Clinical trial results:
Efficacy and safety of paracetamol in comparison to ibuprofen for patent ductus arteriosus treatment in preterm infants. A randomized, open label, comparator-controlled, prospective study.

Summary

EudraCT number	2013-003883-30
Trial protocol	IT
Global end of trial date	17 April 2019

Results information

Result version number	v1 (current)
This version publication date	20 November 2019
First version publication date	20 November 2019

Trial information

Trial identification

Sponsor protocol code	044CF13273

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02422966
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F. S.p.A
Sponsor organisation address	Piazzale della Stazione s.n.c. S.Palomba-Pomezia (Rome) Italy, Rome, Italy, 00071
Public contact	A.C.R.A.F. HQMD Clinical Operations, ACRAF S.p.A, +39 0691945349, paola.lipone@angelinipharma.com
Scientific contact	A.C.R.A.F. HQMD Clinical Operations, ACRAF S.p.A, +39 0691945349, paola.lipone@angelinipharma.com

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	17 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 April 2019
Global end of trial reached?	Yes
Global end of trial date	17 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study objective is to assess the efficacy and safety of paracetamol in comparison to ibuprofen in the treatment of patent ductus arteriosus in preterm infants.

Protection of trial subjects:

The study was carried out according to ICH guidelines of Good Clinical Practices (CPMP/ICH/135/95) and Helsinki Declaration (Fortaleza - Brasil 2013)

Background therapy:

Not applicable

Evidence for comparator:

Pedea (ibuprofen) 5 mg/ml solution for injection has been selected as treatment comparator because it represents the only drug authorised in the EU since 29 July 2004 for the treatment of a hsPDA in preterm newborn infants less than 34 weeks of gestational age [EU/3/01/020]. Doses of ibuprofen to be administered to the patients are consistent with those reported in the relevant SPC.

Actual start date of recruitment	18 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 109
Worldwide total number of subjects	109
EEA total number of subjects	109

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	109
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:

Recruitment of 110 patients was planned. 110 patients were randomised to allocated intervention (52 in Ibuprofen group and 58 in Paracetamol) from 8 December 2015 to 22 January 2019.One patient was erroneously randomised to Ibuprofen group but did not receive medication.

Pre-assignment

Screening details:

One patient was erroneously randomised to Ibuprofen group but did not receive medication.

Period 1

Period 1 title	PERIOD 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	IBUPROFEN 5mg/ml

Arm description:

Ibuprofen intravenous solution administered at an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 h and 5 mg/kg at 48 h.

Arm type	Active comparator
Investigational medicinal product name	Ibuprofen
Investigational medicinal product code	
Other name	Pedea
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Ibuprofen intravenous solution at an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 h and 5 mg/kg at 48 h.

Arm title	PARACETAMOL 10 mg/ml

Arm description:

Paracetamol intravenous solution 15 mg/kg (corresponding to 1.5 ml/kg) per dose every 6 hours for 3 days, for a total amount of 12 doses.

Arm type	Experimental
Investigational medicinal product name	Paracetamol
Investigational medicinal product code	044
Other name	Tachipirina i.v.
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paracetamol intravenous solution 15 mg/kg (corresponding to 1.5 ml/kg) per dose every 6 hours for 3 days, for a total amount of 12 doses.

Number of subjects in period 1	IBUPROFEN 5mg/ml	PARACETAMOL 10 mg/ml
Started	51	58
Completed	37	29
Not completed	14	29
Adverse event, serious fatal	1	3
DA reopening during follow up period	-	8
Adverse event, non-fatal	-	1
DA reopening during follow up	5	-
Worsening from not hsPDA to hsPDA	3	6
Other reasons	3	3
Any condition listed in the exclusion criteria	2	5
Protocol deviation	-	3

Baseline characteristics

Reporting groups	
Reporting group title	IBUPROFEN 5mg/ml
Reporting group description:	
Ibuprofen intravenous solution administered at an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 h and 5 mg/kg at 48 h.	
Reporting group title	PARACETAMOL 10 mg/ml
Reporting group description:	
Paracetamol intravenous solution 15 mg/kg (corresponding to 1.5 ml/kg) per dose every 6 hours for 3 days, for a total amount of 12 doses.	

Reporting group values	IBUPROFEN 5mg/ml	PARACETAMOL 10 mg/ml	Total
Number of subjects	51	58	109
Age categorical Units: Subjects			
Gestational age <37 weeks	51	58	109
Age continuous Units: weeks			
arithmetic mean	28.31	28.18	
standard deviation	± 2.02	± 1.47	-
Gender categorical Units: Subjects			
Female	28	34	62
Male	23	24	47

Subject analysis sets	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population (SP) was defined as all randomised patients who took at least one dose of the study medication.	
Subject analysis set title	Modified Intention to Treat (m-ITT) population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified Intention-to-Treat (m-ITT) population: all randomized patients completing the first treatment course, and having the baseline and the day 3 echocardiographic assessments. The Per Protocol (PP) population was defined as patients from the mITT population with no major protocol violations. Since no major protocol violations were detected the m-ITT and the PP population were the same.	

Reporting group values	Safety population	Modified Intention to Treat (m-ITT) population	
Number of subjects	109	101	
Age categorical Units: Subjects			
Gestational age <37 weeks	109	101	

Age continuous Units: weeks			
arithmetic mean	28.4	28.26	
standard deviation	± 1.74	± 1.73	
Gender categorical Units: Subjects			
Female	62	59	
Male	47	42	

End points

End points reporting groups

Reporting group title	IBUPROFEN 5mg/ml
Reporting group description:	
Ibuprofen intravenous solution administered at an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 h and 5 mg/kg at 48 h.	
Reporting group title	PARACETAMOL 10 mg/ml
Reporting group description:	
Paracetamol intravenous solution 15 mg/kg (corresponding to 1.5 ml/kg) per dose every 6 hours for 3 days, for a total amount of 12 doses.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population (SP) was defined as all randomised patients who took at least one dose of the study medication.	
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Primary: Rate closure of PDA

End point title	Rate closure of PDA
End point description:	
The primary endpoint of the study was the evaluation of the success rate in closing PDA using paracetamol in comparison to ibuprofen after the first 3 days of treatment. Success was defined as the closing PDA after 3 days of treatment with paracetamol or ibuprofen assessed echocardiographically at Visit 3.	
End point type	Primary
End point timeframe:	
Day 3	

End point values	IBUPROFEN 5mg/ml	PARACETAMOL 10 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	51		
Units: event				
DA Closure-Yes	38	27		
DA Closure-No	11	25		

Statistical analyses

Statistical analysis title	Group comparison

Statistical analysis description:

Comparisons between groups was performed by χ2 test. Tests were performed at an alpha level of 5% two-sided

Comparison groups	PARACETAMOL 10 mg/ml v IBUPROFEN 5mg/ml
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared
Parameter estimate	success percent

Secondary: Rate in closing PDA after the second treatment course of ibuprofen as rescue medication;

End point title	Rate in closing PDA after the second treatment course of ibuprofen as rescue medication;

End point description:

Success rate in closing PDA after the second treatment course of ibuprofen as rescue medication.

End point type	Secondary

End point timeframe:

Day 6

End point values	IBUPROFEN 5mg/ml	PARACETAMOL 10 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[1]	10[2]		
Units: event				
DA Closure - Yes	2	4		
DA Closure - No	2	6		

Notes:

[1] - The group refers to subjects with hsPDA at Visit 3

[2] - The group refers to subjects with hsPDA at Visit 3

Statistical analyses

Statistical analysis title	Group comparison
Comparison groups	IBUPROFEN 5mg/ml v PARACETAMOL 10 mg/ml
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared
Parameter estimate	success percent

Secondary: Number of re-openings at 30 days

End point title	Number of re-openings at 30 days

End point description:

End point type	Secondary

End point timeframe:

From Day 0 to Day 30

End point values	IBUPROFEN 5mg/ml	PARACETAMOL 10 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	39		
Units: event				
Re-opening - Yes	8	14		
Re-opening - No	35	25		

Statistical analyses

Statistical analysis title	Group comparison

Statistical analysis description:

Comparisons between groups was performed by $\chi 2$ test. Tests were performed at an alpha level of 5% two-sided

Comparison groups	IBUPROFEN 5mg/ml v PARACETAMOL 10 mg/ml
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared
Parameter estimate	Success percent

Secondary: Incidence of surgical ligations at 30 days

End point title	Incidence of surgical ligations at 30 days

End point description:

End point type	Secondary

End point timeframe:

From Day 0 to Day 30

End point values	IBUPROFEN 5mg/ml	PARACETAMOL 10 mg/ml		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: event				
Surgical ligation - Yes	1	1		
Surgical ligation - No	46	48		

Statistical analyses

Statistical analysis title	Group comparison

Statistical analysis description:

Comparisons between groups was performed by $\chi 2$ test. Tests were performed at an alpha level of 5% two-sided

Comparison groups	IBUPROFEN 5mg/ml v PARACETAMOL 10 mg/ml
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared
Parameter estimate	Success percent

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) were recorded from the signature of the Informed Consent up to the last visit scheduled in the study protocol (40 weeks post conception).

Adverse event reporting additional description:

Safety was assessed by monitoring the frequency of adverse events in each treatment group. Changes from baseline in physical examination, vital signs and urine output were also assessed. Laboratory analyses were evaluated on the basis of the normal range, the Investigator's judgment, and mean changes from screening.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	IBUPROFEN 5mg/ml

Reporting group description:

51 subjects treated with Ibuprofen intravenous solution 5mg/ml.

Reporting group title	PARACETAMOL 10 mg/ml

Reporting group description:

58 subjects treated with paracetamol 10 mg/ml

Serious adverse events	IBUPROFEN 5mg/ml	PARACETAMOL 10 mg/ml	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 51 (9.80%)	10 / 58 (17.24%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	2	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Intestinal malrotation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Atrial thrombosis			

subjects affected / exposed	1 / 51 (1.96%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 51 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising colitis			
subjects affected / exposed	0 / 51 (0.00%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Intestinal obstruction			
subjects affected / exposed	0 / 51 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	0 / 51 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IBUPROFEN 5mg/ml	PARACETAMOL 10 mg/ml	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 51 (74.51%)	34 / 58 (58.62%)	
Vascular disorders			
Hyperaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Astringent therapy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	3 / 51 (5.88%)	1 / 58 (1.72%)	
occurrences (all)	3	1	
Reproductive system and breast disorders			
Vaginal prolapse			
subjects affected / exposed	1 / 51 (1.96%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Apnoea neonatal			
subjects affected / exposed	3 / 51 (5.88%)	1 / 58 (1.72%)	
occurrences (all)	3	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 51 (1.96%)	2 / 58 (3.45%)	
occurrences (all)	1	2	
Investigations			

Cardiac murmur			
subjects affected / exposed	1 / 51 (1.96%)	0 / 58 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	0 / 51 (0.00%)	3 / 58 (5.17%)	
occurrences (all)	0	3	
Congenital, familial and genetic disorders			
Congenital hyperthyroidism			
subjects affected / exposed	2 / 51 (3.92%)	1 / 58 (1.72%)	
occurrences (all)	2	1	
Cardiac disorders			
Bradycardia neonatal			
subjects affected / exposed	2 / 51 (3.92%)	0 / 58 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Anaemia neonatal			
subjects affected / exposed	9 / 51 (17.65%)	11 / 58 (18.97%)	
occurrences (all)	14	16	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 51 (1.96%)	2 / 58 (3.45%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 51 (1.96%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	1 / 51 (1.96%)	1 / 58 (1.72%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	3 / 51 (5.88%)	0 / 58 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			

Sepsis subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 6	7 / 58 (12.07%) 9	
Metabolism and nutrition disorders Metabolic acidosis subjects affected / exposed occurrences (all)	15 / 51 (29.41%) 18	13 / 58 (22.41%) 19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2015	• The substantial Amendment no. 1 (March 04th, 2015) was carried out to be fully compliant with the Italian Guideline for the treatment of personal data in clinical trials (Deliberazione n° 52 del 24 Luglio 2008 del Garante per la Protezione dei Dati Personali – "Linee Guida per i Trattamenti di Dati Personali nell'ambito delle Sperimentazioni Cliniche dei Medicinali"). In addition, changes regarding Sponsor Personnel involved in the study and contact details of a vendor were also proposed in the study protocol. Some minor changes were performed to correct typing errors and provide more detailed instructions for the adverse events recording/reporting. An updated version of the Investigator's Brochure (IB) (version no. 3 of March 04th, 2015) including new Sponsor personnel, new available clinical and post-marketing data was also provided with this Study Amendment. The changes proposed were applied to all sites where the study was submitted/approved. The Study Amendment no. 1 was approved by the National applicable Ethics Committees and the Italian Competent Authority, when applicable.
05 October 2016	• The substantial Study Amendment no. 3 (October 5th, 2016) proposed the replacement of the Principal Investigator of the investigational site IT5 – UOC Neonatologia e Terapia Intensiva Neonatale, Fondazione Policlinico Agostino Gemelli (Roma) due to his retirement, starting from the 1st of November 2016. The proposed Study Amendment was applied only to the investigational site IT5 of the present clinical trial. The Study Amendment no.3 was approved notified to the applicable by National Ethics Committee and Competent Authority, when applicableonly

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: