



Clinical trial results:

A Randomised Controlled Trial of Early Targeted Patent Ductus Arteriosus Treatment Using a Risk Based Severity Score

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-004526-33 |
| Trial protocol | IE |
| Global end of trial date | 05 August 2020 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 25 November 2021 |
| First version publication date | 25 November 2021 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | PDARCT1 |
|-----------------------|---------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Royal College of Surgeons Ireland |
| Sponsor organisation address | 111 St Stephens Green, dublin, Ireland, Dublin 2 |
| Public contact | Mandy Jackson, Royal College of Surgeons Ireland, +353 18093863, sponsorship@rcsi.ie |
| Scientific contact | Afif-El-Khuffash, Royal College of Surgeons Ireland, +353 18093863, sponsorship@rcsi.ie |

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 | 07 September 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 August 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 August 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

We aim to identify infants at high risk of developing CLD/Death by utilising the PDAsc, and randomise those infants to early treatment with Ibuprofen versus placebo. We hypothesise that:

- in preterm infants less than 29 weeks gestation;
- at high risk of developing CLD/Death (Primary outcome) based on a PDAsc ≥ 5.0 ;
- obtained using echocardiography carried out between 36 and 48 hours of life;

,early treatment with non-steroidal anti-inflammatory drugs (Ibuprofen) compared with placebo will result in a reduction of CLD/Death by 36 weeks post menstrual age (PMA). Infants with a PDAsc < 5 will not be enrolled in the study but will be followed up to discharge to confirm their low risk status.

Protection of trial subjects:

The Patient Information leaflet clearly outlined that echocardiogram used in this study is routine practice at the hospital site, and no unpleasant effects were expected. More than 1000 babies have been monitored with this tool over the past 5 years and it has not resulted in any additional discomfort or complications. The echocardiogram is well-tolerated by babies and is safe. If any baby participating in the trial did not bear the procedure for any reason, the investigator ceased testing immediately.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 04 July 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 | Ireland: 60 |
| Worldwide total number of subjects | 60 |
| EEA total number of subjects | 60 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 60 |
| 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:

A sample of 30 infants per arm (a total of 60 infants) were recruited over the recruitment period. Recruitment started on 04-Jul-2016 and the last patient was recruited in January 2020.

Pre-assignment

Screening details:

Parents of eligible infants were approached over the first 36 hours of the newborns age to obtain written informed consent before carrying out the echocardiogram and assessing the inclusion/exclusion criteria. 145 subjects were assessed for eligibility and 85 were excluded based on not meeting the eligibility criteria.

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 |

Blinding implementation details:

The unblinded trial pharmacist or delegate prepared the trial drug or placebo and issued the syringe for infusion to the blinded trial investigator team for administration. The Ibuprofen preparation is colourless and odorless and was indistinguishable from the saline preparation used for the placebo arm. The designated pharmacist or delegate was aware of the treatment allocation in order to facilitate correct assignment and drug/placebo preparation.

Arms

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

Arm description:

Infants in the intervention arm received intravenous Ibuprofen (Pedea 5mg/1ml) at a dose of 10mg/kg (2ml/kg), followed by 2 doses of 5mg/kg (1ml/kg) 24 hours apart administered as a short infusion over 15 minutes.

| | |
|--|--------------------------------------|
| Arm type | Ibuprofen (Intervention) arm |
| Investigational medicinal product name | IBUPROFEN |
| Investigational medicinal product code | ATC code C01 EB16 |
| Other name | Pedea 5 mg/ml solution for injection |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Injection |

Dosage and administration details:

Infants in the intervention arm received intravenous Ibuprofen (Pedea 5mg/1ml) at a dose of 10mg/kg (2ml/kg), followed by 2 doses of 5mg/kg (1ml/kg) 24 hours apart administered as a short infusion over 15 minutes.

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

Arm description:

Infants in the control group received an intravenous dose of placebo (normal saline) at a volume equivalent to that in the intervention group (2ml/kg 1st dose; 1ml/kg 2nd & 3rd doses) administered as a short infusion over 15 minutes.

| | |
|--|-----------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Sodium Chloride (NaCL) 0.9%W/V |
| Investigational medicinal product code | Pharmacotherapeutic group:B05BB01 |
| Other name | NaCL |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Injection |

Dosage and administration details:

Sodium chloride was delivered intravenously

| Number of subjects in period 1 | Ibuprofen Arm | Placebo Arm |
|---------------------------------------|---------------|-------------|
| Started | 30 | 30 |
| Completed | 30 | 30 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall Trial |
| Reporting group description: - | |

| Reporting group values | Overall Trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 60 | 60 | |
| Age categorical | | | |
| Age data was also captured as mean+/- standard deviation per treatment arm | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 60 | 60 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Mean Age | 0 | 0 | |
| Age continuous | | | |
| Gestational age was captured in (weeks) for all subjects at the baseline visit. The overall median gestational age was captured. | | | |
| Units: weeks | | | |
| median | 26.3 | | |
| full range (min-max) | 25.3 to 27.4 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 24 | 24 | |
| Male | 36 | 36 | |
| Birthweight | | | |
| Birthweight was captured at the baseline visit for all subjects enrolled. Birthweight was captured in grams and the median birthweight overall was reported. | | | |
| Units: gram(s) | | | |
| median | 873 | | |
| full range (min-max) | 709 to 1075 | - | |

End points

End points reporting groups

| | |
|---|---------------|
| Reporting group title | Ibuprofen Arm |
| Reporting group description: Infants in the intervention arm received intravenous Ibuprofen (Pedea 5mg/1ml) at a dose of 10mg/kg (2ml/kg), followed by 2 doses of 5mg/kg (1ml/kg) 24 hours apart administered as a short infusion over 15 minutes. | |
| Reporting group title | Placebo Arm |
| Reporting group description: Infants in the control group received an intravenous dose of placebo (normal saline) at a volume equivalent to that in the intervention group (2ml/kg 1st dose; 1ml/kg 2nd & 3rd doses) administered as a short infusion over 15 minutes. | |

Primary: Chronic Lung Disease or Death

| | |
|---|-------------------------------|
| End point title | Chronic Lung Disease or Death |
| End point description: CLD was defined as the need for oxygen supplementation at 36 weeks corrected gestational age with typical chest radiograph changes. | |
| End point type | Primary |
| End point timeframe: The Primary end point was Chronic Lung Disease and / or death before discharge (CLD/Death). | |

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of subjects | 16 | 18 | | |

Statistical analyses

| | |
|--|-----------------------------------|
| Statistical analysis title | Statistical analysis of Endpoints |
| Statistical analysis description: The primary outcome and most of the secondary outcomes are dichotomous variables. Continuous variables was tested for normality by comparing the mean and median, a histogram representation of data, and the Shapiro-Wilk test for normality and was presented as means (standard deviation) or median [inter-quartile range] as appropriate. Dichotomous variables was presented as proportions and summarised in contingency tables. | |
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | < 0.05 ^[2] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.8 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 2.1 |
| Variability estimate | Standard deviation |

Notes:

[1] - All enrolled infants were analysed on an intention-to-treat basis. Analysis for the feasibility study was conducted once the recruitment of all patients was completed. No interim analysis of treatment effect was conducted.

[2] - P value for this outcome measure was 0.80

Secondary: Use of Inotropes in first week

| | |
|---|--------------------------------|
| End point title | Use of Inotropes in first week |
| End point description: | |
| Number of inotropes used (numeric) | |
| Duration of inotrope used in Days (numeric) | |
| End point type | Secondary |
| End point timeframe: | |
| First week of enrolment | |

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of Subjects | 2 | 2 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
| Statistical analysis description: | |
| A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | < 0.05 ^[4] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 7.6 |
| Variability estimate | Standard deviation |

Notes:

[3] - We will use IBM SPSS® (Version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[4] - P value for this outcome was 1.0

Secondary: Use of Frusemide (yes/no)

| | |
|---------------------------------|---------------------------|
| End point title | Use of Frusemide (yes/no) |
| End point description: | |
| Frusemide administration yes/no | |
| End point type | Secondary |
| End point timeframe: | |
| Duration of study participation | |

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of Subjects | 21 | 18 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
| Statistical analysis description: | |
| A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Placebo Arm v Ibuprofen Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | < 0.05 ^[6] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 4.5 |
| Variability estimate | Standard deviation |

Notes:

[5] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[6] - P value is 0.59

Secondary: Median Day of Frusemide Use

| | |
|-----------------|-----------------------------|
| End point title | Median Day of Frusemide Use |
|-----------------|-----------------------------|

| | |
|---------------------------------|-----------|
| End point description: | |
| Frusemide day of life (numeric) | |
| End point type | Secondary |
| End point timeframe: | |
| trial duration | |

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: day | | | | |
| median (full range (min-max)) | 22 (16 to 39) | 25 (19 to 33) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
|-----------------------------------|---|

Statistical analysis description:

A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes

| | |
|---|-----------------------------|
| Comparison groups | Placebo Arm v Ibuprofen Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| P-value | < 0.05 ^[8] |
| Method | Chi-squared |

Notes:

[7] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[8] - P value is 0.75

Secondary: Red cell transfusions

| | |
|-----------------|-----------------------|
| End point title | Red cell transfusions |
|-----------------|-----------------------|

End point description:

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| trial duration | |

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of subjects | 26 | 25 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
| Statistical analysis description: A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| P-value | < 0.05 ^[10] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 5.4 |
| Variability estimate | Standard deviation |

Notes:

[9] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[10] - P value is 1

Secondary: PDA treatment with Paracetamol

| | |
|--|--------------------------------|
| End point title | PDA treatment with Paracetamol |
| End point description: | |
| End point type | Secondary |
| End point timeframe: trial duration | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | Ibuprofen Arm | Placebo Arm | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of subjects | 5 | 10 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
| Statistical analysis description: A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Placebo Arm v Ibuprofen Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| P-value | < 0.05 ^[12] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 1.4 |
| Variability estimate | Standard deviation |

Notes:

[11] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[12] - p value is 0.23

Secondary: PDA Ligation

| | |
|--|--------------|
| End point title | PDA Ligation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: trial duration | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | Ibuprofen Arm | Placebo Arm | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of subjects | 6 | 6 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
| Statistical analysis description: A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Ibuprofen Arm v Placebo Arm |

| | |
|---|------------------------|
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[13] |
| P-value | < 0.05 ^[14] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 3.5 |
| Variability estimate | Standard deviation |

Notes:

[13] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[14] - p value is 1

Secondary: Pulmonary Haemorrhage

| | |
|------------------------|-----------------------|
| End point title | Pulmonary Haemorrhage |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Trial Duration | |

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of subjects | 1 | 1 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
| Statistical analysis description: | |
| A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Placebo Arm v Ibuprofen Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[15] |
| P-value | < 0.05 ^[16] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 16.8 |
| Variability estimate | Standard deviation |

Notes:

[15] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[16] - p value is 1

Secondary: Necrotising Enterocolitis

| | |
|------------------------|---------------------------|
| End point title | Necrotising Enterocolitis |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Trial duration | |

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of subjects | 6 | 4 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
| Statistical analysis description: | |
| A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[17] |
| P-value | < 0.05 ^[18] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 6.5 |
| Variability estimate | Standard deviation |

Notes:

[17] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[18] - p value is 0.73

Secondary: Postnatal steroids

| | |
|-----------------|--------------------|
| End point title | Postnatal steroids |
|-----------------|--------------------|

End point description:

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

End point timeframe:

trial duration

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: number of subjects | 5 | 2 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
|----------------------------|---|

Statistical analysis description:

A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes

| | |
|---|-----------------------------|
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[19] |
| P-value | < 0.05 ^[20] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 15.7 |
| Variability estimate | Standard deviation |

Notes:

[19] - we will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[20] - p value is 0.42

Secondary: Culture proven sepsis

| | |
|-----------------|-----------------------|
| End point title | Culture proven sepsis |
|-----------------|-----------------------|

End point description:

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

End point timeframe:
trial duration

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of subjects | 7 | 7 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
|----------------------------|---|

Statistical analysis description:

A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes

| | |
|---|-----------------------------|
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[21] |
| P-value | < 0.05 ^[22] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 3.3 |
| Variability estimate | Standard deviation |

Notes:

[21] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[22] - p value is 1

Secondary: Retinopathy of Prematurity requiring intervention

| | |
|-----------------|---|
| End point title | Retinopathy of Prematurity requiring intervention |
|-----------------|---|

End point description:

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

End point timeframe:
trial duration

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of subjects | 4 | 5 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
| Statistical analysis description: | |
| A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[23] |
| P-value | < 0.05 ^[24] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 3.2 |
| Variability estimate | Standard deviation |

Notes:

[23] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[24] - p value is 1

Secondary: Grade 3/4 Intraventricular Haemorrhage

| | |
|------------------------|--|
| End point title | Grade 3/4 Intraventricular Haemorrhage |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| trial duration | |

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of subjects | 1 | 1 | | |

Statistical analyses

| Statistical analysis title | Statistical analysis of secondary Endpoints |
|--|---|
| Statistical analysis description: | |
| A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[25] |
| P-value | < 0.05 ^[26] |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 16.8 |
| Variability estimate | Standard deviation |

Notes:

[25] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[26] - p value is 1

Secondary: Periventricular Leukomalacia

| | |
|------------------------|------------------------------|
| End point title | Periventricular Leukomalacia |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| trial duration | |

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: Number of subjects | 4 | 0 | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
|-----------------------------------|---|

Statistical analysis description:

A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes

| | |
|---|-----------------------------|
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[27] |
| P-value | < 0.05 ^[28] |
| Method | Chi-squared |

Notes:

[27] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[28] - p value is 0.12

Secondary: Ventilation Days

| | |
|-----------------|------------------|
| End point title | Ventilation Days |
|-----------------|------------------|

End point description:

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

End point timeframe:

trial duration

| | | | | |
|-------------------------------|-----------------|-----------------|--|--|
| End point values | Ibuprofen Arm | Placebo Arm | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: days | | | | |
| median (full range (min-max)) | 3 (1 to 8) | 3 (1 to 14) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
|-----------------------------------|---|

Statistical analysis description:

A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes

| | |
|---|-----------------------------|
| Comparison groups | Placebo Arm v Ibuprofen Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[29] |
| P-value | < 0.05 ^[30] |
| Method | Chi-squared |

Notes:

[29] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[30] - p value is 0.50

Secondary: CPAP Days

| | |
|-----------------|-----------|
| End point title | CPAP Days |
|-----------------|-----------|

End point description:

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

End point timeframe:

trial duration

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: days | | | | |
| median (full range (min-max)) | 38 (26 to 47) | 34 (28 to 47) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
|----------------------------|---|

Statistical analysis description:

A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes

| | |
|-------------------|-----------------------------|
| Comparison groups | Ibuprofen Arm v Placebo Arm |
|-------------------|-----------------------------|

| | |
|---|----|
| Number of subjects included in analysis | 60 |
|---|----|

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

| | |
|---------------|-----------------------|
| Analysis type | other ^[31] |
|---------------|-----------------------|

| | |
|---------|------------------------|
| P-value | < 0.05 ^[32] |
|---------|------------------------|

| | |
|--------|-------------|
| Method | Chi-squared |
|--------|-------------|

Notes:

[31] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[32] - p value is 0.56

Secondary: HFNC Days

| | |
|-----------------|-----------|
| End point title | HFNC Days |
|-----------------|-----------|

End point description:

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

End point timeframe:

trial duration

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: days | | | | |
| median (full range (min-max)) | 14 (9 to 25) | 16 (8 to 22) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis of secondary Endpoints |
|---|---|
| Statistical analysis description: A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[33] |
| P-value | < 0.05 ^[34] |
| Method | Chi-squared |

Notes:

[33] - we will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[34] - p value is 0.88

Secondary: Oxygen Days

| End point title | Oxygen Days |
|------------------------|-------------|
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| trial duration | |

| End point values | Ibuprofen Arm | Placebo Arm | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: days | | | | |
| median (full range (min-max)) | 9 (1 to 20) | 12 (2 to 26) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
| Statistical analysis description: A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[35] |
| P-value | < 0.05 ^[36] |
| Method | Chi-squared |

Notes:

[35] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[36] - p value is 0.66

Secondary: Hospital Days

| | |
|--|---------------|
| End point title | Hospital Days |
| End point description: | |
| End point type | Secondary |
| End point timeframe: trial duration | |

| | | | | |
|-------------------------------|-----------------|-----------------|--|--|
| End point values | Ibuprofen Arm | Placebo Arm | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: day | | | | |
| median (full range (min-max)) | 87 (75 to 97) | 87 (74 to 97) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis of secondary Endpoints |
| Statistical analysis description: A chi squared test will be used for the primary analysis of the dichotomous primary and secondary outcomes | |
| Comparison groups | Ibuprofen Arm v Placebo Arm |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[37] |
| P-value | < 0.05 ^[38] |
| Method | Chi-squared |

Notes:

[37] - We will use IBM SPSS® (version 22) to perform the statistical analysis. All enrolled infants will be analysed on an intention-to-treat basis. Analysis for the feasibility study will only be conducted once the recruitment of all patients is completed. No interim analysis of treatment effect will be conducted

[38] - p value is 0.87

Adverse events

Adverse events information

Timeframe for reporting adverse events:

baseline to 120-168 hour visit (Visit 4)

Adverse event reporting additional description:

Investigator performed check of adverse event from baseline to 120-168 hour visit (Visit 4) by reviewing the subject chart.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Intervention |
|-----------------------|--------------|

Reporting group description: -

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

Reporting group description:

Infants in the control group received an intravenous dose of placebo (normal saline) at a volume equivalent to that in the intervention group (2ml/kg 1st dose; 1ml/kg 2nd & 3rd doses) administered as a short infusion over 15 minutes. The patency of the ductus was assessed 24 hours after the last placebo dose using echocardiography. If the PDA remained open (PDA diameter > 1.5 mm), then a second course of placebo was given.

| Serious adverse events | Intervention | Placebo | |
|---|-----------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 30 (16.67%) | 15 / 30 (50.00%) | |
| number of deaths (all causes) | 2 | 4 | |
| number of deaths resulting from adverse events | 2 | 4 | |
| Congenital, familial and genetic disorders | | | |
| Ventricular septal defect | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Intraventricular haemorrhage neonatal | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 30 (6.67%) | 3 / 30 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Premature baby | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Necrotising enterocolitis neonatal | | | |
| subjects affected / exposed | 3 / 30 (10.00%) | 4 / 30 (13.33%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neonatal intestinal perforation | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Infections and infestations | | | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis neonatal | | | |
| subjects affected / exposed | 3 / 30 (10.00%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Intervention | Placebo | |
|--|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 30 / 30 (100.00%) | 30 / 30 (100.00%) | |
| Vascular disorders | | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypotension | | | |

| | | | |
|--|------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Thrombosis subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Pregnancy, puerperium and perinatal conditions Jaundice neonatal subjects affected / exposed occurrences (all) | 28 / 30 (93.33%) 28 | 29 / 30 (96.67%) 29 | |
| Weight decrease neonatal subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 4 / 30 (13.33%) 4 | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 2 / 30 (6.67%) 2 | |
| Hyperthermia subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Hypothermia subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Acute respiratory distress syndrome subjects affected / exposed occurrences (all) | 24 / 30 (80.00%) 24 | 30 / 30 (100.00%) 30 | |
| Apnoea subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 1 / 30 (3.33%) 1 | |
| Neonatal aspiration subjects affected / exposed occurrences (all) | 6 / 30 (20.00%) 6 | 9 / 30 (30.00%) 9 | |
| Respiratory failure subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |

| | | | |
|---|---------------------|---------------------|--|
| Respiratory disorder neonatal subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Pleural effusion subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Pulmonary haemorrhage subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 2 / 30 (6.67%) 2 | |
| Pulmonary hypertension subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 1 / 30 (3.33%) 1 | |
| Upper airway obstruction subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Investigations | | | |
| Blood calcium increased subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 0 / 30 (0.00%) 0 | |
| Blood magnesium increased subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Body temperature fluctuation subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Urine output increased subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Brain scan abnormal | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 30 (10.00%) 3 | 3 / 30 (10.00%) 3 | |
| Ultrasound abdomen abnormal subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 2 / 30 (6.67%) 2 | |
| Blood sodium decreased subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 1 / 30 (3.33%) 1 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 2 / 30 (6.67%) 2 | |
| Skin laceration subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Cardiac disorders | | | |
| Cardiopulmonary failure subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Ventricular septal defect subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Nervous system disorders | | | |

| | | | |
|--|------------------------|------------------------|--|
| Intraventricular haemorrhage neonatal subjects affected / exposed occurrences (all) | 8 / 30 (26.67%) 10 | 14 / 30 (46.67%) 15 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 12 / 30 (40.00%) 19 | 11 / 30 (36.67%) 14 | |
| Leukopenia subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 2 / 30 (6.67%) 2 | |
| Leukocytosis subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Neutropenia subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 0 / 30 (0.00%) 0 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 4 / 30 (13.33%) 4 | 2 / 30 (6.67%) 2 | |
| Gastrointestinal disorders | | | |
| Necrotising colitis subjects affected / exposed occurrences (all) | 4 / 30 (13.33%) 4 | 3 / 30 (10.00%) 3 | |
| Abdominal distension subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Meconium ileus subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Inguinal hernia subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Upper gastrointestinal haemorrhage subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|----------------------|----------------------|--|
| Skin discolouration subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Pigmentation disorder subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 2 / 30 (6.67%) 2 | |
| Umbilical erythema subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 2 / 30 (6.67%) 2 | |
| Decubitus ulcer subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Rash subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Skin disorder subjects affected / exposed occurrences (all) | 9 / 30 (30.00%) 9 | 4 / 30 (13.33%) 4 | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 0 / 30 (0.00%) 0 | |
| Haematuria subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Hypercalciuria subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 1 / 30 (3.33%) 1 | |
| Musculoskeletal and connective tissue disorders Muscle rigidity subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Intervertebral disc protrusion | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Sepsis neonatal | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Omphalitis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Metabolism and nutrition disorders | | | |
| Feeding intolerance | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 3 / 30 (10.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 3 | 3 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 18 / 30 (60.00%) | 10 / 30 (33.33%) | |
| occurrences (all) | 19 | 10 | |
| Hyperkalaemia | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 12 / 30 (40.00%) | 14 / 30 (46.67%) | |
| occurrences (all) | 12 | 14 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 3 / 30 (10.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 3 | 2 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 8 / 30 (26.67%) | 11 / 30 (36.67%) | |
| occurrences (all) | 8 | 12 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 4 / 30 (13.33%) | 3 / 30 (10.00%) | |
| occurrences (all) | 4 | 3 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 25 August 2016 | <p>Paragraph modified to clarify that all statistical tests will be two tailed and that Fisher's exact test (in place of the chi-squared test) will be used when the counts in one or more cells have an expected frequency of five or less (for 2 by 2 table).</p> <p>Control Arm: The administration of the Placebo was clarified and altered to exactly mirror the administration of the Intervention.</p> <p>Timing of ECHO 3 corrected from 120 hours to 192 hours.</p> <p>Randomisation method clarified to state that infants will be stratified into two gestational age brackets: 23 – 26 weeks and 27 – 28 weeks.</p> <p>Placebo: The administration of the Placebo was clarified and altered to exactly mirror the administration of the Intervention.</p> <p>Paragraph modified to clarify that all statistical tests will be two tailed and that Fisher's exact test (in place of the chi-squared test) will be used when the counts in one or more cells have an expected frequency of five or less (for 2 by 2 table).</p> <p>The sample size justification was corrected to state that the sample size will be sufficient to demonstrate a significant difference in the primary outcome between the groups if the event rate is reduced from 90% in the control arm to 55% (rather than 60%) in the intervention arm.</p> |
| 26 March 2019 | <p>Updated recruitment timeframe/window.</p> <p>Sponsor/site team details updated</p> <p>Anticipated recruitment period updated to align with amended Study end date, reflecting delay in recruitment.</p> <p>Timeframe for recording concomitant medication specified for clarity.</p> <p>Safety Section updated to reflect current Safety practices and Sponsor designated SOPs.</p> <p>Sponsor pharmacovigilance email address changed to reflect the current email for reporting Serious Adverse Events</p> |

Notes:

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/33069668>