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 hosptial 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 wasconducted.

[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 Entercolitis

End point title	Necrotising Entercolitis

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)		

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

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

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

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

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

subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	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	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). Control Arm: The administration of the Placebo was clarified and altered to exactly mirror the administration of the Intervention. Timing of ECHO 3 corrected from 120 hours to 192 hours. Randomisation method clarified to state that infants will be stratified into two gestational age brackets: 23 – 26 weeks and 27 – 28 weeks. Placebo: The administration of the Placebo was clarified and altered to exactly mirror the administration of the Intervention. 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). 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.
26 March 2019	Updated recruitment timeframe/window. Sponsor/site team details updated Anticipated recruitment period updated to align with amended Study end date, reflecting delay in recruitment. Timeframe for recording concomitant medication specified for clarity. Safety Section updated to reflect current Safety practices and Sponsor designated SOPs. Sponsor pharmacovigilance email address changed to reflect the current email for reporting Serious Adverse Events

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