Clinical trial results:
A prospective, randomised, double-blind crossover study comparing 0.15 g/L rhBSSL added to pasteurized breast milk versus placebo during one week of treatment in preterm infants born before week 32 of gestational age

Summary

EudraCT number	2007-002434-10
Trial protocol	FR IT
Global end of trial date	17 February 2010

Results information

Result version number	v1 (current)
This version publication date	28 April 2016
First version publication date	28 April 2016

Trial information

Trial identification

Sponsor protocol code	BVT.BSSL-021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00659243
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swedish Orphan Biovitrum
Sponsor organisation address	Tomtebodavägen 23, Stockholm, Sweden, 11276
Public contact	Medical Director, Swedish Orphan Biovitrum, 0046 86970000,
Scientific contact	Medical Director, Swedish Orphan Biovitrum, 0046 86970000,

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 1901/2006 apply to this trial?	No
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	17 February 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2010
Global end of trial reached?	Yes
Global end of trial date	17 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the fat absorption (coefficient of fat absorption) in preterm infants following treatment with rhBSSL to that with placebo when administered in pasteurized breast milk.

Protection of trial subjects:

The study was performed in accordance with the recommendations guiding physicians in biomedical research involving patients adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions ( ). The study was also conducted in accordance with the general principles of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and European Union (EU) Directives 2001/20/EC and 2005/28/EC and under the ICH 11 Guidance for Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99). The recommendations of the Ad Hoc group for the development of guidelines for the implementing of Directive 2001/20/EC: Ethical Considerations for Clinical Trials Performed in Children was also considered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2008
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	France: 27
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	32
EEA total number of subjects	32

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	32
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: -

Pre-assignment

Screening details:

Preterm infants born before week 32 of gestation and who were ≤32weeks and 6 days of gestation (extrapolated age) at the time of first study dose, whose size was approprate for their gestational age, who were receiving pasteurized breast milk, and who were receiving enteral nutrition (bottle or nasal tube).

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	rhBSSL

Arm description: -

Arm type	Experimental
Investigational medicinal product name	rhBSSL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The amount of milk given was based on the patient’s body weight as recorded on the CRF each morning. The concentration of rhBSSL in pasteurized breast milk remained constant at 0.15 g/L. Patients received pasteurized breast milk with or without rhBSSL for 7 days depending on the randomization schedule. A matching amount of sterile water for injection (WFI) was added to the pasteurized breast milk without rhBSSL when the patient was assigned to placebo. The amount of milk given each day was recorded on the CRF.
Infants were to receive approximately 150 to 180 mL milk/kg body weight per day. The feeding amount on a mL/kg basis for a particular infant was to remain constant for both treatment periods.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The amount of milk given was based on the patient’s body weight as recorded on the CRF each morning. Patients received pasteurized breast milk with or without rhBSSL for 7 days depending on the randomization schedule. A matching amount of sterile water for injection (WFI) was added to the pasteurized breast milk without rhBSSL when the patient was assigned to placebo. The amount of milk given each day was recorded on the CRF.
Infants were to receive approximately 150 to 180 mL milk/kg body weight per day. The feeding amount on a mL/kg basis for a particular infant was to remain constant for both treatment periods.

Number of subjects in period 1	rhBSSL	Placebo
Started	29	29
Completed	27	28
Not completed	2	1
Adverse event, non-fatal	2	1

Baseline characteristics

Reporting groups

Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	32	32	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	32	32	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Extrapolated gestational age at screening visit			
Units: weeks			
arithmetic mean	32.51		
standard deviation	± 0.535	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	16	16	

Subject analysis sets

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

Subject analysis set description:

All randomized patients who received at least one dose of randomized study medication (rhBSSL or placebo). The analysis of all safety and tolerability variables were performed using the safety analysis set.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized patients who received at least one dose of randomized study medication in both treatment periods.

Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients included in FAS who had reasonable compliance and no other major protocol violations.

Subject analysis set title	rhBSSL - Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description: rhBSSL - Per Protocol	
Subject analysis set title	rhBSSL - FAS
Subject analysis set type	Full analysis
Subject analysis set description: rhBSSL - FAS	
Subject analysis set title	Placebo - Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: Placebo - Per Protocol	
Subject analysis set title	Placebo - FAS
Subject analysis set type	Full analysis
Subject analysis set description: Placebo - FAS	

Reporting group values	Safety Analysis Set	Full Analysis Set	Per Protocol Set
Number of subjects	30	27	20
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	30	27	20
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			
Extrapolated gestational age at screening visit			
Units: weeks			
arithmetic mean	32.51		
standard deviation	± 0.535	±	±
Gender categorical Units: Subjects			
Female			
Male			

Reporting group values	rhBSSL - Per Protocol	rhBSSL - FAS	Placebo - Per Protocol
Number of subjects	20	27	20
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			

Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Extrapolated gestational age at screening visit			
Units: weeks arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			

Reporting group values	Placebo - FAS		
Number of subjects	27		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Extrapolated gestational age at screening visit			
Units: weeks arithmetic mean standard deviation	±		
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	rhBSSL
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized patients who received at least one dose of randomized study medication (rhBSSL or placebo). The analysis of all safety and tolerability variables were performed using the safety analysis set.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients who received at least one dose of randomized study medication in both treatment periods.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients included in FAS who had reasonable compliance and no other major protocol violations.	
Subject analysis set title	rhBSSL - Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
rhBSSL - Per Protocol	
Subject analysis set title	rhBSSL - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
rhBSSL - FAS	
Subject analysis set title	Placebo - Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Placebo - Per Protocol	
Subject analysis set title	Placebo - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo - FAS	

Primary: Coefficient of fat absorption (CFA) measured in stool collected for a 72 hour period during the final 3 days of each treatment period.

End point title	Coefficient of fat absorption (CFA) measured in stool collected for a 72 hour period during the final 3 days of each treatment period.
End point description:	
End point type	Primary
End point timeframe:	
The collection of feces for the determination of coefficient of fat absorption (CFA) was performed over a period corresponding to the fat (formula) ingestion during 72 hours toward the end of each treatment.	

End point values	rhBSSL - Per Protocol	Placebo - Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: percentage				
arithmetic mean (standard deviation)	68.46 (± 15.333)	63.82 (± 17.875)		

Statistical analyses

Statistical analysis title	ANOVA CFA

Statistical analysis description:

The primary efficacy outcome, CFA from the last three days of each treatment period, will be analyzed by an analysis of variance (ANOVA) with treatment, period, and sequence as factors with patient as a random effect nested within sequence.

Comparison groups	rhBSSL - Per Protocol v Placebo - Per Protocol
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.073
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	4.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	10.22

Notes:

[1] - Please note that this is a crossover study and each subject receives both treatments in a randomized order. The number of subjects stated below does not account for the crossover design and is therefore stated as twice as high as the correct number of patients.

Secondary: Change in body weight (g/kg/day) between the start and end of each treatment period - Per Protocol

End point title	Change in body weight (g/kg/day) between the start and end of each treatment period - Per Protocol

End point description:

End point type	Secondary

End point timeframe:

The patient’s weight in grams (g) was recorded each day and entered on the CRF. To the extent possible, body weight was measured at approximately the same time each day using a scale with an accuracy of at least ±5 g.

End point values	rhBSSL - Per Protocol	Placebo - Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: g/kg/day				
arithmetic mean (standard deviation)	16.16 (± 4.856)	14.59 (± 4.63)		

Statistical analyses

Statistical analysis title	Change in body weight - Per Protocol

Statistical analysis description:

The secondary efficacy outcomes will be analyzed by an analysis of variance (ANOVA) with treatment, period, and sequence as factors with patient as a random effect nested within sequence.

Comparison groups	rhBSSL - Per Protocol v Placebo - Per Protocol
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.271
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	4.88

Notes:

[2] - Please note that this is a crossover study and each subject receives both treatments in a randomized order. The number of subjects stated below does not account for the crossover design and is therefore stated as twice as high as the correct number of patients.

Secondary: Change in body weight (g/kg/day) between the start and end of each treatment period - FAS

End point title	Change in body weight (g/kg/day) between the start and end of each treatment period - FAS

End point description:

End point type	Secondary

End point timeframe:

First measurement done at Screening Visit (Day -7 to -1) and thereafter daily on Day 1 to Day 17 and at Follow up visit (Day 20-26).

End point values	rhBSSL - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: g/kg/day				
arithmetic mean (standard deviation)	15.54 (± 4.88)	13.63 (± 5.292)		

Statistical analyses

Statistical analysis title	Change in body weight - FAS

Statistical analysis description:

The secondary efficacy outcomes will be analyzed by an analysis of variance (ANOVA) with treatment, period, and sequence as factors with patient as a random effect nested within sequence.

Comparison groups	Placebo - FAS v rhBSSL - FAS
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.119
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	4.43

Notes:

[3] - Please note that this is a crossover study and each subject receives both treatments in a randomized order. The number of subjects stated below does not account for the crossover design and is therefore stated as twice as high as the correct number of patients.

Secondary: Change in length from knee-to-heel (mm) between the start and end of each treatment period - Per Protocol

End point title	Change in length from knee-to-heel (mm) between the start and end of each treatment period - Per Protocol

End point description:

End point type	Secondary

End point timeframe:

First measurement done at Screening Visit (Day -7 to -1) and thereafter daily on Day 1 to Day 17 and at Follow up visit (Day 20-26). To the extent possible, length was measured at approximately the same time each day.

End point values	rhBSSL - Per Protocol	Placebo - Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: mm				
arithmetic mean (standard deviation)	2.43 (± 1.621)	1.83 (± 3.032)		

Statistical analyses

Statistical analysis title	Change of Knee-to heel Length in PP population

Statistical analysis description:

The secondary efficacy outcomes will be analyzed by an analysis of variance (ANOVA) with treatment, period, and sequence as factors with patient as a random effect nested within sequence.

Comparison groups	rhBSSL - Per Protocol v Placebo - Per Protocol
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.361
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	1.65

Notes:

[4] - Please note that this is a crossover study and each subject receives both treatments in a randomized order. The number of subjects stated below does not account for the crossover design and is therefore stated as twice as high as the correct number of patients.

Secondary: Change in length from knee-to-heel (mm) between the start and end of each treatment period - FAS

End point title	Change in length from knee-to-heel (mm) between the start and end of each treatment period - FAS

End point description:

End point type	Secondary

End point timeframe:

First measurement done at Screening Visit (Day -7 to -1) and thereafter daily on Day 1 to Day 17 and at Follow up visit (Day 20-26)
To the extent possible, length was measured at approximately the same time each day.

End point values	rhBSSL - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: mm				
arithmetic mean (standard deviation)	2.17 (± 1.95)	1.7 (± 2.796)		

Statistical analyses

Statistical analysis title	Change of Knee-to heel Length in FAS population

Statistical analysis description:

The secondary efficacy outcomes will be analyzed by an analysis of variance (ANOVA) with treatment, period, and sequence as factors with patient as a random effect nested within sequence.

Comparison groups	rhBSSL - FAS v Placebo - FAS
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.376
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	1.34

Notes:

[5] - Please note that this is a crossover study and each subject receives both treatments in a randomized order. The number of subjects stated below does not account for the crossover design and is therefore stated as twice as high as the correct number of patients.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period for this study began upon administration of the first dose of investigational medication (Baseline visit) and ended 1 week ± 3 days after last dose of study drug intake (follow-up visit).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	rhBSSL
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	rhBSSL	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Septic shock			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	rhBSSL	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 28 (57.14%)	14 / 29 (48.28%)	
Investigations			
Cardiac murmur			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Oxygen saturation decreased			

subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	4	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 28 (3.57%)	3 / 29 (10.34%)	
occurrences (all)	2	13	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 28 (7.14%)	3 / 29 (10.34%)	
occurrences (all)	2	3	
Anaemia neonatal			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Thrombocythaemia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Application site discolouration			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Retinopathy of prematurity			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Anal fissure			

subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Colitis ulcerative			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 29 (3.45%)	
occurrences (all)	3	1	
Necrotising colitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Regurgitation			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	9 / 28 (32.14%)	8 / 29 (27.59%)	
occurrences (all)	15	10	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Renal tubular acidosis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Infections and infestations			
Fungal infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Viral infection			

subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	3 / 28 (10.71%)	2 / 29 (6.90%)	
occurrences (all)	3	2	
Hyponatraemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Metabolic acidosis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 29 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2009	• Changed enrollment age requirement from ≤32 weeks and 6 days of gestation at the time of enrollment to ≤32 weeks and 6 days of gestation at the time of first study drug dose • Added exploratory analysis of long-chain polyunsaturated fatty acids measure in stool collected • Changed sample processing where complete diapers were to be sent to the central laboratory
01 June 2009	• Harmonised the unit for the secondary efficacy variable change in body weight as gram per kg per day across all sections of the protocol • Added a statistical hypothesis of change in body weight as part of the confirmatory strategy • Pre-defined that a statistical analysis with respect to the change in body weight and CFA was performed using combined data from this study and study BVT.BSSL 020 • Added the definition of change in body weight • Harmonized the text in the statistical analysis section with earlier sections of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported