

**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        | <ul style="list-style-type: none"><li>• New data added to full data set</li><li>1) Results for the period 12-24 months corrected age has been added as analysis of these endpoints has now been finalized.</li><li>2) Link to publication added.</li><li>3) Correction of wrongful allocation of data within the "Adverse Events" section caused by EudraCT software issues.</li></ul> |

**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)                    | EMA-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:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | 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.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 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 |
|------------------------------|-----|

|                  |            |
|------------------|------------|
| <b>Arm title</b> | 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.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 2<sup>[2]</sup></b> | rhBSSL EES | Placebo EES |
|---|------------|-------------|
| Started   | 35         | 37          |
| Completed   | 35         | 37          |

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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<br>Units: Weeks<br>arithmetic mean<br>standard deviation | 28.74<br>± 1.675  | 28.86<br>± 1.731   | ± |
| Baseline Body Weight<br>Units: gram(s)<br>arithmetic mean<br>standard deviation           | 1386.8<br>± 268.9 | 1383.1<br>± 258.85 | ± |
| Baseline Body Length<br>Units: cm<br>arithmetic mean<br>standard deviation                | 39.75<br>± 2.718  | 39.48<br>± 2.364   | ± |
| Head Circumference at Baseline<br>Units: cm<br>arithmetic mean<br>standard deviation      | 27.86<br>± 1.605  | 27.77<br>± 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<br>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<br>arithmetic mean<br>standard deviation   | ±                                     | ±  | ±                                     |
| Gender categorical<br>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<br>Units: Weeks<br>arithmetic mean<br>standard deviation | $\pm$ | $\pm$ | $\pm$ |
| Baseline Body Weight<br>Units: gram(s)<br>arithmetic mean<br>standard deviation           | $\pm$ | $\pm$ | $\pm$ |
| Baseline Body Length<br>Units: cm<br>arithmetic mean<br>standard deviation                | $\pm$ | $\pm$ | $\pm$ |
| Head Circumference at Baseline<br>Units: cm<br>arithmetic mean<br>standard deviation      | $\pm$ | $\pm$ | $\pm$ |

| 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<br>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<br>arithmetic mean<br>standard deviation   | $\pm$                                     | $\pm$                                | $\pm$                                |
| Gender categorical<br>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  | ± | ± | ± |

| <b>Reporting group values</b>  | 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)<br>Appropriate for gestational age (AGA)  |       |       |       |
| Gestational Age at Time of Birth<br>Units: Weeks<br>arithmetic mean<br>standard deviation   | $\pm$ | $\pm$ | $\pm$ |
| Baseline Body Weight<br>Units: gram(s)<br>arithmetic mean<br>standard deviation   | $\pm$ | $\pm$ | $\pm$ |
| Baseline Body Length<br>Units: cm<br>arithmetic mean<br>standard deviation  | $\pm$ | $\pm$ | $\pm$ |
| Head Circumference at Baseline<br>Units: cm<br>arithmetic mean<br>standard deviation  | $\pm$ | $\pm$ | $\pm$ |

## 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  $\geq 2$  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  $\geq 2$  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 ( $\pm$ 3.53)     | 17.201 ( $\pm$ 3.3579)    | 16.333 ( $\pm$ 3.0247)               | 17.302 ( $\pm$ 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 ( $\pm$ 3.6694)                   | 15.875 ( $\pm$ 2.7538)                | 17.989 ( $\pm$ 3.4448)                    | 18.547 ( $\pm$ 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 ( $\pm$ 3.4588)               | 16.615 ( $\pm$ 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   |

|                                   |        |
|-----------------------------------|--------|
| <b>Statistical analysis title</b> | 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   |

|                                   |        |
|-----------------------------------|--------|
| <b>Statistical analysis title</b> | 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  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | 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  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | 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  |

|   |  |
|---|--|
| <b>Secondary: Body Weight: Change from Baseline at 4 Weeks</b>                            |  |
| 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. |  |

| <b>End point values</b>              | 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

| <b>Statistical analysis title</b> | 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 ( $\pm$ 567.2)    | 2823.8 ( $\pm$ 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 ( $\pm$ 1334.25)  | 8845.9 ( $\pm$ 1239.8)    |  |  |

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | 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. |   |

|                                      |                          |                           |  |  |
|--------------------------------------|--------------------------|---------------------------|--|--|
| <b>End point values</b>              | 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



|                                   |        |
|-----------------------------------|--------|
| <b>Statistical analysis title</b> | 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

|  |        |
|--|--------|
| <b>Statistical analysis title</b>  | 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:<br>Change from baseline = post baseline value — baseline value.                             |   |
| End point type   | Secondary                                     |
| End point timeframe:<br>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:<br>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.<br>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 ( $\pm$ 4.128)     | 73.49 ( $\pm$ 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 until 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 ( $\alpha$ ) which is defined by the differential equation  $(dm/dt) = \alpha V(t)$ ,  $t \geq 1$

where

- $\alpha$  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  $\alpha$ , separately for each patient.  $\alpha$  will be constrained to be  $\geq 0$ , 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  $\alpha$  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 ( $\pm$ 23.625)   | 109.72 ( $\pm$ 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**

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|                 |                                      |
|-----------------|--------------------------------------|
| 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**

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|                 |                                      |
|-----------------|--------------------------------------|
| 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | 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:  |   |
| <p>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.</p> <p>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.</p> |   |
| 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)                |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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

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|                 |  |
|-----------------|--|
| 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

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| 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.

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|                |           |
|----------------|-----------|
| 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)                |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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

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|                 |  |
|-----------------|--|
| 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 ( $\pm$ 0.1942)      | 0.061 ( $\pm$ 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 ( $\pm$ 10.64)        | 69.9 ( $\pm$ 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 ( $\pm$ 9.12)         | 39.3 ( $\pm$ 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 ( $\pm$ 9.29)         | 40.4 ( $\pm$ 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 ( $\pm$ 12.38)           | 1.1 ( $\pm$ 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 ( $\pm$ 12.75)       | 154.4 ( $\pm$ 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 ( $\pm$ 253.92)      | 528.1 ( $\pm$ 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 ( $\pm$ 12.8054)     | 10.428 ( $\pm$ 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 ( $\pm$ 95.4933)    | 96.212 ( $\pm$ 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 ( $\pm$ 94.6279)   | 106.64 ( $\pm$ 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 ( $\pm$ 0.2965)      | 0.428 ( $\pm$ 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 ( $\pm$ 32.478)         | 36.03 ( $\pm$ 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 ( $\pm$ 3.3)         | 138.4 ( $\pm$ 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 ( $\pm$ 1.691)        | 3.05 ( $\pm$ 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:<br>$GV = (1000 \times (W_n \times W_1)) / (W_n (D_n - D_1))$ 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 ( $\pm$ 5.6001)   | 21.938 ( $\pm$ 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 <sup>[1]</sup> | 34 <sup>[2]</sup> |  |  |
| 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 <sup>[3]</sup> | 34 <sup>[4]</sup> |  |  |
| 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 <sup>[5]</sup> | 35 <sup>[6]</sup> |  |  |
| 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

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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End point timeframe:

24 Months Corrected Age Visit

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| 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               |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Body Weight at 24 Months Corrected Age**

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|                 |  |
|-----------------|--|
| End point title | Body Weight at 24 Months Corrected Age |
|-----------------|--|

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End point description:

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

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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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 ( $\pm$ 1.4591) | 11.078 ( $\pm$ 1.3523) |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Body Height at 24 Months Corrected Age**

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

|                                      |                      |                      |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| <b>End point values</b>              | 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 ( $\pm$ 4.307) | 85.65 ( $\pm$ 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:<br>Only includes assessments performed within 24 months corrected age +/- 28 days |   |
| End point type   | Secondary                                     |
| End point timeframe:<br>24 Months Corrected Age Visit  |   |

|                                      |                      |                      |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| <b>End point values</b>              | 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 ( $\pm$ 1.735) | 47.28 ( $\pm$ 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:<br>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 |           |

| <b>End point values</b>     | rhBSSL<br>Extension<br>safety set: 12<br>to 24 months<br>CA | Placebo<br>Extension<br>safety set: 12<br>to 24 months<br>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

### 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  $\geq 2$  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  $\geq 2$  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  $\geq 2$  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  $\geq 2$  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  $\geq 2$  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  $\geq 2$  vials of rhBSSL

| <b>Serious adverse events</b>                                       | rhBSSL Safety<br>Analysis Set:<br>Baseline to week 4 | Placebo Safety<br>Analysis Set:<br>Baseline to week 4 | rhBSSL Safety<br>Analysis Set: 4<br>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           |
| <b>Investigations</b>                             |                 |                 |                 |
| 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           |
| <b>Congenital, familial and genetic disorders</b> |                 |                 |                 |
| 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-hypodermatitis                            |                 |                 |                 |
| 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           |

|                               |                |               |                |
|-------------------------------|----------------|---------------|----------------|
| <b>Serious adverse events</b> | Placebo Safety | rhBSSL Safety | Placebo Safety |
|-------------------------------|----------------|---------------|----------------|

|   | Analysis Set: 4<br>weeks to 3 months | Analysis Set: 3<br>months to 12<br>months CA | Analysis Set: 3<br>months to 12<br>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           |
| <b>Investigations</b>                             |                 |                 |                 |
| 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           |
| <b>Congenital, familial and genetic disorders</b> |                 |                 |                 |
| 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-hypodermatitis                            |                 |                 |                 |
| 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 %

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

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

| <b>Non-serious adverse events</b>   | Placebo Safety<br>Analysis Set: 4<br>weeks to 3 months | rhBSSL Safety<br>Analysis Set: 3<br>months to 12<br>months CA | Placebo Safety<br>Analysis Set: 3<br>months to 12<br>months CA |
|---|--|---|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed   | 104 / 200 (52.00%)                                     | 16 / 212 (7.55%)  | 11 / 200 (5.50%)   |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)<br>Haemangioma<br>subjects affected / exposed<br>occurrences (all) | 5 / 200 (2.50%)<br>7                                   | 0 / 212 (0.00%)<br>0  | 0 / 200 (0.00%)<br>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<br>occurrences (all)   | 0 / 200 (0.00%)<br>0                             | 0 / 212 (0.00%)<br>0                             | 0 / 200 (0.00%)<br>0                             |
| Musculoskeletal and connective tissue disorders<br>Osteopenia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 200 (0.00%)<br>0                             | 0 / 212 (0.00%)<br>0                             | 0 / 200 (0.00%)<br>0                             |
| Infections and infestations<br>Rhinitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 8 / 200 (4.00%)<br>8<br><br>0 / 200 (0.00%)<br>0 | 0 / 212 (0.00%)<br>0<br><br>0 / 212 (0.00%)<br>0 | 0 / 200 (0.00%)<br>0<br><br>0 / 200 (0.00%)<br>0 |
| Metabolism and nutrition disorders<br>Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 200 (0.00%)<br>0                             | 0 / 212 (0.00%)<br>0                             | 0 / 200 (0.00%)<br>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:

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### 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:

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### Online references

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