

**Clinical trial results:
Efficacy and Safety of Inhaled Budesonide in Very Preterm Infants at
Risk for Bronchopulmonary Dysplasia****Summary**

| | |
|--------------------------|-------------------------|
| EudraCT number | 2009-012203-26 |
| Trial protocol | DE FI FR EE CZ BE GR NL |
| Global end of trial date | 31 July 2016 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 25 March 2022 |
| First version publication date | 25 March 2022 |
| Summary attachment (see zip file) | Safety outcomes (Safety outcomes.jpeg) |

Trial information**Trial identification**

| | |
|-----------------------|-----------------------------------|
| Sponsor protocol code | Grand_Award_Health-F5_2009-223060 |
|-----------------------|-----------------------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01035190 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University Children's Hospital Tuebingen |
| Sponsor organisation address | Calwerstr. 7, Tuebingen, Germany, 72976 |
| Public contact | Christian F. Poets, Dirk Bassler, University Children's Hospital Tuebingen Department of Neonatology, +49 7071-298 6175/61, neurosis.studycoordinator@med.uni-tuebingen.de |
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 15 October 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine if the early (within 12 hours of life) prophylactic use of inhaled corticosteroids (Budesonide) in very preterm infants (gestational age 23 0/7-27 6/7 weeks) requiring any form of positive pressure support (mechanical or nasal ventilation or continuous positive airway pressure (CPAP)) increases survival without bronchopulmonary dysplasia (BPD) at 36 weeks gestational age.

Protection of trial subjects:

NEuroSIS will be conducted in accordance with the Declaration of Helsinki, as well as with the International Conference on Harmonization Good Clinical Practice Guidelines (ICH GCP). At present there is general agreement that further studies investigating inhaled corticosteroids in the population of preterm infants are needed and equipoise remains. It has been highlighted repeatedly that future studies need to address both the short-term and longterm benefits and adverse effects, with particular attention to neurodevelopmental outcome.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 10 April 2010 |
| 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 | Israel: 125 |
| Country: Number of subjects enrolled | Germany: 252 |
| Country: Number of subjects enrolled | Netherlands: 11 |
| Country: Number of subjects enrolled | Czechia: 179 |
| Country: Number of subjects enrolled | Estonia: 8 |
| Country: Number of subjects enrolled | Finland: 103 |
| Country: Number of subjects enrolled | France: 100 |
| Country: Number of subjects enrolled | Italy: 51 |
| Country: Number of subjects enrolled | Belgium: 34 |
| Worldwide total number of subjects | 863 |
| EEA total number of subjects | 738 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 863 |
| 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:

Infants with a gestational age of 23 weeks 0 days to 27 weeks 6 days and a chronologic age of 12 hours or less who required any form of positive pressure support were eligible.

Pre-assignment

Screening details:

2233 infants met the inclusion criteria, however, 466 patients were excluded due to several reasons. 1767 patients were available, but only 913 underwent randomization. Finally the ITT population consisted of 863 patients

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Data relating to patients/parents, caregivers and outcome assessors will be blinded (the pharmacist will be the only person with knowledge of treatment assignments). Randomization must take place within the first 12 hours of life.

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Budesonide arm |

Arm description:

Eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygen saturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The dose of budesonide was two puffs (200 µg per puff) administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Budesonide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oromucosal suspension |
| Routes of administration | Inhalation use |

Dosage and administration details:

The dose of budesonide was two puffs (200 µg per puff) administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered.

| | |
|------------------|-------------|
| Arm title | Placebo arm |
|------------------|-------------|

Arm description:

To ensure that all the infants received the study drug within 24 hours after birth, eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygen saturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The placebo contained only hydrofluoroalkane propellant.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|-------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

The dose was two puffs administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered. Study drugs were administered until infants no longer needed supplemental oxygen and positive pressure support or reached a postmenstrual age of 32 weeks 0 days, regardless of ventilator status.

| Number of subjects in period 1 | Budesonide arm | Placebo arm |
|---------------------------------------|----------------|-------------|
| Started | 441 | 422 |
| Completed | 437 | 419 |
| Not completed | 4 | 3 |
| Consent withdrawn by subject | 4 | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Budesonide arm |
|-----------------------|----------------|

Reporting group description:

Eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygensaturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The dose of budesonide was two puffs (200 µg per puff) administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered.

| | |
|-----------------------|-------------|
| Reporting group title | Placebo arm |
|-----------------------|-------------|

Reporting group description:

To ensure that all the infants received the study drug within 24 hours after birth, eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygensaturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The placebo contained only hydrofluoroalkane propellant.

| Reporting group values | Budesonide arm | Placebo arm | Total |
|--|----------------|-------------|-------|
| Number of subjects | 441 | 422 | 863 |
| Age categorical | | | |
| Infants with a gestational age of 23 weeks 0 days to 27 weeks 6 days and a chronologic age of 12 hours or less who required any form of positive pressure support were eligible. | | | |
| Units: Subjects | | | |
| Preterm newborn infants (gestational age < 37 wks) | 1 | 1 | 2 |
| Newborns (0-27 days) | 439 | 420 | 859 |
| Infants and toddlers (28 days-23 months) | 1 | 1 | 2 |
| Age continuous | | | |
| Units: weeks | | | |
| arithmetic mean | 26.1 | 26.1 | |
| standard deviation | ± 1.3 | ± 1.2 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 219 | 209 | 428 |
| Male | 222 | 213 | 435 |

End points

End points reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Budesonide arm |
|-----------------------|----------------|

Reporting group description:

Eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygensaturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The dose of budesonide was two puffs (200 µg per puff) administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered.

| | |
|-----------------------|-------------|
| Reporting group title | Placebo arm |
|-----------------------|-------------|

Reporting group description:

To ensure that all the infants received the study drug within 24 hours after birth, eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygensaturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The placebo contained only hydrofluoroalkane propellant.

Primary: Death or bronchopulmonary displasia at 36 weeks postmenstrual age

| | |
|-----------------|---|
| End point title | Death or bronchopulmonary displasia at 36 weeks postmenstrual age |
|-----------------|---|

End point description:

The primary outcome was a composite of death or bronchopulmonary dysplasia at 36 weeks of postmenstrual age. Bronchopulmonary dysplasia was defined as the requirement for positive pressure support, the requirement for supplemental oxygen at a fraction of inspired oxygen exceeding 0.30, or, in infants receiving low amounts of oxygen, an inability to maintain an oxygen-saturation value above 90% during a structured, short period of saturation monitoring coupled with gradual weaning from oxygen to ambient air (the oxygen-reduction test).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

36 weeks

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: patients | 175 | 194 | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Statistical analysis of the primary endpoint |
| Comparison groups | Budesonide arm v Placebo arm |

| | |
|---|-----------------|
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.05 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1 |

Secondary: Frequency of a patent ductus arteriosus requiring surgery

| | |
|--|---|
| End point title | Frequency of a patent ductus arteriosus requiring surgery |
| End point description: The frequency of a patent ductus arteriosus that was considered by clinical staff to require surgical ligation | |
| End point type | Secondary |
| End point timeframe: 36 weeks | |

| End point values | Budenoside arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: patients | 31 | 54 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis secondary outcome |
| Comparison groups | Placebo arm v Budenoside arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.004 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.36 |
| upper limit | 0.83 |

Secondary: Frequency of the need for reintubation after the last administration of the study drug

| | |
|-----------------|--|
| End point title | Frequency of the need for reintubation after the last administration of the study drug |
|-----------------|--|

End point description:

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

End point timeframe:

36 weeks

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: patients | 23 | 38 | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical analysis of the secondary outcome |
|-----------------------------------|---|

| | |
|-------------------|------------------------------|
| Comparison groups | Budesonide arm v Placebo arm |
|-------------------|------------------------------|

| | |
|---|-----|
| Number of subjects included in analysis | 856 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-----------------|
| Analysis type | non-inferiority |
|---------------|-----------------|

| | |
|---------|--------|
| P-value | = 0.03 |
|---------|--------|

| | |
|--------|-------|
| Method | ANOVA |
|--------|-------|

| | |
|--------------------|-----------------|
| Parameter estimate | Risk ratio (RR) |
|--------------------|-----------------|

| | |
|----------------|------|
| Point estimate | 0.58 |
|----------------|------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|------|
| lower limit | 0.35 |
|-------------|------|

| | |
|-------------|------|
| upper limit | 0.96 |
|-------------|------|

Secondary: The median postmenstrual age at the last use of supplemental oxygen

| | |
|-----------------|---|
| End point title | The median postmenstrual age at the last use of supplemental oxygen |
|-----------------|---|

End point description:

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

End point timeframe:

36 weeks

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: weeks | 32 | 33 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis of the secondary outcome |
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.05 |
| Method | ANOVA |

Secondary: Retinopathy of prematurity

| | |
|------------------------|---|
| End point title | Retinopathy of prematurity |
| End point description: | The endpoint was to assess how many participants developed stage 2 or higher retinopathy of prematurity |
| End point type | Secondary |
| End point timeframe: | 36 weeks |

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 361 | | |
| Units: patients | 127 | 113 | | |

Statistical analyses

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Stratified relative risk |
| Comparison groups | Budesonide arm v Placebo arm |

| | |
|---|-----------------|
| Number of subjects included in analysis | 724 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.23 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.38 |

Secondary: Brain injury

| | |
|---|--------------|
| End point title | Brain injury |
| End point description: The endpoint was to assess how many patients suffered from brain injury | |
| End point type | Secondary |
| End point timeframe: 36 weeks | |

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 428 | 410 | | |
| Units: patients | 91 | 70 | | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Stratified Relative Risk |
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 838 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.12 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.65 |

Secondary: Necrotizing enterocolitis or intestinal perforation

| | |
|-----------------|---|
| End point title | Necrotizing enterocolitis or intestinal perforation |
|-----------------|---|

End point description:

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

End point timeframe:

36 weeks

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: patients | 51 | 44 | | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Statistical analysis |
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.47 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.35 |

Secondary: Frequency of intestinal perforation

| | |
|-----------------|-------------------------------------|
| End point title | Frequency of intestinal perforation |
|-----------------|-------------------------------------|

End point description:

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

End point timeframe:

36 weeks

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: patients | 29 | 44 | | |

Statistical analyses

| Statistical analysis title | Statistical analysis |
|---|------------------------------|
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.95 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 1.58 |

Secondary: Patent ductus arteriosus treated with drugs

| | |
|------------------------|---|
| End point title | Patent ductus arteriosus treated with drugs |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks | |

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: patients | 189 | 207 | | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Stratified Relative Risk |
| Comparison groups | Placebo arm v Budenoside arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.07 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.01 |

Secondary: Patent ductus arteriosus treated by surgical ligation

| | |
|------------------------|---|
| End point title | Patent ductus arteriosus treated by surgical ligation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks | |

| End point values | Budenoside arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: patients | 31 | 54 | | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Stratified Relative Risk |
| Comparison groups | Budenoside arm v Placebo arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.004 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.55 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.36 |
| upper limit | 0.83 |

Secondary: Culture-proven infection: sepsis

| | |
|------------------------|----------------------------------|
| End point title | Culture-proven infection: sepsis |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | Budesonide arm | Placebo arm | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: patients | 148 | 125 | | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Stratified Relative Risk |
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.2 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.38 |

Secondary: Culture-proven infection: meningitis

| | |
|------------------------|--------------------------------------|
| End point title | Culture-proven infection: meningitis |
| End point description: | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks | |

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 422 | | |
| Units: patients | 5 | 4 | | |

Statistical analyses

| Statistical analysis title | Stratified Relative Risk |
|---|------------------------------|
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 859 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.79 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.32 |
| upper limit | 4.43 |

Secondary: Adverse treatment effects

| | |
|---|---------------------------|
| End point title | Adverse treatment effects |
| End point description: | |
| Adverse treatment effects were defined as either oral candidiasis requiring treatment (in 28 patients in the budesonide group and 32 patients in the placebo group), hyperglycemia requiring insulin treatment (in 86 patients in the budesonide group and 85 patients in the placebo group), or hypertension requiring treatment (in 6 patients in the budesonide group and 10 patients in the placebo group). | |
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks | |

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: patients | 95 | 98 | | |

Statistical analyses

| Statistical analysis title | Stratified Relative Risk |
|---|------------------------------|
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.55 |
| Method | ANOVA |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.18 |

Secondary: Days of hospitalization

| | |
|------------------------|-------------------------|
| End point title | Days of hospitalization |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | n.a |

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: days | 91 | 93 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in weight from baseline to day 28

| | |
|---------------------------------|--|
| End point title | Change in weight from baseline to day 28 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: 28 days | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | Budesonide arm | Placebo arm | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 441 | 422 | | |
| Units: grams (g) | 274 | 278 | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | p value for the change in weight |
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 863 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.72 |
| Method | ANOVA |

Secondary: Change in head circumference from baseline to day 28

| | |
|---------------------------------|--|
| End point title | Change in head circumference from baseline to day 28 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: 28 days | |

| | | | | |
|--------------------------------------|-----------------|-----------------|--|--|
| End point values | Budesonide arm | Placebo arm | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | 1.6 (± 1.2) | 1.4 (± 1.4) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | P-value for the change in head circumference |
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.21 |
| Method | ANOVA |

Secondary: Postmenstrual age at last use of respiratory support: Positive-pressure support

| | |
|------------------------|---|
| End point title | Postmenstrual age at last use of respiratory support: Positive-pressure support |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| n.a | |

| End point values | Budesonide arm | Placebo arm | | |
|---------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: weeks | | | | |
| median (inter-quartile range (Q1-Q3)) | 33.1 (30.7 to 35.4) | 33.4 (31.4 to 36.3) | | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | P-value |
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.07 |
| Method | ANOVA |

Secondary: Postmenstrual age at last use of respiratory support: supplemental oxygen

| | |
|------------------------|---|
| End point title | Postmenstrual age at last use of respiratory support: supplemental oxygen |
| End point description: | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | n.a |

| End point values | Budesonide arm | Placebo arm | | |
|---------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: weeks | | | | |
| median (inter-quartile range (Q1-Q3)) | 31.6 (27.9 to 35.4) | 33.1 (28.3 to 37.1) | | |

Statistical analyses

| Statistical analysis title | P-value |
|---|------------------------------|
| Comparison groups | Budesonide arm v Placebo arm |
| Number of subjects included in analysis | 856 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.05 |
| Method | ANOVA |

Secondary: Long term neurodevelopmental disability

| | |
|------------------------|---|
| End point title | Long term neurodevelopmental disability |
| End point description: | The only prespecified secondary long-term outcome was neurodevelopmental disability among survivors, defined as a composite of cerebral palsy, cognitive delay, deafness, or blindness at a corrected age of 18 to 22 months. |
| End point type | Secondary |
| End point timeframe: | 18 to 22 months |

| End point values | Budesonide arm | Placebo arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 437 | 419 | | |
| Units: patients | 148 | 165 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

The long term effects were measured at 18 to 22 months

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|-----|
| Dictionary name | n.a |
|-----------------|-----|

| | |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: The information regarding safety outcomes can be found in the attached chart.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26465983>