



Clinical trial results:

Mindex: The efficacy and safety of very low dose dexamethasone used to facilitate the extubation of ventilator dependent preterm babies who are at high risk of bronchopulmonary dysplasia

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-005342-63 |
| Trial protocol | GB |
| Global end of trial date | 24 June 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 10 May 2019 |
| First version publication date | 10 May 2019 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | UoL001206 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN81191607 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University of Liverpool / Liverpool Joint Research Office |
| Sponsor organisation address | 2nd Floor Block D Waterhouse Building, 3 Brownlow Street, Liverpool, United Kingdom, L69 3GL |
| Public contact | NPEU Clinical Trials Unit, National Perinatal Epidemiology Unit, +44 01865289737, minidex@npeu.ox.ac.uk |
| Scientific contact | NPEU Clinical Trials Unit, National Perinatal Epidemiology Unit, +44 01865289737, minidex@npeu.ox.ac.uk |

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 | 04 September 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 April 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 June 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine if treatment with very low dose dexamethasone facilitates the extubation of ventilator dependent preterm babies of less than 30 weeks' gestation who are at high risk of developing BPD.

The main outcome measure is the time from randomisation to first extubation, when the baby remains extubated for more than 24 hours.

Protection of trial subjects:

Safety data was reviewed by the DMC which, if appropriate, make recommendations regarding continuation of the trial or modification of the trial protocol. The Trial Steering Committee (TSC) will have ultimate responsibility for deciding whether the trial should be stopped on safety grounds.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 01 August 2016 |
| 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 | United Kingdom: 22 |
| Worldwide total number of subjects | 22 |
| EEA total number of subjects | 22 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 22 |
| 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:

The trial recruitment took place in 11 tertiary neonatal units across the United Kingdom. Recruitment stopped on the 14th April 2018 after 22 babies had been randomised to the trial over a period of 9 months. This was a decision made by the funder due to poor recruitment.

Pre-assignment

Screening details:

330 babies were screened and 44 were eligible for the trial.

22 babies were not enrolled for the following reasons: 9 due to clinician decision, 11 due to parent(s) declining consent and 2 for unknown reasons.

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, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Dexamethasone (Hospira, dexamethasone 3.3 mg/ml solution for injection) was supplied as a clear sterile solution at a concentration of 3.3 mg per 1 ml in 2 ml vials. Cartons containing 14 single-use vials were provided.

Placebo was supplied as a clear sterile solution of 0.9% saline solution for injection. Cartons identical to those for dexamethasone, each containing 14 identical single-use vials were provided.

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Dexamethasone |

Arm description:

very low dose dexamethasone (50 mcg/kg /day for 13 doses)

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Dexamethasone (Hospira, dexamethasone 3.3 mg/ml solution for injection) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Nasogastric use , Intravenous use, Oral use |

Dosage and administration details:

Doses of 50 mcg/kg (0.015 ml/kg of 3.3 mg/ml solution) of dexamethasone will be administered daily on days 1 to 10 after randomisation (10 doses) then alternate days on days 12, 14 and 16, making a total of 13 doses.

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

Arm description:

matched placebo

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use, Nasogastric use , Oral use |

Dosage and administration details:

Placebo will be supplied as a clear sterile solution of 0.9% saline solution for injection. Cartons identical to those for dexamethasone, each containing 14 identical single-use vials will be provided. Volume of IMP to be withdrawn from the vial will be calculated following the calculations for dexamethasone dosing and then diluted with dextrose or normal saline for administration.

| Number of subjects in period 1 | Dexamethasone | Placebo |
|---------------------------------------|---------------|---------|
| Started | 12 | 10 |
| Completed | 12 | 10 |

Baseline characteristics

Reporting groups

| | |
|---|---------------|
| Reporting group title | Dexamethasone |
| Reporting group description: very low dose dexamethasone (50 mcg/kg /day for 13 doses) | |
| Reporting group title | Placebo |
| Reporting group description: matched placebo | |

| Reporting group values | Dexamethasone | Placebo | Total |
|---|---------------|----------|-------|
| Number of subjects | 12 | 10 | 22 |
| Age categorical | | | |
| Gestational age at birth (completed weeks) | | | |
| Units: Subjects | | | |
| Preterm newborns (gestational age <=25 weeks) | 10 | 7 | 17 |
| Preterm newborns (gestational age 26 to 27 weeks) | 2 | 1 | 3 |
| Preterm newborns (gestational age 28 to 29 weeks) | 0 | 2 | 2 |
| Age continuous | | | |
| Gestational age at birth (completed weeks) | | | |
| Units: days | | | |
| median | 25 | 25 | |
| inter-quartile range (Q1-Q3) | 24 to 25 | 23 to 26 | - |
| Gender categorical | | | |
| Baby's sex | | | |
| Units: Subjects | | | |
| Female | 4 | 6 | 10 |
| Male | 8 | 4 | 12 |
| Mother's ethnic group | | | |
| Units: Subjects | | | |
| White | 11 | 9 | 20 |
| Asian | 1 | 0 | 1 |
| Black | 0 | 1 | 1 |
| Neonatal Unit | | | |
| Recruiting neonatal unit | | | |
| Units: Subjects | | | |
| Hull Royal Infirmary | 2 | 3 | 5 |
| Leicester Royal Infirmary | 1 | 2 | 3 |
| Liverpool Women's Hospital | 3 | 0 | 3 |
| Birmingham Women's Hospital | 2 | 0 | 2 |
| University Hospital Coventry | 1 | 1 | 2 |
| Bradford Royal Infirmary | 1 | 1 | 2 |
| Leeds General Infirmary | 2 | 0 | 2 |
| Royal Preston Hospital | 0 | 2 | 2 |
| Royal Victoria Infirmary, Newcastle | 0 | 1 | 1 |
| Antenatal steroids | | | |
| Units: Subjects | | | |

| | | | |
|---|----|----|----|
| Yes | 10 | 7 | 17 |
| No | 2 | 3 | 5 |
| Time between rupture of membranes and birth Units: Subjects | | | |
| <24 hours | 6 | 7 | 13 |
| >= 24 hours | 4 | 3 | 7 |
| Missing | 2 | 0 | 2 |
| Clinical chorioamnionitis evidence Units: Subjects | | | |
| Yes | 0 | 1 | 1 |
| No | 12 | 9 | 21 |
| Level of NNU at site of birth Units: Subjects | | | |
| Level II | 2 | 0 | 2 |
| Level III | 10 | 10 | 20 |
| Baby received diuretics for >24 hours at randomisation Units: Subjects | | | |
| Yes | 3 | 2 | 5 |
| No | 9 | 8 | 17 |
| Actual mode of delivery Units: Subjects | | | |
| Vaginal delivery | 10 | 6 | 16 |
| Caesarean section | 2 | 4 | 6 |
| Multiple pregnancy Units: Subjects | | | |
| Singleton | 11 | 8 | 19 |
| Multiple | 1 | 2 | 3 |
| Ibuprofen received before trial entry Units: Subjects | | | |
| Yes | 4 | 2 | 6 |
| No | 8 | 8 | 16 |
| Hydrocortisone received before trial entry Units: Subjects | | | |
| Yes | 2 | 0 | 2 |
| No | 10 | 10 | 20 |
| Ventilation method at trial entry Units: Subjects | | | |
| IPPV | 8 | 10 | 18 |
| HFOV | 4 | 0 | 4 |
| Most recent results at trial entry Units: Subjects | | | |
| No abnormality seen | 4 | 7 | 11 |
| IVH/ Hydrocephalus/ PVL/ Other white matter injury | 7 | 3 | 10 |
| Cranial ultrasound not performed | 1 | 0 | 1 |
| Maternal age | | | |
| Mother's age in years | | | |
| Units: years | | | |
| median | 26 | 28 | |

| | | | |
|--|------------------|------------------|---|
| inter-quartile range (Q1-Q3) | 21 to 31 | 23 to 34 | - |
| Birth weight Units: gram(s) arithmetic mean standard deviation | 730.4 ± 175.1 | 756.5 ± 191.1 | - |
| Birth weight centile Units: centile arithmetic mean standard deviation | 43.5 ± 32.5 | 45.6 ± 20.1 | - |
| Postnatal age at trial entry Units: day median inter-quartile range (Q1-Q3) | 13 11 to 20 | 16 14 to 18 | - |
| Temperature at admission to NNU (°C) | | | |
| Units: degree arithmetic mean standard deviation | 36.8 ± 1.1 | 37.4 ± 1.1 | - |
| Worst base deficit in first 24 hours after birth Units: milliequivalent(s)/litre arithmetic mean standard deviation | 10.9 ± 5.7 | 9.6 ± 5.1 | - |
| Apgar score at five minutes Units: score median inter-quartile range (Q1-Q3) | 5 0 to 8 | 5 2 to 8 | - |
| CRIB II Score Units: score median inter-quartile range (Q1-Q3) | 15 12 to 16 | 15 9 to 16 | - |
| Baby's actual weight at trial entry Units: gram(s) arithmetic mean standard deviation | 862.1 ± 252.7 | 851.1 ± 227.5 | - |
| Head circumference at trial entry Units: centimeter arithmetic mean standard deviation | 22.9 ± 1.5 | 23.9 ± 2.6 | - |
| FiO2 at trial entry Units: percent arithmetic mean standard deviation | 49.8 ± 12.9 | 41.2 ± 8.0 | - |
| Mean airway pressure at trial entry Units: cmHO arithmetic mean standard deviation | 8.9 ± 3.9 | 11.5 ± 3.4 | - |

End points

End points reporting groups

| | |
|---|---------------|
| Reporting group title | Dexamethasone |
| Reporting group description: very low dose dexamethasone (50 mcg/kg /day for 13 doses) | |
| Reporting group title | Placebo |
| Reporting group description: matched placebo | |

Primary: Time to first extubation (if extubated for >24 hours) after first IMP dose

| | |
|--|---|
| End point title | Time to first extubation (if extubated for >24 hours) after first IMP dose ^[1] |
| End point description: Time to event analysis | |
| End point type | Primary |
| End point timeframe: Up to 16 days post randomisation | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the trial was stopped early, no comparative analysis was performed due to the small number of participants recruited. Only descriptive statistics are reported.

| End point values | Dexamethason e | Placebo | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 ^[2] | 2 ^[3] | | |
| Units: hour | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Not censored (extubated for >24 hours by day 16) | 58.5 (47.9 to 91.5) | 58.4 (47.3 to 69.5) | | |

Notes:

[2] - Subjects extubated for >24 hours by day 16

[3] - Subjects extubated >24 hours by day 16

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first extubation after first IMP dose

| | |
|--|---|
| End point title | Time to first extubation after first IMP dose |
| End point description: Time-to-event analysis | |
| End point type | Secondary |
| End point timeframe: Up to 16 days post-randomisation | |

| End point values | Dexamethasone | Placebo | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 ^[4] | 6 ^[5] | | |
| Units: hour | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Not censored | 65.7 (47.9 to 91.5) | 58.4 (18.3 to 123.4) | | |

Notes:

[4] - Subjects extubated by day 16

[5] - Subjects extubated by day 16

Statistical analyses

No statistical analyses for this end point

Secondary: Extubation by day 7 (if extubated for >24 hours)

| | |
|----------------------------|--|
| End point title | Extubation by day 7 (if extubated for >24 hours) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Day 7 after first IMP dose | |

| End point values | Dexamethasone | Placebo | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[6] | 6 ^[7] | | |
| Units: subjects | 5 | 2 | | |

Notes:

[6] - Subjects not discontinued by Day 7

[7] - Subjects not discontinued by Day 7

Statistical analyses

No statistical analyses for this end point

Secondary: Extubation by day 7 (whether or not for more than 24 hours)

| | |
|----------------------------|---|
| End point title | Extubation by day 7 (whether or not for more than 24 hours) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Day 7 after first IMP dose | |

| End point values | Dexamethasone | Placebo | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[8] | 6 ^[9] | | |
| Units: subjects | 5 | 4 | | |

Notes:

[8] - Subjects not discontinued by Day 7

[9] - Subjects not discontinued by Day 7

Statistical analyses

No statistical analyses for this end point

Secondary: Alive at 36 weeks' PMA or discharge if sooner

| | |
|--------------------------------------|---|
| End point title | Alive at 36 weeks' PMA or discharge if sooner |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks' PMA or discharge if sooner | |

| End point values | Dexamethasone | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 10 | | |
| Units: Subjects | | | | |
| Yes | 10 | 9 | | |
| No | 2 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total duration of invasive ventilation through ET

| | |
|--------------------------------------|---|
| End point title | Total duration of invasive ventilation through ET |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks' PMA or discharge if sooner | |

| End point values | Dexamethasone | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 10 | | |
| Units: day | | | | |
| median (inter-quartile range (Q1-Q3)) | 23 (20 to 27) | 31 (20 to 47) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total duration of non-invasive respiratory support nasal CPAP, nasal ventilation or high flow oxygen therapy

| | |
|--------------------------------------|--|
| End point title | Total duration of non-invasive respiratory support nasal CPAP, nasal ventilation or high flow oxygen therapy |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks' PMA or discharge if sooner | |

| End point values | Dexamethasone | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 10 | | |
| Units: day | | | | |
| median (inter-quartile range (Q1-Q3)) | 40 (27 to 50) | 40 (28 to 46) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total duration of supplemental oxygen

| | |
|--------------------------------------|---------------------------------------|
| End point title | Total duration of supplemental oxygen |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks' PMA or discharge if sooner | |

| End point values | Dexamethasone | Placebo | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 10 | | |
| Units: day | | | | |
| median (inter-quartile range (Q1-Q3)) | 15 (2 to 19) | 4 (0 to 8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Open-label treatment with corticosteroids received after randomisation (cumulative dose)

| | |
|--------------------------------------|--|
| End point title | Open-label treatment with corticosteroids received after randomisation (cumulative dose) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks' PMA or discharge if sooner | |

| End point values | Dexamethasone | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 10 | | |
| Units: subjects | | | | |
| Yes | 5 | 4 | | |
| No | 7 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Diuretics received for >48 hours after randomisation

| | |
|--------------------------------------|--|
| End point title | Diuretics received for >48 hours after randomisation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 36 weeks' PMA or discharge if sooner | |

| End point values | Dexamethason e | Placebo | | |
|-----------------------------|-------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 10 | | |
| Units: subjects | | | | |
| Yes | 8 | 9 | | |
| No | 4 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: BPD assessment at 36 weeks' PMA or discharge if sooner

| | |
|-----------------|--|
| End point title | BPD assessment at 36 weeks' PMA or discharge if sooner |
|-----------------|--|

End point description:

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

End point timeframe:

At 36 weeks' PMA or discharge if sooner

| End point values | Dexamethason e | Placebo | | |
|-----------------------------|-------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 10 | | |
| Units: subjects | | | | |
| Mild | 2 | 0 | | |
| Moderate | 2 | 2 | | |
| Severe | 6 | 7 | | |
| Not assessed/died | 2 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Until 36 weeks post menstrual age

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

Dictionary used

| | |
|-----------------|----------------|
| Dictionary name | Not applicable |
|-----------------|----------------|

| | |
|--------------------|-----|
| Dictionary version | n/a |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Dexamethasone |
|-----------------------|---------------|

Reporting group description:

very low dose dexamethasone (50 mcg/kg /day for 13 doses)

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

Reporting group description:

matched placebo

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: Non-serious adverse events are not reported for this population.

| Serious adverse events | Dexamethasone | Placebo | |
|---|---|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | |
| number of deaths (all causes) | 2 | 1 | |
| number of deaths resulting from adverse events | | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Hypoglycaemia neonatal | Additional description: Severity: Mild. Causality: not related. Resolved. | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Dexamethasone | Placebo | |
|---|----------------|----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 01 September 2016 | <p>[Protocol v2.0 15/08/2016]</p> <p>Exclusion criteria edited for clarity: removal of the word 'concurrent' and 'previous' from exclusion criteria 1, 4 and 5.</p> <p>Secondary objectives updated to clarify recording at 36 weeks +/- 2 weeks or at discharge home if earlier.</p> <p>Typos/Removed ET abbreviation and replaced with 'endotracheal tube'/Consistency of phrasing: '36 weeks (or discharge home if sooner)' (Across the protocol).</p> <p>Clarification that 'existing diuretic therapy' is for the 24 hours prior to randomisation.</p> <p>Error in criteria for stopping trial medications – '48' hours changed to '72' hours.</p> <p>Clarification that the IMP can be administered orally as per the MHRA approved IMP labels (Section 5.5).</p> <p>All IMP stock will be stored on the neonatal unit rather than having separate stocks at pharmacy and on the neonatal unit (Section 5.5).</p> <p>Changed 'Trial Solution Request Form' to 'Pack Allocation Form' to reflect change in name of document.</p> <p>Addition of liver failure, left ventricular hypertrophy and hydrocephalus to foreseeable adverse events as recommended by the Chief Investigator and Clinical Lead. Removal of chronic lung disease as a separate foreseeable adverse event as this is considered the same as bronchopulmonary dysplasia. Changed 'focal' to 'gastro' for consistency (Section 6.4).</p> <p>Clarification of the process for reporting SAEs (Section 6.5).</p> <p>Oxygen reduction test flow diagram updated (Appendix 2).</p> <p>Signature section for the Chief Investigator and the Statistician have been removed. These signatures are now documented separately and stored in the Trial Master File (front page).</p> |
| 26 October 2017 | <p>[Protocol v4.0 04/10/2017]</p> <p>Change of Trial Statistician to Louise Linsell.</p> <p>'Changes to the inflammatory cytokine profile' now listed as an exploratory outcome rather than secondary outcome (as requested by the Sponsor's GCP expert).</p> <p>Addition of text to section 4.6 to provide further detail about the storage and analysis of blood and ET secretion microsamples (as requested by the Sponsor's GCP expert).</p> <p>Further clarity of the circumstances in which trial medications should be stopped.</p> <p>Further clarity on the recording of open-label corticosteroids.</p> |

| | |
|---------------|--|
| 12 March 2018 | <p>[Protocol v5.0 14/02/2018]</p> <p>Correction of abbreviations.</p> <p>Clarification of outcomes: time to first extubation after first IMP dose and extubation by day 7 (this refers to 7 completed days after first IMP dose).</p> <p>Correction of typos and minor grammatical errors.</p> <p>Increase in number of sites to ≤ 25.</p> <p>Clarification of timing of completion of Diary of Care and cytokine sampling.</p> <p>Addition of text regarding cytokine profiling, as requested by the laboratory team responsible for this aspect of the trial.</p> <p>Removal of 'continuation of a treatment course of antibiotic therapy beyond 72 hours duration' for stopping trial medication.</p> <p>Addition of text clarifying that study medication should be stopped if treatment is required which would be contra-indicated with use of steroids in the opinion of the treating clinical team</p> <p>Clarification of censoring of babies and exclusions from analyses</p> <p>Removal of 'temporarily' discontinued, as babies will only be permanently discontinued</p> <p>Removal of text regarding adjustment of effect estimates and exploratory analysis</p> <p>Change of risk ratios from 99 to 95% CI</p> <p>Clarification that the '28 days' for assessing BPD and suitability for an oxygen reduction test should be considered cumulative</p> |
|---------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported