analysis uses analysis of variance model including factors for treatment, feeding regimen (PBM or Infant formula) and size for gestational age category (SGA or AGA).

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	1.18

Secondary: AA Concentration in S-PC in 4 weeks

End point title	AA Concentration in S-PC in 4 weeks

End point description:

AA = Arachidonic acid
S-PC = Serum phosphatidylcholine fraction

End point type	Secondary

End point timeframe:

4 weeks

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	133		
Units: µg/mL				
arithmetic mean (standard deviation)	110.68 (± 30.219)	108.15 (± 25.678)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Analysis uses analysis of variance model including factors for treatment, feeding regimen (PBM or Infant formula) and size for gestational age category (SGA or AGA).

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.519
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.41
upper limit	8.72

Secondary: Bayley III Cognitive Domain at 12 Months Corrected Age: Scaled Scores

End point title	Bayley III Cognitive Domain at 12 Months Corrected Age: Scaled Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Scaled scores represent a child’s performance on a subtest relative to his or her same-age peers. They are derived from the total raw scores (which is the sum of the number of points earned for a subtest) on each of the subtests and are scaled to a metric with a range of 1 to 19, a mean of 10, and a standard deviation of 3.

End point type	Secondary

End point timeframe:

12 Months Corrected Age Visit

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	179		
Units: Scaled score				
arithmetic mean (standard deviation)	9.5 (± 2.52)	9.3 (± 2.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley III Cognitive Domain at 12 Months Corrected Age: Composite Scores

End point title	Bayley III Cognitive Domain at 12 Months Corrected Age: Composite Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Composite scores are based on various sums of subtest scaled scores for the Language, Motor , and Adaptive Behaviors composites, and composite equivalents for the scaled scores from the Cognitive and Social-Emotional Scales. The composite scores are scaled to a metric with a range of 40 to 160, a mean of 100, and a standard deviation of 15.

End point type	Secondary

End point timeframe:

12 Months Corrected Age Visit

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	181	179		
Units: Composite Scores				
arithmetic mean (standard deviation)	97.6 (± 12.61)	96.6 (± 12.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley III Language Domain at 12 Months Corrected Age: Receptive Communication: Scaled Scores

End point title	Bayley III Language Domain at 12 Months Corrected Age: Receptive Communication: Scaled Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Scaled scores represent a child's performance on a subtest relative to his or her same-age peers. They are derived from the total raw scores (which is the sum of the number of points earned for a subtest) on each of the subtests and are scaled to a metric with a range of 1 to 19, a mean of 10, and a standard deviation of 3.

End point type	Secondary

End point timeframe:

12 Months Corrected Age Visit

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	181	179		
Units: Scaled Score				
arithmetic mean (standard deviation)	8.9 (± 3.12)	8.7 (± 3.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley III Language Domain at 12 Months Corrected Age: Expressive Communication: Scaled Scores

End point title	Bayley III Language Domain at 12 Months Corrected Age: Expressive Communication: Scaled Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Scaled scores represent a child's performance on a subtest relative to his or her same-age peers. They are derived from the total raw scores (which is the sum of the number of points earned for a subtest) on each of the subtests and are scaled to a metric with a range of 1 to 19, a mean of 10, and a standard deviation of 3.

End point type	Secondary

End point timeframe:

12 Months Corrected Age Visit

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	181	179		
Units: Scaled Score				
arithmetic mean (standard deviation)	9.1 (± 2.57)	8.9 (± 2.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley III Language Domain at 12 Months Corrected Age: Composite Scores

End point title	Bayley III Language Domain at 12 Months Corrected Age: Composite Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Composite scores are based on various sums of subtest scaled scores for the Language, Motor , and Adaptive Behaviors composites, and composite equivalents for the scaled scores from the Cognitive and Social-Emotional Scales. The composite scores are scaled to a metric with a range of 40 to 160, a mean of 100, and a standard deviation of 15.

End point type	Secondary

End point timeframe:

12 Months Corrected Age Visit

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	181	179		
Units: Composite Score				
arithmetic mean (standard deviation)	94.5 (± 14.3)	93 (± 14.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley III Motor Domain at 12 Months Corrected Age: Fine Motor: Scaled Scores

End point title	Bayley III Motor Domain at 12 Months Corrected Age: Fine Motor: Scaled Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Scaled scores represent a child's performance on a subtest relative to his or her same-age peers. They are derived from the total raw scores (which is the sum of the number of points earned for a subtest) on each of the subtests and are scaled to a metric with a range of 1 to 19, a mean of 10, and a standard deviation of 3.

End point type	Secondary

End point timeframe:

12 Months Corrected Age Visit

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	181	179		
Units: Scaled score				
arithmetic mean (standard deviation)	9.2 (± 2.2)	9.7 (± 2.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley III Motor Domain at 12 Months Corrected Age: Gross Motor: Scaled Scores

End point title	Bayley III Motor Domain at 12 Months Corrected Age: Gross Motor: Scaled Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Scaled scores represent a child's performance on a subtest relative to his or her same-age peers. They are derived from the total raw scores (which is the sum of the number of points earned for a subtest) on each of the subtests and are scaled to a metric with a range of 1 to 19, a mean of 10, and a standard deviation of 3.

End point type	Secondary

End point timeframe:

12 Months Corrected Age Visit

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	181	179		
Units: Scaled Score				
arithmetic mean (standard deviation)	7.7 (± 2.98)	8.2 (± 2.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley III Motor Domain at 12 Months Corrected Age: Composite Scores

End point title	Bayley III Motor Domain at 12 Months Corrected Age: Composite Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Composite scores are based on various sums of subtest scaled scores for the Language, Motor , and Adaptive Behaviors composites, and composite equivalents for the scaled scores from the Cognitive and Social-Emotional Scales. The composite scores are scaled to a metric with a range of 40 to 160, a mean of 100, and a standard deviation of 15.

End point type	Secondary

End point timeframe:

12 Months Corrected Age Visit

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	181	179		
Units: Composite Score				
arithmetic mean (standard deviation)	90.7 (± 12.54)	93.7 (± 12.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of vomiting episodes/day

End point title	Mean number of vomiting episodes/day

End point description:

Mean number of vomiting episodes per day = total number of vomiting episodes / number of days on treatment.
Number of days on treatment = (End of treatment date — treatment start date) + 1.
Patients experiencing no vomiting episodes were included in the summary statistics using zero as the

mean number of episodes/day.

End point type	Secondary
End point timeframe: Baseline to Week 4	

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	212	200		
Units: Number of vomiting episodes/day				
arithmetic mean (standard deviation)	0.069 (± 0.1942)	0.061 (± 0.1449)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Blood Pressure at Baseline

End point title	Systolic Blood Pressure at Baseline
End point description:	

End point type	Secondary
End point timeframe: Baseline. Baseline is defined as last non-missing measurement prior to dosing	

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	211	197		
Units: mmHg				
arithmetic mean (standard deviation)	69.6 (± 10.64)	69.9 (± 10.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Blood Pressure at 4 weeks

End point title	Systolic Blood Pressure at 4 weeks
End point description:	

End point type	Secondary

End point timeframe:
Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	207	191		
Units: mmHg				
arithmetic mean (standard deviation)	74.1 (± 11.32)	71.6 (± 11.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Blood Pressure: Change from Baseline at 4 Weeks

End point title	Systolic Blood Pressure: Change from Baseline at 4 Weeks

End point description:
Change from baseline = post baseline value — baseline value

End point type	Secondary

End point timeframe:
Baseline and Week 4. Baseline is defined as last non-missing measurement prior to dosing

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	207	191		
Units: mmHg				
arithmetic mean (standard deviation)	4.5 (± 13.88)	1.8 (± 13.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic Blood Pressure at Baseline

End point title	Diastolic Blood Pressure at Baseline

End point description:

End point type	Secondary

End point timeframe:
Baseline. Baseline is defined as last non-missing measurement prior to dosing

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	197		
Units: mmHg				
arithmetic mean (standard deviation)	39.3 (± 9.12)	39.3 (± 8.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic Blood Pressure at 4 weeks

End point title	Diastolic Blood Pressure at 4 weeks

End point description:

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	206	191		
Units: mmHg				
arithmetic mean (standard deviation)	41.2 (± 9.29)	40.4 (± 9.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic Blood Pressure: Change from Baseline at 4 Weeks

End point title	Diastolic Blood Pressure: Change from Baseline at 4 Weeks

End point description:

Change from baseline = post baseline value — baseline value.

End point type	Secondary

End point timeframe:

Baseline and Week 4. Baseline is defined as last non-missing measurement prior to dosing

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	206	191		
Units: mmHg				
arithmetic mean (standard deviation)	2 (± 12.38)	1.1 (± 12.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Heart Rate at Baseline

End point title	Heart Rate at Baseline

End point description:

End point type	Secondary

End point timeframe:

Baseline. Baseline is defined as last non-missing measurement prior to dosing

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	212	200		
Units: bpm				
arithmetic mean (standard deviation)	153.3 (± 12.75)	154.4 (± 12.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Heart Rate at 4 weeks

End point title	Heart Rate at 4 weeks

End point description:

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	209	197		
Units: bpm				
arithmetic mean (standard deviation)	151.5 (± 15.2)	151.4 (± 13.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Heart Rate: Change from Baseline at 4 Weeks

End point title	Heart Rate: Change from Baseline at 4 Weeks

End point description:

Change from baseline = post baseline value — baseline value.

End point type	Secondary

End point timeframe:

Baseline and Week 4. Baseline is defined as last non-missing measurement prior to dosing.

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	209	197		
Units: bpm				
arithmetic mean (standard deviation)	-1.9 (± 17.64)	-3 (± 16.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vitamin A Concentration at 4 weeks

End point title	Vitamin A Concentration at 4 weeks

End point description:

End point type	Secondary

End point timeframe:

4 weeks

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	206	194		
Units: nmol/L				
arithmetic mean (standard deviation)	517.8 (± 253.92)	528.1 (± 347.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vitamin D2 Concentration at 4 weeks

End point title	Vitamin D2 Concentration at 4 weeks

End point description:

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	204	194		
Units: nmol/L				
arithmetic mean (standard deviation)	9.813 (± 12.8054)	10.428 (± 15.4648)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vitamin D3 Concentration at 4 weeks

End point title	Vitamin D3 Concentration at 4 weeks

End point description:

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	204	194		
Units: nmol/L				
arithmetic mean (standard deviation)	96.018 (± 95.4933)	96.212 (± 93.0384)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sum Vitamin D2 & D3 Concentrations at week 4

End point title	Sum Vitamin D2 & D3 Concentrations at week 4

End point description:

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	204	194		
Units: nmol/L				
arithmetic mean (standard deviation)	105.831 (± 94.6279)	106.64 (± 91.4863)		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibodies to rhBSSL at Baseline

End point title	Antibodies to rhBSSL at Baseline

End point description:

A positive sample is defined as a sample which when analyzed in a confirmatory batch produces a ratio (ratio of instrument response obtained in the presence of rhBSSL) which is below the confirmatory cut point of 0.598, confirming the presence relative to absence of antibodies specific to rhBSSL.

End point type	Secondary

End point timeframe:

Baseline

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	198		
Units: number of patients				
Positive	4	2		
Negative	206	196		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibodies to rhBSSL at 4 weeks

End point title	Antibodies to rhBSSL at 4 weeks

End point description:

A positive sample is defined as a sample which when analyzed in a confirmatory batch produces a ratio (ratio of instrument response obtained in the presence of rhBSSL) which is below the confirmatory cut point of 0.598, confirming the presence relative to absence of antibodies specific to rhBSSL.

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	208	194		
Units: number of patients				
Positive	196	193		
Negative	12	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibodies to rhBSSL at 3 months

End point title	Antibodies to rhBSSL at 3 months

End point description:

A positive sample is defined as a sample which when analyzed in a confirmatory batch produces a ratio (ratio of instrument response obtained in the presence of rhBSSL) which is below the confirmatory cut point of 0.598, confirming the presence relative to absence of antibodies specific to rhBSSL.

End point type	Secondary

End point timeframe:

Month 3

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	202	189		
Units: number of patients				
Positive	178	172		
Negative	24	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibodies to rhBSSL at 6 months

End point title	Antibodies to rhBSSL at 6 months

End point description:

A positive sample is defined as a sample which when analyzed in a confirmatory batch produces a ratio (ratio of instrument response obtained in the presence of rhBSSL) which is below the confirmatory cut point of 0.598, confirming the presence relative to absence of antibodies specific to rhBSSL.

The 6 month sample is only displayed for those patients who have a positive result for the 3 month sample.

End point type	Secondary

End point timeframe:

Month 3

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	15		
Units: number of patients				
Positive	5	3		
Negative	17	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibodies to rhBSSL at 12 months

End point title	Antibodies to rhBSSL at 12 months

End point description:

A positive sample is defined as a sample which when analyzed in a confirmatory batch produces a ratio (ratio of instrument response obtained in the presence of rhBSSL) which is below the confirmatory cut point of 0.598, confirming the presence relative to absence of antibodies specific to rhBSSL.

The 12 month sample is only displayed for those patients who have a positive result for the 6 month sample.

End point type	Secondary

End point timeframe:

Month 12

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	10		
Units: number of patients				
Positive	6	1		
Negative	10	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of Amylase at 4 weeks

End point title	Levels of Amylase at 4 weeks

End point description:

Blood samples will be collected at the end of treatment for safety analyses unless at least 1 sample had been drawn following a minimum of 2 weeks treatment with study drug. Lab results are analyzed by local laboratories.
Week 4 results are included in the summary statistics if the assessment is taken not more than three days after treatment stop. Where multiple samples are taken, the last sample taken during treatment will be used.
For laboratory values recorded as less than the limit of quantification (LOQ), the LOQ value * 0.5 was used in the summary statistics.

End point type	Secondary

End point timeframe:

Week 4.

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	165		
Units: ukat/L				
arithmetic mean (standard deviation)	0.103 (± 0.091)	0.096 (± 0.0577)		

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of Alanine Aminotransferase at 4 weeks

End point title	Levels of Alanine Aminotransferase at 4 weeks

End point description:

Blood samples will be collected at the end of treatment for safety analyses unless at least 1 sample had been drawn following a minimum of 2 weeks treatment with study drug. Lab results are analyzed by local laboratories.
Week 4 results are included in the summary statistics if the assessment is taken not more than three days after treatment stop. Where multiple samples are taken, the last sample taken during treatment will be used.
For laboratory values recorded as less than the limit of quantification (LOQ), the LOQ value * 0.5 was used in the summary statistics.

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	196	181		
Units: ukat/L				
arithmetic mean (standard deviation)	0.266 (± 0.2266)	0.23 (± 0.1521)		

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of Aspartate Aminotransferase at 4 weeks

End point title	Levels of Aspartate Aminotransferase at 4 weeks

End point description:

Blood samples will be collected at the end of treatment for safety analyses unless at least 1 sample had been drawn following a minimum of 2 weeks treatment with study drug. Lab results are analyzed by local laboratories.
Week 4 results are included in the summary statistics if the assessment is taken not more than three days after treatment stop. Where multiple samples are taken, the last sample taken during treatment will be used.
For laboratory values recorded as less than the limit of quantification (LOQ), the LOQ value * 0.5 was used in the summary statistics.

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	178		
Units: ukat/L				
arithmetic mean (standard deviation)	0.447 (± 0.2965)	0.428 (± 0.1905)		

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of Bilirubin at week 4

End point title	Levels of Bilirubin at week 4

End point description:

Blood samples will be collected at the end of treatment for safety analyses unless at least 1 sample had been drawn following a minimum of 2 weeks treatment with study drug. Lab results are analyzed by local laboratories.
Week 4 results are included in the summary statistics if the assessment is taken not more than three days after treatment stop. Where multiple samples are taken, the last sample taken during treatment will be used.
For laboratory values recorded as less than the limit of quantification (LOQ), the LOQ value * 0.5 was used in the summary statistics.

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	191	178		
Units: umol/L				
arithmetic mean (standard deviation)	35 (± 32.478)	36.03 (± 30.965)		

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of Sodium at 4 weeks

End point title	Levels of Sodium at 4 weeks

End point description:

Blood samples will be collected at the end of treatment for safety analyses unless at least 1 sample had been drawn following a minimum of 2 weeks treatment with study drug. Lab results are analyzed by local laboratories.
Week 4 results are included in the summary statistics if the assessment is taken not more than three days after treatment stop. Where multiple samples are taken, the last sample taken during treatment will be used.
For laboratory values recorded as less than the limit of quantification (LOQ), the LOQ value * 0.5 was

used in the summary statistics.

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	185		
Units: mmol/L				
arithmetic mean (standard deviation)	138.2 (± 3.3)	138.4 (± 3.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of Urea at 4 weeks

End point title	Levels of Urea at 4 weeks

End point description:

Blood samples will be collected at the end of treatment for safety analyses unless at least 1 sample had been drawn following a minimum of 2 weeks treatment with study drug. Lab results are analyzed by local laboratories.
Week 4 results are included in the summary statistics if the assessment is taken not more than three days after treatment stop. Where multiple samples are taken, the last sample taken during treatment will be used.
For laboratory values recorded as less than the limit of quantification (LOQ), the LOQ value * 0.5 was used in the summary statistics.

End point type	Secondary

End point timeframe:

Week 4

End point values	rhBSSL Safety Analysis Set	Placebo Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	198	181		
Units: mmol/L				
arithmetic mean (standard deviation)	3.04 (± 1.691)	3.05 (± 1.856)		

Statistical analyses

No statistical analyses for this end point

Secondary: Growth velocity calculated using a 2-point weight model

End point title	Growth velocity calculated using a 2-point weight model

End point description:

A sensitivity analysis will be performed for the primary endpoint. Growth velocity (g/kg/day) will be calculated using a 2-Point weight model (Patel, 2009). The net weight gain over time will be divided by the weight at Day 1. For each patient, growth velocity will be calculated using the following formula:
GV= (1000 x (Wn x W1)) / (Wn (Dn - D1))
where w1=weight in grams at Day 1 and wn=weight in grams at Day n (Day n being the last available weight assessment during the treatment period, taken on or before Day 29).

End point type	Secondary

End point timeframe:

Baseline to Week 4

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	204		
Units: g/kg/day				
arithmetic mean (standard deviation)	22.353 (± 5.6001)	21.938 (± 5.2548)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.448
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.508
upper limit	1.404

Secondary: Growth restriction, 10 percentile

End point title	Growth restriction, 10 percentile

End point description:

Growth restriction is defined as having a weight below the 10th percentile for the gestational age on the gender specific intrauterine growth curve (based on Olsen et al 2010) during the 4-week treatment period

End point type	Secondary

End point timeframe:

Baseline to Week 4

End point values	rhBSSL Full Analysis Set	Placebo Full Analysis Set		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	204		
Units: Patients with growth restriction	68	74		

Statistical analyses

Statistical analysis title	Logistic regression model

Statistical analysis description:

Adjusted percentage of patients below the 10th percentile, odds ratio and p-value obtained from a logistic regression model with treatment, feeding regimen (PBM or infant formula), and size for gestational age category (SGA/AGA) as explanatory variables.
Odds ratio is defined as rhBSSL / Placebo.
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Comparison groups	rhBSSL Full Analysis Set v Placebo Full Analysis Set
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.29

Secondary: Bayley III Cognitive Domain at 24 Months Corrected Age: Composite Scores

End point title	Bayley III Cognitive Domain at 24 Months Corrected Age: Composite Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Composite scores are based on various sums of subtest scaled scores for the Language, Motor , and Adaptive Behaviors composites, and composite equivalents for the scaled scores from the Cognitive and Social-Emotional Scales. The composite scores are scaled to a metric with a range of 40 to 160, a mean of 100, and a standard deviation of 15.

End point type	Secondary

End point timeframe:

24 Months Corrected Age Visit

End point values	rhBSSL EES	Placebo EES		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[1]	34[2]		
Units: Composite Score				
arithmetic mean (standard deviation)	90.8 (± 14.64)	91.5 (± 14.64)		

Notes:

[1] - Two patients with missing composite score

[2] - One patient with invalid composite score and two patients with missing composite score

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Analysis uses analysis of variance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA).
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Invalid composite scores were not included

Comparison groups	rhBSSL EES v Placebo EES
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.849
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.91
upper limit	6.53

Secondary: Bayley III Language Domain at 24 Months Corrected Age: Composite Scores

End point title	Bayley III Language Domain at 24 Months Corrected Age: Composite Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Composite scores are based on various sums of subtest scaled scores for the Language, Motor , and Adaptive Behaviors composites, and composite equivalents for the scaled scores from the Cognitive and Social-Emotional Scales. The composite scores are scaled to a metric with a range of 40 to 160, a mean of 100, and a standard deviation of 15.

End point type	Secondary

End point timeframe:

24 Months Corrected Age Visit

End point values	rhBSSL EES	Placebo EES		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[3]	34[4]		
Units: Composite Scores				
arithmetic mean (standard deviation)	90.5 (± 17.38)	89 (± 14.45)		

Notes:

[3] - Two patients with missing composite score

[4] - Three patients with missing composite score

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Analysis uses analysis of variance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA).
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Invalid composite scores were not included

Comparison groups	rhBSSL EES v Placebo EES
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.742
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.57
upper limit	9.17

Secondary: Bayley III Motor Domain at 24 Months Corrected Age: Composite Scores

End point title	Bayley III Motor Domain at 24 Months Corrected Age: Composite Scores

End point description:

The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age, across five domains: cognitive, motor (including the fine and gross motor subtests), language (including the receptive and expressive communication subtest), social-emotional, and adaptive behavior. Assessments of the cognitive, motor and language domains are conducted using items administered to the child; assessment of the social-

emotional and adaptive behavior domains are conducted using parent/primary caregiver response to a questionnaire.

Composite scores are based on various sums of subtest scaled scores for the Language, Motor , and Adaptive Behaviors composites, and composite equivalents for the scaled scores from the Cognitive and Social-Emotional Scales. The composite scores are scaled to a metric with a range of 40 to 160, a mean of 100, and a standard deviation of 15.

End point type	Secondary
End point timeframe:	
24 Months Corrected Age Visit	

End point values	rhBSSL EES	Placebo EES		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[5]	35[6]		
Units: Composite Scores				
arithmetic mean (standard deviation)	95.5 (± 10.73)	96.3 (± 13.38)		

Notes:

[5] - Two patients with missing composite score

[6] - Two patients with missing composite score

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Analysis uses analysis of variance model including factors for treatment, feeding regimen (PBM or Infant formula), size for gestational age category (SGA or AGA).
PBM = Pasteurized breast milk; SGA = Small for gestational age; AGA = Appropriate for gestational age.

Invalid composite scores were not included

Comparison groups	rhBSSL EES v Placebo EES
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.755
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.92
upper limit	5.04

Secondary: Number of Patients with Neurodevelopment Disability at 24 Months Corrected Age Visit

End point title	Number of Patients with Neurodevelopment Disability at 24 Months Corrected Age Visit

End point description:

The Neurodevelopment Disability Composite is defined as presence of any of the one following:
- A composite score of less than 70 on any of the cognitive, language or motor domains of Bayley III
- Bilateral deafness, defined as need for bilateral amplification
- Bilateral blindness, defined as corrected visual acuity of less than 20/200 (or equivalent) in the better eye
- Cerebral palsy, defined as hypotonia, spastic diplegia, hemiplegia or quadriplegia causing functional deficits that require rehabilitation services

End point type	Secondary

End point timeframe:

24 Months Corrected Age Visit

End point values	rhBSSL EES	Placebo EES		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: Number of Patients	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Body Weight at 24 Months Corrected Age

End point title	Body Weight at 24 Months Corrected Age

End point description:

Only includes assessments performed within 24 months corrected age +/- 28 days

End point type	Secondary

End point timeframe:

24 Months Corrected Age Visit

End point values	rhBSSL EES	Placebo EES		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: gram(s)				
arithmetic mean (standard deviation)	11.385 (± 1.4591)	11.078 (± 1.3523)		

Statistical analyses

No statistical analyses for this end point

Secondary: Body Height at 24 Months Corrected Age

End point title	Body Height at 24 Months Corrected Age
End point description:	
Only includes assessments performed within 24 months corrected age +/- 28 days	
End point type	Secondary
End point timeframe:	
24 Months Corrected Age Visit	

End point values	rhBSSL EES	Placebo EES		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: cm				
arithmetic mean (standard deviation)	86.45 (± 4.307)	85.65 (± 3.709)		

Statistical analyses

No statistical analyses for this end point

Secondary: Head Circumference at 24 Months Corrected Age

End point title	Head Circumference at 24 Months Corrected Age
End point description:	
Only includes assessments performed within 24 months corrected age +/- 28 days	
End point type	Secondary
End point timeframe:	
24 Months Corrected Age Visit	

End point values	rhBSSL EES	Placebo EES		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: cm				
arithmetic mean (standard deviation)	47.77 (± 1.735)	47.28 (± 1.379)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serious Adverse Drug Reactions

End point title	Serious Adverse Drug Reactions
End point description:	
Serious Adverse Drug Reactions were to be recorded from the 12 to the 24 months CA visit.	

End point type	Secondary

End point timeframe:

12 to 24 months Corrected Age Visits

End point values	rhBSSL Extension safety set: 12 to 24 months CA	Placebo Extension safety set: 12 to 24 months CA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	135	131		
Units: Number of Patients	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Non-serious AEs were recorded from the start of treatment on Day 1 through the 3-month f-u visit. SAEs were recorded from informed consent to the 12 months CA visit. In addition, Serious ADRS were recorded from the 12 to the 24 months CA visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	rhBSSL Safety Analysis Set: Baseline to week 4

Reporting group description:

The SAF consisted of a total of 412 patients who received at least one dose of study drug; 212 patients were included in the rhBSSL group and 200 patients were included in the placebo group. Five patients randomized to placebo treatment were included in the rhBSSL group since they incorrectly had received ≥2 vials of rhBSSL

Reporting group title	Placebo Safety Analysis Set: Baseline to week 4

Reporting group description:

The SAF consisted of a total of 412 patients who received at least one dose of study drug; 212 patients were included in the rhBSSL group and 200 patients were included in the placebo group. Five patients randomized to placebo treatment were included in the rhBSSL group since they incorrectly had received ≥2 vials of rhBSSL

Reporting group title	rhBSSL Safety Analysis Set: 4 weeks to 3 months

Reporting group description:

The SAF consisted of a total of 412 patients who received at least one dose of study drug; 212 patients were included in the rhBSSL group and 200 patients were included in the placebo group. Five patients randomized to placebo treatment were included in the rhBSSL group since they incorrectly had received ≥2 vials of rhBSSL

Reporting group title	Placebo Safety Analysis Set: 4 weeks to 3 months

Reporting group description:

The SAF consisted of a total of 412 patients who received at least one dose of study drug; 212 patients were included in the rhBSSL group and 200 patients were included in the placebo group. Five patients randomized to placebo treatment were included in the rhBSSL group since they incorrectly had received ≥2 vials of rhBSSL

Reporting group title	rhBSSL Safety Analysis Set: 3 months to 12 months CA

Reporting group description:

The SAF consisted of a total of 412 patients who received at least one dose of study drug; 212 patients were included in the rhBSSL group and 200 patients were included in the placebo group. Five patients randomized to placebo treatment were included in the rhBSSL group since they incorrectly had received ≥2 vials of rhBSSL

Reporting group title	Placebo Safety Analysis Set: 3 months to 12 months CA

Reporting group description:

The SAF consisted of a total of 412 patients who received at least one dose of study drug; 212 patients were included in the rhBSSL group and 200 patients were included in the placebo group. Five patients randomized to placebo treatment were included in the rhBSSL group since they incorrectly had received ≥2 vials of rhBSSL

Serious adverse events	rhBSSL Safety Analysis Set: Baseline to week 4	Placebo Safety Analysis Set: Baseline to week 4	rhBSSL Safety Analysis Set: 4 weeks to 3 months
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 212 (9.43%)	13 / 200 (6.50%)	46 / 212 (21.70%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	0 / 212 (0.00%)	1 / 200 (0.50%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioma			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cyst			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	2 / 212 (0.94%)	1 / 200 (0.50%)	2 / 212 (0.94%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary dysplasia			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	2 / 212 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 212 (0.00%)	1 / 200 (0.50%)	2 / 212 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stridor			

subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Apparent life threatening event			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neonatal respiratory failure			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			

subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Laryngomalacia			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial septal defect			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder congenital			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phenylketonuria			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyloric stenosis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cleft palate			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Craniosynostosis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Persistent foetal circulation			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic infantile neurological cutaneous and articular syndrome			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac hypertrophy			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral calcification			
subjects affected / exposed	0 / 212 (0.00%)	1 / 200 (0.50%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periventricular leukomalacia			
subjects affected / exposed	0 / 212 (0.00%)	1 / 200 (0.50%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Poor sucking reflex			
subjects affected / exposed	0 / 212 (0.00%)	1 / 200 (0.50%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotonia			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White matter lesion			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	6 / 212 (2.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Retinopathy of prematurity			
subjects affected / exposed	4 / 212 (1.89%)	6 / 200 (3.00%)	6 / 212 (2.83%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 212 (0.00%)	1 / 200 (0.50%)	3 / 212 (1.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising enterocolitis neonatal			
subjects affected / exposed	4 / 212 (1.89%)	1 / 200 (0.50%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia strangulated			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Growth retardation			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Parotitis			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 212 (0.94%)	1 / 200 (0.50%)	8 / 212 (3.77%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory tract infection			
subjects affected / exposed	0 / 212 (0.00%)	1 / 200 (0.50%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 212 (0.47%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 212 (0.00%)	1 / 200 (0.50%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenovirus infection			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	3 / 212 (1.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	3 / 212 (1.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	2 / 212 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningococcal sepsis			

subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus infection			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	2 / 212 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	2 / 212 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	1 / 212 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute tonsillitis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermo-hypodermitis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			

subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exanthema subitum			

subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pertussis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Feeding disorder			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight gain poor			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	0 / 212 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo Safety	rhBSSL Safety	Placebo Safety

	Analysis Set: 4 weeks to 3 months	Analysis Set: 3 months to 12 months CA	Analysis Set: 3 months to 12 months CA
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 200 (22.00%)	61 / 212 (28.77%)	55 / 200 (27.50%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioma			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	2 / 200 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cyst			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	3 / 200 (1.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary dysplasia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 200 (0.00%)	2 / 212 (0.94%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Stridor			

subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Apparent life threatening event			
subjects affected / exposed	1 / 200 (0.50%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neonatal respiratory failure			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 200 (0.00%)	2 / 212 (0.94%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			

subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Laryngomalacia			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial septal defect			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder congenital			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phenylketonuria			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyloric stenosis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cleft palate			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Craniosynostosis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Persistent foetal circulation			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic infantile neurological cutaneous and articular syndrome			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac hypertrophy			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral calcification			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periventricular leukomalacia			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Poor sucking reflex			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotonia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White matter lesion			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Retinopathy of prematurity			
subjects affected / exposed	3 / 200 (1.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	8 / 200 (4.00%)	6 / 212 (2.83%)	2 / 200 (1.00%)
occurrences causally related to treatment / all	0 / 8	0 / 8	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising enterocolitis neonatal			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	2 / 200 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 200 (0.50%)	2 / 212 (0.94%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia strangulated			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Growth retardation			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Parotitis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	11 / 200 (5.50%)	11 / 212 (5.19%)	7 / 200 (3.50%)
occurrences causally related to treatment / all	0 / 11	0 / 15	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory tract infection			
subjects affected / exposed	0 / 200 (0.00%)	3 / 212 (1.42%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenovirus infection			
subjects affected / exposed	1 / 200 (0.50%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	9 / 200 (4.50%)	7 / 212 (3.30%)	12 / 200 (6.00%)
occurrences causally related to treatment / all	0 / 10	0 / 12	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	3 / 200 (1.50%)	8 / 212 (3.77%)	13 / 200 (6.50%)
occurrences causally related to treatment / all	0 / 3	0 / 9	0 / 20
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 200 (0.50%)	6 / 212 (2.83%)	3 / 200 (1.50%)
occurrences causally related to treatment / all	0 / 1	0 / 7	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	2 / 200 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningococcal sepsis			

subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	1 / 200 (0.50%)	2 / 212 (0.94%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 200 (0.00%)	2 / 212 (0.94%)	5 / 200 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	2 / 200 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute tonsillitis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 200 (0.00%)	6 / 212 (2.83%)	4 / 200 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 7	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermo-hypodermitis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			

subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exanthema subitum			

subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 200 (0.00%)	2 / 212 (0.94%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pertussis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	2 / 200 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Feeding disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	0 / 200 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight gain poor			
subjects affected / exposed	0 / 200 (0.00%)	1 / 212 (0.47%)	1 / 200 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	rhBSSL Safety Analysis Set: Baseline to week 4	Placebo Safety Analysis Set: Baseline to week 4	rhBSSL Safety Analysis Set: 4 weeks to 3 months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	174 / 212 (82.08%)	156 / 200 (78.00%)	117 / 212 (55.19%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	5 / 212 (2.36%)	7 / 200 (3.50%)	7 / 212 (3.30%)
occurrences (all)	5	7	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	114 / 212 (53.77%)	100 / 200 (50.00%)	50 / 212 (23.58%)
occurrences (all)	134	121	56
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	10 / 212 (4.72%)	12 / 200 (6.00%)	0 / 212 (0.00%)
occurrences (all)	10	12	0
Eye disorders			
Retinopathy of prematurity			
subjects affected / exposed	34 / 212 (16.04%)	29 / 200 (14.50%)	10 / 212 (4.72%)
occurrences (all)	34	30	10
Conjunctivitis			
subjects affected / exposed	23 / 212 (10.85%)	20 / 200 (10.00%)	0 / 212 (0.00%)
occurrences (all)	23	20	0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 212 (3.30%)	5 / 200 (2.50%)	6 / 212 (2.83%)
occurrences (all)	7	5	6
Flatulence			
subjects affected / exposed	7 / 212 (3.30%)	3 / 200 (1.50%)	0 / 212 (0.00%)
occurrences (all)	7	3	0
Abdominal distension			
subjects affected / exposed	7 / 212 (3.30%)	1 / 200 (0.50%)	0 / 212 (0.00%)
occurrences (all)	8	1	0
Umbilical hernia			

subjects affected / exposed	5 / 212 (2.36%)	7 / 200 (3.50%)	11 / 212 (5.19%)
occurrences (all)	5	7	11
Inguinal hernia			
subjects affected / exposed	0 / 212 (0.00%)	0 / 200 (0.00%)	7 / 212 (3.30%)
occurrences (all)	0	0	7
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary dysplasia			
subjects affected / exposed	17 / 212 (8.02%)	11 / 200 (5.50%)	0 / 212 (0.00%)
occurrences (all)	17	11	0
Apnoea			
subjects affected / exposed	17 / 212 (8.02%)	8 / 200 (4.00%)	0 / 212 (0.00%)
occurrences (all)	17	15	0
Musculoskeletal and connective tissue disorders			
Osteopenia			
subjects affected / exposed	3 / 212 (1.42%)	8 / 200 (4.00%)	0 / 212 (0.00%)
occurrences (all)	3	8	0
Infections and infestations			
Rhinitis			
subjects affected / exposed	13 / 212 (6.13%)	7 / 200 (3.50%)	5 / 212 (2.36%)
occurrences (all)	13	9	6
Urinary tract infection			
subjects affected / exposed	7 / 212 (3.30%)	2 / 200 (1.00%)	0 / 212 (0.00%)
occurrences (all)	8	2	0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	5 / 212 (2.36%)	6 / 200 (3.00%)	0 / 212 (0.00%)
occurrences (all)	5	6	0

Non-serious adverse events	Placebo Safety Analysis Set: 4 weeks to 3 months	rhBSSL Safety Analysis Set: 3 months to 12 months CA	Placebo Safety Analysis Set: 3 months to 12 months CA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 200 (52.00%)	16 / 212 (7.55%)	11 / 200 (5.50%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	5 / 200 (2.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	7	0	0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	49 / 200 (24.50%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	59	0	0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Retinopathy of prematurity			
subjects affected / exposed	4 / 200 (2.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	5	0	0
Conjunctivitis			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 200 (4.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	8	0	0
Flatulence			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	0	0	0
Umbilical hernia			
subjects affected / exposed	10 / 200 (5.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	10	0	0
Inguinal hernia			
subjects affected / exposed	8 / 200 (4.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	9	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	0	0	0
Apnoea			

subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Osteopenia			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Rhinitis			
subjects affected / exposed	8 / 200 (4.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	8	0	0
Urinary tract infection			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 200 (0.00%)	0 / 212 (0.00%)	0 / 200 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2011	Amendment 1 was completed before the first patient entered the study and included mostly clarifications and corrections.
15 February 2013	Amendment 2 was prepared to prolong the study from 12 to 24 months corrected age to study health economy and effect on neurodevelopment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Based on the limited number of patients expected to complete the 24 month CA visit due to the sponsors decision to terminate the study early, only a subset of the pre-planned analyses and data presentations for the extension were performed.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27244221